The making of liqui-pellet and liqui-tablet, the next generation oral dosage form

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DECLARATION

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another university for the award of any other degree

Signature:

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List of abbreviation

API: Active pharmaceutical ingredient

BSC: Biopharmaceutical classification system

DSC: Differential scanning calorimetry

f_1: Difference factor

f_2: Similarity factor

F_M: Fraction of molecularly dispersed drug

GIT: Gastro-intestinal tract

HCTZ: Hydrochlorothiazide

HLB: Hydrophile-lipophile balance

HPMC: hydroxypropyl methylcellulose

HTS: High throughput screening

L_f: Load factor

MCC: Microcrystalline cellulose

MUPS: Multi-unit pellet system

PEG: polyethylene glycol

PG: Propylene glycol

PVP: polyvinylpyrrolidone

R value: Ratio of carrier and coating material

SEM: Scanning electron microscopy

SSA: Specific surface area

SUDS: Single unit dosage system

TMUPS: Tablet multi-unit pellet system

XRPD: X-ray powdered diffraction

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ADDITIONAL RESEARCH ACTIVITY

The technology invented in this project was filed for patent. Patent application number is 1812022.0.

ABSTRACT

The aim of the project is to use concept from liquisolid technology to improve dissolution rate, which is the rate limiting step for bioavailability for poorly water-soluble drug. This is a major challenge in the pharmaceutical industry. In fact, approximately 60% of drugs in the market are considered poorly soluble in gastrointestinal fluids, and around 40% of drugs in development are identified as poorly water-soluble; both of which is based on biopharmaceutical classification system (BCS). There are various other technologies with the same purpose of improving dissolution rate, however, liquisolid technology hold key advantages making it appealing to formulation scientist. These advantages include: simplistic approach (advance machinery and technique not required); cost effective; use green technology and excipient used are conventional and easily obtainable. Despite such appealing advantages, in reality liquisolid technology is hampered from being commercially used due to major drawbacks such as, inability to produce high dose drug without being too bulky for swallowing and poor flow property, which poses difficulty in manufacturing. This give rise to the invention of liqui-pellet and liqui-tablet in this project, which successfully overcome liquisolid drawbacks. These new dosage form can have high liquid load factor whilst achieving excellent flow property as well as maintaining acceptable weight for high dose drug.

Liqui-pellet stems from the combination of concept from liquisolid technology and pelletization technology. Poorly water-soluble API (active pharmaceutical ingrideint) such as, naproxen and hydrochlorothiazide (HCTZ) were used as the model API. Naproxen and HCTZ liqui-pellet were successfully made, including their optimized formulations. Some of these optimized formulations included effervescent agent (sodium bicarbonate), superdisintegrant and high specific surface area carrier (neusilin US2). This demonstrate that liqui-pellet is versatile for formulation design modification via addition of functional excipient/s whilst maintaining acceptable weight for swallowing. In fact, all formulation made was of acceptable weight for swallowing. Almost all of the formulations have relatively high liquid load factor whilst achieving excellent flowability, which has not been seen in liquisolid formulation before. Furthermore, the optimized naproxen was able to achieve remarkably rapid drug release rate of 100% in 20 min at an acidic pH of 1.2, which naproxen is known to be practically insoluble in. As for optimized HCTZ liqui-pellet, 100% drug release rate was achieved after 15 min at pH 1.2. Such rapid drug release rate is shown to be more superior than other technologies including liquisolid compact, solid dispersion and solid self-dispersing micelle when compared with other studies.

From liqui-pellet, the focus of the project shift to liqui-tablet, which in its simplest form is essentially compressed liqui-pellet. The aim is to explore the potential to diversify this new technology and to respond to the strong incentive for tablet dosage form (tablet being the most favored oral dosage form and more cost-effective than capsule). Naproxen liqui-tablet was successfully made, verifying liqui-tablet feasibility. The liqui-tablet was able to revert back to its multi-unit pellet system, which maintain the inherent advantages of liqui-pellet; but also, able to maintain the rapid drug dissolution rate.

The final investigation was to see if high dose liqui-tablet was feasible (ketoprofen 100mg). Ketoprofen 100mg liqui-tablet was successfully made, verifying its feasibility. Not only was it feasible, it also only weighed 483.8mg whilst having excellent to good pre-compressed flow property. This is a major advancement as it takes liquisolid concept into a commercially feasible direction for high dose drug, which has never been achieved in liquisolid formulation before.

Throughout the project, various other physicochemical properties were analyzed such as: flowability test; saturation solubility test; friability test; particle size analysis by sieve method; stereoscopic analysis; tablet hardness test; scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and stability test. In general, most formulation achieve good robustness and excellent flow properties with narrow size distribution, which is ideal for manufacturing and quality control test.

Overall, liqui-pellet and liqui-tablet have demonstrated itself a promising next generation oral dosage form with capability of remarkably rapid drug release, and array of advantages including versatility for formulation manipulation (i.e. addition of functional excipient/s), cost-effective, simple to produce, inherent advantages from liquisolid technology and inherent advantages from pelletization technology.

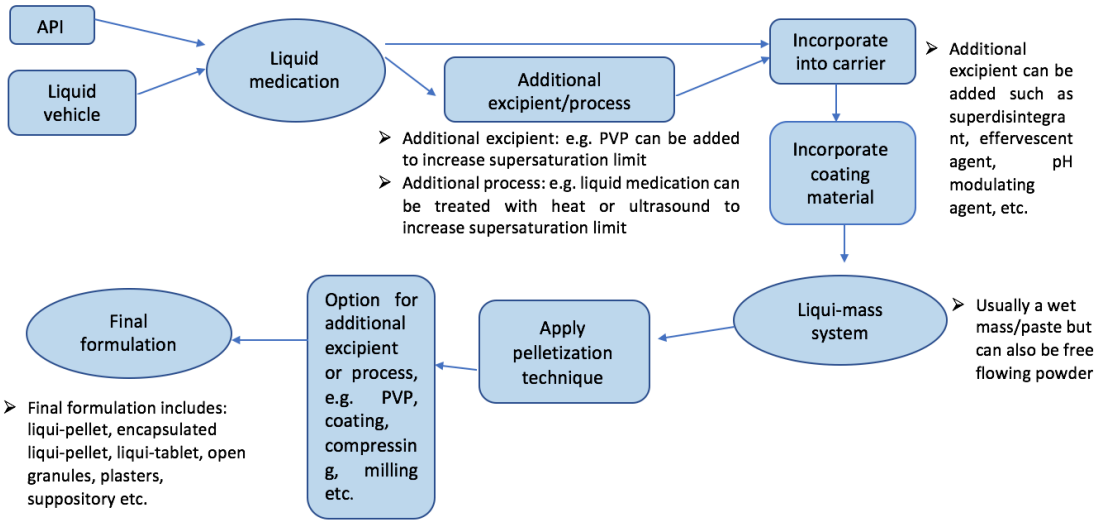
Chapter 1: Introduction

1.1 Liqui-pellet and liqui-tablet overview

At the time of writing this thesis, the author has invented liqui-pellet and liqui-tablet, which is considered the next generation oral dosage form; and is under the process of being filed for patent. For this reason, there is currently no literature on these dosage form; however, the author of the current PhD thesis believes an overview on these dosage form and the technology behind it will be beneficial in giving the reader a grasp of this study.

Liqui-pellet and liqui-tablet (compacted liqui-pellet) are aimed at improving absorption of poorly water-soluble drug mainly through enhanced dissolution rate. Liqui-pellet primarily stem from combining the concept of liquisolid technology with pelletization technology, which then can be compressed into liqui-tablet. It is noteworthy to point out that liqui-pellet and liqui-tablet are fundamentally different from liquisolid formulation in that it does not fit under the liquisolid system, but instead comes under liqui-mass system. A summary of liui-pellet and liqui-tablet under liqui-mass system is shown in Figure. 1.1 (I). In brief, wet mass is made through incorporating carrier and coating materials to the liquid medication, which then undergoes pelletization process.

The structure of a single liqui-pellet composed of carrier, liquid medication, coating material and possibly additional excipient is shown in Figure. 1.1. (II). Details of this technology will be further explained in the introduction section of chapter 2 to 11.



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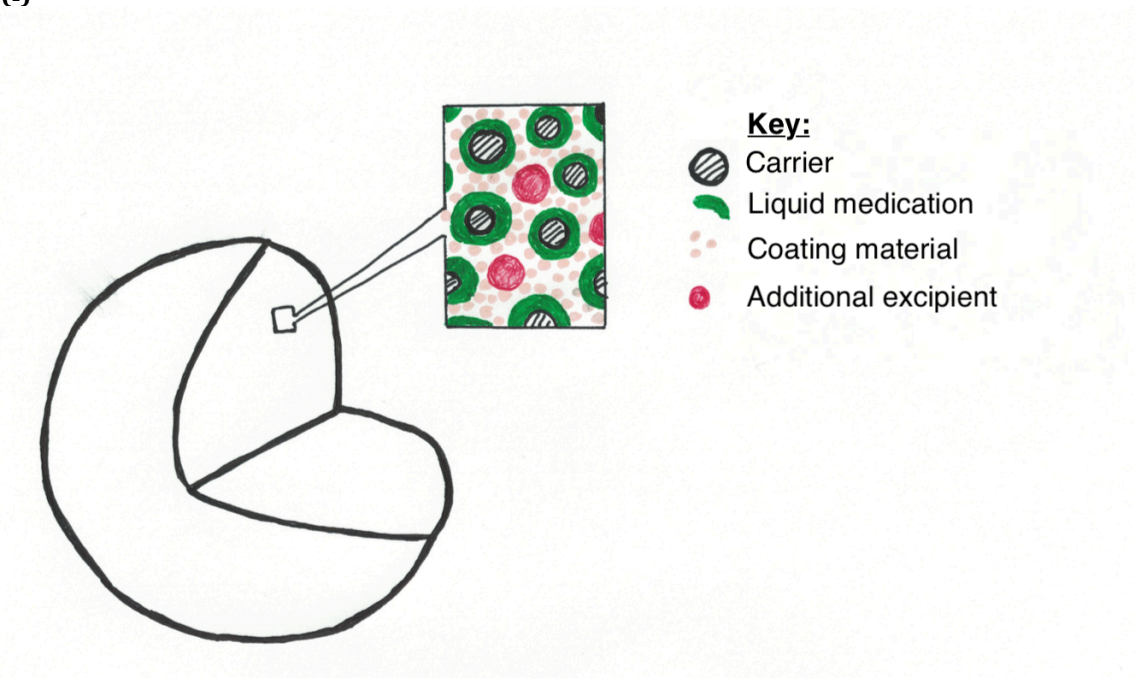


(II)

Figure. 1.1. (I) Diagram summarizing the novel liqui-mass system which is used to make liqui-pellet and liqui-tablet. **(II)** Diagram of a single liqui-pellet and its component.

Since this technology uses a concept from liquisolid technology and pelletization technology, it is prudent to have an understanding of the mentioned technologies, which will be described in chapter 1 (Introduction).

1.2 Liquisolid technology

This section of the introduction will focus mainly on the fundamental knowledge of liquisolid technology.

1.2.1 Introduction to liquisolid technology

Key points:

- *Liquisolid technology is a novel approach in improving bioavailability of poorly water-soluble drugs by increasing dissolution rate.*
- *The concept of liquisolid system comprise of an active pharmaceutical ingredient (API), which is solubilized in a non-volatile co-solvent (also known as liquid vehicle), forming the liquid medication. This liquid medication is then incorporated into a carrier and coated with nano-sized coating material, producing powders that are dry looking, free flowing and readily compressible.*
- *Powdered solution technology is the predecessor of liquisolid technology.*
- *Liquisolid technology is capable of fast and slow release formulation.*

Liquisolid technology is a relatively new approach in oral drug dosage form design to improve the bioavailability of poorly water-soluble drugs via increasing dissolution rate. This poor dissolution rate of poorly water-soluble drugs is in fact a major issue confronting the pharmaceutical industry [1]. To appreciate the potential implication of the concept from liquisolid technology, it is worth pointing out that around 60% of synthesized drugs are poorly soluble, which is based on biopharmaceutical classification system (BCS); and around 40% of drugs in development are identified as poorly water soluble [2].

Apart from improving dissolution rate, which can also be achieved in liquid form of medication, there are preferences to produce the seemingly solid dosage form. Due to majority of patients being elderly, administration of liquid medication can pose an issue in terms of dexterity limitation in handling liquid medication. Also, there are other advantages such as prolong shelf life and capacity for drug modification in dosage form design, which makes solid dosage form more favourable than the liquid dosage form. Liquid form of medication can be encapsulated in a capsule; however, this method is not cost effective. Hence, there is an incentive for alternative solid oral dosage form.

The fundamental components in liquisolid technology is shown as a diagram in Figure 1.2, which was taken from Spireas *et al* [3] and Nokhochi *et al* [4], and further modified by the author. The concept of liquisolid system comprises of an API, which is solubilized in a non-volatile co-solvent (also termed liquid vehicle), forming the liquid medication. The term liquid medication refers to liquid lipophilic drug, suspension of water-insoluble drug or solid water-insoluble drug dissolved in a liquid vehicle [3]. This liquid medication is then incorporated into a carrier and coated with nano-sized coating material. Ideally, this should give the admixture of API and excipient (in a seemingly powder form) a dry, free-flowing and readily compressible properties. This admixture can then be made into a dosage form called liquisolid compact, which includes liquisolid tablet and liquisolid capsule, or made into a liquisolid microsystem [5].

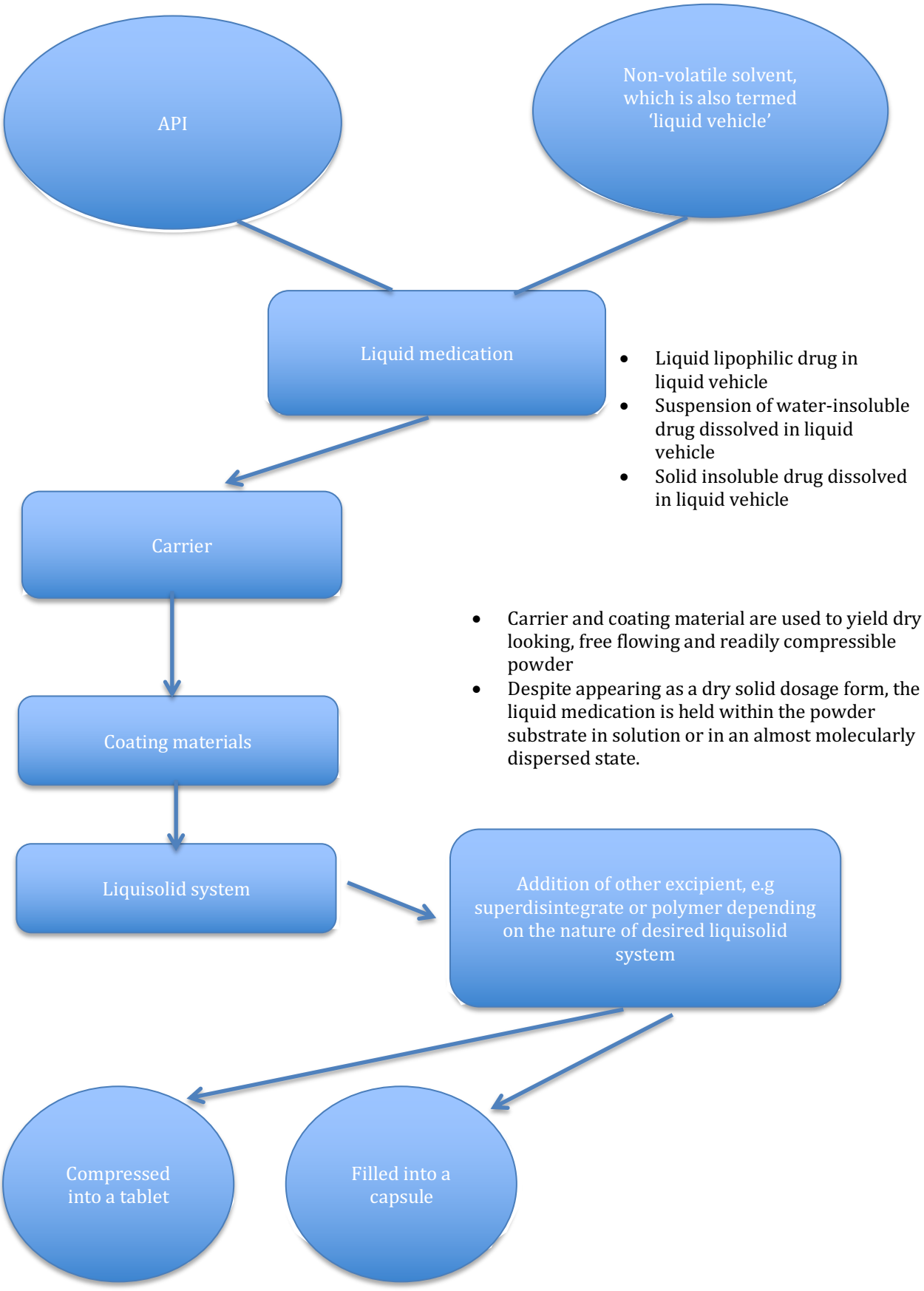


Figure 1.2. Outline of liquisolid preparation

Liquisolid technology stems from an older technology called powdered solutions. This older technique incorporates drug, which is solubilized in a co-solvent, into silica with large specific surface area; giving the admixture a dry looking and non-adherent properties [6,7]. Despite its improvement in drug release rate, the powdered solution could not be compressed into a tablet. This led to another technology called modified powdered solution, which incorporates microcrystalline cellulose in order to enhance compressibility [8]. Even though compressibility did improve, there were still a number of major limitations such as, the requirement of large quantities of silica; the squeezing out of the liquid portion of the admixture and formation of soft tablet [8]; thus, this technology is not commercially viable. It should also be noted that liquisolid system introduced the concept of liquid medication which is broader in comparison to powdered solutions where only drug solution applies [3]. Spireas *et al* [3] modified this technology into what is currently known as liquisolid technology. This technology is able to overcome some of the limitations of its predecessor; and according to Spireas, is now industrially applicable. In spite of such claim, it has been made clear from a number of studies that liquisolid technology still have major limitations, hampering it from materializing into commercial use [4]. The limitations such as, poor flowability and compressibility of liquisolid powder admixture, and the inability to make acceptable weight and size of high dose liquisolid compact are crucial drawbacks in this technology [4,9].

The mechanism of how liquisolid compact improves the bioavailability is through enhancing drugs dissolution rate. In brief, it is proposed that the enhancement of dissolution rate is due to increased wetting properties, increased surface area of drug available for dissolution [3] and increased solubility [4]. All of which will be discussed more thoroughly in chapter 1 section 1.2.3.

Liquisolid technology is also capable of sustaining drug release whilst maintaining an almost zero order kinetics [10,11], making it a very appealing oral delivery system for drugs that requires sustained release. This zero order kinetics of sustain drug release has significant implication in therapeutic treatment, especially for drugs with a short half-life and narrow therapeutic window. The sustained release pattern is achieved by manipulating the excipients in liquisolid compacts.

In order to have a good grasp of the concept involving liquisolid compacts, it is worth mentioning briefly the key terms relating to liquisolid system. These key terms will be explained further in later subsection in the introduction. Key terms are as below:

- '*Liquid load factor*' (L_f) is the ratio of the weight of liquid medication (W) over the weight of carrier excipient (Q) in the liquisolid system, whilst maintaining acceptable flowability and compressibility [12]. This is an important factor to consider in terms of dosage per liquisolid compact. It is also a valuable component in several mathematical equations involving liquisolid compacts. Liquid load factor can be expressed as below (Equation 1.1) [4,5,12]:

$$L_f = W/Q \qquad \text{(Equation 1.1)}$$

- *Fraction of molecularly dispersed drug* (F_M) is the ratio between the drug's saturation solubility (S_d) in the non-volatile solvent and the actual drug concentration (C_d) in the liquid medication. Since in liquisolid compacts the API are solubilized in the liquid vehicle and held in a molecularly dispersed state, it is important to quantify this. The reason why F_M value is important is that API in molecularly dispersed state is thought to be one of the major reason for the enhanced drug release capability. In general, dissolution rate increases with increasing F_M value. The F_M can be expressed as shown below (Equation 1.2) [3]:

$$F_M = S_d/C_d \qquad \text{(Equation 1.2)}$$

- *Flowable liquid-retention potential* (ϕ*-value*) in liquisolid system denotes the maximum amount of liquid vehicle that can be incorporated into the bulk (w/w) whilst maintaining acceptable flow property [3].

- *Compressible liquid-retention potential* (ψ*-value*) in liquisolid system denotes the maximum amount of liquid vehicle that can be incorporated into the bulk (w/w) whilst maintaining acceptable compressibility [3], yielding tablets with satisfactory mechanical strength and not showing liquid squeezing out phenomena [13].

1.2.2 Advantages & limitations of liquisolid compacts and other competitors

Key points

- *The key advantage of liquisolid technology is that it is simple and cost-effective*
- *The limitations of this technology are poor flowability, poor compactability and inability to produce high dose drug without being too bulky and heavy for real life use*

Liquisolid technology is still relatively new (patent documentded during 1996); however, it holds key advantages over other technologies and has been mentioned to envisaged to play a major role in the next generation tablets [4]. It is capable of improving bioavailability via significantly enhancing the dissolution rate of water-insoluble drugs [1] in a cost-effective and simplistic approach, which is favourable when considering manufacturing at a commercial scale [4]. In fact, the production process is similar to that of conventional tablets; and the excipients used are conventional and commonly available in the market [4]. In addition to enhancing the drug release, the formulation can be manipulated to produce sustained release dosage form with a near zero order kinetics [4].

In comparison to liquid dosage form, where improved bioavailability can also be achieved, the seemingly solid dosage form of liquisolid compact holds inherent advantages of appearing as a solid form. The solid form gives capacity for a more diverse formulation manipulation and improves stability through reduced thermodynamic energy. Various studies have demonstrated liquisolid compact achieving good stability [14–17].

Although there are other various technologies confronting the issue of poor bioavailability of water-insoluble drugs; they may require advance preparation technique, sophisticated machinery, complicated technology or are not cost effective [4]. The other technologies include conversion of crystalline drug into its amorphous state [18]; micronization [19–22]; solid dispersion [23]; co-grinding [24–26]; nanosuspension [27,28]; self-emulsifying drug delivery system [29,30]; co-precipitation and inclusion of drug solution in soft gelatin capsule [31]. Some of these technologies are not cost effective and in most cases the long-termed stability is an issue. For example, on storage, highly amorphous materials can be converted to crystalline state with poor dissolution [32,33].

In spite of the major advantages liquisolid technology offers; it has yet to overcome major issues hampering it from progressing into commercial phase. The reason for this is mainly due to major limitations of poor flowability, poor compactability and inability to produce high dose drug without being too bulky and heavy for real life use [1,4]. The flow property of the liquisolid blend is of critical importance in the production of pharmaceutical dosage forms, such as capsule and tablet, in order to attain a uniform feed and reproducible filling [34]. In fact, the flow property is such an important factor that formulation design is dictated by a mathematical model introduced by Spireas *et al*, which is governed by flow property [5].

In brief, Spireas mathematical model dictates the amount of carrier and coating materials required in order to maintain acceptable flow property and compactibility [5]. Details of this model will be explained in chapter 1 section 1.2.6. To achieve acceptable flow property and compactibility, high amount of carrier and coating materials are usually required [9]. In the enhanced drug release liquisolid formulation, the release rate is directly proportional to the fraction of molecularly dispersed drug (F_M). Therefore higher dose of drug in the formulation would require a larger amount of liquid vehicle in order to achieve good release profile [4,35]. This consequently required higher amount of carrier and coating material to maintain good flowability and compressibility [35]. Such outcome would ultimately increase the weight and size of the liquisolid compact, which is generally higher than conventional tablets [4], resulting into a dosage form that would be difficult to swallow [4].

There has been some attempt to tackle the weight issue for high dose formulation. This is demonstrated in studies by Javadzadeh *et al*, where it is claimed that drug loading factor can be increased with the use of hydrophilic polymer additives, such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) or polyethylene glycol (PEG 35000) [36]. They observed an increase of carbamazepine L_f from 0.25 to 0.6, which is considered high [36]. This method can reduce the weight of dosage form as it reduces the amount of carrier and coating material required without compromising flowability and compactability [36].

Another approach to reduce liquisolid tablet weight is to incorporate highly compactable excipients such as microcrystalline cellulose (MCC). However, it is reported that considerable squeezing out phenomena occurs during compression of these formulation [4]. There is also a study by Hentzschel *et al* [35] where the focus is on increasing

liquid load factor via using high specific surface area (SSA) carrier and coating materials, such as neusilin (amorphous form of magnesium aluminometasilicate). By replacing commonly used carrier and coating materials with an alternative, which has higher SSA, considerably higher liquid adsorption capacity can be achieved [35]. Hentschel *et al* [35] state that the liquid adsorption capacity increased by a factor of 7 after replacing avicel and aerosil with neusilin as carrier and coating material. This increased in liquid adsorption effectively reduced liquisolid compact weight which is confirmed by Hentzschel *et al* [37]. Liquid load factor increased from 0.22 to 1.58 when neusilin is used instead of avicel and aerosil; and yet acceptable flowability and tablet hardness is achieved [37]. Despite such claim, Hentzschel *et al* [37] did not provide data on flowability test, thus, such claimed should be carefully examined. The drug griseofulvin was used for study and result showed a reduction in tablet weight from 2026mg to 600mg [37]. Nonetheless, these mention attempts are insufficient for high dose drug.

1.2.3 Mechanism of enhanced drug release in liquisolid formulation

Key points:

- *It is thought that the enhanced dissolution rate of liquisolid compacts are chiefly due to increase in surface area available for dissolution, increased solubility of drug and improved wettability of drug particles*

Since the application of combinatorial chemistry and high throughput screening (HTS) for investigating new chemical entity, drugs molecular weight and lipophilicity has increased, which consequently decreases their aqueous solubility [38]. As mentioned in the introduction to liquisolid technology, around 60% of drugs synthesized are poorly water-soluble, which is based on biopharmaceutical classification system (BCS), and around 40% of drugs in development are identified as poorly water-soluble [2]. It is obvious that pharmaceutical industries are facing a technological challenge where poor bioavailability is solely caused by poor water solubility [39].

Oral drug bioavailability is primarily affected by the drugs' solubility profile, dissolution rate and permeability [9]. In terms of physicochemical aspect, drug dissolution rate and solubility of water-insoluble drug are major reasons for poor bioavailability of BCS Class II drugs [1]. This is because drug dissolution rate is often the rate limiting step for absorption for such drug [1].

In order for an active ingredient in a solid dosage form to be available for absorption in the gastrointestinal tract (GIT), it must undergo dissolution [36]. The well-known 'Noyes-Whitney equation' (Equation 1.3) can be used to explain the enhanced drug release mechanism of liquisolid formulation. The equation is as followed:

$$D_R = (D/h)S(C_s\text{-}C) \qquad \text{(Equation 1.3)}$$

Dissolution rate (D_R) is directly proportional to the surface area (S) available for dissolution and to concentration gradient (C_s-C), where C_s is the saturated solubility of the drug in dissolution medium and C is the concentration of solute in dissolution medium at a specific time [40]. Since dissolution test are generally standardized with parameters in constant conditions such as, temperature, dissolution medium and agitation, it can be assumed that the thickness of boundary layer (h) and diffusion coefficient (D) are also constant [40]. It is postulated that the enhanced dissolution rate of liquisolid formulation are chiefly due to

increase in surface area available for dissolution, increased solubility of drug and improved wettability of drug particles [3,4].

The increased in the surface area available for dissolution (S) can be explained by the dissolved drug in the liquid vehicle being held in the powder substrate in a solubilized or molecularly dispersed state [3]. According to the Noyes-Whitney equation, it is expected that the increase in surface area available for dissolution (S) is directly proportional to dissolution rate (D_R). It should be pointed out that F_M is linked to *S.* The S would increase with the increase of F_M. If drug content increased above solubility limit, for example drug's saturation solubility (S_d) in non-volatile solvent is less than the actual drug concentration (C_d) in liquid medication, then the fraction of undissolved drug will increase. In terms of fraction, more drug would precipitate and less drug will be solubilized or held in a molecularly dispersed state. This consequently reduces dissolution rate as both F_M and D_R are directly proportional [3]. If $S_d \geq C_d$ then $F_M = 1$, which is the maximum limit [3]. D_R increases linearly with increasing F_M but this is observed only above a certain F_M limit [4].

It is speculated that the drug's saturation solubility (C_s) is increased at the microenvironment level in the liquisolid system [3]. Indeed the relatively small amount of liquid vehicle contained in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium [3]. However, at interfacial point between individual liquisolid primary particles and the release medium, where stagnant diffusion layer forms, it is possible that in this microenvironment the liquid medication diffusing out of a single liquisolid particle, may be sufficient to enhance the solubility of the drug by acting as co-solvent with the aqueous dissolution medium of the diffusion boundary layer [3]. The increase in C_s results in increasing difference between C_s and C which is proportional to D_R [40].

The improved wetting properties are caused by the water miscible liquid vehicle acting as a wetting agent on liquisolid primary particle [4] or on potentially precipitated crystal [3]. The wetting agent improves the dispersion resulting in the greater surface area (S) for dissolution, which is directly proportional to D_R [41].

It is interesting to note that in studies by Spireas and Sadu [3], they found that dissolution rate of hydrocortisone and prednisolone liquisolid compacts are independent of the volume of dissolution medium; unlike a conventional compressed tablet. This is

rather advantageous in the physiological conditions in that dissolution rate may be kept more consistent under the varying condition presented in the GIT [3].

Liquisolid compacts with enhance dissolution rate has been successfully achieved for low dose drug [1,3], but still remains a challenge for high dose drug due to its heavy high weight [4]. In literature, there has been a number of studies where liquisolid technology have been applied to enhance drug release. A list of some of these drugs is shown in Table 1.1.

Table 1.1. List of drugs that has been made into liquisolid compact for enhancing dissolution

Prednisolone [1]	Famotidine [34]	Furosemide [42]	Ketoprofen [43]
Piroxicam [44]	Candesartan [45]	Hydrochlorothiazide [14,46]	Olmesartan medoxomil [47]
Indomethacin [48]	Griseofulvin [37]	Rosuvstatin [49]	Meloxicam [50]
Hydrocortisone [3]	Clonazepam [16]	Paliperidone [51]	Fenofibrate [52]
Naproxen [15]	Spironolactone [17]	Lovastatin [53]	Diclofenac sodium [54]
Carbamazepine [36]	Valsartan [55]	Lercanidipine [56]	

This list is not exhaustive and there are current undergoing studies on liquisolid technology.

1.2.4 Factors affecting drug dissolution rate of liquisolid formulation

There are quite a few important factors that affect dissolution rate of liquisolid formulations. These factors include, API and excipients' physicochemical properties; concentration of drug; the amount of excipient used; ratio of carrier and coating material; and addition of disintegrant or retarding agent. This section will look into the finer details of each of these factors.

1.2.4.1 Liquid vehicle & drug concentration

In general, non-volatile co-solvent (liquid vehicle) increase dissolution rate by increasing wetting properties and solubility of the drug [48]. The liquid vehicle can reduce the interfacial surface tension between the dosage form and dissolution medium [44,45]. The drug's solubility in a liquid vehicle is one of the key factors that can determine the drug release profile [9]. Usually, liquid vehicle in which the API is highly soluble in, results in a larger faction of API being solubilized or in a molecularly dispersed state (in other words F_M increases) [3]. This effectively increases drug release rate, as there will be larger surface area for dissolution. Also, with higher saturation solubility, there could be enhanced solubility of the drug at microenvironment. The liquid vehicle with the drug diffusing out of a single liquisolid particle may be sufficient to enhance the solubility of the drug by acting as co-solvent with the aqueous dissolution medium at the diffusion boundary layer [3].

If drug concentration increases above saturation solubility limit, precipitation of the drug's crystallized form may occur, which will affect dissolution rate. It is claimed in a study on indomethacin liquisolid compact by Nokhodchi *et al* [48], that drug concentration in liquid medication has major influences on drug release rate. The crystallized form of API undergoes two key stages during dissolution; firstly, there is an interfacial reaction where solute molecules are liberated from the solid phase into the liquid phase, which is a challenge for poorly water-soluble API; secondly, these solute molecules need to pass through the boundary layer and into the bulk medium. As for solubilized drug, only the second stage applies; therefore, it can be seen that solubilized form will have faster drug release rate than the crystallized form [41]. The solubilized API just simply need to leak out of the solid dosage form. Another example of drug concentration affecting dissolution rate is shown in Spirea *et al* work where increased hydrocortisone concentration reduces

dissolution rate [3]. Despite the drug's solubility in liquid vehicle being an important factor in determining drug release rate, there are also other physicochemical characteristics of liquid vehicle that may affect drug release rate such as, lipophilicity, viscosity, polarity, chemical structure and molecular mass [1].

Pharmaceutical scientists who have worked on liquisolid compact will notice that different APIs have a different liquid vehicle that is most appropriate to them. In practice, it is actually difficult to predict the best liquid vehicle for a particular drug due to the different contributing factors involved. There are cases where solubility studies do not match up with the drug dissolution rate. Such cases are shown in a number of publications; to name a few, results obtained by Spireas and Sadu [1], Suliman *et al* [57] and even the author of this thesis own studies. Thus, the best approach to determine most suitable liquid vehicle is the trial and error method; to run dissolution tests of the drug with various liquid vehicles and observe which gives the best enhanced drug release rate.

1.2.4.2 Carrier & coating materials

The properties of carrier and coating materials can influence drug release profile of liquisolid formulation. For enhanced drug release formulation, these excipients should disintegrate in such that disintegration is not the rate-limiting step of the drug release [4]. In the case for sustaining drug release, the disintegration should be kept to a minimal. In addition they both require having properties to make non-adherent, free-flowing and readily compressible powdered admixture (with liquid medication incorporated) in order to produce a successful liquisolid tablet or capsule that is acceptable from the perspective of manufacturing [3]. The typical carriers used in this technology are: cellulose, starch and lactose of various grades [58]. To be specific, the commonly used carrier in fast and slow release formulations respectively are microcrystalline cellulose (MCC) and eudragit RL & eudragit RS [35]. Carrier such as Avicel (MCC) has disintegrating properties, which could facilitate enhanced drug release rate [4]. The presence of this cellulose can be associated with enhanced wicking, which can speed up disintergration [36]. As for eudragit RL and eudragit RS, which are hydrophobic carriers, the hydrophobic properties can reduce wettability, slowing down disintegration process [59]. This effectively reduces the drug release rate and is the choice of carrier for sustained release formulation [35].

There has also been a study where carriers with large specific surface area (SSA), namely neusilin (synthetic amorphous form of magnesium aluminometasilicate) and fujicalin (spherically granulated dicalcium phosphate anhydrous), being used to increase L_f [35]; however, the study did not include dissolution test; thus, it is unclear whether the large SSA has any influence on drug release rate. However, it is found that the different carriers with different SSA have different surface morphological structure [35]. Different morphological structure can potentially influence drug release behavior. In addition, it was found that liquisolid compact with avicel disintegrates faster than the formulation with fujicalin, which is suggestive that fujicalin could have major influences on dissolution rate [35].

Amorphous silicon dioxide such as aerosil® of various grade is usually used as a coating material in liquisolid system. This hydrophobic silica material in high amount can slow down drug release [36,60]. This leads to another parameter to consider, which is the ratio of carrier:coating material commonly known as the R-value in liquisolid technology. The R-value can be calculated using Equation 1.4, where Q is the amount of carrier and q is the amount of coating material [3].

$$R = Q/q \qquad \text{(Equation 1.4)}$$

Since hydrophobic silica coating material can retard drug release, it can be deduced that low R-value is suitable for sustained drug release and high R-value are suitable for enhancing drug release formulation. Although high R-value is required for enhanced drug releasing formulation, the amount of coating material still needs to be in sufficient amount for good flowability. Thus, Spireas *et al* recommend a minimum R-value of 20 for fast release formulation [60]. In regards to MCC and aerosil, high R-value would improve disintegration and prevent precipitation of drug; this is because when more carriers are used the L_f is reduced, preventing oversaturation and precipitation; thus, improving drug release rate [36,60].

Currently, there have been no extensive studies on the effect of silicon dioxide of different grades on dissolution rate. There have been studies in using different high SSA coating material. Neusilin (a synthetic amorphous form of magnesium aluminometasilicate) and florite (calcium silicate) were used as novel coating material [35]. These coating materials have marked effect on surface morphology of liquisolid compact which can be seen using

SEM [35]. Despite this, no dissolution studies have been recorded with such liquisolid formulation.

1.2.4.3 Superdisintegrant

In the enhanced drug release liquisolid formulation, superdisintegrant is one of the major excipient required to achieve the fast drug release rate. It is often used to ensure that disintegration is not the rate-limiting step of the drug releasing process. Superdisintegrants are modified disintegrants that are defined as a substance which facilitates or increase disintegration at a low concentration, typically 1-10% of dosage unit total weight [61]. The three commonly used superdisintegrant are sodium starch glycolate, croscarmellose sodium and crospovidone; each of them have variation in the mechanism of how they work and hold different advantages or disadvantages to one another [61].

The four main mechanism of action of superdisintegrants are: swelling, capillary/ wicking, deformation and electrostatic repulsion [61]. Swelling action occurs in certain disintegrating agent where water is taken up, reducing the adhesiveness of other ingredients in the tablet; therefore, the tablet falls apart [62]. Capillary/ wicking action works by enhancing porosity and creating pathways in the tablet for liquid to get drawn up (wicked) via capillary action, which disrupts interparticulate bonds, breaking the tablet [61]. This is due to these disintegrating agent inherent physical properties of low cohesiveness and compressibility [63]. Deformation action occurs in disintegrant that is believed to have elastic nature such as, potato or corn starch [61]. In tableting, the compaction force deforms the material from elastic to plastic, creating energy-rich potential. In exposure to aqueous environment, the energy potential of the disintegrant will be triggered and cause disintegration [63]. Electrostatic repulsion mechanism for non-swelling disintegrant requires water to trigger the repulsive force in order for disintegration to occur [61].

Sodium starch glycolate is a cross linked polymer of carboxymethyl starch and works by swelling [61]. The large hydrophilic carboxymethyl groups disrupt the hydrogen bonding within the polymer structure, allowing water to penetrate. The cross-linking reduces water-soluble fraction and viscosity of dispersion in water [64]. The carboxymethyl group and cross-linking effectively leads to rapid water absorption and swelling. This causes uniform disintegration [61]. Natural pre-dried starch can swell and increase volume by 10-20%, whereas modified starch can increase by 200-300% [61]. In tablet dosage form, this

superdisintegrant can cause disintegration in less than 2 minutes [61]. However large amount of sodium starch glycolate can slow down the disintegration due to gelling and subsequent increase in viscosity [65].

Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose is said to have higher disintegrating rate than sodium starch glycolate [63]. Croscarmellose sodium has excellent swelling properties and its fibrous nature results in excellent wicking action [61]. Nonetheless, it can form a gel when fully hydrate [61], which reduces disintegration time and effectively reduces drug release rate.

Crospovidones are insoluble cross-linked homopolymers of N-vinyl-2-pyrrolidone [61]. It has high cross-linked density; thus, it is able to absorb water and swells rapidly without forming gel [63]. The disintegrating mechanism of action of crospovidone includes swelling, wicking and deformation [61].

When choosing superdisintegrant it is crucial to consider complexation. For example, anionic disintegrant such as, sodium starch glycolate and croscarmellose sodium, may complex with cationic drug, consequently decreasing dissolution [61]. A non-ionic disintegrant like crospovidone does not complex with cationic drug [61]; thus, may be the most suitable choice for such drug.

1.2.4.4 Hydrophilic polymers

Studies from Javadzadeh *et al* showed that hydrophilic polymer such as polyvinylpyrrolidine (PVP), hydroxypropyl methyl cellulose (HPMC) and polyethylene glycol (PEG 35000) can increase loading factor when incorporated into the liquid medication microsystem [36]. With these polymers, it is possible to use less carrier whilst improving L_f and ultimately reducing the weight of the final dose unit, which is a major obstacle in current liquisolid technology. In studies by Javadzadeh *et al*, amongst the hydrophilic polymer mentioned, liquisolid containing PVP gave the fastest dissolution rate [36].

The hydrophilic polymer may increase L_f but they can also influence drug release rate. According to Javadzadeh *et al*, liquisolid tablet containing PEG 35000 disintegrate slower and has slower dissolution rate; which may be due to increase in viscosity of the stagnant diffusion layer [36]. A formulation containing HPMC showed fast disintergration of

tablet due to swelling but slow dissolution rate due to gel formation [36]. Liquisolid tablet containing PVP showed increased drug release rate. It is postulated that the main reason for dissolution rate to increase in the presence of PVP is due to crystal growth inhibition [36]. Precipitation inhibitor can maintain supersaturation either by inhibiting nucleation, crystal growth or both [66]. In the case for PVP, crystal growth is inhibited [36] but does not stop or prevent nucleation; the nucleation is nearly instantaneous [67]. Simonelli *et al* have shown that PVP can inhibit precipitation of drug in a supersaturated solution [68]. Despite Javadzadeh *et al* claimed on PVP increasing dissolution rate [36], on closer inspection, there is no test comparing liquisolid tablet with and without the hydrophilic polymeric additive; thus, it is reasonable to assume that PVP increase dissolution rate is not yet conclusive. However, their results did show that by increasing PVP concentration from 10% or 20% to 30%, the dissolution rate increased during the first 30 min, but afterwards there was no significant difference ($P>0.05$) [36].

The mechanism of how precipitation inhibitor achieved inhibitory effect is lacking and remain generally unknown. Hence, there has been studies on PVP to understand the relationship between adsorption and crystal growth inhibition [66]. The degree of effectiveness of precipitation inhibitor depend on their mechanisms of action, intermolecular interaction and its physico-chemical properties as well as hydrophobicity, semi-rigid structure, and amphiphilic nature [66,69–71]. Note that the lack of understanding on mechanism of inhibitory effects of precipitation inhibitor could be due to lack of simple techniques and model to study it [66].

1.2.4.5 Retarding agent

HMPC is a hydrophilic polymer which has been used in sustained release liquisolid formulation as an additive to retard drug release [11]. In studies by Nokhodchi *et al*, different concentration of HMPC was used in the liquisolid formulation to investigate the effect of this excipient on dissolution rate. HPMC concentration between 0-15% was used on theophylline liquisolid [11]. It is found that higher concentration of HPMC in the liquisolid formulation results in a significantly reduced drug release rate [11]. Furthermore, in their studies, 15% of HPMC was incorporated in the liquisolid and conventional tablet formulation; the dissolution test results interestingly showed that the liquisolid formulation had a significantly retarded drug release rate compared to the conventional tablet [11]. Another key retarding excipients are the various type of eudragits.

1.2.6 Mathematical model for liquisolid

There are quite a few important equations in liquisolid technology, which will be briefly introduced in this section; some of them have been developed by the Spireas and Sadu [1,5]. Equations 1.1 and 1.2 have been explained in chapter 1 section 1.2.1. In brief, Equation 1.1 is used to calculate the L_f where W is the weight of liquid medication and Q is the weight of carrier [4,5,12]. Equation 1.2 is used to calculate the fraction of molecularly dispersed drug, where S_d is the drug's saturation solubility and C_d is the actual drug concentration in the liquid medication [3].

$$L_f = W/Q \qquad \text{(Equation 1.1)}$$

$$F_M = S_d/C_d \qquad \text{(Equation 1.2)}$$

The ratio of carrier and coating material, also known as the R-value (Equation 1.4) have been explained in chapter 1 section 1.2.4.2. In brief, Q is the amount of carrier and q is the amount of coating material [3]. These amounts are usually in weight. The R-value is an important parameter that can influence liquisolid compact dissolution profile and physicochemical properties [36,60].

$$R = Q/q \qquad \text{(Equation 1.4)}$$

Equations 1.5 and 1.6 are used to find the L_f that ensures acceptable flowability and compactability [4,5]. Note that the flowable liquid-retention potential (*ϕ-value*) and compactable liquid retention potential (*ψ-value*) in liquisolid system denotes the maximum amount of liquid vehicle that can be incorporated into the bulk (w/w) whilst maintaining acceptable flow or compressible property respectively [3]. This can also be interpreted as how much carrier and coating material is required to maintain acceptable flow and compressibility properties. In Equation 1.5 Φ and $\mathbf{\Phi}$ correspond to *ϕ-value* of carrier and coating material respectively [4] . The Ψ and $\mathbf{\Psi}$ in Equation 1.6 correspond to *ψ-value* of the carrier and coating material respectively [4]. The compactability is determined by studying the pactisity [5,72], describing the maximum crushing strength of 1 g tablet that was compacted at sufficiently high compression force [4].

$$^{\Phi}L_f = \Phi + \mathbf{\Phi}\ (1/R) \qquad \text{(Equation1.5)}$$

$$^{\Psi}L_f = \Psi + \mathbf{\Psi}\ (1/R) \qquad \text{(Equation 1.6)}$$

The optimum liquid load factor (L_o) can be determined using Equation 1.5 and 1.6; the one with the lowest L_f between ${}^{\Phi}L_f$ and ${}^{\Psi}L_f$ will be the L_o [4,5]. After determining the L_o, it is possible to find the amount of carrier and coating material which gives acceptable flow and compressible properties [5]. This leads into Equation 1.7 where the optimal carrier (Q_o) can be determined; W is the weight of liquid medication and L_o is the optimal liquid load factor [5].

$$Q_o = W/L_o \qquad \text{(Equation 1.7)}$$

Once Q_o is determined from Equation 1.7, optimal coating material (q_o) can be determined via using Equation 1.8; R is the ratio of carrier and coating material respectively [5].

$$q_o = Q_o/R \qquad \text{(Equation 1.8)}$$

1.3 Extrusion-spheronization technology

This section of the introduction will focus mainly on the fundamental aspect of extrusion-spheronization technology.

1.3.1 Introduction to extrusion-spheronization technology

In brief, extrusion-spheronization technology is one of the several techniques used to produce pellets, which may also be known as beads, spheroids, matrix pellet or spherical granules [73–75]. From the early 1950's to the present time, there is much attention to pelletization from the pharmaceutical industry due to its ability for multiparticulate drug delivery and other inherent advantages pellets offers [76]. Some key advantages of pellets are: reduced risk of side effects that are due to dose dumping; combining incompatible drugs or drugs with different release profiles in same dose unit [77]; predictable transportation in the gastrointestinal tract (GIT), flexibility for modification [76]; advantageous for acid-sensitive drug due to reduce gastric transit time [78] and having good flow properties [79].

Extrusion-spheronization is the most commonly used technique among the other pelletization methods that is applied to controlled release pharmaceutical dosage form

design [73,80]. Other techniques for making pellets include, solution/suspension layering; powder layering; balling; compression; spray drying and spray congealing [76]. Among these technologies, extrusion-spheronization is favoured due to its ability to produce uniform pellet size with smooth surface morphology (important for application of coating technology), good flow properties, narrow size distribution, high drug loading capacity, good strength and low friability [73].

Reynold and Conine & Hadley first reported the extrusion-spheronization process in 1970 [79,81]. However, it should be noted that the spheronization technique (also known as Merumerization) was already invented by Nakaharra in 1964 [73,82]. The extrusion-spheronization process consists of stages shown in Figure 1.3. The powders of API and excipients are mixed then moisten with a granulating liquid. This forms a wet mass during granulation stage, which then goes through an extruder. During the extrusion process, the wet mass is pushed through a die forming rod-like mass termed extrudate, which then gets spheronized. Spheronization involves placing the extrudate onto a plate with a specific groove (termed friction plate), which rotates, breaking the extrudate into smaller cylinders; then eventually smoothing the cylinder into spherical particles due to frictional force [83]. Once the wet pellets are formed, they can be dried via a different method, which will be mention later in chapter 1 section 1.3.2.4.

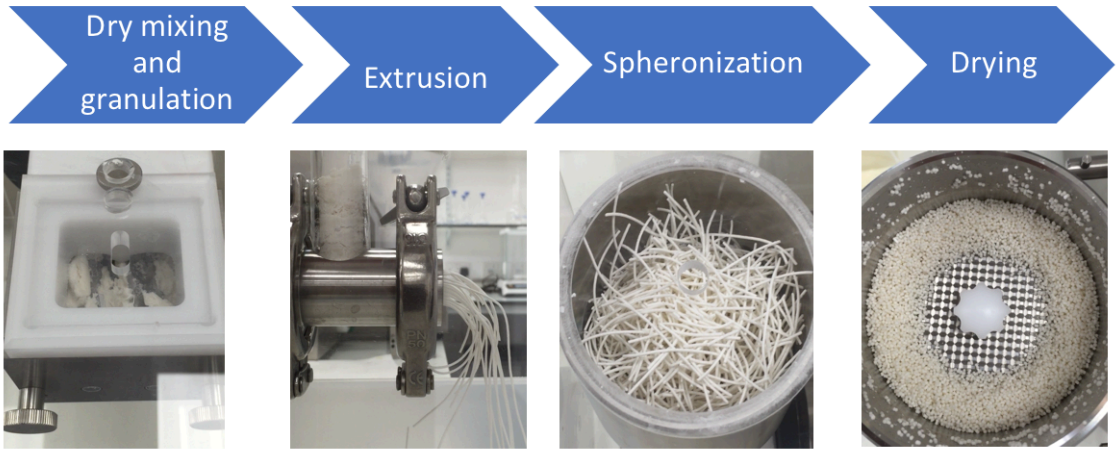


Figure 1.3. Outline of extrusion-spheronization process.

Microcrystalline cellulose is the gold standard carrier used in extrusion-spheronization because it can form a wet mass with unique properties, such as good rheological properties, good plasticity and good cohesiveness [73]. The high internal porosity and large surface area of MCC allow a large quantity of water to be absorbed and retained,

which gives it its unique properties [84]. Such properties are required for a successful production of pellets. In addition, pellets produced from MCC have shown to have good sphericity, smooth surface, high density and low friability [73].

It is worth mentioning that the mechanism of how MCC achieve the ideal properties for extrusion-spheronization is not completely understood. In fact, there have been two different models postulating how MCC is able to achieve its properties; one model uses the crystallite gel model and the other model explain MCC as a molecular sponge [85]. In the crystallite gel model, it is described that MCC particles in formulation are broken down into smaller particles by shear force during extrusion. It is suggested that the shear force would eventually result to crystallite of colloidal size occurring, which form gel in presence of water. The gel network aid both the extrusion and spheronization process [85]. However, in the molecular sponge model, water is filled in pores between particles. Parts of water is localize within the cellulose fibres in pores and amorphous region and parts is localize between fibres [85]. The interaction is complex and subject to much debate. During extrusion, the sponge like MCC is squeezed and water comes out to lubricate the partice through the screen of the extruder [85]. Despite the different models, it is clear that MCC is currently the gold standard carrier in extrusion-spheronization technology.

At the present time, there are already commercial products produced via pelletization, showing its growing popularity in pharmaceutical industry. Some of these products are shown in Table 1.2. In brief, it may be useful to look into the production methods and parameters of some of these products to gain an insight of commercial standard of pellet production. For more information on these products refer to Lavanya and Dandapani review articles [73,86].

Table 1.2. List of commercially available marketed pellet products [86]

Product	API	Company
Bontril SR	Phendimetrazine Tartrate	Carnick laboratories, Inc.
Brexin L.A	Chlorphenamine and Pseudoephedrine	Savage Laboratories, Bangalore.
Catazyme S	Catalase	Organon pharmaceuticals, USA.
Compazine	Prochlorperazine	Smith & French, MUMBAI.
Dilgard XL 180	Diltiazem	Smith kline & French, MUMBAI.
Elixophyline	Theophylline	CIPLA Ltd, Ahmedabad.
Fastin	Phentermine hydrochloride	Berlex Laboratories, USA.
Hispril	Dphenylpyraline	Berlex Laboratories, USA.
Ibugesic S.R 300	Ibuprofen	CIPLA Ltd, Ahmedabad.
Indocin S.R	Indomethacin	Merck Sharp, MUMBAI.
Nicobid T.S	Nicotinic acid	U.S Vitamin, USA.
Ornade	Chlorpheniramine-Phenylpropan	Smith Kline.

1.3.2 Extrusion-spheronization processes

1.3.2.1 Dry mixing and granulation process

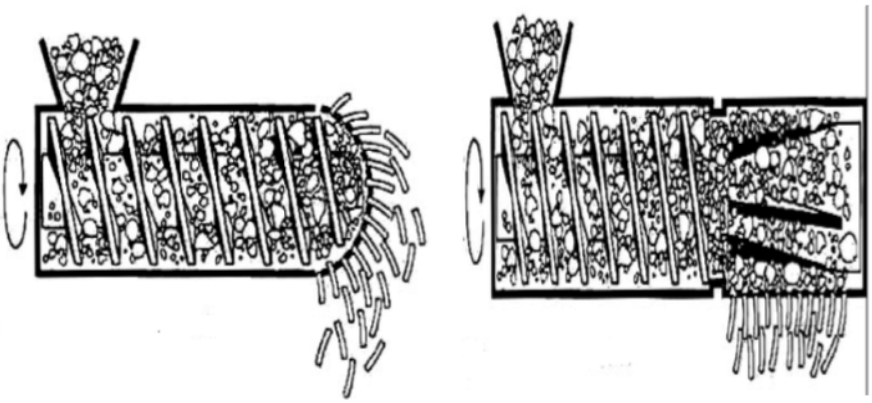
The initial stage of making pellet via extrusion-spheronization is mixing the API and excipients in dry powder form. Homogenous powder blending can be achieved via various mixers such as high shear mixer, tumbler mixer, twin shell blender and planetary mixer [81–83,87]. Granulating liquid is then added to the admixture, which includes MCC, and blending continue to form the wet mass [73]. The mechanism of how wet mass is form has two proposed models. The crystallite gel model and sponge model which have been explained earlier in chapter 1 section 1.3.1. Care must be taken into account when granulation liquid is added as the mixing process, high shear mixer in particular, can generate a large amount of heat that can cause evaporation of the granulating liquid, consequently affecting the wet mass extrusion properties [88].

1.3.2.2 Extrusion process

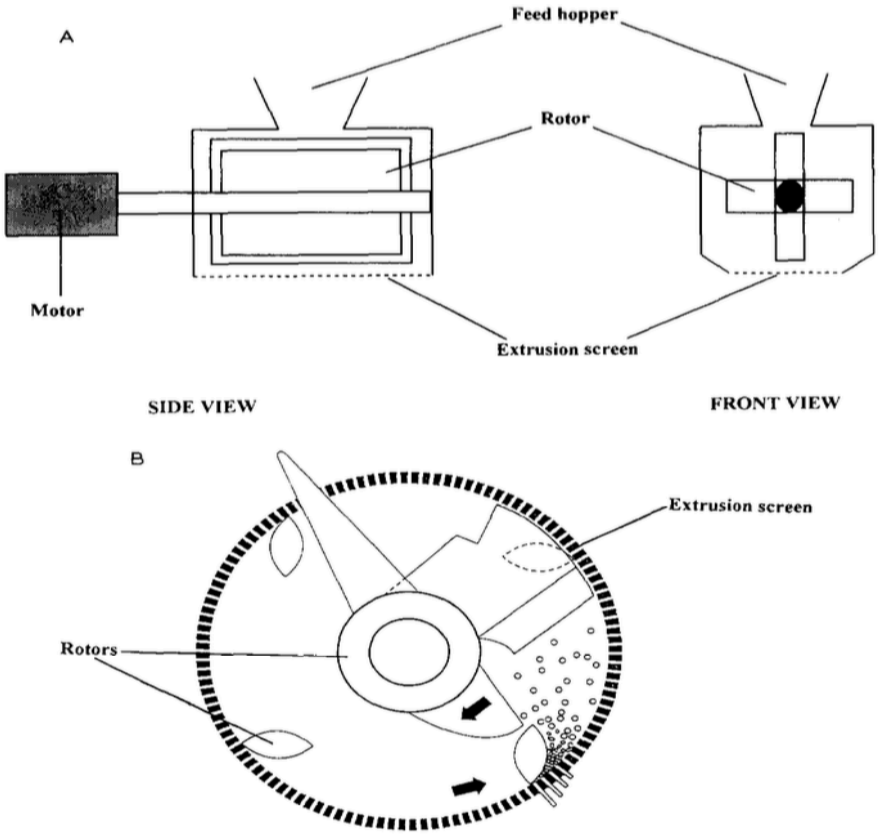
Once the wet/ plastic mass is formed, the second stage is the extrusion process. In the extrusion process, the wet plastic mass is forced through a die, which produces an elongated plastic mass known as an extrudate. There are four main different types of extruder: screw feed extruder; sieve and basket extruder; gravity feed/roll extruder and piston feed/ram extruder [73,75,80]. Details of how these extruders work are shown in Table 1.3. It should be noted that there has been a report on the influences of different types of extruders on the quality of pellets produced [79,88–90]. This implies that it is important to consider the types of extruder being used to obtain the desired properties of the pellet.

Table 1.3. Types of extruder and the mechanism of how it works

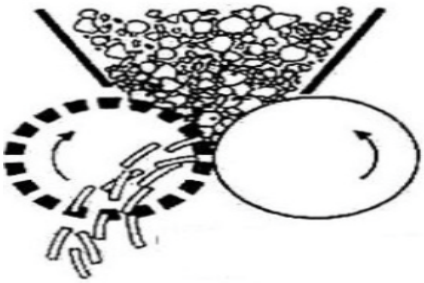
Extruder types	Mechanism of how the extruder works
Screw feed extruder	The screw extruder consist of either single or twin screws feeding the wet granulate mass to an radial or axial extrusion die [79,89] as shown in Figure 1.4 (I).
Sieve and basket extruder	Sieve and basket extruders consist of an oscillating or rotating device that pushes the wet plastic mass through the die of the screen [80]. The wet mass is fed into this screen via screw or gravity [80]. The difference between the sieve and basket extruder is said to be similar to that between radial and axial screw extruder. Figure 1.4 (II) shows the sieve and basket extruder.
Gravity feed/roll extruder	Gravity feed extruder (also known as roll extruder) consists of two counter-rotating cylinders, which can have two variations. First is called cylinder roll type where only one of the cylinder is perforated; second is called gear roll type where two of the cylinder is perforated (Figure 1.4 (III)) [73,80].
Piston feed/ram extruder	The piston feed extruder (also known as the ram extruder) is probably the oldest type of extruder. It works by having the wet plastic mass pushed through a screen via a piston [73,80,91]. Figure 1.4 (IV) shows the piston feed extruder.



(I)


A
Feed hopper
Rotor
Motor
Extrusion screen
SIDE VIEW
FRONT VIEW
B
Extrusion screen
Rotors

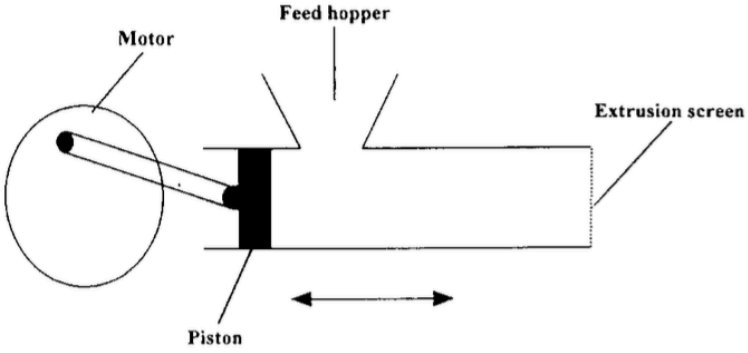
(II)



Cylinder roll type

Gear roll type

(III)



(IV)

Figure 1.4. (**I**) Axial screw feed extruder (left) and radial screw feed extruder (right) [92,93]. (**II**) Side and front view of sieve extruder (A) and basket extruder (B) [91]. (**III**) Top image is the cylinder roll type gravity feed extruder, and the bottom image is the gear roll type gravity feed extruder [73]. (**IV**) Piston feed extruder [80]

In order to successfully make good pellets, the rheological properties of the extrudate are a crucial factor in determining this success. The wet mass must display sufficient plastic properties to allow shaping and cohesiveness to retain the desired shape of the extrudate. The extrudate for pellet production should be self-lubricating and eventually brittle but not friable [94]. Moisture in the mass ready for extrusion is one of the major factors necessary for providing plasticity for extrusion and spheronization, which have been subjected to much research [95–100]. Water content, which is the most common granulating liquid in this technology, is found to be one of the most important parameters

influencing the success of pellet production and its quality [99]. Other parameters that can affect pellets' properties include water temperature, extrusion speed, spheronization speed, spheronization duration and more, which will be explained in more details in chapter 1 section 1.3.5.

1.3.2.3 Spheronization process

Once extrudates are produced, the third stage is the spheronization stage. At this stage, the cylindrical extrudate is placed in a spheronizer, which is simply a chamber with a spinning plate/disk at the bottom [82]. This spinning plate is termed frictional plate and is the key component for producing spherical pellets via breaking the cylindrical extrudate into smaller cylinders, achieving a shape where the length may equivalent to their diameter [81]. It is claimed that the rounding of the plastic mass is due to the frictional force produced by the spinning friction plate [83]. The friction plate has a characteristic grooved surface that is responsible for the enhanced frictional force [73]. There are two types of groove geometry; first is the cross hatch geometry where grooves form a right angle (Figure 1.5); second is the radial geometry where the radial pattern is used (Figure 1.5) [89] .

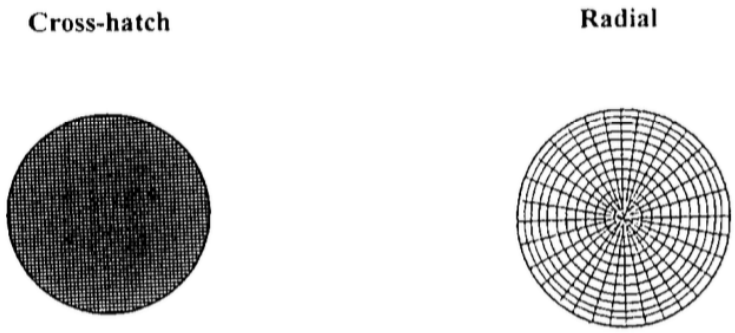


Figure 1.5. Two types of friction plate, cross-hatch (left) and radial (right) friction plate.

There are two proposed mechanisms of the spheronization process; one is proposed by Rowe and the other by Baert. Rowe suggested that the cylindrical extrudate is rounded to form pellets via the frictional forces [89]. First, the cylindrical plastic particles transform into a rounded edge cylinders then into dumb-bells and elliptical particles, which eventually become spherical in shape (Figure 1.6) [89]. Baert and Remon proposed that due to frictional and rotational forces, the cylinder twist and break apart before rounding into spheres [101]. Initially, the cylinder twist forming what is known as a rope, then further twist into a dumb-bell shape, which breaks apart into a sphere with cavity outside and eventually rounded into a sphere (Figure 1.7) [80]. The spheres with cavity have a flat and round side. During

spheronization, the flat side folds together, which is described as a flower forming a cavity observed in certain pellet [80].

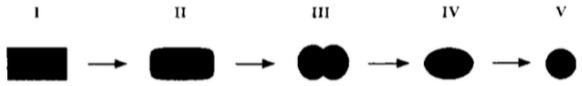


Figure 1.6. Rowe postulated pellet forming mechanism [89]. I, cylinder; II, rounded edges cylinder; III, dumb-bell; IV, ellipse; V, sphere.

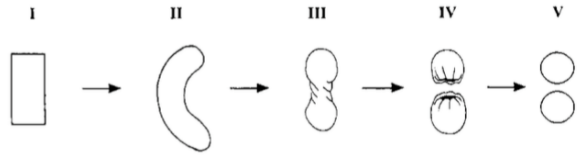


Figure 1.7. Baert and Remon postulated pellet forming mechanism. I, cylinder; II, rounded edges cylinder; III, dumb-bell; IV, ellipse; V, sphere.

The spheronization process has a major influence on the success and quality of pellet production, which will be explained in detail in chapter 1 section 1.3.5. In brief, the key spheronization process parameters affecting pellets properties are spheronization speed, duration and the amount of extrudate loaded.

1.3.2.4 Drying process

The final stage of pellet production via extrusion-spheronization is the drying process of the pellet. Once the spherical particles are formed after spheronizing, it is subject to drying to remove the excess water. At this stage, the porosity of the pellet is easily affected by the drying method applied [102]. The drying techniques include evaporation at room temperature [103,104], oven-drying [105], fluidized bed dryer [106–108], microwave-drying [105], freeze-drying [109] and desiccation with silica-gel [110,111].

The difference in removal of moisture; means of heat and mass transfer; static or dynamic nature of the bed and drying techniques are the cause of pellets with different structural and mechanical properties [102]. Pellets' porosity is considered the most crucial properties affected by various drying method where different technique results in different extent and rate of pellets shrinkage [102]. It has been seen that rapid evaporation of water via fluidized bed dryer, and the direct evaporation of the expanded ice via freeze drying suppresses the shrinkage of the pellets, forming pellets with higher porosity and greater mean diameter [105]. It can be postulated that methods which give slow evaporation of water

such as, oven or desiccation with silica-gel results in pellet with greater shrinkage and lower porosity [105].

The degree of porosity gives us useful information about the strength of the pellet. When porosity increases, the strength of the pellet tends to decrease [102,105]. Figure 1.8 shows the relative pellets' porosity and strength made from various drying method.

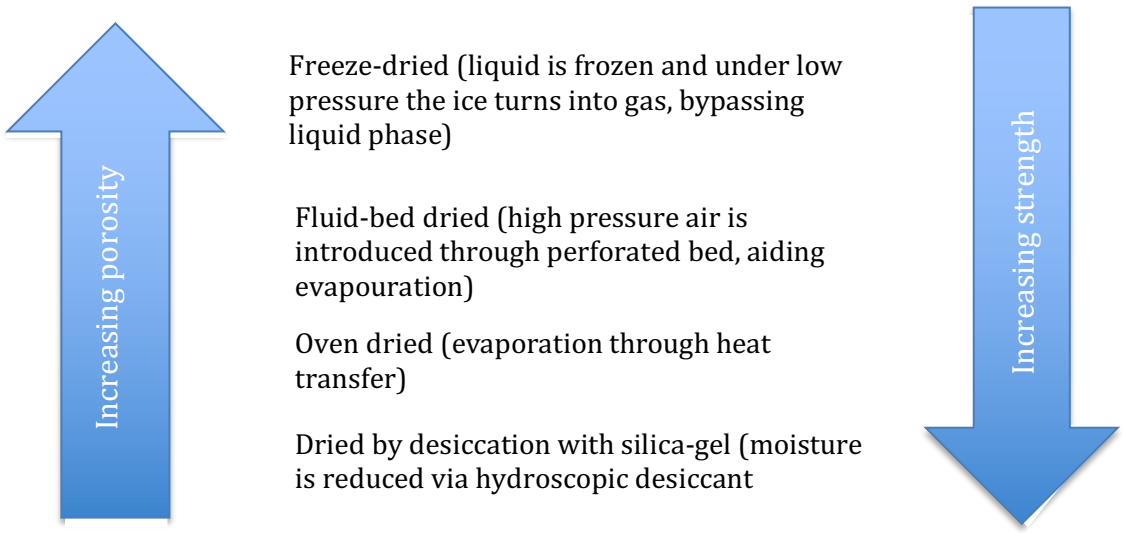


Figure 1.8. Porosity and strength of pellets dried by different technique.

Claims on the effect of drying method on pellets' porosity and strength can be seen in various studies. In studies by Dryer *et al*, ibuprofen pellet made with lactose carrier that was tray-dried was mechanically stronger than fluid-bed dried counterpart [111]. Bataille *et al* claimed that the pellets containing Avicel PH101 and lactose that were dried via microwave differ from that dried by oven; the microwaved dried pellets were more porous with rougher surface and reduced hardness [105]. Berggren and Alderborn found that an increase in drying rate resulted in more porous pellets made from MCC [112].

1.3.4 Advantages & limitations of extrusion-spheronization

The inherent advantages of pellets are shown in details in Table 1.4. As see from this table there are many reasons for using pellets as a choice of dosage form. The advantages include: reduced risk of side effects [77,113–115]; reduced irritation of GIT [115–117]; improved flow properties [79]; resistant to friability [79]; easily coated [79]; uniform packing; capable of controlled drug release dosage form [73,118,119]; capability for taste masking [120–123]; capable for improved drug release rate [73]; ease of adjusting dose strength; multi-unit dosage system [73,77]; advantageous for acid-sensitive drugs due to reduced stomach transit time [75] and predictable dispersion & transportation in the GIT [76,77] .

Table 1.4. List of advantages of pelletization

Advantages of pelletization	Explanation
Reduced risk of side effects	Since the API is in more than one unit of dosage form, this reduces the risk of side effects in controlled release formulation caused by dose dumping [77,113]. In addition, the small size of the pellet allows better distribution in the GIT. This could improve bioavailability due to better drug absorption, and reduce peak plasma fluctuation which can reduce risk of side effects [114]. Furthermore, since the drug is freely distributed in the GIT, there is reduced risk of high drug concentration at the local site; thus, implying reduced risk of toxicity and side effects [115].
Reduced irritation of the GIT	With improved bioavailability, which potentially could reduce local drug concentration, risk of toxicity at local site in the GIT can be reduced [115]. Furthermore, premature degradation of dosage form enteric coat, which can lead to irritation of the stomach can be reduced in pellet dosage form. This is due to pellet small size (usually <2mm), which gets emptied out from the stomach relatively quick similar to liquids; thus, its transit time in the stomach is shorter than larger tablet dosage form [116,117].
Improve of flow properties, less friable,	The spherical shape of pellet has smaller surface of contact amongst one another, thus, less friction and cohesive force, resulting better flow property.

easily coated and uniform packing [79]	Pellet form is commonly known to be robust and less friable, hence, reducing pellets from being damage and loss during transportation. Spherical pellets with smooth surface can be coated with ease.
Producing controlled dosage form	The nature of controlled release formulation being determined via multi-unit dosage form system allows predictable and reproducible drug release over time [118,119]. In addition, due to the spherical shape and low surface area to volume ratio, successive coating can be applied to the pellet dosage form [73].
Capability for taste masking	Since the spherical shape of pellet can be coated at ease, it is possible to use taste masking polymer [120–123].
Improve drug release rate [73]	Larger surface area inherent in pellet multi-unit dosage form can increase dissolution rate. This can be mathematically explained by Noyes-Whitney equation (Equation 1.3).
Ease of adjusting dose strength	Dosage strength can be adjusted by changing the amount of pellet filled in capsule.
Multi-pellet unit systems (MUPs)	Allows chemically incompatible drug to be able to mixed and made into a single dosage unit. This effectively means it is also possible to make a single dosage unit that can deliver different APIs at different sites of the GIT [73]. In addition, it is possible to combine drugs with different release profile in the same dose unit [77].
Advantageous for acid-sensitive drugs	Due to pellets short transit time in the stomach, it can be considered advantageous for acid-sensitive drug [78].
Predictable dispersion and transportation in the GIT	The reduced risk of dose dumping and small uniform size of pellets allows a more predictable drug dispersion and transportation in the GIT [76]. Also, there are less variation in gastric emptying; hence, inter and intra variability of plasma drug profile is minimized [77].

Among various pelletization techniques, extrusion-spheronization technique is the most popular in pharmaceutical production due to key advantages shown in Table 1.5. In brief, these advantages are high loading capacity [73,75]; good properties for commercial manufacturing [73]; uses green technology; simple process and high throughput with low wastage [124].

Table 1.5. List of advantages of extrusion-spheronization method for pelletization

Advantages of extrusion-spheronization	Explanation
High loading capacity	It is possible to have high loading of API in matrix-based pellets without producing very large particles [73,75]. The API is integrated within the pellet structure unlike some pellets where the API is only present at the surface of the pellet.
Good properties for commercial manufacturing	It is possible to produce pellets with uniform size, good flowability, narrow size distribution and smooth surface, which is important for successful coating [73].
Green technology	The process of making the pellet does not require heat such as hot melt extrusion. This saves energy and cost.
Simple process	Extrusion-spheronization is a relatively simple technology in terms of operation; the machine can be commonly found in pharmaceutical industry.
High throughput with low wastage [124]	Able to obtain high yield.

Despite the apparent advantages of pelletization, particularly via extrusion-spheronization method, there are some limitations. The limitations of pelletization and extrusion-spheronization method are shown in details in Table 1.6 and Table 1.7 respectively. In brief, limitation of pelletization includes: not being suitable for low-potency and highly dose drug [125]; not suitable for drugs targeting the stomach organ (although floating pellet system can resolve this [126]) and not ideal for weakly basic drugs due to quick gastric emptying into small intestine, where the drug will be in basic condition, which weakly basic drug are poorly soluble in. As for extrusion-spheronization technique, the limitation includes: not suitable for fast drug release formulation [127]; not suitable for water

labile drug and if MCC is used as a bulk agent, the amount of water that can be added is restricted to the upper and lower limit.

Table 1.6. List of limitation of pelletization

Limitation of pelletization	Explanation
Not suitable for low-potency, highly dosed drug	It is not considered advisable for low-potency, highly dosed drug to be made into MUPs due to large capsule size can reduce patient compliance [125].
Not suitable for drugs targeting the stomach organ	Since the pellets are small, its transit time in the stomach will be relatively short and it gets emptied out from the stomach into small intestine quickly as liquid does [116,117].
Poor dissolution of weakly basic drug	Weakly basic drug dissolve faster in an acidic environment such as the stomach. Since pellets are small the drug transit time in the stomach will be short; hence, the weakly basic drug has less time to dissolute at the pH it is soluble in.

Table 1.7. List of limitation of extrusion-spheronization method for pelletization

Limitation of extrusion-spheronization	Explanation
Not suitable for fast drug releasing formulation	MCC is the gold standard for making pellet via extrusion-spheronization. Despite its excellent rheological property to achieve this, it is resistant to disintegration; thus, not suitable for fast drug releasing formulation [127]. Currently, there is no standard excipient to make rapid drug releasing formulation via extrusion-spheronization.
Not suitable to water-labile drug	Since MCC is mainly used in the extrusion-spheronization to make pellets, water is required for MCC to achieve its unique rheological property in order to successfully produce the pellets. This would mean water-labile drugs would not be suitable for this technique. According to the author, it is not known at present of a carrier excipient that does not require water in extrusion-spheronization technique.

Assuming MCC is used, the success of spheronization is restricted to the lower and upper limit of the amount of water added.	There is a lower and upper limit range of water required for producing pellets with acceptable quality [95,128,129]. Water level below the lower limit will result in formation of large yields of fines/dust; and above the upper limit would lead to agglomerated product during the spheronization process [80].

1.3.5 Factors affecting pellets physicochemical properties

In extrusion-spheronization technology, there is an array of parameters/ factors that can influence the physicochemical properties of the end product. These parameters/ factors will be categorized into different stages of the extrusion-spheronization process and the excipient used. The stages include mixing and granulation, extrusion, spheronization and drying process.

A summary of parameters during the mixing and granulation process affecting the physicochemical properties of the pellets is shown in Table 1.8.

Table 1.8. Effects of parameters in the mixing and granulation process on the physicochemical properties of the pellets

Mixing and granulation	Effect on pellets' physicochemical properties
Water content in granulating liquid	It has been observed that increase in water content in granulating liquid has led to an increase in hardness of pellets, which can lead to slower drug release rate [80]. This increase in hardness and effectively reduced friability is explained by Otsuka *et al* as a result of a decrease in internal porosity of pellets with increased water content [130].
Alcohol in granulating liquid	When alcohol-water mixture is used as granulating liquid as opposed to just water, the pellets that are produced have reduced hardness, sphericity and disintegration time with increase in friability and drug dissolution rate [131]. According to Sarkar, the increase in friability (or reduced cohesiveness) can be explained in terms of MCC particle de-aggregation [131]. MCC is made of aggregates of sub-unit, which is held by hydrogen bonds (H-

	bonds). The de-aggregation of the MCC particles requires breaking of the H-bonds, which is dependent on the polarity of the granulating liquid; thus, granulating liquid with a lower polarity such as high alcohol content in water-alcohol mixture, reduces the extent of de-aggregation, yielding larger particles [131]. The MCC with larger particle size and lower surface tension of granulating liquid produce moistened mass with reduced cohesive strength. This limits the agglomerate growth by coalescence and close packing of the component during spheronzation; hence, producing more friable pellets [131]. Friable pellets can suggest that such pellet will disintegrate better, leading to improved drug dissolution rate.
Glycerol solution produce porous pellets	Glycerol solution as granulating liquid produces pellets with greater porous structure than with water as granulating liquid [132].
Moisture content	Moisture content affects the internal porosity, friability, mechanical strength/ cohesiveness, particle size distribution, shape and size of the pellets [74,95].
Drug solubility	The increased solubility of API in the granulating liquid will lead to an increase in granulation liquid volume. This can result in over wetting which effectively can influence the physicochemical properties of the final product [92].

A summary of parameters during the extrusion process affecting the physicochemical properties of the pellets is shown in Table 1.9.

Table 1.9. Effects of parameters and methods of extrusion on the physicochemical properties of the pellets

Extrusion	Effect on pellets' physicochemical properties
Extruder type	Different types of extruder produce pellets with different size distribution, density and sphericity [79,89,133]. This may be caused by various extruder having different optimal amount of granulating liquid range, different length to radius ratio of extrusion screen or differences in shear rate [90,134–136].
Extrusion speed	It has been claimed in a number of research work that extrusion speed affect the quality of pellets [83,97–99,104,137–139]. High extrusion speed results in pellets with rougher surface/ shark skinning (a term often used in extrusion where extrudate surface resemble a creased shark skin), which causes wider particle size distribution due to surface defect leading to uneven initial breakup of the extrudate during spheronization process [97]. However, there have been other claims that extrusion speed has no influence on pellets size [103,139–141]. It is claimed by Mesiha and Valles that surfactant with high HLB (hydrophilic-lipophilic balance) value can be used as a lubricant to reduce this sharkskin effect [142].
Extrusion screen	The diameter of the die and thickness of extrusion screen influences the extrudate, consequently affecting the physical properties of the pellets [97,99,135,140,141]. The size of the pellets produced is determined by the diameter of the die [97,135]; big die diameter results in larger pellet size than small die diameter. It is noted in studies by Baert *et al* and Hellen *et al* that reduced thickness of extrusion screen produces rougher surface extrudate [135,143]. Surface impairment of extrudate should be avoided to achieve pellets that are considered of good quality.
Extrusion temperature	During the extrusion process, temperature can rise which can significantly alter the water/ moisture content of the processed mass via evaporation. This may result in differences of extrudates' properties at the beginning and the end of the batch [144]. Evaporation is made possible in bulking agent like avicel due to water being available as free water [144].

A summary of parameters during the spheronization process affecting the physicochemical properties of the pellets is shown in Table 1.10.

Table 1.10. Effects of parameters in the spheronization process on the physicochemical properties of the pellets

Spheronization	Effect on pellets' physicochemical properties
Spheronization speed	It is well documented that spheronization speed can influence the size of the pellet produced [98,103,106,138,140,145,146]. It has been observed that increase in spheronization speed leads to an increase in mean diameter of the pellets [80]. It has also been observed that spheronization speed influences pellet roundness [138,146–148], hardness [105], porosity [105,138], bulk and tapped densities [106,145], flow rate [145], friability [145] and surface structure [105]. There has been a suggestion that spheronization speed should be optimized to obtain desired densification [89]. Low spheronization speed would lead to insufficient densification, resulting increased of imperfection of sphere; and high speed could potentially result to agglomeration of pellets [80].
Spheronization time	It has been stated in various research work that extended spheronization time resulted in narrower particle size distribution [138]; higher sphericity [148]; change in yield of particular size range [145] and changed in tapped and bulk density [145] which is indirectly linked to flow property.
Spheronization load	At low spheronization load and high spheronization speed, the yield of pellet of specific range decreases [140]. It is observed in Hazsnos *et al* studies that the particle mean diameter increased with spheronization load [103]. However, in Hellen *et al* studies, it is observed that pellet size decreased with increasing spheronization load [104]. This ambiguity reflects the complexity of the spheronization process and its parameters.

As explained in chapter 1 section 1.3.2.4, slow drying results to greater shrinkage of the pellet, which reduces the porosity. The reduction of porosity improves the pellet mechanical strength. Table 1.11 shows the different methods of drying and its effect on pellets' physical properties.

Table 1.11. Effects of drying methods on the physical properties of the pellets

Drying method	Effect on pellets' physical properties
Freeze-dried	Direct evaporation of expanded ice pellet (freeze-drying) results in suppression of shrinkage process of pellet, which increases porosity and mean diameter [102].
Fluid-bed dried	Rapid evaporation of water via turbulent motion of fluidized pellet (fluidized bed), results in suppression of shrinkage process of pellet, which increases porosity and mean diameter [102].
Microwave	Microwaved dried pellet have shown to be more porous and less robust than oven dried pellet [105].
Oven dried	Slower manner of evaporation in comparison to the above method results in greater shrinkage of pellet, which reduces porosity and size of pellets [102].
Dried by desiccation with silica-gel	This has the slowest manner of evaporation in comparison to all of the above method, resulting in the greatest shrinkage of pellet, which reduces porosity and size of pellets [102].

The key effects of different excipients on the properties of the pellets are shown in Table 1.12. In brief, the physicochemical properties of the bulking agent and presence of plasticizer & surfactant can influence the pellet physicochemical properties.

Table 1.12. Effects of excipients on the physicochemical properties of the pellets

Excipients	Effect on pellets' physicochemical properties
Type of bulking agent	Different bulking agent/ carrier can exhibit different physicochemical characteristic of the final product.
Supplier of MCC	It has been seen that MCC from different supplier can alter the pellets' characteristic [149,150].
Plasticizer	According to Wang *et al*, reducing the amount of plasticizer in granulating polymer results to increase tensile strength and brittle fracture under compression [151]. However, increase in plasticizer content results to pellets with better plastic property because the polymer transits from glassy to rubbery state [151].
Surfactant	A surfactant that has high HLB value which tends to reduce sharkskinning of extrudate (in other words reduces the rough surface extrudate), as a result of decreased frictional force at the die wall of extrusion screen, producing pellets with higher sphericity [142]. In addition, it can facilitate permeability of API through GIT wall [152] and create the possibility of hydrophobic drug in pellets dosage form [153].

1.4 Compaction of pellets

1.4.1 Introduction to compacted pellets

Compaction of multiparticulates into tablets can be called multi-unit tablet, pellet-based tablet, tablet of multi-unit pellet system (MUPS) or compacted pellet. Although it has many names it is essentially compressed pellet, which may result to a tablet reverting back to its multiparticulate system in the GIT; or an intact tablet due to fusion of multiparticulates [102]. The MUPS can be categorized into two different types; type 1 consisting of uncoated or matrix pellet and type 2 consisting coated pellet [102]. In the compacted matrix pellet, Abdul *et al* have stated that such compacted pellet does not function as a MUPS and remain as a monolithic system [102]. However, such statement may not be accurate if compacted matrix pellet reverts back to its pellet form in dissolution medium.

Ideally, the compacted pellet should rapidly revert back to MUPS with similar drug release profile as the uncompressed MUPS [102,154]. The pellet core should be soft enough to deform under the compression force without brittle fracture, but hard enough to resist compression force to prevent permanent fusion of the pellets [102,154]. In other words, the major mechanism during compaction of the pellet should be elastic deformation as opposed to plastic deformation [155]. For coated pellet, the rupturing of the coating posed a major issue when a compression force is applied; thus, it is suggested that polymeric coating should have adequate strength, ductility and thickness [154].

The compaction of uncoated pellet will be part of the authors' investigation; hence, this introduction will be focused mainly on compaction of uncoated pellet instead of compaction of coated pellet. However, it should be pointed out that the compaction of coated pellet is a major challenge and there have been extensive studies in this field. In compaction of uncoated pellets, it has been suggested that there are four stages involved. They are 1) rearrangement of pellets, 2) surface deformation, 3) bulk deformation and 4) cessation of volume reduction [102,156], which are explained in more details in Table 1.13. During the rearrangement of pellet and surface deformation stages, there is a marked reduction in volume; however, there is insufficient inter-granular bonding force; thus, the pellet cannot form a compact [102,156]. At high compaction force during the bulk deformation stage, the inter-granular bonding is stronger, which is likely to form a compact. Further increase of compaction force can further increase inter-granular bonding but volume reduction may cease or be minute [102,156].

Table 1.13. Stages of compaction of pellets into tablets.

Stages in compaction of pellets	Details of the stages
1) Rearrangement of pellets	At low compaction force, the reduction of volume is due to pellets rearrangement, where pellets fill the inter-particle void [102,156].
2) Surface deformation	At moderate compaction force, the reduction of volume is caused by local surface deformation, where the surface of pellets is flatten [102,156].
3) Bulk deformation	At high compaction force, bulk deformation of pellets occurs, which mean the change in pellet dimension is in parallel to densification of pellet [102,156].
4) Cessation of volume reduction	Still under high compaction force, however, there is no further volume reduction due to low inter-granular and intra-granular porosity.

Since the author of this thesis will mainly use MCC-based pellet, it is noteworthy to point out some of the observation in studies relating to compression of MCC-base pellet by Johansson *et al* [156,157]. They observed that MCC-based pellet compressed by deformation and the incidence of pellet fragmentation is very low or non-existence. It is also reported that the porosity of MCC-based pellet has an influence on the degree of deformation and densification. During compression, low porosity MCC pellet undergoes limited permanent deformation, whereas high porosity MCC pellet undergoes high compression induced change, including a marked reduction in pellet porosity.

Although compaction of coated pellet is not the main focus in the investigation of this thesis, there are numerous reason it will become relevant to the author's invention in the near future. There are many reasons for film coating to be applied to compacted pellets which include: modifying drug release profile; taste masking; improved appearance; improved stability and improved mechanical integrity [102]. The polymer film coating can be categorized into two main groups, 1) cellulosic polymer and 2) acrylic polymer [158,159]. The main cellulosic polymer used in sustained release is ethylcellulose, and the main acrylic polymers used are Eudragit® and Kollicoat® [102]. It has been stated that among these two

types of polymer, acrylic polymer is more flexible; thus, it is a more suitable for coating pellet-based tablet [160]. Furthermore, since the rupturing of film coating is a major issue as it can cancel the function of the coating film, cushioning excipients is an important factor in compaction of coated pellet [102].

1.4.2 Advantages of tablet multi-unit pellet system (TMUPS)

The compacted pellet maintains the advantages of the MUPS provided that the compact can revert back to its MUPS [161]. The advantages of pellet dosage form are covered in chapter 1 section 1.3.4. In brief, MUPS is an attractive system as opposed to single unit dosage system (SUDS) due some key inherent advantages including, potential to combine incompatible drugs or drugs with different release profiles in same dose unit; flexibility for modification via coating technology; reduced likelihood of side effects due to fast gastric emptying; reduced inter and intra-variation in bioavailability caused by food effect and reduced risk of dose dumping as subunit of the MUPS can be distributed more evenly in the GIT [77,162,163], which also improves bioavailability and reduce variability in drug release [154]. In terms of production, the benefits of pellet-based tablet over powder tableting is the reduction of dust problems [81] and capability of improved flow property for machine handling. Furthermore, MUPS represents a higher technical barrier to deter the introduction of generic products; hence, potentially extending the commercial value of a given drug [154].

It is a well-known fact that tablet dosage form is a more commercially favourable dosage form than capsule in terms of cost-effectiveness. Producing tablet have lower production cost and higher production rate compared to capsule [164], and costly control steps to ensure capsule integrity is eliminated [77,165]. Other advantages of tablet over capsule includes: lower tendency of dosage form adhering to oesophagus during ingestion [166]; ability to be administered at higher dose strength per unit than capsule [167]; reduces the risk of dosage form being tampered with [164]; improves patient compliance, particularly for those who prefer not to ingest gelatin capsule [110]. It is also worth mentioning that the issue with gelatin capsule is not just an individual preference but extends to chemical instability [168], varying dissolution rate of capsule due to varying structure and composition of gelatin [169], and questionable source, particularly from waste leather which has been treated with harmful substance [170]. Hence, there is an incentive to explore pellet-base tablet as an alternative to pellet filled capsule, which is reflected in the growing popularity in compressing pellet into a tablet as opposed to filling them in capsule [167].

1.4.3 Problems in compacting pellets

In spite of TMUPS array of advantages, the manufacturing of TMUPS is an extremely challenging area of study. The content uniformity of TMUPS can be influenced by the size of the pellets, its size distribution and the size of additional excipients. In general, compaction of pellets together with an excipient of smaller particle size results in high variation in mass and size due to a segregation phenomenon [171]. The main challenge in TMUPS however, concerns with coated pellet. The induced damage of functional coating due to compression process pose a major issue in TMUPS; hence, there are only a few pharmaceutical TMUPS currently on the market [154], such as Beloc® ZOK (Metoprolol) [172], Antra® MUPS (Omeprazole) [173] and Prevacid® SoluTab™ (Lansoprazole) [174].

In some case, it may be acceptable for the coating film to deform but not rupture as rupturing would lead to loss of coating function [102]. It has been mentioned that additional excipient/s is required for particle of about 1 mm to be compressed into a stable tablet without film coating rupturing. To add to the challenge of making successful TMUPS, the coating film may not rupture during compaction but this does not ensure the TMUPS will have appropriate tensile strength, friability and disintegration time [167].

Another potential problem in compacted pellets is the fusion of the pellets, which may prevent the tablet reverting back to MUPS [102]. This would take away the inherent advantages of the MUPS. The MUPS advantages are mentioned in chapter 1 section 1.4.2. In order to avoid or overcome problem arising from compaction of pellets, comprehensive knowledge of how pellets behave during compression process and parameters affecting it should be understood, which is covered in chapter 1 section 1.4.4.

1.4.4 Factors affecting TMUPS

When making TMUPS there are many factors that impact the formulation design. As mention in chapter 1 section 1.4.3, the polymeric functional coating integrity is a key issue in compacting pellets. If the coating is cracked or ruptured it will have a negative impact on its desired function, particularly if the function is for controlled drug release. Thus, the type of coating film, size of pellet and excipients, properties of pellet, properties of additional excipient/s, and compression force must be carefully controlled to achieve the desired drug release profile [175]. Factors that can impact the design of TMUPS are summarized in Figure 1.9. Within the process of producing TMUPS, there are components which can be categorized as 1) pellet core, 2) coating, 3) tableting excipient and 4) equipment.

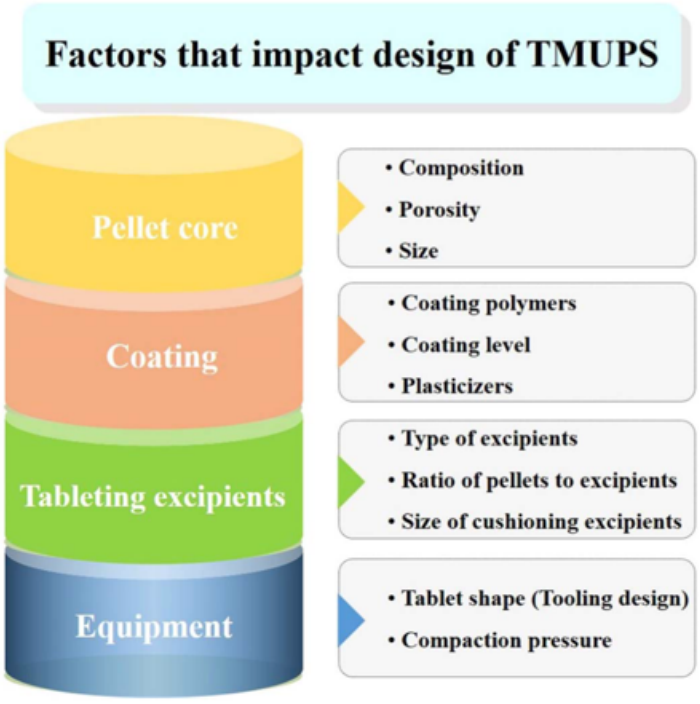


Figure 1.9. Diagram summarizing factors that impact the design of TMUPS [154]

Within the components mentioned above, there are factors that affect these components and effectively the whole TMUPS. Key factors affecting pellet core include: composition, porosity and size, which is explained in more details in Table 1.14. It has been mentioned that MCC-based pellet is inappropriate for an enhanced drug release pellet-based tablet as such pellet core does not disintegrate quickly [176].

Table 1.14. Factors affecting the core pellet in TMUPS

Factors affecting core pellets	Details about the factor
Composition	Composition of core pellet determines its deformability, which in turn influences pellet tabletability and integrity of functional coating layer after compaction [154]. The more rigid the pellet core is the better it is for coated TMUPS because there will be a smaller degree of deformation during compression, which protects the integrity of the polymeric coating film [154]. Therefore, naturally, the formulation that incorporates excipient with hard characteristic would be considered more compression resistant [154]. However, this would increase risk of fracture during compression.
Porosity	The porosity of the pellet influences its deformation and densification [177], which in turn affect the compression of the pellet and the drug release profile [154].
Size	It is observed that large pellets undergo a higher degree of deformation than smaller pellet [178], due to reducing number of force transmission points, which increases contact stress at each contact point [154]. This means larger pellet may cause greater damage to coating layer than smaller pellets.

Key factors affecting coating films are the type of coating polymers, coating level (number of coating layers or thickness) and plasticizers, which is explained in more details in Table 1.15. Successful TMUPS can be achieved when coating composition and cushioning excipient/s are optimized [154].

Table 1.15. Factors affecting the coating film in TMUPS

Factors affecting the coating	Details about the factor
Type of coating polymer	Different types of coating polymer have different mechanical properties. The key mechanical property is usually described as percentage elongation of the coating film. High elongation would mean the coating is more resistant to rupturing under compression force [154].

Coating level	Coating layers are directly linked to the film thickness. Thick film could make it more resilient to damage and rupture under compression force [179]. However, coating film thickness influences drug release profile [180,181] and although thicker film is more resilient under compression, it further delays drug release. This may not produce the desired drug release profile that is intended.
Plasticizer	Plasticizers are used to increase film coating flexibility to prevent it from rupturing during the compaction process. The plasticizer reduces the glass transition temperature [154].

Key factors in tableting excipients include types of excipient, ratio of pellet to excipient and size of cushioning excipients, which is explained in more details in Table 1.16.

Table 1.16. Factors in tableting excipients in TMUPS

Factors in tableting excipients	Details about the factor
Type of excipients	Different excipients added together with the pellets for compaction can influence the TMUPS properties, such as mechanical strength, friability and integrity of the TMUPS. One of the key excipients is a cushioning agent. This excipient undergoes extensive deformation so that the pellet coating deformation is reduced; thus, protecting the coating film [154].
Ratio of pellets to excipients	This is another important factor that can significantly influence TMUPS properties such as friability, disintegration time, integrity of coating film, drug content uniformity and drug release profile [182].
Size of cushioning excipients	Differences in size of cushioning excipient can affect its cushioning effect and its influence on drug content uniformity. Smaller cushioning excipient have better cushioning effect; however, larger granules of cushioning excipients that matches the size of the pellet generally favour better drug content uniformity due to less separation [154].

Finally, the key factors involved in equipment includes tablet shape and compression pressure, which is explained in more details in Table 1.17.

Table 1.17. Factors involving equipment in TMUPS

Factors involving equipment	Details about the factor
Tablet shape	Tooling design used to produce different shaped tablet affects stress distribution inside the tablet which influences the deformation of the components in the tablet during compression [183]. This can influence the TMUPS physical properties.
Compression pressure	It has been stated that compression force significantly influences tablet properties such as, strength, disintegration time and friability. It is observed that increase in compression pressure reduces friability of TMUPS [179,184]. The compaction pressure does not seem to affect drug dissolution rate provided that the coating film is not damaged and the tablet revert back to MUPS [154].

Aims & objectives

The key objective of this project is to create a new oral dosage form called liqui-pellet and liqui-tablet (invented by the author of this thesis), which directly addresses the grand challenge of improving the bioloavailability of poorly water-soluble drugs in a cost-effective manner. Liqui-pellet and liqui-tablet uses liqui-mass system and stems from combining pelletization technology with concepts from liquisolid technology. The classical liquisolid formulation holds many keys advantages in terms of drug dissolution performance and the manufacturing aspect, mainly simple and cost-effective. However, there are main hurdles such as, (1) poor flowability (2) poor compactability and (3) inability to produce high dose dosage form within acceptable size and weight for swallowing. This restricts liquisolid application in pharmaceutical formulations, hindering its commercial feasibility. Therefore, the main aim of the current research is to overcome these restrictions and bring forward concepts from liquisolid technology to a commercial direction through the author newly invented technology. Investigations on factors affecting its physicochemical properties and drug release performance was another key ojective. In addition, tests which is typically used for quality control was investigate to study the potential commercial feasibility.

Each experimental chapter of this thesis have specific objectives and the chapters are arranged in such that previous chapter will contribute to the next chapter. In chapter 2, the objective is to investigate the feasibility of making naproxen liqui-pellet for the first time in order to resolve the poor flowability issue prevalent in liquisolid technology. This leads into chapter 3 where naproxen liqui-pellet is optimized to improve drug release rate. Observation in this chapter reveals two key parameters influencing drug release rate, which becomes the key ojective of chapter 4, where the author investigates the effect of the amount of water and co-solvent have on liqui-pellet, particularly the drug release rate.

In chapter 5, effervescent agent (sodium bicarbonate) is incorporated into liqui-pellet as a functional excipient to improve drug release rate. Chapter 6 objective is to study naproxen liqui-pellet potential as a fast release dosage form through incorporating all the knowledge from previous chapters to optimize the formulation. In addition, a large specific surface area carrier called neusilin US2 is introduced to investigate its influence on physicochemical properties.

So far, the mentioned chapters uses naproxen as the API. In order to truly claim liqui-pellet is a new oral dosage form, it is prudent to use another API. Chapter 7 investigate

the feasibility of hydrochlorothiazide liqui-pellet as well as optimizing the formulation to study its potential for rapid drug release. This serves as a way to establish and confirm the understanding of parameters affecting liqui-pellet.

Chapter 8 objective is to investigate the feasibility of liqui-tablet which stems from liqui-pellet. This is to diversify the invented technology and a response to the strong incentive for tablet dosage form. Another key purpose of the investigation is to see if rapid drug release rate can be maintained in liqui-tablet form. Finally, in chapter 9, investigation is conducted to see if liqui-tablet can produce a high dose dosage form within a reasonable size and weight for swallowing. This has never been achieved before with liquisolid technology. Such development can bring concepts from liquisolid or powdered solution technology into an attractive commercial direction.

Chapter 2: Liqui-pellet: the emerging next generation oral dosage form which stems from liquisolid technology in combination with pelletization technology

2.1 Abstract

In spite of the major advantages that liquisolid technology offers, particularly in tackling poor bioavailability of poorly water-soluble drugs (i.e. BSC Class II drugs), the inability of high liquid loading, poor flowability and poor compressibility of liquisolid powder is one of the biggest hurdles, hampering this technology from being commercially feasible. Henceforth an attempt is made to overcome these drawbacks whilst maintaining liquisolid inherent advantages. This results in the emerging next generation oral dosage form called liqui-pellet, which stems from liquisolid concept in combination with pelletization technology. All formulations were incorporated into capsules as the final product. Solubility studies were conducted in naproxen with different liquid vehicles, namely polyethylene glycol 200 (PEG 200), propylene glycol (PG), tween 80, labrafil, labrasol and kolliphor EL. Flowability and dissolution tests confirmed that this next generation oral dosage formulation have excellent-good flow property, whilst maintaining the typical liquisolid enhanced drug release performance. The liqui-pellet also have a high liquid load factor of 1, where 29% of the total mass is co-solvent. This shows that high liquid load factor can be achieved in liqui-pellet without compromising flowability. The scanning electron microscopy (SEM) studies indicated that co-solvent tends to reduce surface roughness of the pellet. Solid-state study, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) indicated a reduced crystalline structure and increase in amorphousness in liqui-pellet. Overall, the results showed that poor flowability of liquisolid formulation could be overcome with liqui-pellet, which is believed to be a major advancement into commercial feasibility of liquisolid concept.

2.2 Introduction

Liqui-pellet is an emerging novel oral dosage form, which improves the bioavailability of poorly water-soluble drugs via increasing drug release rate in the GIT. The poor drug dissolution rate of water-insoluble drugs is, in fact, a major issue confronting the pharmaceutical industry [1]. It is worth pointing out that around 60% of drugs in the market are poorly soluble in gastrointestinal fluids, which is based on biopharmaceutical

classification system (BCS), and around 40% of drugs in development are identified as poorly water soluble [185,186].

Liqui-pellet stems from combining liquisolid concept with pelletization technology. It is fundamentally different from liquisolid technology in that it does not fit under the definition of liquisolid system; hence, it is called liqui-pellet instead of liquisolid pellet. Liquisolid formulation is described to be under liquisolid system, which refers to a powdered form of liquid medication formulated by transforming liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble drugs in appropriate non-volatile liquid vehicle into dry looking nonadherent, free flowing and readily compressible powder admixtures by incorporating specific carriers and coating materials [5]. In this study, the liqui-pellet cannot be described as a liquisolid system because it is not necessarily in powder form and the admixture is not necessarily free-flowing, but rather a cohesive wet mass. The formulation only becomes free-flowing after becoming a pellet. In addition, the purpose of entitling the new dosage form as liqui-pellet, is to emphasize the high liquid load factor or high amount of liquid vehicle it is capable of containing. The new system is described as liqui-mass system, which is summarized in Figure 2.1. The liqui-mass system is versatile and different modification can be applied to it. In this study, the key focus is producing liqui-pellet via liqui-mass system. However, it should be noted that this novel technology is still in its infancy; there is a high degree of flexibility for modification regarding liqui-pellet and the liqui-mass composition as shown in Figure 2.1.

In order to have a good grasp of liqui-pellet, it is important to understand liquisolid technology. Liquisolid technology's simplistic approach and cost-effectiveness are desirable when considering manufacturing at a commercial scale [4]. In fact, the excipients used are conventional and commonly available in the market [4]. In addition to enhancing the drug release, the formulation can be manipulated to achieve sustained drug release with a near zero order release kinetic [10,11]. Despite the advantages, it has yet to overcome drawbacks, which hampers it from becoming a commercial product. This is mainly due to major issues such as poor flowability, poor compressibility and the inability to produce high dose drug without being too bulky and heavy, which is not ideal for swallowing [1,4]. The flow property of the liquisolid blend is of critical importance in terms of manufacturing, particularly tablet or capsule form, as flow property determines uniform feed and reproducible filling [34].

In brief, the concept of liquisolid system is comprised of an active pharmaceutical ingredient (API), which is solubilized in a liquid vehicle, forming the liquid medication. This

liquid medication is then incorporated into a carrier which is coated with a nano-sized coating material to give the admixture of API and excipients a dry, free-flowing and readily compressible properties [1,3].

Although there are other various technologies confronting the issue of poor drug dissolution rate of water insoluble drugs, they may require advance technique, sophisticated machinery, complicated technology or not cost-effective [4]. The other technologies include conversion of crystalline drug into its amorphous state [18], micronization [19–22], solid dispersion [23], co-grinding [24–26], nanosuspension [27,28], self-emulsifying drug delivery system [29,30] and inclusion of drug solution in soft gelatin capsule [31]. But in most cases the long-termed stability is an issue. For example, on storage, highly amorphous materials can be converted to crystalline state which usually change drug release profile [32,33].

Since the focus of this study involves combining concept from liquisolid technology with pelletization technology, specifically extrusion-spheronization technology, the understanding of optimal extrudate properties for spheronization and parameters affecting the formation of pellets is prudent. In order to carry out wet extrusion, the material must display sufficient plastic property and cohesiveness to allow shaping and retention of the extrudate. The extrudate for pellet production should be self-lubricating and eventually brittle but not friable [94]. Moisture in the powder mass is one of the major factors necessary for providing plasticity for extrusion and spheronization, which have been subjected to much research [95–100]. Water content is found to be one of the most important parameters [99]. Other factors that can affect pellets' properties are water/ granulating liquid temperature, extrusion speed, spheronization speed and spheronization duration [98].

The aim of the present study is to make liqui-pellet, which has the inherent advantages from both liquisolid and pelletization technologies. The extrusion-spheronization technique can improve flow property and the inherent advantages from the liquisolid aspect can enhance the drug release rate. The author has termed this next generation oral dosage form as liqui-pellet. This is to distinguish itself from the classical liquisolid compact; to emphasize the high liquid loading factor it is capable of; and most importantly to make clear that it is fundamentally different from liquisolid formulation in that it does not correspond to liquisolid system, but instead to liqui-mass system. The excellent flowability of liqui-pellet means there is more room to increase liquid load factor or the amount of liquid vehicle. The inherent advantages from pelletization technology

include reduced risk of side effects due to dose dumping, combining incompatible drugs or drugs with different release profiles in same dose unit [77] and having good flow property [79].

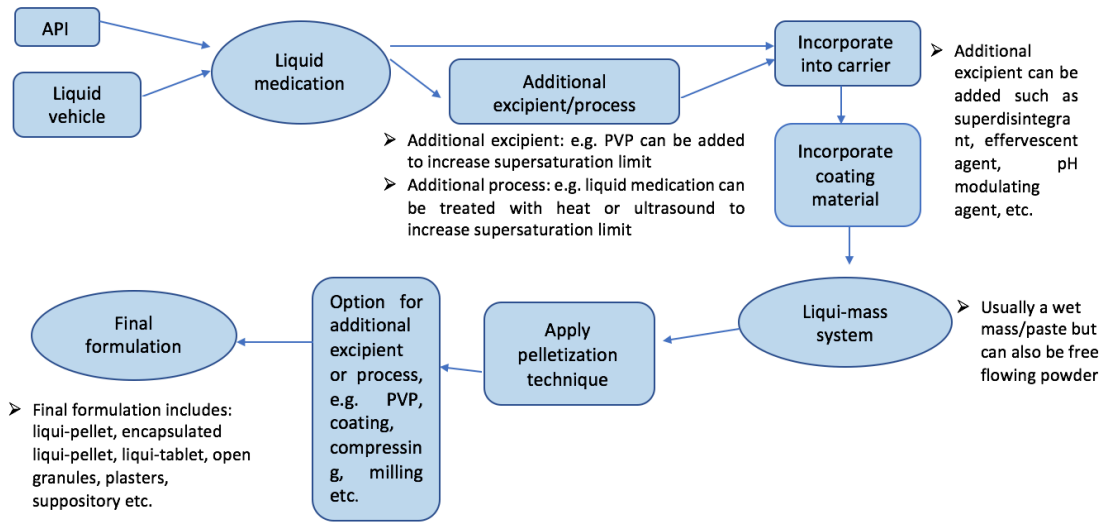


Figure 2.1. Diagram summarizing the novel liqui-mass system which is used to make liqui-pellet

2.3 Materials and methods

2.3.1 Materials

Naproxen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); polyethylene glycol 200 (Fisher Scientific, Leicester, UK); propylene glycol (SAFC, Spain); polysorbate 80 (tween 80), (Acros, Netherlands); linoleoyl macrogol-6 glycerides (Labrafil), (Gattefosse, Saint Priest, France); caprylocaproyl macrogol-8 glycerides (Labrasol), (Gattefosse, Saint Priest, France) and macrogolglycerol ricinoleate 35 (Kolliphor EL), (BASF SE, Ludwigshafen, Germany). All other reagents and solvent were of analytical grades.

2.3.2 Solubility studies

Saturated solubility studies were carried out using 6 different liquid vehicles, i.e. polyethylene glycol 200 (PEG 200), propylene glycol (PG), tween 80, labrafil, labrasol and kolliphor EL. Saturated solutions were prepared by adding excess pure naproxen into a small vial containing 10ml of specified liquid vehicle. The sample was then left in a bath

shaker (OLS Aqua Pro, Grant Instruments Ltd, UK) for 48 h under a constant temperature of 37°C and shaking speed of 40rpm. The supernatant was then filtered through a pre-heated filter (pore size 0.22 μm, Millex GP, Merck Millipore Ltd, Ireland), and diluted with phosphate buffer solution. This was then analyzed via UV/vis spectrophotometer (Biowave II, Biochrom Ltd, UK) to determine the concentration of naproxen in each sample. Each test was carried out in triplicates.

2.3.3 Preparation of naproxen liqui-pellet

The liqui-pellets were prepared by mixing pure naproxen in a chosen liquid vehicle (PEG 200, PG, tween 80, labrafil, labrasol and kolliphor EL) using pestle and mortar method. All formulations contained avicel PH-101 and aerosil 300 as carrier and coating materials respectively, with a weight ratio of carrier to coating material of 20 (R-value). Avicel PH-101 was mixed into the admixture to make sure the wet liquid medication was absorbed by the carrier and not leaving residual in the mortar when transferred into a mixer (Caleva Multitab, Caleva Process Solutions Ltd, UK). The sample was mixed for 10 min at a constant rate of 125 rpm with deionized water added bit by bit to achieve desirable plasticity for extrusion (Caleva Multitab, Caleva Process Solutions Ltd, UK). The preliminary studies indicated that water content was a crucial factor to achieve extrudate with optimal plasticity for quality spherical pellet after spheronization (Caleva Multitab, Caleva Process Solutions Ltd, UK), which was further supported by the data published in literature [99]. Aerosil 300 was then added into the admixture and further mixed for 10 min before extrusion-spheronization process. Spheronization was set at an almost constant rotation at 4000rpm (decrease to 3500 rpm if agglomeration seemed likely or increase to 4500 rpm to increase pellet sphericity), however in each formulation, spheronization time varied depending on the extrudate plasticity property. Pellets were then placed in an oven under a constant temperature of 50°C overnight to remove water from pellets. Table 2.1 shows the details of each formulation with different liquid vehicles.

Table 2.1. Key formulation characteristics of the investigate liqui-pellet capsule

Formulation	Liquid vehicle	Liquid vehicle concentration (%w/w)	Mass of carrier (mg)	Mass of coating material (mg)	Liquid load factor	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet			68.97	3.13		90.63
LP-1	PEG 200	29.27	62.50	3.12	1	128.13
LP-2	PG	29.27	62.50	3.12	1	128.13
LP-3	Tween 80	29.27	62.50	3.12	1	128.13
LP-4	Labrafil	29.27	62.50	3.12	1	128.13
LP-5	Labrasol	29.27	62.50	3.12	1	128.13
LP-6	Kolliphor EL	29.27	62.50	3.12	1	128.13

Note all formulation contain 25mg of naproxen and the carrier to coating material is at a ratio of 20:1

2.3.4 Assay of drug content

Assays were carried out in all naproxen liqui-pellet samples in order to confirm that all formulations contained expected amount of drug that meets USP standard of 90-110%. Assays were carried out via crushing specified amount (in weight) of liqui-pellets and dissolving the sample in a specified amount of phosphate buffer solution (pH 7.4) for spectrophotometric analysis (Biowave II, Biochrom Ltd, UK) at a wavelength of 271 nm where naproxen can be detected. Wavelength of 271nm was determined using studies by Tiong *et al* [15].

2.3.5 Flowability test on liqui-pellet

Techniques of measuring flow property of the liqui-pellet that were used were: flow rate in g/sec (Flowability tester, Copley Scientific, UK), angle of repose (Flowability tester, Copley Scientific, UK and Digimatic height gage, Mitutoyo, Japan) and Carr's compressibility index using the SVM tapped density tester (D-63150, Erweka, Germany). Flow rate was measured by recording the weight (g) and time (sec) of pellets flowing through a 10 mm diameter orifice. Shutter was applied before funnel became empty of the sample. As for the angle of repose, the pellets were placed in a funnel with 10 mm diameter orifice and let to flow onto a 100 mm diameter circular test platform. The digimatic height gauge and micrometer were used to measure the height and diameter of the heap of the sample, so that the angle of

repose could be determined. Carr's compressibility index (CI%) was calculated from the poured (P_b) and tapped (P_t) densities using CI equation (Equation 2.1). Tapped density was measured using the tapped density tester, which was set for 100 taps. All measurements were done in triplicates.

$$CI\% = (P_t - P_b)/P_t \times 100 \quad \text{(Equation 2.1)}$$

2.3.6 Friability test on liqui-pellet

Since there is no official standard for friability test on pellets, friability test were adapted using similar method used by Hu *et al.* [187]. All formulations were tested. Pellets (3 g) and glass beads (3 g) were placed in Erweka friabilator (D-63150, Erweka, Germany) under constant rotation of 25 rpm for 4 minutes. Note that the friabilator was sealed in order to prevent pellets from leaving the container. The weight of the pellets before and after the friability test was recorded in order to calculate % weight loss.

2.3.7 Particle size analysis via sieve method

Sieves (Test sieve, Retsch, Germany) were used to determine the size distributions of all formulations. Pellets (5 g) were sieved under vibration via mechanical shaker (AS 200, Retsch, Germany) for 1 min with amplitude of 50, then a further 9 min with amplitude of 40, using 2000, 1000, 850, 500, 250 μm sieves. The pellets yield was determined based on the pellet fraction between 250 μm and 2000 μm and shown as the % of total pellet weight.

2.3.8 Stereoscopic analysis

Stereoscopic analysis was performed on all formulations using an optical microscope (Nikon Labophot, Nikon, Japan), which was attached to a camera (Panasonic camera WVCL310, Panasonic, Japan). This allowed the mean Feret's diameter, roundness and elongation ratio to be calculated using particle size analysis software V1999 (designed in-house at King's College London). Note that 100 pellets per formulation were analyzed and roundness and elongation ratio was calculated using Equation 2.2 and 2.3 respectively [188].

$$\text{Roundness} = (\text{perimeter})^2/(4 \times \pi \times \text{Area}) \quad \text{(Equation 2.2)}$$

$$\text{Elongation ratio} = \text{Maximum Feret diameter} / \text{Minimum Feret diameter} \quad \text{(Equation 2.3)}$$

2.3.9 Scanning electron microscope (SEM) analysis

Scanning electron microscope (Jeol JMS 820, Freising, Germany) was used to observe the morphology of the pellets of each formulation. Each sample was placed in a double-sided carbon tape and sputter-coated with gold using a sputter coater (Edwards S-150 sputter coater, Edwards High Vacuum Co. International, USA) before placing in the SEM machine. The surface structure was then observed and recorded at magnification of × 80, × 200 and × 800, using the SEM which was operating at 3kV.

2.3.10 In-vitro drug release test

All dissolution tests were carried out using USP paddle method (708-DS Dissolution Apparatus & Cary 60 UV-Vis, Agilent Technologies, USA). The formulations in the form of liqui-pellets in capsule were under constant condition of 900 ml of dissolution medium, paddle agitation of 50rpm and temperature of 37.3 ± 0.5^{o}C. Dissolution medium was either HCl buffer solution of pH 1.2 or phosphate buffer solution of pH 7.4 to simulate gastric fluid and intestinal fluid respectively without enzymes. Absorbance (at 271 nm) was taken at time interval of 5 min until 1 hour then time interval of 10 min for another hour. Wavelength of 271nm was determined using studies by Tiong *et al* [15].

All formulations contained 25mg of naproxen. The reason for choosing 25mg of naproxen was because of naproxen poor solubility profile at pH 1.2 due to its weak acidic properties. Naproxen would need to be able to dissolve completely at pH 1.2 in order for the dissolution test to be reliable. According to studies by Mora and Martinez [189], naproxen solubility at 35^{o}C and pH 1.2 was 1.16×10^{-4}mol/L or 27mg/L, hence 25mg used in test seemed reasonable. As for pH 7.4, naproxen was extremely soluble with solubility of 1.455×10^{-2}mol/L or ~3347mg/L. It should be noted that pH 1.2 sink condition was not maintained and this pH was only used for comparison of various formulations.

2.3.11 Kinetic model analysis of drug release

Kinetic release models (zero order, first order and Higuchi) were applied to the results from drug release studies. Zero-order release model describes a system where drug release rate is independent of its concentration. The data from cumulative drug release can be plotted against time [190]. First-order release model describes a system where drug release rate is dependent of its concentration and can be obtained by plotting logarithm percentage release of remaining drug vs the time [190]. Higuchi model suggests that drug release from

insoluble matrix is directly proportional to square root of time and is based on Fick's law of diffusion [191]. The plot of cumulative percent drug release against square root of time should be linear if drug release is a controlled release [191]. The most appropriate kinetic model for a formulation is based on the highest square of correlation coefficient known as R^2 value [192].

2.3.12 Differential scanning calorimetry (DSC) studies

DSC (DCS 4000, Perkin Elmer, USA) was performed on the excipients, pure naproxen and the chosen formulations with the fastest drug release rate in order to assess their thermal behavior. Samples weighing between 3-6mg were sealed in aluminum pan and thermal behavior was investigated at a scanning rate of 10 ^{o}C/min, from 25 ^{o}C to 200 ^{o}C under nitrogen atmosphere.

2.3.13 X-ray powder diffraction (XRPD) studies

XRPD was performed using X-ray diffractometer (D5000, Siemens, Germany) on naproxen, excipients and selected formulations to characterize the solid state of the materials used. Samples were scanned over a range of 2θ at a voltage of 40 kV and current of 30 mA, with scanning angle ranged from 5^{o} to 40^{o} and scan rate of 0.2^{o}/s.

There were 2 methods of analyzing the % relative crystallinity, which were integrated peak method (Equation 2.4) and peak height method (Equation 2.5) [193]. For integrated peak method, the area under the peak was measured via trapezoid method. In Equation 2.4, A_s is the integrated peak value of a sample and A_r is the integrated peak value of a reference, which is usually the pure API. In Equation 2.5, H_s is the peak height value of a sample and H_r is peak height value of a reference, which is usually the pure API.

$$\% \text{ XRD relative crystallinity} = (A_s/A_r) \times 100 \qquad \text{(Equation 2.4)}$$

$$\% \text{ XRD relative crystallinity} = (H_s/H_r) \times 100 \qquad \text{(Equation 2.5)}$$

2.3.14 Statistical & mathematical analysis

Mean cumulative % drug release (reading point at 2h) from dissolution test were statistically analyzed by one-way analysis of variance (ANOVA). Results were quoted as significant where $p<0.05$.

Specific mathematical equations were used to analyze and compare dissolution profiles, which includes difference factor (f_1) equation Equation 2.6 and similarity factor (f_2) equation Equation 2.7 as described by Moore and Flanner [194]. Both methods have been recommended by the US FDA (Food and drug administration) [195] and implemented by the FDA in various guidance documents [196,197]. In brief, f_1 value between 0-15 and f_2 value between 50-100 indicates equivalence of the two dissolution profiles [198]. Details of the equations can be found in various literature [195,199–201]. The *n* represents the number of dissolution sample times and R_t & T_t represent the mean % of drug dissolved at each time point (t).

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|]/[\sum_{t=1}^{n} R_t]\} \bullet 100 \qquad \text{(Equation 2.6)}$$

$$f_2 = 50 \bullet \log\{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\} \qquad \text{(Equation 2.7)}$$

2.4 Results and discussion

2.4.1 Solubility studies

As shown in Table 2.2, naproxen is most soluble in kolliphor EL liquid vehicle and least soluble in tween 80. Despite this, the formulation containing tween 80 (LP-3) unexpectedly shows the fastest dissolution rate at pH 1.2 (Figure 2.6). It is generally thought that formulation containing the liquid vehicle with the highest solubility to the drug would exhibit the fastest drug release rate. This is due to less drugs in crystalline form and more drugs are in solubilized or in molecularly dispersed state in the carrier, thus increasing surface area for dissolution [3].

It is noteworthy to point out that apart from drug solubility, other physicochemical characteristics of liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure and molecular mass may affect drug release behavior [1]. Hence, this may be the reason why the solubility result does not strictly match with the drug release result. Nonetheless, solubility of drug in a liquid vehicle is a major factor that could greatly influence drug release profile.

Table 2.2. Solubility of naproxen in various liquid vehicles at 37°C (n=3)

Non-volatile solvent	Mean concentration (mg/ml) ± SD[a]	Inference
PEG 200	7.88 ± 4.87	Slightly soluble
PG	5.13 ± 0.78	Slightly soluble
Tween 80	2.99 ± 1.01	Slightly soluble
Labrafil	10.73 ± 1.15	Sparingly soluble
Labrasol	5.14 ± 2.44	Slightly soluble
Kolliphor EL	15.83 ± 0.77	Sparingly soluble

For the composition of each formulation refer to Table 2.1
[a] SD, standard deviation

2.4.2 Extrusion and Spheronization

It should be noted that in the preliminary work, the moisture level or plastic property of extrudates greatly affect the success of spheronization. Extrudate plastic property is directly linked to the amount of water added, which is the granulating liquid. The more water added the greater the degree of plasticity. When the extrudate's plasticity reaches above a critical point it would usually be in a form of long threads rather than short threads (usually 3-5cm) as shown in Figure 2.2 (A). This extrudate's degree of plasticity was above the critical point, resulting in agglomeration during the spheronization as shown in Figure 2.3 (A). Thus, finding the optimal water content in extrudate has been seen prudent in making liqui-pellets. In addition, spheronization speed and time should be taken into account as high speed and long duration of spheronization could lead to agglomeration.

It can also be seen in Figure 2.3 that the quality of the pellets from formulation (B) can be similar or better than that of pellets without liquid vehicle (C). This could be due to liquid vehicle improving the rheological property of the extrudate to form good spherical pellets.

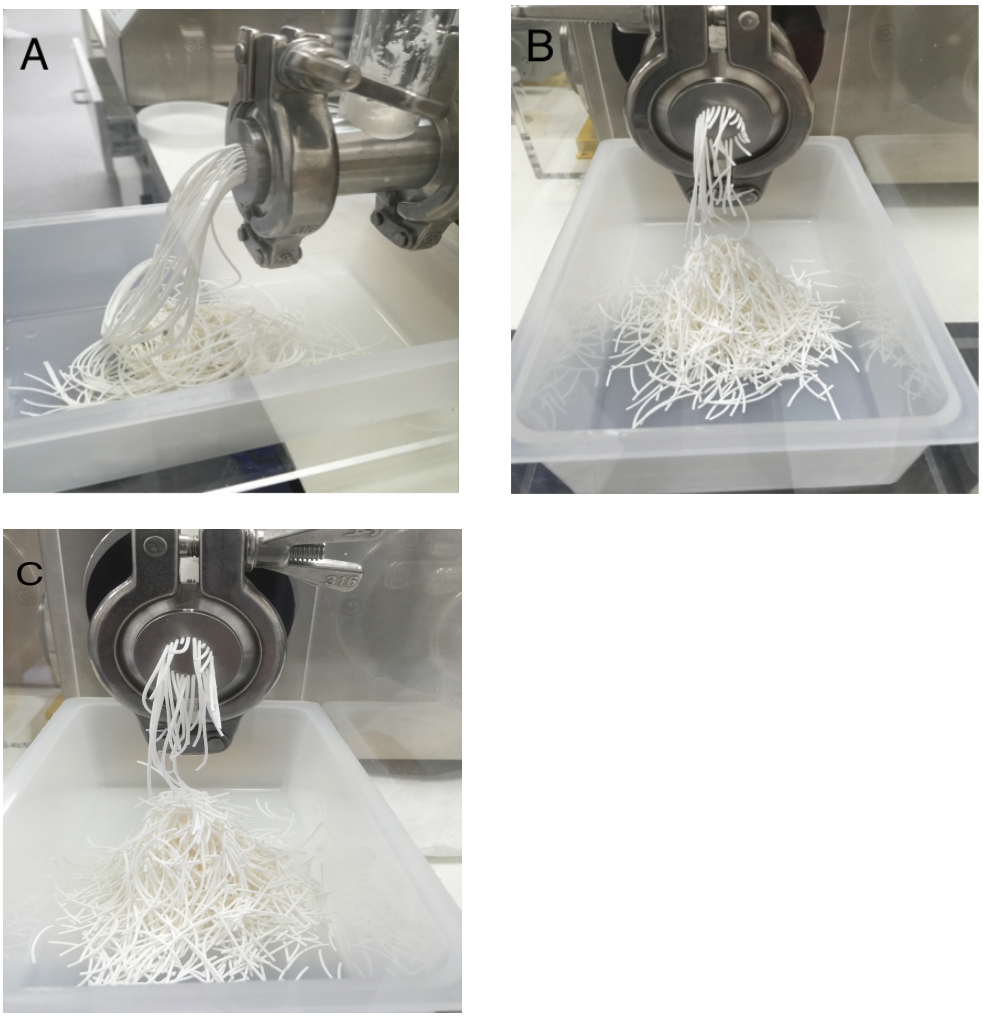


Figure 2.2. Image (A) of extrudate of a formulation (naproxen, tween 80, avicel and aerosil) containing high water content, exhibiting high plasticity. Image (B) of extrudate of a formulation (naproxen, PG, avicel and aerosil) containing lower water content, exhibiting lower plasticity. Image (C) of extrudate of physical mixture formulation (naproxen, avicel and aerosil)

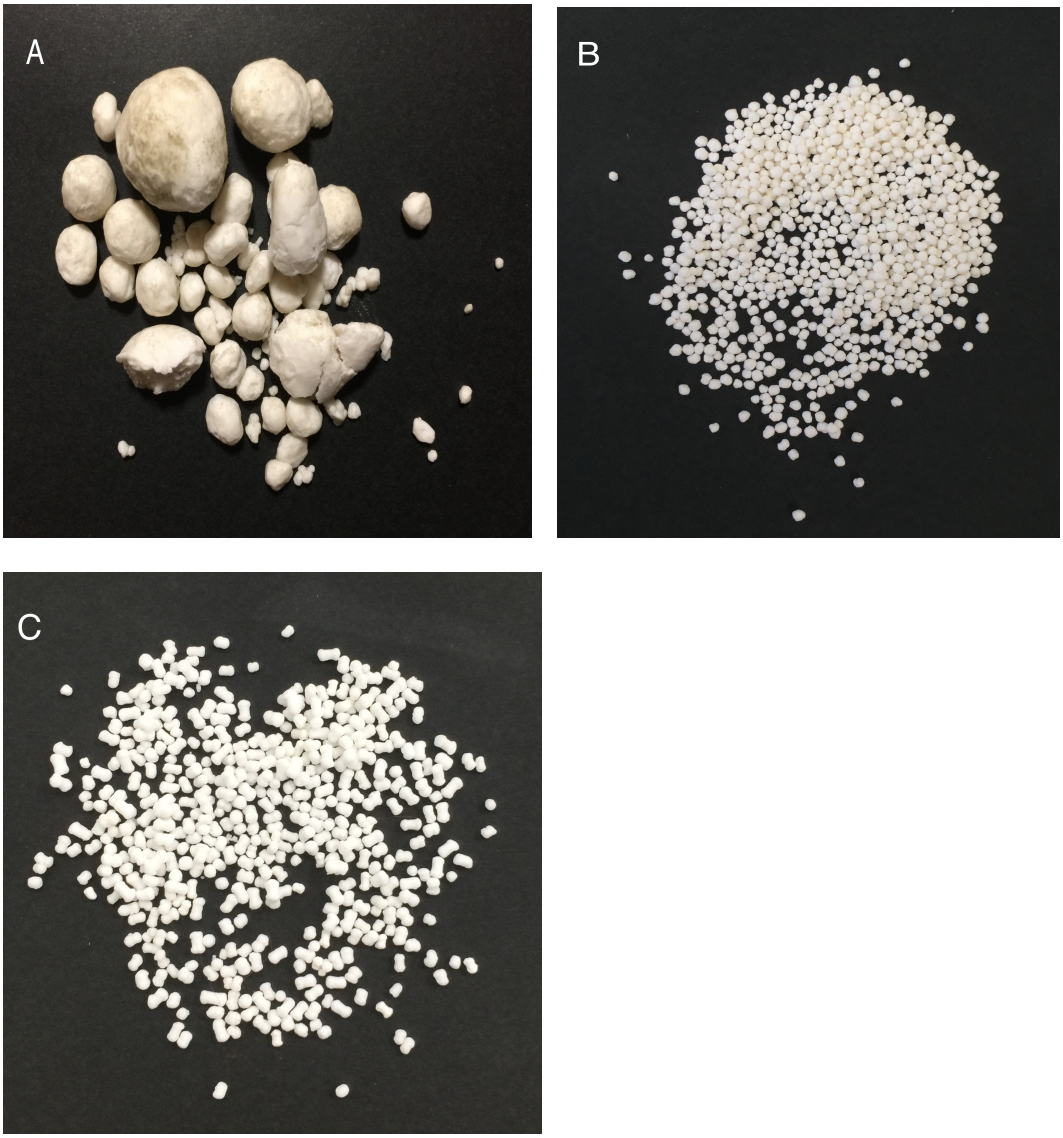


Figure 2.3. Image (A) of agglomerated product after spheronizing a formulation (naproxen, Tween 80, Avicel and Aerosil) containing high water content and longer threads. Image (B) of good quality pellets after spheronizing a formulation (naproxen, PG, avicel and aerosil) containing lower water content and shorter threads. Image (C) of reasonable quality pellets of physical mixture formulation (naproxen, avicel and aerosil)

2.4.3 Liqui-pellet flow property

The results obtained from the flowability studies (Table 2.3) indicate that liqui-pellet is indeed a very promising approach to overcome poor flowability with high liquid load factor, which is one of the biggest hurdles in current liquisolid technology. According to the angle of repose results, all formulations achieved excellent flow property apart from LP-3, which is in the borderline between excellent to good flow property. CI% results show that all formulations achieved excellent flow property. Such results have never been achieved in liquisolid formulation with high liquid load factor before.

It is interesting to see that the liquid load factor (L_f) in liqui-pellet formulations are as high as 1 (Table 2.1), which is considered very high in liquisolid formulations. In fact, 28% of the total mass of the pellets is co-solvent and yet the flow property is excellent. To put this into perspective a comparison with various studies will be discussed. For example, in studies by Tiong *et al.*, the naproxen liquisolid composition highest L_f is 0.9 with very poor flow property (Carr's index of 31.58) [15]. Even the formulation with L_f of 0.168 only had fair flow property (Carr's index of 20) [15]. In studies by Javadzadeh *et al.* it is claimed that with the use of additive, such as PEG 3500, the L_f can be increased [36]. They observed an increase of carbamazepine L_f from 0.25 to 0.6, which is considered high [36]. It can be seen clearly that liqui-pellet L_f is much higher than the formulations in the mentioned studies, and yet there are more rooms for liqui-pellet to be optimized such as incorporating polymeric additive. In studies by Hentzschel *et al*. a commonly used carrier (avicel of specific grade) and coating material (aerosil of specific grade) is replaced with neusilin, which have a much larger specific surface area (SSA) than avicel to make tocopherol acetate liquisolid tablet [35]. This large SSA increased the L_f from 0.22 to 1.58 (factor of ~7), however it is still limited by its flow property; their formulations' flow rate were below 1 g/s [35] (funnel with 7mm orifice used), whereas the poorest liqui-pellet flow rate (LS-3) in the present study is still significantly better with flow rate of 5.67 g/s (funnel with 10mm orifice used).

With such high L_f in liqui-pellet whilst still achieving excellent flow property, the implication for commercial use is very appealing as currently there is no liquisolid formulation in the market. Liquisolid technology in itself has great merits in the advantages it offers, but its drawbacks of poor flowability and larger mass of excipients in dosage form for high dose drug have made it difficult to establish itself for commercial use. In fact, with high L_f and excellent flowability, it would seem possible that liqui-pellet can achieve acceptable weight for high dose drug (this is proven by the authors investigation in chapter 10). It would be fundamentally reasonable to postulate that liqui-pellet is highly commercially feasible without having the inherent advantages of liquisolid formulation compromised.

It is also worth mentioning that due to flow property not being a major drawback in liqui-pellet, this effectively reduces the reliance on the current liquisolid mathematical model introduced by Spireas. Flowable liquid-retention potential and compressible liquid-retention need less attention in liqui-pellet. In other words, high L_f can be achieved whilst maintaining excellent flow property, and compressibility is not a major factor for liqui-

pellet. Other parameters such as R-value and choices of excipients may not need to be compromised by flow property.

Despite results obtained in this study, liqui-pellet and liqui-mass system is still in its infancy; there are still areas for further optimization in order to realize liqui-pellet full potential, which at present is undergoing studies by the author.

Table 2.3. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all liqui-pellet formulation (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	8.02 ± 0.24	27.95 ± 0.14	9.08 ± 0.87	Excellent flow property	Excellent flow property
LP-1	8.85 ± 0.16	25.89 ± 0.95	6.07 ± 1.71	Excellent flow property	Excellent flow property
LP-2	8.88 ± 0.07	23.53 ± 0.19	8.93 ± 0.93	Excellent flow property	Excellent flow property
LP-3	5.67 ± 0.28	30.26 ± 0.09	3.38 ± 0.71	Excellent-good flow property	Excellent flow property
LP-4	6.64 ± 0.23	27.37 ± 0.21	4.16 ± 1.67	Excellent flow property	Excellent flow property
LP-5	7.10 ± 0.16	27.52 ± 0.24	3.18 ± 1.58	Excellent flow property	Excellent flow property
LP-6	7.12 ± 0.07	29.24 ± 0.57	3.42 ± 0.00	Excellent flow property	Excellent flow property

[a] For the composition of each formulation refer to Table 2.1
[b] SD, standard deviation from the mean

2.4.4 Determination of the amount of drug in liqui-pellet formulations

Assay via spectrophotometer (Table 2.4) shows that all formulations except LP-2 have good amount of drug nearing to 100%. What is unusual is that LP-2 shows ~30% more naproxen than expected. Initially it is thought that this is due to experimental or processing error and so the LP-2 is remade but the assay still shows ~130% drug content. It is still unclear as to why liqui-pellet with propylene glycol as liquid vehicle show that it contains more drugs than expected. This could be due to the presence of PG in the formulation causing

interference in the absorption reading. According to Dastidar and Sa studies [202], PG can interfere with absorbance of diazepam, causing an increase in the absorbance at the wavelength used for diazepam [202]. Perhaps the PG is causing interference in the absorption reading for naproxen too. It should be pointed out that since PG is not the chosen suitable liquid vehicle for naproxen liqui-pellet, there is no major issue concerning the interaction between naproxen and PG.

Table 2.4. Spectrophotometric assay (wavelength 271 nm) showing % drug release in 25mg naproxen formulations and pure naproxen powder (n=3)

Formulation[a]	Mean % drug release ± SD[b]
Pure naproxen powder	98.78 ± 0.23
Physical mixture pellet	96.54 ± 2.30
LP-1	95.68 ± 1.22
LP-2	129.68 ± 0.58
LP-3	100.88 ± 1.10
LP-4	101.84 ± 0.66
LP-5	99.94 ± 0.46
LP-6	101.79 ± 1.27

[a] For the composition of each formulation refer to Table 2.1.
[b] SD, standard deviation from the mean.

2.4.5 Friability test

The results obtained from the friability test (Table 2.5) show all formulations having % weight loss below 1%, which is considered acceptable for tablets under USP standard. This indicates that liqui-pellets are ideal for commercial manufacturing as it is robust to friability. The microcrystalline cellulose carrier forms strong bonding within its structure when water is added, producing pellets with strong structure which is resistant to being friable. Also, the liquid vehicle in the liqui-pellet increases the pellet plasticity, which effectively increases the pellet resistant to friability.

Table 2.5. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.54
LP-1	0.03
LP-2	0.00
LP-3	0.29
LP-4	0.53
LP-5	0.30
LP-6	0.43

2.4.6 Particle size of liqui-pellet via sieve method

In Figure 2.4, it is clear that all formulations are mostly below 2 mm in size. Formulations LP-1, LP-3, LP-4 and LP-6 are mostly within 1 mm. This shows that it is possible to produce uniform size of liqui-pellet, which is important in regards to quality control in manufacturing for commercial use.

Formulations LP-2 and LP-5 have broader size distribution with smaller size pellets compared to the rest of the liqui-pellet formulations. In regards to formulation LP-2, ~45% and ~35% of total pellet fall within 850 μm and 500 μm respectively. As for formulation LP-5, ~51% and ~5.8% of total pellet fall within 850 μm and 500 μm respectively. This indicates the liquid vehicle can have an effect on liqui-pellet size distribution, which can be assumed to be due to its effect on extrudate plasticity. As for physical mixture pellet, which does not contain liquid vehicle, ~77% of total pellet are within 500 μm. Hence it seems to indicate liquid vehicle tends to increase pellet size.

Since all of the pellets are almost entirely equal or less than 2 mm, it will be emptied from the stomach into the small intestine relatively fast, similar to how liquid is emptied [115]. This is advantageous for weakly acidic drugs (i.e. naproxen), as they undergo dissolution at a faster rate in less acidic and more alkaline environment such as the small intestine. Hence it is suggested that the bioavailability and speed of drug absorption may improve.

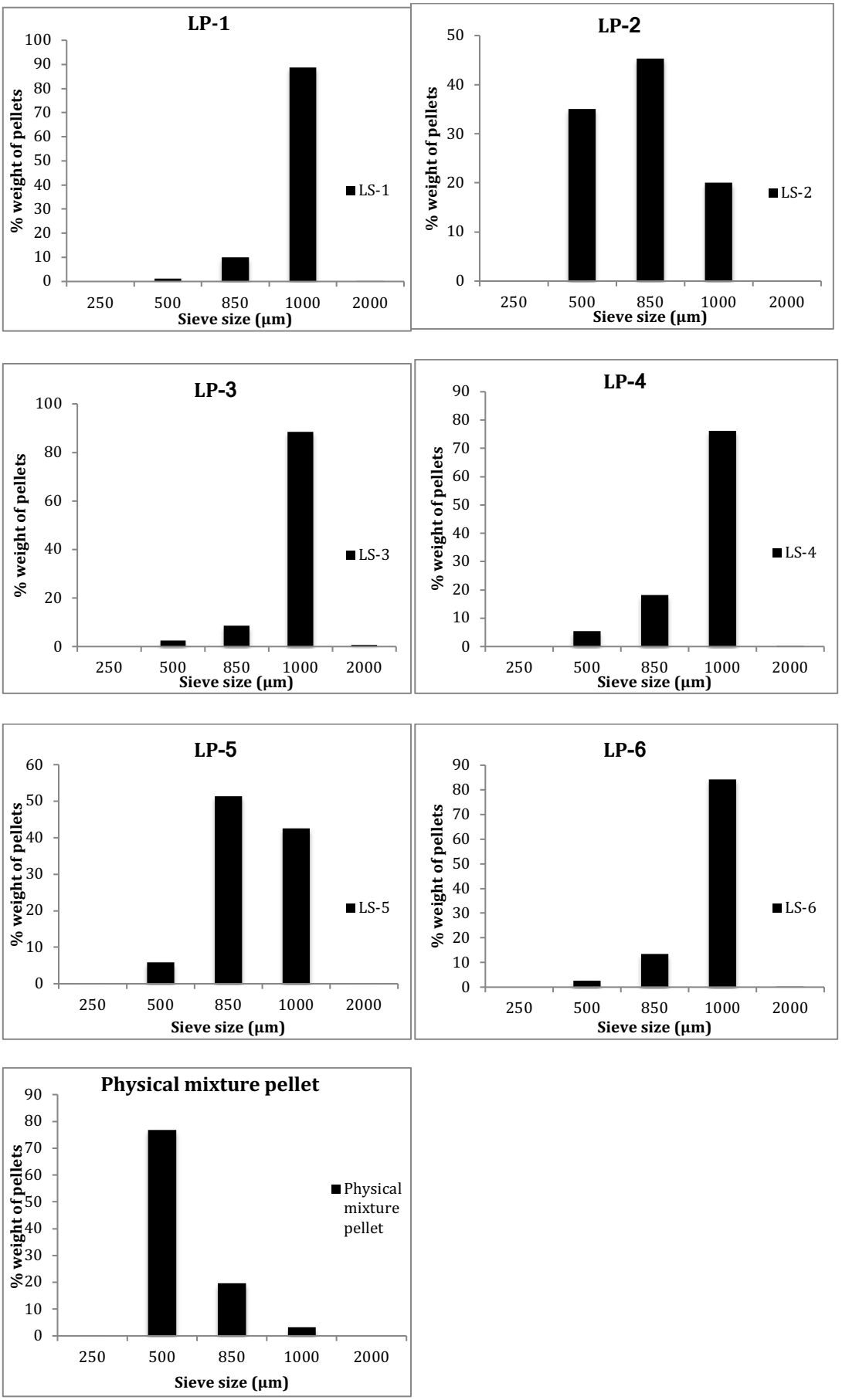


Figure 2.4. Graph showing particle size distribution of all formulations via sieve method

2.4.7 Stereoscopic analysis

In general, the Feret's diameter (Table 2.6) of the pellets seems to agree with most of the results from particle size analysis. Thus, supporting the claim that different liquid vehicles can influence pellet size and generally increases the pellet size. However, there are some discrepancies between the stereoscopic and particle size analysis. It can be seen that the mean Ferret diameter of the physical mixture pellet, LP-2 and LP-5 could be overestimated. In fact, since the pellets are not perfectly spherical and are usually in the most stable orientation, meaning that the smallest dimension is orientated vertically; therefore, overestimation is likely to occur [41]. In reality, it is actually difficult to attain a perfect spherical particle.

Formulations LP-6, LP-5 and physical mixture pellet showed the least roundness and largest elongation ratio. Among them, LP-6 has the highest deviation from perfect roundness (1.38) and largest mean elongation ratio (1.47). Nevertheless, the pellets are good enough to achieve excellent flowability (Table 2.3). As for the rest of the formulations, the results seem to suggest the rest of the liqui-pellets have good roundness and minimal elongation.

Table 2.6. Stereoscopic analysis showing the mean Feret's diameter, mean roundness and mean elongation of each formulation (n=100)

Formulations	Mean Feret's diameter (mm)	Mean roundness ± SD[b]	Mean elongation ratio ± SD[b]
Physical mixture pellet	1.028	1.25 ± 0.12	1.41 ± 0.19
LP-1	1.294	1.12 ± 0.07	1.15 ± 0.10
LP-2	1.000	1.12 ± 0.03	1.17 ± 0.09
LP-3	1.517	1.14 ± 0.09	1.18 ± 0.17
LP-4	1.303	1.18 ± 0.07	1.25 ± 0.11
LP-5	1.268	1.24 ± 0.11	1.41 ± 0.21
LP-6	1.535	1.38 ± 0.18	1.47 ± 0.18

[a] For the composition of each formulation refer to Table 2.1
[b] SD, standard deviation from the mean.

2.4.8 Morphological studies on pellets via SEM

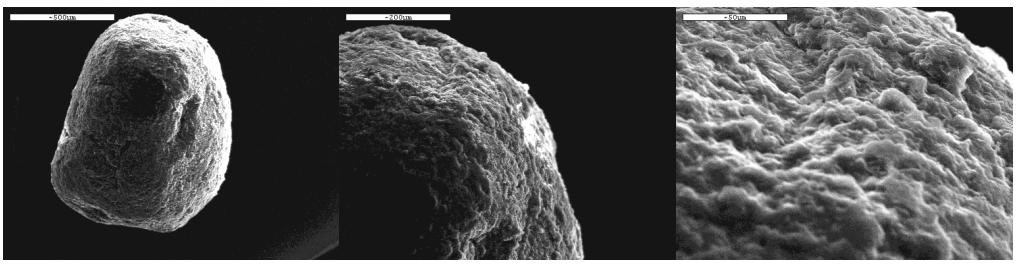
According to Figure 2.5, it can be seen that physical mixture pellet (PMP) has the roughest surface structure compared to the rest of the formulations. This seems to suggest that the co-solvent in liqui-pellet formulations has an influence on the pellet surface morphology, resulting to a smoother surface. Perhaps this is the result of liquid vehicle reducing the crystallinity of the pellet. Given that all formulation resisted disintegration after dissolution

test, surface morphology after dissolution test was observed. The physical mixture pellet surface structure is not much different from before the dissolution test. As for the rest of the formulation containing different types of co-solvent, it is observed that their surface structure became rougher after undergoing dissolution test. This could be due to liquid medication moving out from the pellet into the dissolution medium, resulting the pellet reverting back to a more crystalline structure or shrinking into a rougher surface structure. Also, there may have been slight disintegration around the surface when the liquid medication leaves the pellet. The fact that it is possible to study the morphology of the pellets after undergoing dissolution test, demonstrates the strong bonding within the microcrystalline cellulose structure, rendering the pellet non-disintegrating.

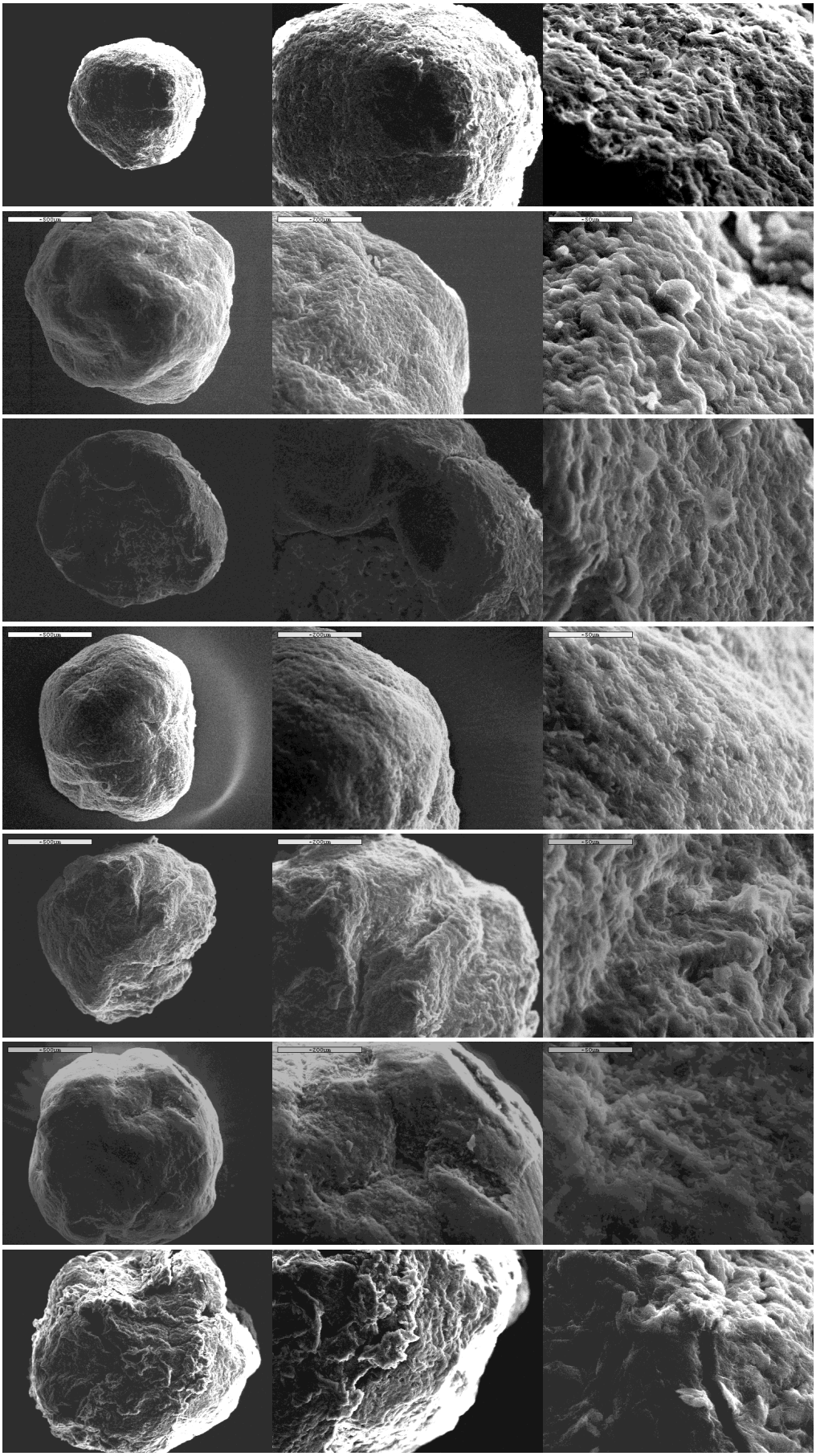
When observing liqui-pellet surface structure before dissolution test (Figure 2.5), it can be observed that different liquid vehicles give different surface structure. Formulation containing PEG 200 (LP-1) or tween 80 (LP-3) have similar surface structure and both produces relatively rough surface in comparison to the other liqui-pellet formulations. Such surface structure is different from formulation containing PG (LP-2) or kolliphor EL (LP-6) where both produces smooth surface liqui-pellet. Liqui-pellet containing labrafil (LP-4) and labrasol (LP-5) have similar surface structure to one another. As shown in Figure 2.5, both of their surface structure is relatively smooth but interestingly has a smooth round bump that resembles micron size pebbles.

The results from the morphology studies and dissolution studies showed no significant correlation between surface structures affecting dissolution rate. This could be due to the drug release rate being affected by many additional factors as well as surface properties including drug solubility and physicochemical characteristics of liquid vehicle [1]. Hence this may be the reason why it does not appear to be clear how surface structure affects drug release rate. Further studies on surface structure are needed on liqui-pellet to determine its impact on drug release.

I **II** **III**



PMP[a]


PMP[b]
LP-1[a]
LP-1[b]
LP-2[a]
LP-2[b]
LP-3[a]
LP-3[b]

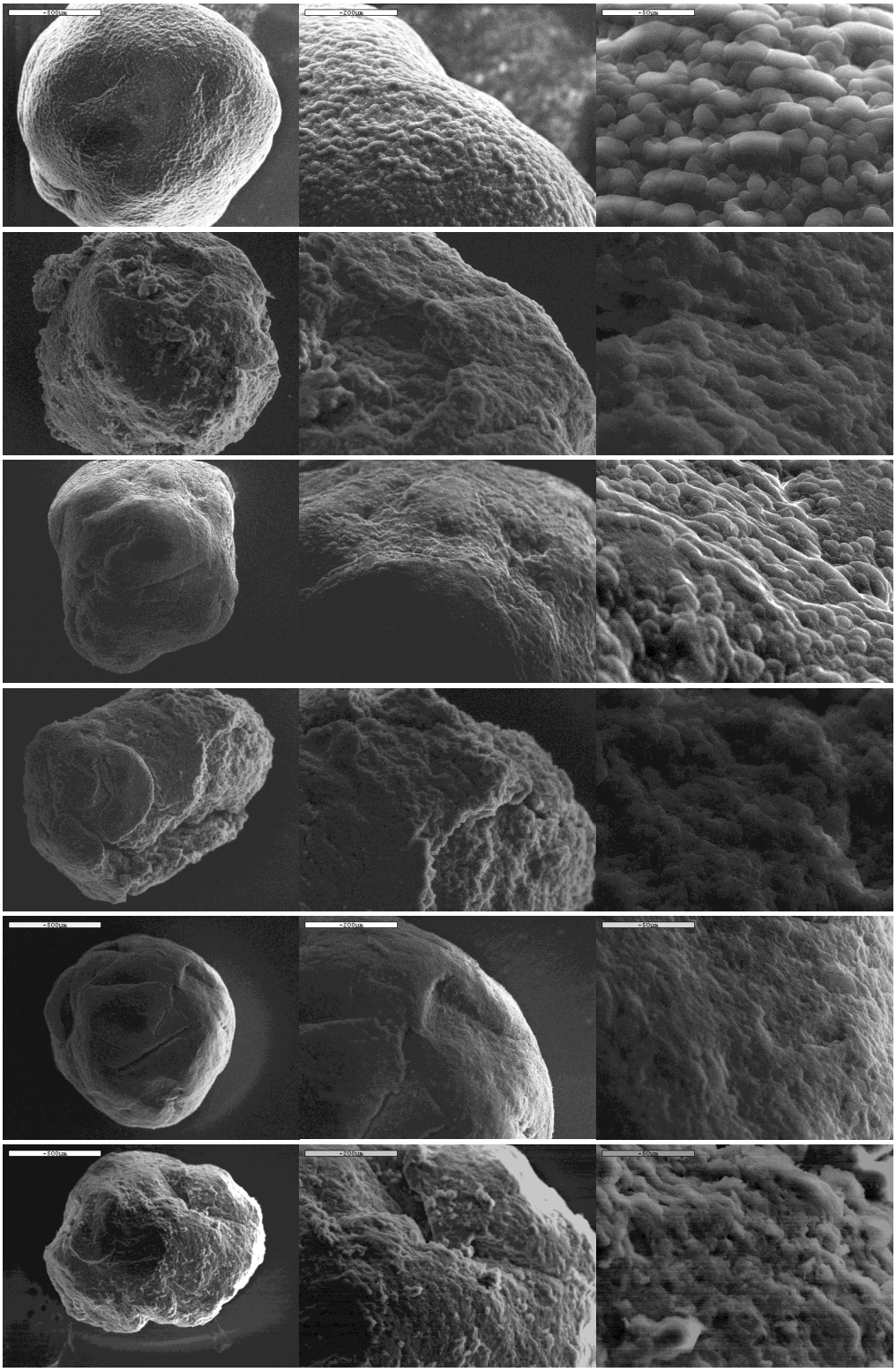


Figure 2.5. Images from SEM of all formulation; I. × 80 magnification, II. × 200 magnification and III. × 800 magnification. Note [a] refers to pellet before undergoing dissolution test and [b] SD refers to after dissolution test

2.4.9 Drug release study

The dissolution profiles of all formulations at pH 1.2 are shown in Figure 2.6. It should be noted that, although, naproxen is poorly soluble in acidic condition and the dissolution test should be carried out at higher pH or with sink condition, for comparison purpose the dissolution of liqui-pellets was initially carried out at pH 1.2. It can be seen clearly in Figure 2.6 and Figure 2.7 that liquid vehicle causes considerable enhancement of drug release rate compared to physical mixture pellet ($p<0.05$), which does not contain a liquid vehicle. The difference factor (F_1) and similarity factor (F_2) of the best formulation (LP-3) and physical mixture at acidic condition are 73.16 and 53.53 respectively. As seen, the F_1 value indicate a marked difference in dissolution profile. The P value and F_1 value indicate that there is a difference in dissolution profile. The enhanced drug release via API solubilized or held at molecularly dispersed state is maintained even after extrusion and spheronization. This demonstrates the enhanced drug release mechanism via liquisolid concept can be combined with pelletization technique.

Despite the solubility test (Table 2.2), the dissolution results at pH 1.2 (Figure 2.6) show formulation with tween 80 (LP-3) achieving the fastest drug release rate in comparison to the other formulations with different liquid vehicles. Tween 80 has the fastest drug release rate followed by kolliphor EL (LP-6) then labrasol (LP-5). Admittedly, even though formulation with tween 80 has the fastest dissolution rate, the percentage cumulative drug release is about 17% after 2 hours, which is poor. Nonetheless, the poor dissolution rate is expected as naproxen is poorly soluble under acidic pH [189] and the microcrystalline-based pellet are not suitable for fast release formulation due to resistance to disintegration [127].

It is obvious that drug release rate increases significantly at pH 7.4 (Figure 2.7); however, what is interesting is that the formulation containing labrasol (LP-5) has the fastest drug release rate of ~75% after 2 h instead of tween 80 (LP-3), which is ~66% after 2h. This shows a different trend compared to the results when the pH is 1.2. Their F_1 and F_2 are 9.23 and 66.04 respectively, indicating little difference in dissolution profile. Also, at pH 7.4, tween 80 (LP-3) and kolliphor EL (LP-6) dissolution profile are almost identical (F_1 = 1.43 and F_2 = 95.66). Furthermore, around 90 min during the dissolution test, labrafil (LP-4) drug release profile are similar to that of tween 80 and kolliphor EL. Such changes in dissolution profile in comparison to the results obtained at pH 1.2 suggests that pH can affect different liquid vehicles' influence on drug release rate; and the degree of this effect depends on the choice of liquid vehicle. Thus, the effect of pH on different liquid vehicles

seems fundamental for future studies, particularly in choosing the most appropriate co-solvent for a specific region of GIT we want the drug to be released most efficiently in. In this case, the author believes that tween 80 is the most suitable liquid vehicle since the aim is to have a fast onset of action and a fast drug release rate. Thus, it is prudent that the drug release rate is high in acidic condition as the drug will be in the stomach before entering the small intestine. It should be noted that although the aim is to have fast onset of action and fast drug release, in reality, drug such as naproxen would have enteric coat due to potential GI irritation and the main site of absorption will be in the small intestine.

Despite labrasol having the best drug release at pH 7.4, tween 80 drug release rate is only ~10% lower than labrasol. Nonetheless, labrasol and kolliphor EL may also be a suitable liquid vehicle for naproxen. In studies by Tiong, liquisolid tablet containing kolliphor EL (formerly known as cremophor EL) and naproxen of 20% w/w gave the fastest drug release, confirming that kolliphor EL may also be a suitable liquid vehicle for naproxen [15].

It should be pointed out that naproxen liqui-pellet formulations have yet to be optimized. The author observes a lower than expected drug dissolution rate could also be due to lack of disintegration of the pellets. It is known that avicel produces pellets which lack disintegrating properties [203]. Therefore, the improvements of liqui-pellet disintegration are currently undergoing studies.

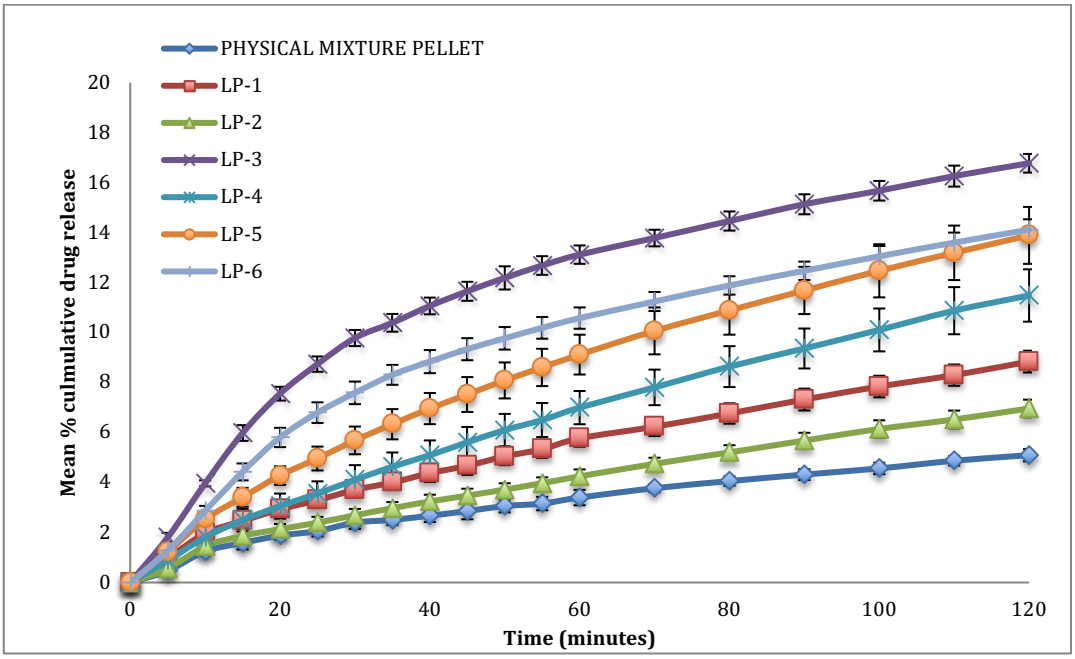


Figure 2.6. Dissolution profile of pellets in capsule for naproxen 25mg with various liquid vehicles and physical mixture pellet (pH 1.2) (n = 3)

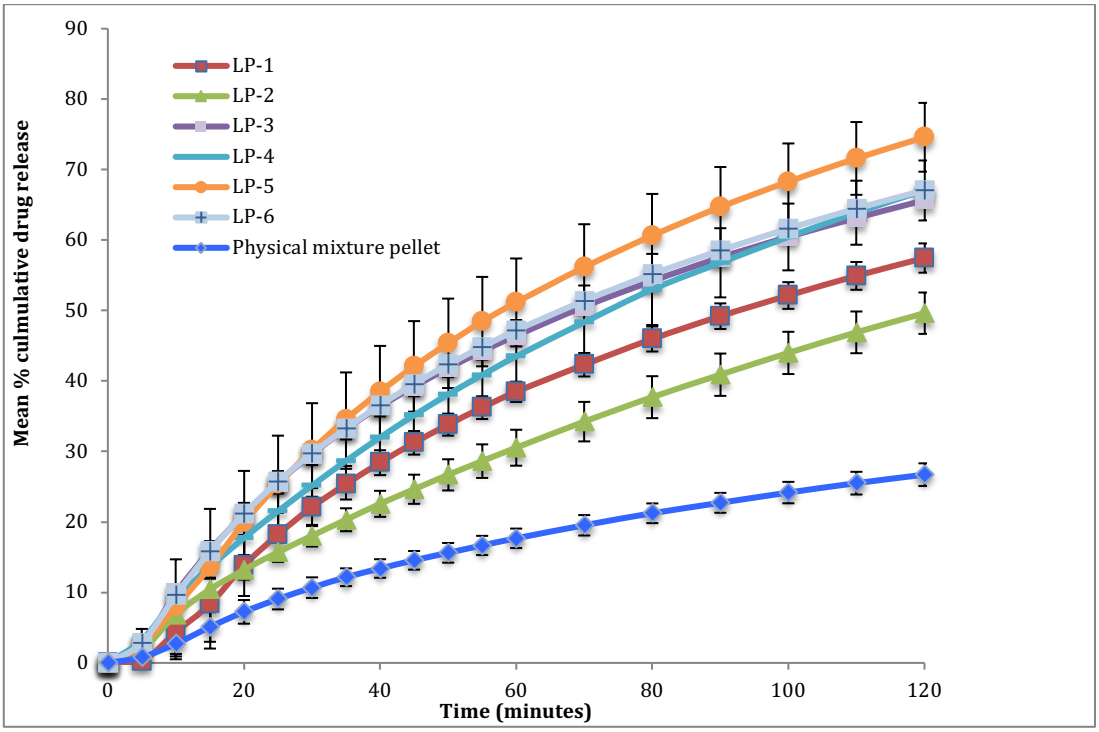


Figure 2.7. Dissolution profile of pellets in capsule for naproxen 25mg with various liquid vehicles and physical mixture pellet (pH 7.4) (n = 3)

2.4.10 Kinetic model analysis of drug release

The information about the correlation coefficients (R^2) of formulations is shown in Table 2.7 (at pH 1.2) and Table 2.8 (at pH 7.4), which uses kinetic release models such as, zero order, first order and Higuchi model. Most appropriate kinetic model was determined by the highest R^2 value. Drug release under pH 1.2 (Table 2.7), show all naproxen liqui-pellet drug release is best described by Higuchi's model, except for LP-4, which is best describe by first order model. Higuchi's model of drug release is based on Fick's law of diffusion [190]. This law states that API concentration gradient between dosage form and bulk of dissolution medium is the driving force for diffusion of API molecules from dosage form to dissolution medium. However, under pH 7.4 (Table 2.8), all naproxen liqui-pellet formulations drug release is best described by First order model. The drug release rate is dependent on its concentration.

Table 2.7. Release parameters of naproxen formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.946	0.949	0.993
LP-1	0.965	0.970	0.990
LP-2	0.976	0.979	0.981
LP-3	0.851	0.869	0.974
LP-4	0.984	0.988	0.975
LP-5	0.964	0.971	0.988
LP-6	0.880	0.894	0.981

Table 2.8. Release parameters of naproxen formulations at pH 7.4

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.955	0.972	0.977
LP-1	0.952	0.989	0.969
LP-2	0.978	0.997	0.976
LP-3	0.929	0.986	0.983
LP-4	0.969	0.999	0.978
LP-5	0.947	0.998	0.976
LP-6	0.934	0.989	0.983

2.4.11 DSC studies

Thermogram obtained from the DSC includes naproxen; avicel; aerosil; primojel; physical mixture pellets; LP-3; LP-5 and LP-6 (Figure 2.8 and 2.9). There is a sharp endothermic peak (T_m = 158.77°C and ΔH = 92.06J/g) for naproxen, indicating its crystalline state. Avicel (T_m = 72.67°C and ΔH = 94.82J/g) and primojel (T_m = 83.82°C and ΔH = 167.36J/g) traces have broad peak, which could be due to water within avicel and primojel evaporating, as they are hygroscopic materials. The evaporation of water was also observed by Tiong *et al.* [15]. Aerosil had no definitive peak.

In the physical mixture pellet trace (Figure 2.9), the peak is at a lower temperature than naproxen (Figure 2.8). The peak shift from 158.77°C to 149.80°C respectively, which could be due to the avicel affecting the overall peak of naproxen in the physical mixture pellets. As temperature increases, API dissolves in the excipients, shifting the peak towards the left. Nevertheless, the crystalline state of naproxen is still present.

However, in formulation LP-3 (T_m = 120°C and ΔH = 1.9060J/g), LS-5 (T_m = 111.98°C and ΔH = 2.4048J/g) and LP-6 (T_m = 121.48°C and ΔH = 3.5034J/g), the DSC traces show the naproxen peak being less prominent and that T_m is lower than physical mixture. This

indicates that liqui-pellets have reduced crystallinity and possibly have become more amorphous; thus, the improvement in drug dissolution rate. Since there is no peak shifting to the right, this indicate no interaction via formation of complex. Complex would usually increase bonding thus increasing the melting point.

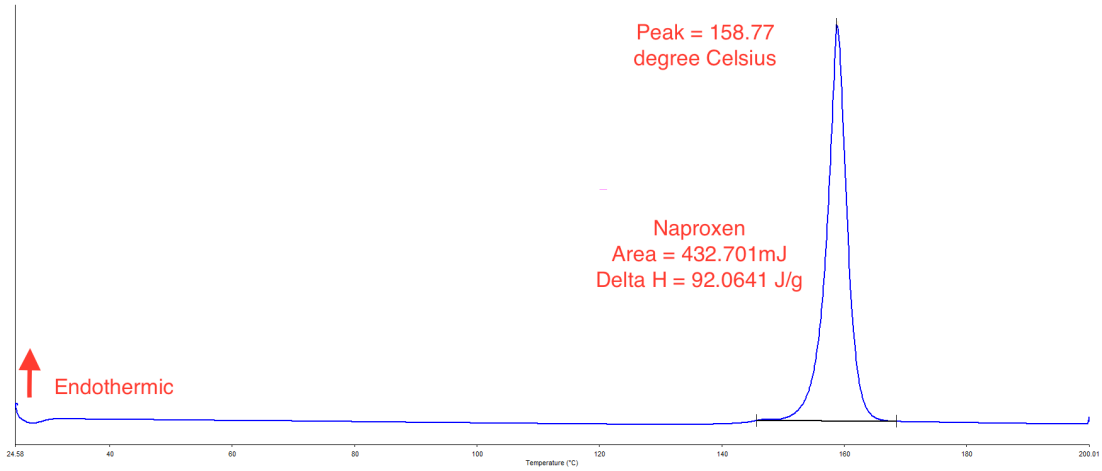


Figure 2.8. DSC thermogram of naproxen

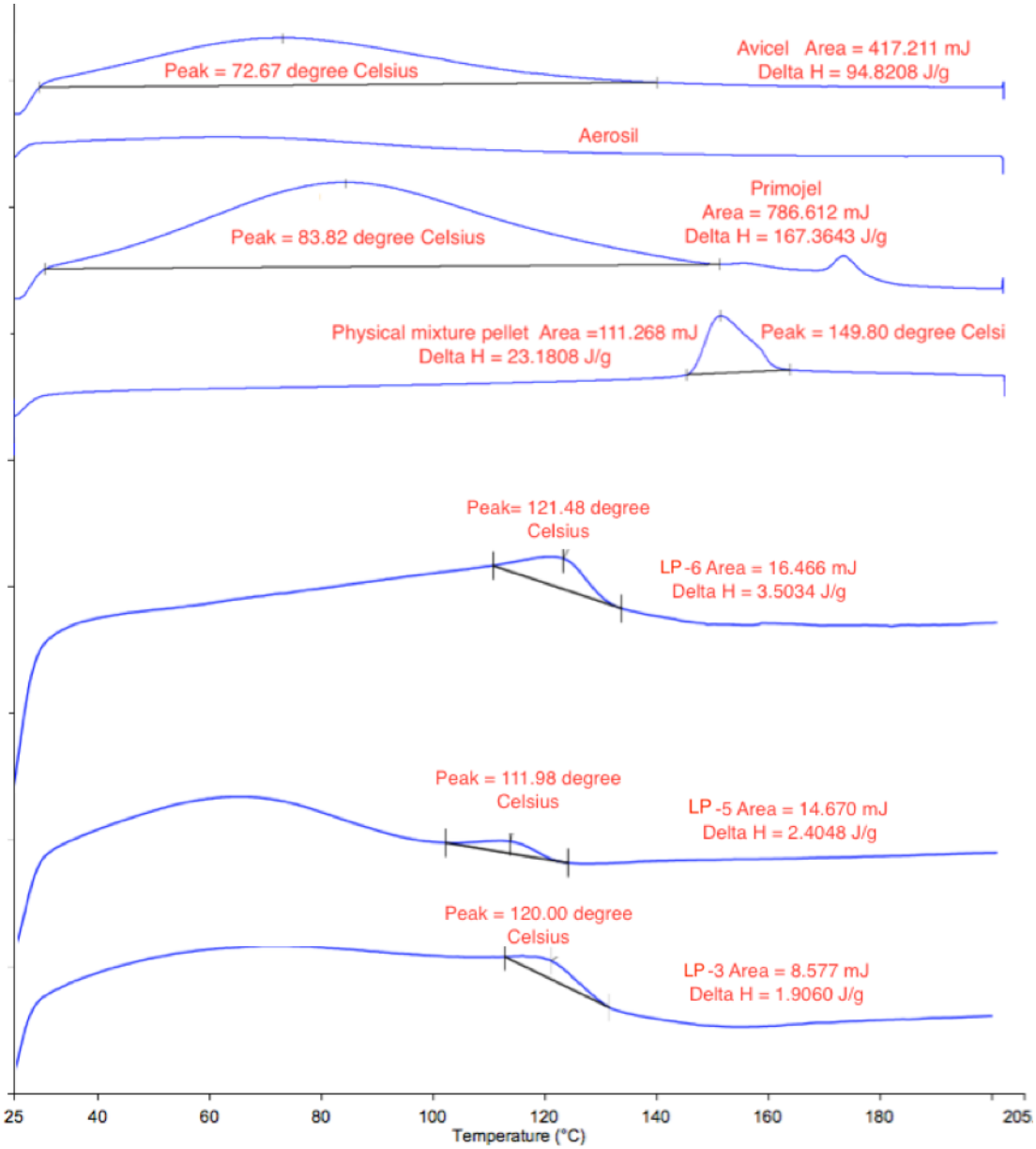


Figure 2.9. DSC traces of avicel, aerosil, primojel physical mixture pellet, LP-3, LP-5 and LP-6. Note the scales of excipients and formulations are different in order to show the peak more clearly

2.4.12 XRPD studies

Naproxen has major peaks at 2θ values of 12.2, 16.2, 18.4, 19.6, 22.2, 23.2, 26.8 and 27.8° (Figure 2.10). These peaks are similar to the naproxen diffractogram in Maghsoodi studies [204]. However, the differences are the presence of a sharp peak at ~7° and the absence of a peak at 26.8° compared to Maghsoodi studies. Naproxen peaks are also similar to naproxen diffractogram in Mello and Ricci-Junior studies [205], but again there are some differences too. This could be due to different scan rate settings. Nonetheless, the main diagnostic peaks of naproxen are present.

The physical mixture and the chosen formulations (LP-3, LP-5 and LP-6) diffractograms (Figure 2.10) have no peaks other than that of naproxen and avicel, which indicates no interaction between the excipients and the API. Data from % relative crystallinity (Table 2.9) shows that physical mixture and formulation LP-3, LP-5 and LP-6 have reduced crystallinity compared to the pure naproxen, agreeing with the result observed in the DSC test.

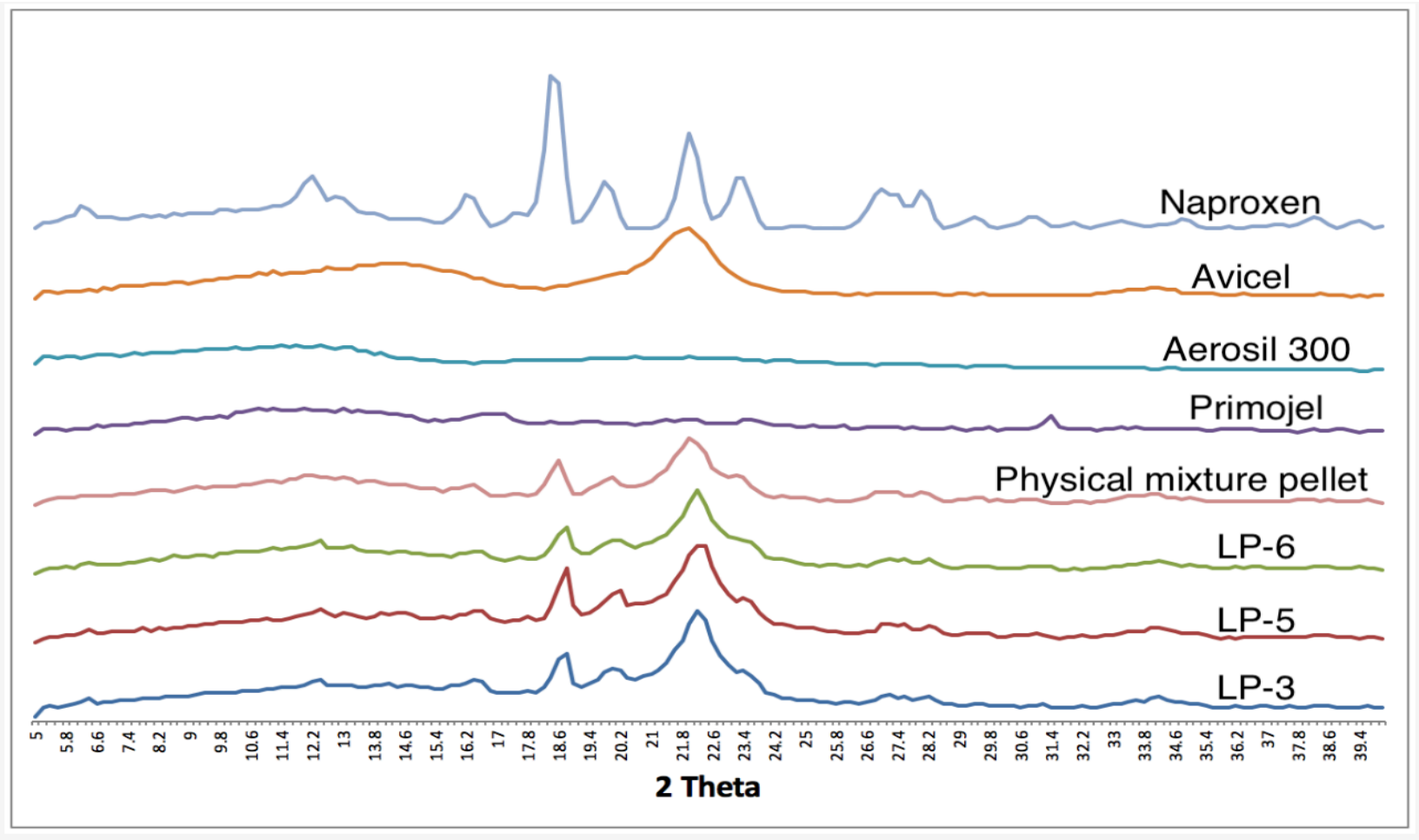


Figure 2.10. Diffractograms of naproxen, avicel, aerosil, primojel, physical mixture pellet, LP-3, LP-5 and LP-6

Table 2.9. % relative crystallinity via integrated peak area and peak height method

Formulation	% relative crystallinity via integrated peak area method	% relative crystallinity via peak height method
Physical mixture	23.26	39.54
LP-3	21.23	55.44
LP-5	24.19	49.77
LP-6	17.10	45.61

2.5 Conclusion

The emerging next generation oral dosage form, liqui-pellet, have shown remarkable results in terms of overcoming the major drawbacks in liquisolid technology. Liqui-pellet is able to achieve high liquid load factor whilst maintaining excellent flow property, which has never been achieved in liquisolid technology before. Excellent to good flow property was obtained from all liqui-pellet formulations which had liquid load factor of 1. The solid-state studies (DSC and XRPD) showed the crystallinity of liqui-pellet being reduced. This is one of the key factors for the observed improvement in enhanced drug release. With major drawbacks of liquisolid technology being overcome using liqui-pellet, the liqui-pellet is anticipated as a highly commercially feasible product. Furthermore, there is potential for further optimization as parameters, such as R-value, and choices of excipients may not need to be compromised by flow property.

Chapter 3: Optimizing the release rate of naproxen liqui-pellet, the emerging next generation oral dosage form, stemming from liquisolid concept and pelletization technologies

3.1 Abstract

Liqui-pellet is a new dosage form stemming from pelletization technology and concept from liquisolid technology. In spite of liqui-pellet overcoming a major hurdle in liquisolid technology through achieving excellent flow property with high liquid load factor, the formulation requires to be optimized in order to improve drug release rate. From previous studies by the author, it was found that tween 80 was the most appropriate liquid vehicle for naproxen liqui-pellet. Using tween 80 as the liquid vehicle, an attempt was made in this study to achieve an enhanced drug release rate of the poorly water-soluble naproxen. It was found that primojel 5% w/w was the most appropriate concentration of superdisintegrant out of 5%, 10% and 15% w/w. Flowability test confirmed that all liqui-pellet formulations have excellent-good flow property, including liqui-pellets with a high liquid load factor of 1.52, where 38% of the total mass is co-solvent. This shows a relatively high liquid load factor can be achieved in liqui-pellet without compromising the flowability, which is one of the key novelty of this work. An optimized formulation containing tween 80 as the liquid vehicle showed considerable enhanced drug release rate in comparison to previously non-optimized liqui-pellet. It was found that the improved drug release rate was due to the remarkably improved disintegration of the supposedly non-disintegrating microcrystalline-based pellet; the optimized liqui-pellet seems to explode into fragments in the dissolution medium. At pH 1.2, the optimized formulation had ~14% more drug release than non-optimized formulation after 2 h, and at pH 7.4 the drug release of the optimized pellet was nearing 100% at ~15 min, whereas the none-optimized pellet only achieved ~66% drug release after 2 h. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) indicated a reduction in crystallinity and possibly increased in amorphousness in the liqui-pellet formulation. Overall results showed that liqui-pellet exhibited an enhanced drug release and the capacity for high liquid load factor whilst maintaining excellent flowability, rendering it a potentially commercially feasible drug delivery system.

3.2 Introduction

The key introductory points are covered in chapter 2 section 2.3; however, further background relating to this chapter will be covered in this section.

It is evident from the flowability studies in chapter 1 section 2.4.5 that flow property does not pose a major issue in liqui-pellet as it does for liquisolid formulation. Hence, Spireas liquisolid mathematical equation that dictates the amount of carrier and coating material does not apply to liqui-pellet. This shows that liqui-pellet is more flexible in terms of formulation design than liquisolid formulation. Again, this is another distinguishing feature of liqui-pellet over liquisolid formulation.

The technology involving liqui-mass system is highly versatile, which becomes more apparent in later chapters. It can be seen in Figure. 2.1 that liqui-mass system encompasses wet mass/paste and but less frequently free-flowing powder. In concept, the technology concerning liqui-mass system can produce free granule, moldable sheets, liqui-pellet, liqui-tablet and more, which will be investigated in future studies when the potential of liqui-mass system is further explored. There is also a considerable flexibility for modifications of the formulation, particularly the coating of liqui-pellet. Such versatility makes this new liqui-mass system interesting and exciting to explore. In addition, this technology has major advantages such as being cost-effective; mainly uses green technology; simplistic approach; easy to scale up platform technology for commercial manufacturing; does not require organic volatile solvent; no need for advanced technique or machinery and excipient are common and easily obtainable [4]. Such advantages may not be present in other various technologies confronting the same issue of improving bioavailability of poorly water-soluble drugs. The inventor of liqui-pellet believes that it is highly commercially feasible and has the potential to play a major role in the future oral dosage forms.

One of the key purposes of liqui-pellet is to take the key advantages of liquisolid formulation into a commercially feasible dosage form. This is done by confronting the major drawbacks in liquisolid technology, such as poor flow property, poor compactibility and inability to produce high dose drug without being too bulky and heavy for real life use [1,4]. In the author's previous studies, it is shown that liqui-pellet can achieve excellent flow property whilst having a high liquid load factor of 1. Liqui-pellet not only contains the advantages of liquisolid technology, but it also has the inherent advantages of being in a pellet form. Such advantages include good flow property [79], potential to combine

incompatible drugs or drugs with different release profiles in same dose unit [77], reduced risk of side effects due to dose dumping and the flexibility for modification via coating technology.

The aim of the present study is to optimize liqui-pellet formulation in order to improve the drug release rate of naproxen, which is a nonsteroidal anti-inflammatory drug (NSAID), belonging to BSC class II. The chosen liquid vehicle used in the investigation is tween 80, as it was considered the most suitable liquid vehicle from previous studies. Tween 80 solubilizes the API as well as acting as a surface active agent which reduces interfacial tension and improve water penetrating into the dosage form.

3.3 Materials and methods

3.3.1 Materials

Naproxen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel), (DFE Pharma, Goch, Germany); croscarmellose (primellose), (DFE Pharma., Goch, Germany), 2-propranol (VWR Chemicals, Fontenay Sous Bois France); polysorbate 80 (tween 80) and PEG mw of 1500. All other reagents and solvent were of analytical grades.

3.3.2 Preparation of naproxen liqui-pellet

The naproxen liqui-pellet formulations were prepared in the same manner as in chapter 2 section 2.3.3; however, there are variations in parameters such as composition of granulating liquid; presence or absence of tween 80 liquid vehicle; concentration of liquid vehicle and concentration of primojel (Table 3.1).

For clarity, it should be mentioned that the liqui-pellet formulations were categorized into two sections. In the first section between LP-1 to LP-6, the main focus was to look into the effect of varying concentration of a primojel (superdisintegrant) with and without the presence of tween 80. The second section, between LP-7 to LP-11, was the modified formulations in an attempt to improve drug release rate.

Table 3.1. Key formulation characteristics of the investigate encapsulated liqui-pellet

Formulation	Liquid vehicle	Amount of liquid vehicle (%w/w)	Liquid load factor	Disintegrant type and amount	Pre-extrusion liquid added	Mass of carrier (mg)	Mass of coating material (mg)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet					Water	68.97	3.13	90.63
LP-1	Tween 80	28.23	1	Primojel 5 %w/w	Water	62.53	3.13	132.95
LP-2	Tween 80	27.12	1	Primojel 10 %w/w	Water	62.57	3.13	138.24
LP-3	Tween 80	26.04	1	Primojel 15 %w/w	Water	62.42	3.12	144.03
LP-4	None			Primojel 5 %w/w	Water	62.41	3.12	95.42
LP-5	None			Primojel 10 %w/w	Water	62.57	3.13	100.81
LP-6	None			Primojel 15 %w/w	Water	62.43	3.12	106.53
LP-7	Tween 80	28.23	1	Primojel 5 %w/w	Water	62.53	3.13	132.95
LP-8	Tween 80	38.34	1.52	Primojel 5 %w/w	Water	50.07	2.50	132.66
LP-9	Tween 80	28.23	1	Primellose 5 %w/w	Water	62.53	3.13	132.95
LP-10	Tween 80	28.23	1	Primojel 5 %w/w	*PEG & water	62.53	3.13	132.95
LP-11	Tween 80	28.23	1	Primojel 5 %w/w	**2-propanol & water	62.53	3.13	132.95

Note all formulation contain 25mg of naproxen and the carrier to coating material is at a ratio of 20:1

* 0.5g of PEG was dissolved in 10ml of water, ** 2-propanol and water was mixed in equal volume

3.3.3 Flowability test on liqui-pellet

Carried out in same manner as described in chapter 1 section 2.3.5.

3.3.4 Friability test on liqui-pellet

Carried out in same manner as described in chapter 2 section 2.3.6.

3.3.5 Particle size analysis via sieve method

Carried out in same manner as described in chapter 2 section 2.3.7.

3.3.6 Stereoscopic analysis

Carried out in same manner as described in chapter 2 section 2.3.8.

3.3.7 Scanning electron microscopy (SEM) analysis

Carried out in same manner as described in chapter 2 section 2.3.9.

3.3.8 In-vitro dissolution test

Carried out in same manner as described in chapter 2 section 2.3.10.

3.3.9 Kinetic model analysis of drug release

Carried out in same manner as described in chapter 2 section 2.3.11.

3.3.10 Differential scanning calorimetry (DSC) studies

Carried out in same manner as described in chapter 2 section 2.3.12.

3.3.11 X-ray powder diffraction (XRPD) studies

Carried out in same manner as described in chapter 2 section 2.3.13.

3.3.12 Statistical and mathematical analysis

Carried out in same manner as described in chapter 2 section 2.3.14.
1

3.4 Results and discussion

3.4.1 Liqui-pellet flow property

Results from the flowability tests is shown in Table 3.2. It is clear that all formulations have excellent or in the borderline between excellent to good flow property. Thus, it is claimed that liqui-pellet is a promising dosage form, which resolves poor flowability issue in liquisolid technology and yet maintains the inherent advantages stemming from liquisolid concept.

The previous studies (chapter 2) by the author demonstrated that liqui-pellets achieved high liquid load factor of 1, whilst maintaining excellent flow property. In fact, before the development of liqui-pellet, it has been proven very difficult to achieve such mentioned results, due to the cohesive nature of liquid powder admixture, which is shown in various studies. Tiong *et al* formulated naproxen liquisolid powder with L_f of 0.9 but the flowability was poor (Carr's index of 31.58) [15]. In studies by Javadzadeh *et al*, an additive such as PEG 3500 was used to increase the L_f [36]. They observed an increase of carbamazepine L_f from 0.25 to 0.6 [36], however, it is clear that liqui-pellet L_f is much more superior and does not need polymeric additive. Hentzschel *et al* replaced a commonly used carrier (avicel) and coating material (aerosil) with neusilin, a material with a much larger specific surface area (SSA) [35]. This enabled an increase of L_f by a factor of ~7, nonetheless it was still limited by its flow property; their formulations' flow rate are below 1g/s [35].

What is exciting and promising in liqui-pellet is that it can be further optimized so that the L_f is further increased. It can be seen in Table 3.1 that LP-8 has L_f is as high as 1.52, where 38% of the pellet total mass is co-solvent, and yet excellent-good flow property is achieved. Such a result further supports the potential of liqui-pellet being commercially feasible. Since flow property and L_f no longer being a major hindrance, this next generation oral dosage form seems commercially feasible. The potential for smooth and cost-effective manufacturing, as well as producing high dose liqui-pellet without being overly bulky and heavy, makes it commercially ideal.

Table 3.2. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all liqui-pellet formulation (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical Mixture pellet	8.02 ± 0.24	27.95 ± 0.14	9.08 ± 0.87	Excellent flow property	Excellent flow property
LP-1	7.60 ± 0.10	26.98 ± 0.74	5.25 ± 0.86	Excellent flow property	Excellent flow property
LP-2	7.61 ± 0.12	27.75 ± 0.31	8.13 ± 1.65	Excellent flow property	Excellent flow property
LP-3	7.42 ± 0.22	28.68 ± 0.53	6.07 ± 1.44	Excellent flow property	Excellent flow property
LP-4	10.68 ± 0.06	23.81 ± 0.40	9.95 ± 0.08	Excellent flow property	Excellent flow property
LP-5	8.59 ± 0.08	28.20 ± 0.16	11.17 ± 0.85	Excellent flow property	Good flow property
LP-6	6.96 ± 0.28	29.21 ± 0.26	10.37 ± 0.79	Excellent flow property	Excellent-good flow property
LP-7	7.13 ± 0.07	28.68 ± 0.22	7.24 ±2.33	Excellent flow property	Excellent flow property
LP-8	5.82 ± 0.09	30.51 ± 0.38	3.90 ± 2.30	Excellent-good flow property	Excellent flow property
LP-9	7.35 ± 0.05	28.57 ± 0.50	7.63 ± 1.42	Excellent flow property	Excellent flow property
LP-10	6.47 ± 0.19	30.13 ± 0.19	9.24 ± 0.73	Excellent-good flow property	Excellent flow property
LP-11	6.03 ±0.25	30.47 ± 0.51	7.76 ± 0.76	Excellent-good flow property	Excellent flow property

[a] For the composition of each formula refer to Table 3.1
[b] SD, standard deviation from the mean

3.4.2 Friability test

Table 3.3 shows the results obtained from the friability test of the physical mixture pellet and two optimized formulations (LP-8 and LP-11). In brief, they all have % weight loss below 1%. Since there is currently no standard for friability test on pellets, USP standard friability test for tablets is adapted, which suggests less than 1% weight loss is acceptable. Therefore, it can be concluded that all tested formulations are robust, which is ideal for commercial manufacturing in terms of quality control.

It can also be postulated that the robustness is due to microcrystalline cellulose (carrier) forming sufficient bonds within its structure when water is added; hence, producing robust pellets. In addition, the tween 80 in the liqui-pellet can increase the pellet

plasticity due to plasticizing effect [206], which effectively increases the pellet resistant to friability.

Table 3.3. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.54
LP-8	0.03
LP-11	0.12

3.4.3 Particle size analysis via sieve method

Results from particle size analysis of the optimized formulation LP-8 (Figure 3.1) indicate that ~97% of the pellets fall in the size of 1mm. This shows that the optimized liqui-pellet LP-8, have good uniformity of size. This is ideal in perspective of manufacturing. There will be less likelihood of variation in the volume of pellet during encapsulation, consequently maintaining uniformity of drug content during the filling process.

Particle size analysis of LP-11 shows a wider size distribution with ~64% fall in the size of 850 microns and ~32% fall in the size of 1mm. This could be due to reduced plastic property due to decreased water content, leading to poorer quality pellet with wider size distribution.

Nonetheless, both of the optimized formulations are almost entirely below 2mm range, which is similar to the previous studies in chapter 2 section 2.4.6. Hence, the liqui-pellet will behave similarly to liquid in the stomach and be emptied into the small intestine relatively fast [115]. This can be beneficial for weakly acidic drugs (i.e. naproxen), as they are more soluble in an alkaline environment, suggesting that bioavailability and onset of action may be improved.

It is also interesting to note that most of the physical mixture pellet falls in 500μm, which is considered small. This supports the claim from the previous studies by the author that co-solvent tends to increase pellet size.

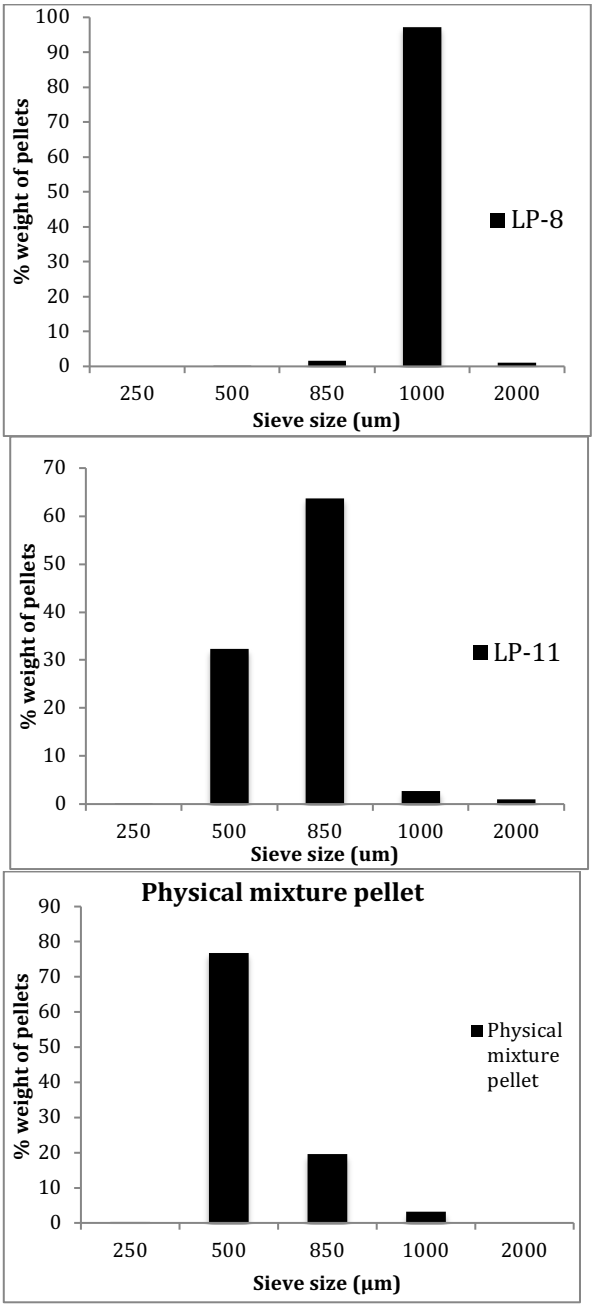


Figure 3.1. Particle size distribution of LP-8, LP-11 and physical mixture pellet

3.4.4 Stereoscopic analysis

The Feret's diameter (Table 3.4) agrees with the trend that co-solvent tend to increase liqui-pellet size. It can be seen that physical mixture and LP-11 mean Ferret diameters overestimated the liqui-pellet size. Since the pellets are not perfectly spherical, they tend to be in their most stable orientation. This means that the smallest dimension is orientated vertically; therefore, overestimation is prone to occur [41].

It is clear that LP-11 is the least round with mean roundness deviating from 1 considerably (1.42). Its mean elongation ratio is also large which supports the visible observation of the cylindrical liqui-pellet. Perhaps the reduced plastic property due to decreased water content leads to incomplete spheres forming. Nonetheless, LP-11 has excellent-good flowability.

Table 3.4. Stereoscopic analysis showing the mean feret's diameter, mean roundness and mean elongation of physical mixture pellet and optimized formulation (n=100)

Formulations[a]	Mean Feret's diameter mm	Mean roundness ± SD[b]	Mean elongation ratio ± SD[b]
Physical mixture pellet	1.028	1.25 ± 0.12	1.41 ± 0.19
LP-8	1.431	1.28 ± 0.14	1.43 ± 0.21
LP-11	1.527	1.42 ± 0.12	1.95 ± 0.35

[a] For the composition of each formula refer to Table 3.1
[b] SD, standard deviation from the mean

3.4.5 Scanning electron microscope (SEM) analysis

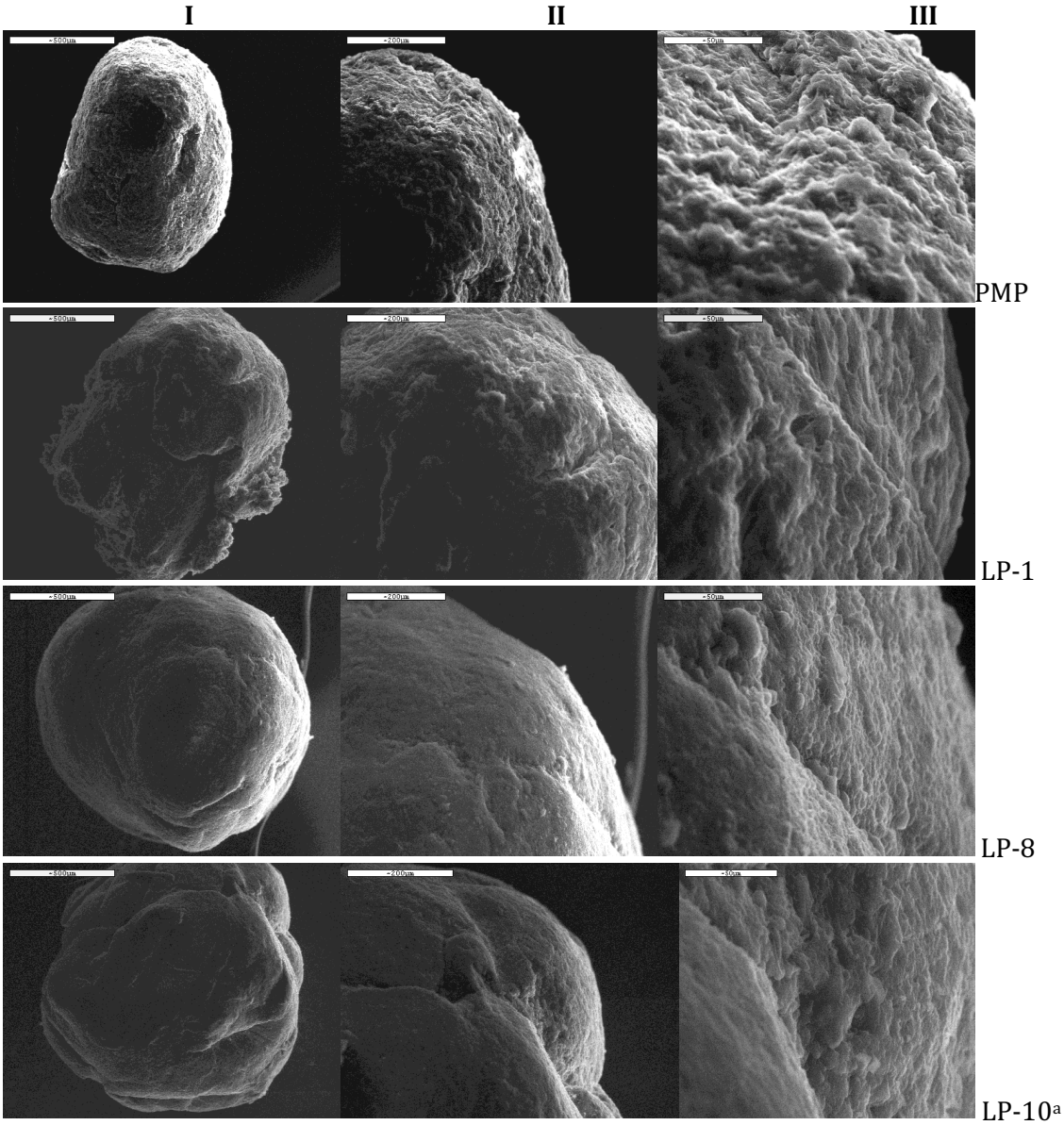
The SEM results (Figure 3.2) show physical mixture pellet (PMP) has the roughest surface structure compared to the rest of the formulation. This can be seen clearly at 800 times magnification. Although formulation LP-1, which contain 28% tween 80, shows surface crack at x 80 magnification, its surface is less rough than the physical mixture pellet. This is more apparent at x 200 and 800 magnification. The formulation LP-8, which contains 38% tween 80, shows a remarkable reduction in surface roughness compared to LP-1. This indicates that surface structure becomes less rough as tween 80 is increased.

The observation supports the claim made from the previous studies in chapter 2 section 2.4.8 where co-solvent influences surface structure, which tends to make the surface smoother. It is speculated from the previous studies that liquid vehicle may reduce the crystallinity of the pellet, resulting in smoother surface structure.

The SEM image of formulation LP-11 shows a large number of cracks in the pellet compared to LP-8. In LP-11, which also contains tween 80 as liquid vehicle, the water content is reduced during the manufacturing of the liqui-pellet. Water and 2-propanol mixture is used instead of just water to reduce overall water content during production. With the reduced amount of water, there will be less bonding within the MCC structure, thus the pellet quality is reduced. Furthermore, the water act as lubricant for the wet mass during extrusion, thus less water would result to rougher surface of extrudate leading to more

varied and brittle surface pellet. Nonetheless, this is advantageous as the pellet was able to disintegrate well in the dissolution medium.

In formulation LP-10, PEG (molecular weight of 1500) and water mixture was used to make the liqui-pellet. It is thought that the PEG at the surface of the pellets will dissolve faster, forming pores. However, it is clear in Figure 3.2 image LP-10^{b}, there is no apparent porous structure but the surface did become rougher.



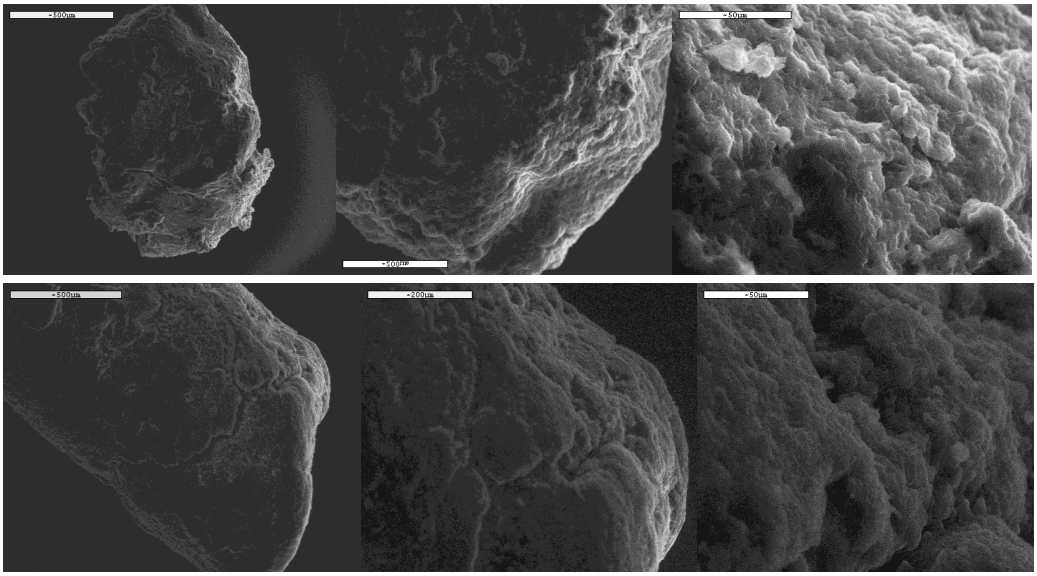


Figure 3.2. Images from SEM of physical mixture pellet, LP-7, LP-8 and LP-11; I. x 80 magnification, II. x 200 magnification and III. x 800 magnification

3.4.6 Drug release study

As mentioned in the previous studies (chapter 2) by the author, naproxen has poor solubility in acidic condition; however, for comparison purpose, the dissolution of liqui-pellets was carried out at pH 1.2. The authors have found that tween 80 appears to be the most suitable co-solvent for naproxen liqui-pellet; hence, tween 80 is the chosen liquid vehicle in this chapter. As observed in the previous dissolution study of liqui-pellet (chapter 2 section 2.4.9), the lack of disintegrating properties of MCC-based pellet led to poor drug dissolution rate. In an attempt to promote disintegration, a superdisintegrant (primojel) of different concentrations (5, 10, 15% w/w) is introduced into the formulation.

Dissolution test of the formulations containing 5%, 10%, 15% w/w of primojel with and without liquid-vehicle is shown in Figure 3.3. Liqui-pellet formulations containing primojel of 5% and 10% w/w (LP-1 and LP-2 respectively) had similar dissolution profiles (F_1 = 3.3 and F_2 = 97.84). It can be seen that increasing primojel concentration to 15% w/w (LP-3) slightly impedes dissolution by ~5% in comparison to 5% w/w (LP-1) and 10% w/w (LP-2) of primojel. When comparing LP-1 (primojel 5% w/w) and LP-3 (primojel 15% w/w), F_1 = 25.16 and F_2 = 77.26, and when comparing LP-2 (primojel 10% w/w) and LP-3 (primogel 15% w/w), F_1 = 21.15 and F_2 = 80.18. It can be seen the F_1 value mentioned is above 15, indicating differences in the drug release profile due to a reduction in drug dissolution rate when primojel is increased to 15% w/w. This may be due to primojel forming gel, which can slow down drug release rate. It is also claimed that the required concentration of primojel to achieve optimum disintegration action is ~4% w/w [207]. Given

this claim, primojel with a concentration of 5% w/w is chosen as opposed to 10% for the other formulations. Results from Figure 3.3 confirm formulation without a liquid vehicle has considerable slower drug release rate compared to the one with liquid vehicle ($p<0.05$). In fact, even with a different concentration of primojel incorporated into the formulation (LP-4, LP-5 and LP-6), the dissolution profiles are similar to that of physical mixture pellet ($p>0.05$). This further confirms that the characteristic of enhanced drug release in liquisolid formulations can be maintained in liqui-pellet.

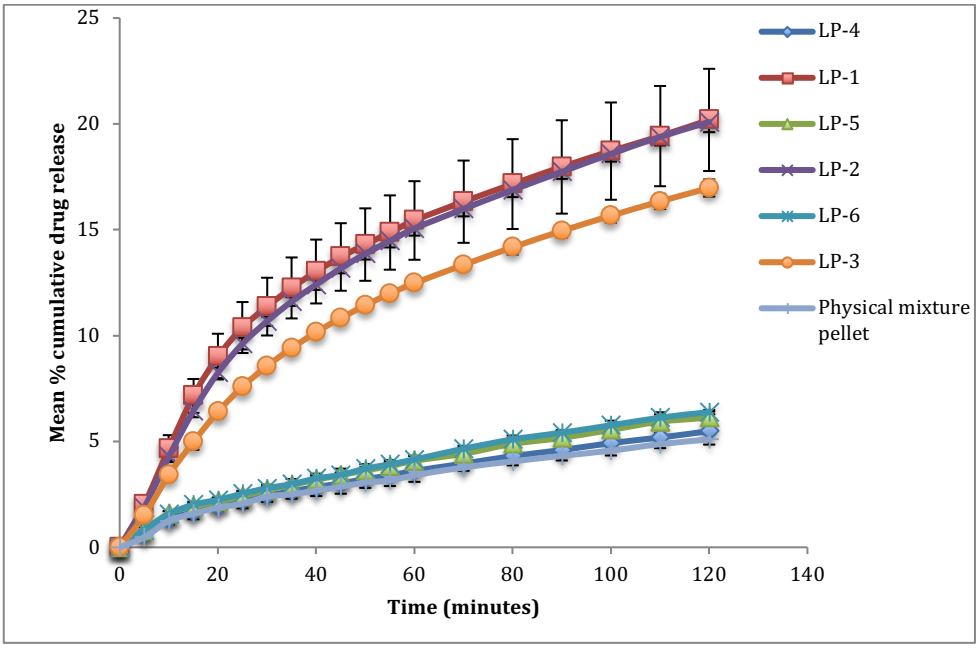


Figure 3.3. Dissolution profile of pellets in capsule for naproxen 25mg with different concentration of primojel (5, 10 and 15% w/w) with and without Tween 80 (pH 1.2) (n = 3)

After the most suitable liquid vehicle and concentration of primojel are chosen, various modifications are applied to the formulation to further improve drug release rate. As seen in Figure 3.4, a formulation containing an increased tween 80 and decreased carrier and coating materials (LP-8) shows the best enhanced drug release profile.

When comparing LP-8 to the non-optimized naproxen liqui-pellet containing tween 80 from the previous studies (chapter 2), it can be seen that the drug release from LP-8 is ~12% higher ($p<0.05$) and ~26% higher than physical mixture pellet ($p<0.05$) after 2 hours. This shows the potential of increasing drug dissolution rate of liqui-pellet when the formulation is optimized. In addition to LP-8 having the fastest drug release rate, its liquid load factor is higher than other formulations ($L_f = 1.52$), whilst still maintaining excellent-good flow property. With the increase in tween 80, less water is required to achieve the appropriate level of plasticity of the extrudate for making quality pellets when spheronized.

This is due to tween 80 plasticizing effect [206]. With less water included in the formulation, it can be deduced that the amount of bonding within the microcrystalline cellulose structure is reduced. Thus, disintegration is more rapid, which is visibly observable during the dissolution test (Figure 3.5). In fact, the disintegration is rather fast and explosive, which is the reason for higher drug release rate. One of the limitations of microcrystalline cellulose carrier in pelletization via extrusion-spheronization is the difficulty of achieving enhanced drug release due to strong bonding, rendering the pellet none disintegrating [203]. In spite of this, microcrystalline cellulose is used because it is the gold standard in extrusion and spheronization technology as it has the proper rheological properties, cohesiveness and plasticity to yield strong spherical pellets [94]. Formulation LP-11 has the second best enhanced drug release rate (~26% within 2 hours). This can be explained in a similar manner to LP-8, where 2-propanol and water mixture is used during the liqui-pellet preparation, which effectively reduces the amount of water. Hence, bonding force within microcrystalline cellulose is reduced, leading to improvement in the propensity for disintegration.

It is found that the stage at which primojel is added during formulation has a slight effect on how well the superdisintegrant performs. When primojel is added into the liqui-mass system after coating material (LP-7), the drug release rate is ~5% lower than the same formulation where primojel is added in the early stage along with the carrier (LP-1). The F_1 = 27.81 and F_2 = 74.83. F_1 indicates a difference in their dissolution profile; thus, the stages of when primojel is added does have an influence on drug release rate. It can be seen that the superdisintegrant is added extragranularly in LP-7 and intragranularly in LP-1. Intragranular incorporation of primojel appears to be more effective than extragranular for improving drug release. This reflects the importance of having an optimum procedure for preparing liqui-pellet. In literature, a combination of intragranular and extragranular incorporation of superdisintegrant is most effective in promoting disintegration [61,62,208].

In formulation LP-9, primojel superdisintegrant is replaced by primellose to see if the sodium starch glycolate or croscarmellose sodium (respectively) will perform better. Results from Figure 3.4 shows primojel (LP-1) have ~4% more drug release than primellose (LP-9) after 2 hours, suggesting primojel is the better superdisintegrant of choice for naproxen liqui-pellet.

In formulation LP-10, PEG (molecular weight of 1500) and water mixture were used to make the liqui-pellet. It is thought that the PEG at the surface of the pellets will dissolve

faster, forming pores which can facilitate the penetration of water into pellets; or that the liquid medication can move out easily via the pores generated as a result of the dissolution of PEG in the dissolution medium. However, the results show similar drug release rate to that of LP-7; thus, no improvement in drug dissolution rate is observed. The SEM results (Figure 3.2) show that LP-10 surface is rougher after the dissolution test, but the porous structure is not apparent. Without the porous structure, the drug release rate would not improve.

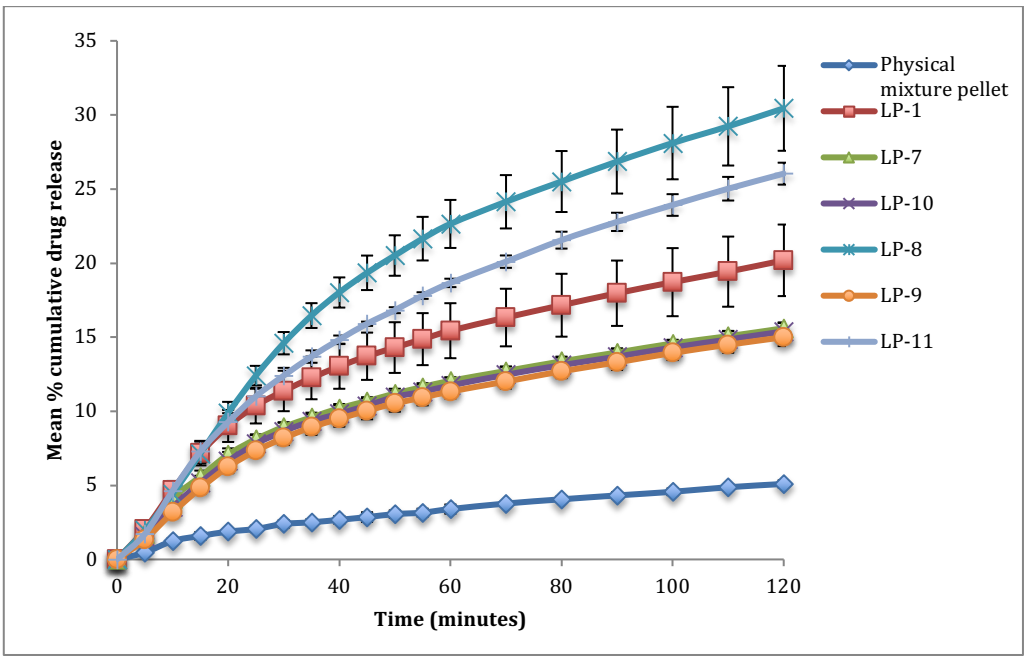


Figure 3.4. Dissolution profile of pellets in capsule for naproxen 25mg with various modifications in attempt to improve dissolution rate (pH 1.2) (n = 3)

Figure 3.5. An image of LP-8 liqui-pellet disintegrates explosively in acidic dissolution medium. Note the small white specks are fragments of the liqui-pellet

USP pharmacopoeia suggests performing the dissolution test at pH 7.4 to maintain sink conditions. On the basis of this, the author believes that those formulations which

shows higher dissolution at pH 1.2 should exhibit the better dissolution at higher pH, therefore only the optimized formulation (LP-8 and LP-11) are selected for dissolution test at pH 7.4 (Figure 3.6). The results show both formulations are reaching near plateau after 20 min (~100% drug release within 20 min). This fast drug dissolution profile is to be expected, as naproxen is a weakly acidic drug, hence it will dissolve more rapidly in a basic environment. In brief, the results show naproxen liqui-pellet is capable of achieving fast release rate even though there have been claims that microcrystalline cellulose-based pellets via extrusion-spheronization tends to prolong drug release [209]. In addition, since the pellets are small, i.e. ~98.8% of both LP-8 and LP-11 fall into the size of 1mm or below, these pellets will undergo gastric emptying relatively fast, similar to liquid [115]. It will be exposed to basic environment relatively quick, thus drug dissolution should occur faster and potentially improve the drug bioavailability. Also, since the pellets are small, it will be well distributed along the gastrointestinal tract, which could further improve bioavailability [115].

According to results shown in Figure 3.6, it seems that water content during the preparation of the liqui-pellet plays a major role in disintegration and drug release. It is clear that reducing the water content causes a significant improvement in drug release rate, most likely due to reduced bonding force within the microcrystalline cellulose structure, which improves disintegration. Furthermore, avicel has disintegrant properties [207], which are displayed with the reduced water content formulations. The drug release rate of the reduced water formulations (LP-8 and LP-11) nearly reached towards the plateau after 20 min, whereas a formulation without reduced water content (LP-1) only achieve ~79% drug release after 2 hours.

When comparing the results from Figure 3.5 and Figure 3.6 to Tiong *et al* studies [15] on naproxen liquisolid compact, liquisolid tablets showed faster drug release rate at pH 1.2; however, at pH 7.4, the drug dissolution rate for the optimized liqui-pellet are similar or slightly better than Tiong *et al*. With excellent-good flow property being achieved in liqui-pellet and the intrinsic advantages of liqui-pellet, including possible room for further modifications, the novel liqui-pellet seems like a promising approach in tackling bioavailability issue of poorly water-soluble drugs in a commercially feasible and cost-effective way.

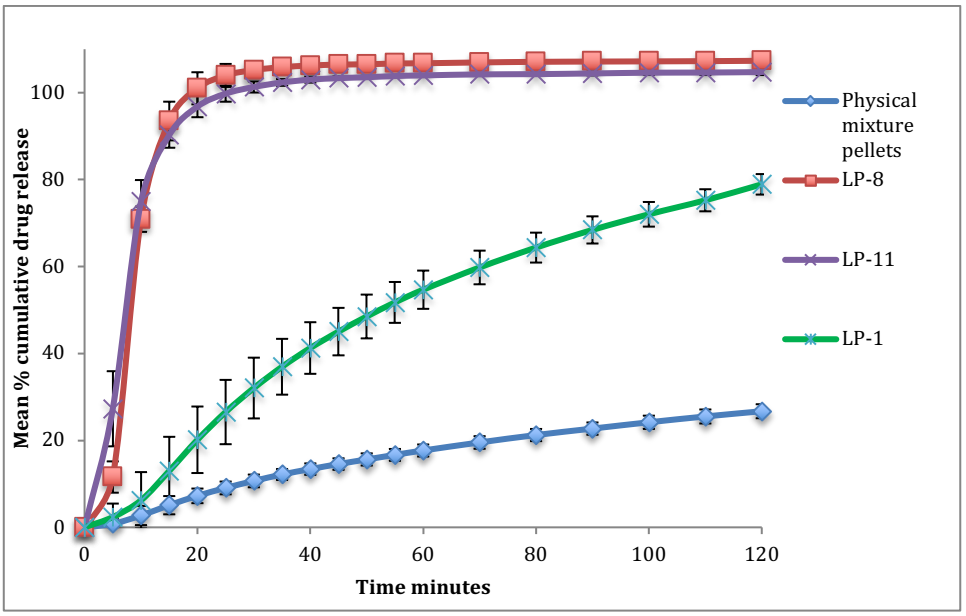


Figure 3.6. Dissolution profile of formulations containing naproxen 25mg with the fastest dissolution rate after modifications, formulation containing tween 80 as liquid vehicle with primojel 5% w/w, and physical mixture pellets (pH 7.4) (n = 3)

3.4.7 Kinetic model analysis of drug release

Naproxen liqui-pellet drug release under pH 1.2 is best described by Higuchi's model as shown by the correlation coefficient value (R^2) in Table 3.5. A similar result was observed in chapter 2 section 2.4.10. As explain in that chapter, Higuchi's model of drug release is based on Fick's law of diffusion [190]. This law states that API concentration gradient between dosage form and bulk of dissolution medium is the driving force for diffusion of API molecules from dosage form to dissolution medium, hence driving drug dissolution. The two best formulations (F-8 and F-11) drug release under pH 7.4 fit the zero order model best (Table 3.6). This model describes a system where the drug release is constant over a period of time. The drug release for these two formulations are independent of concetration.

Table 3.5. Release parameters of naproxen formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.946	0.949	0.993
LP-1	0.861	0.883	0.977
LP-2	0.861	0.883	0.977
LP-3	0.886	0.906	0.984
LP-4	0.955	0.958	0.994
LP-5	0.956	0.960	0.993
LP-6	0.961	0.964	0.991
LP-7	0.858	0.874	0.978
LP-8	0.906	0.932	0.977
LP-9	0.875	0.890	0.980
LP-10	0.866	0.882	0.979
LP-11	0.921	0.943	0.988

Table 3.6. Release parameters of naproxen formulations at pH 7.4

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.955	0.972	0.977
LP-1	0.940	0.997	0.971
LP-8	0.937	0.898	0.796
LP-11	0.967	0.960	0.909

3.4.7 DSC studies

The DSC traces of naproxen, avicel, aerosil, primojel, physical mixture pellets and some optimized liqui-pellet formulations are shown in Figure 3.7 and 3.8. The naproxen trace shows a sharp endothermic peak (T_m = 158.77°C and ΔH = 92.06J/g) indicating its crystalline state. Avicel (T_m = 72.67°C and ΔH = 94.82J/g) and primojel (T_m = 83.82°C and ΔH = 167.36J/g) thermograms displayed broad peak. These peaks could be due to water within avicel and primojel evaporating, as they are hygroscopic materials. Tiong *et al* also observed the evaporation of water from avicel [15]. As for aerosil, there is no definitive peak.

When comparing naproxen and physical mixture pellet thermograms as shown in Figures 3.7 and Figure 3.8, it can be seen that there is a small shift of peak from 158.77°C to 149.80°C respectively. This could be due to avicel influencing the overall peak of naproxen in the physical mixture pellet. Nonetheless, the crystalline state of naproxen is still present. However, when looking at the DSC traces of optimized formulations (liqui-pellets), LP-8 (T_m = 111.01°C and ΔH = 2.04J/g) and LP-11 (T_m = 120.69°C and ΔH = 2.83J/g), the naproxen

peak was less prominent and the T_m lowered, indicating that they were less crystalline and possibly more amorphous, hence the improvement in dissolution.

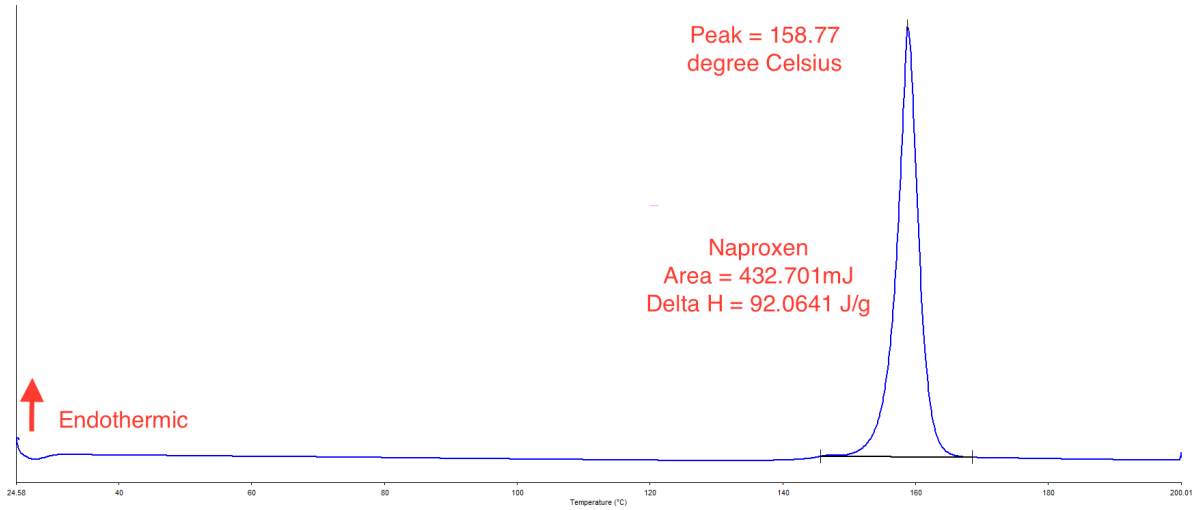


Figure 3.7. DSC thermogram of naproxen

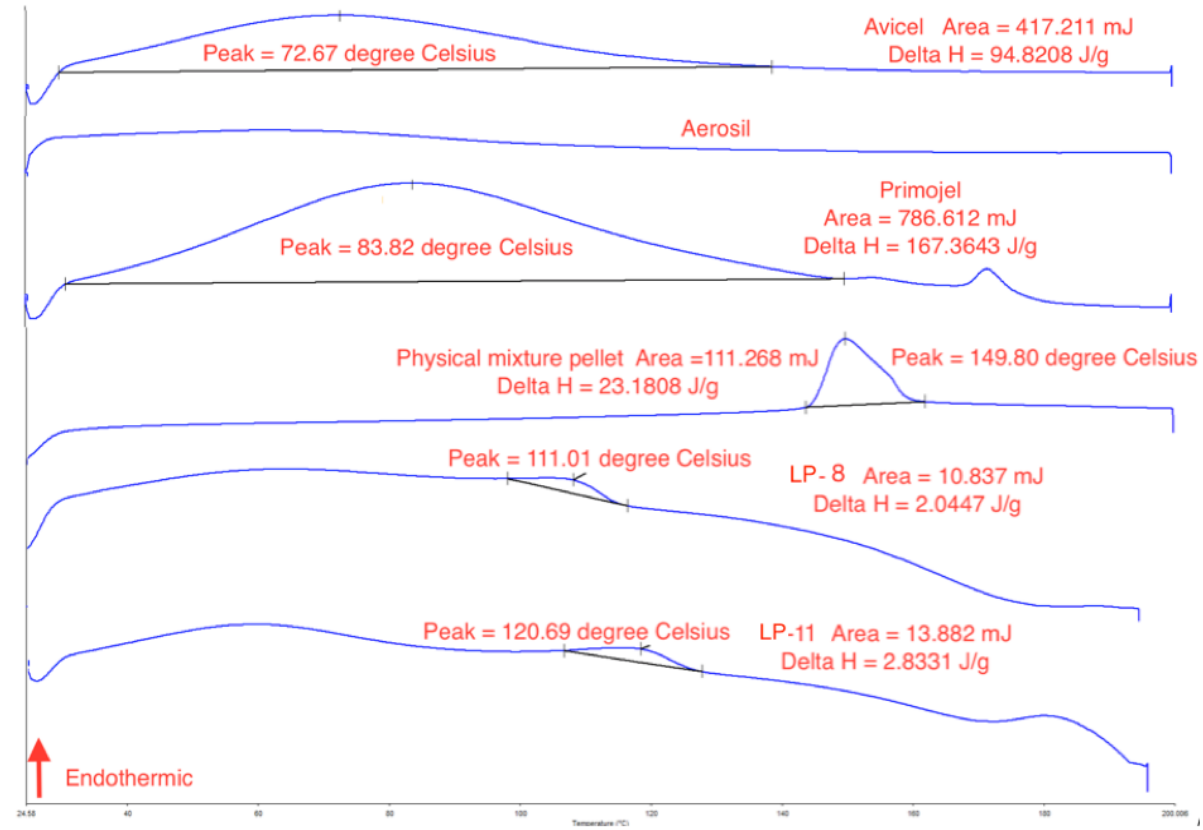


Figure 3.8. DSC thermograms of avicel, aerosil, primojel physical mixture pellet, LP-8 and LP-11. Note the scales of avicel, aerosil and primojel are the same but different from physical mixture, LP-8 and LP-11.

3.4.8 XRPD studies

Naproxen diffractogram (Figure 3.9) shows major peaks at 2θ values of 12.2, 16.2, 18.4, 19.6, 22.2, 23.2, 26.8 and 27.8°. These peaks are similar to the naproxen in Maghsoodi studies [204] with the exception of a sharp peak at ~7° being present and peak at 26.8° being absent in Maghsoodi studies. Naproxen peaks are also slightly different in Mello and Ricci-Junior studies [205], showing some variation in naproxen peaks between different studies. This could be due to different scan rate settings or the actual state or form of the drug used in various studies. Nonetheless, the general peaks of naproxen are present.

The XRPD diffractogram of physical mixture pellet and formulation LP-8 and LP-11 has no peak other than that of naproxen and avicel, which indicates no interaction between the excipients and the drug. Data from % relative crystallinity (Table 3.7) shows that physical mixture and formulation LP-8 and LP-11 have reduced crystallinity compared to the pure naproxen, agreeing with the result observed in the DSC test.

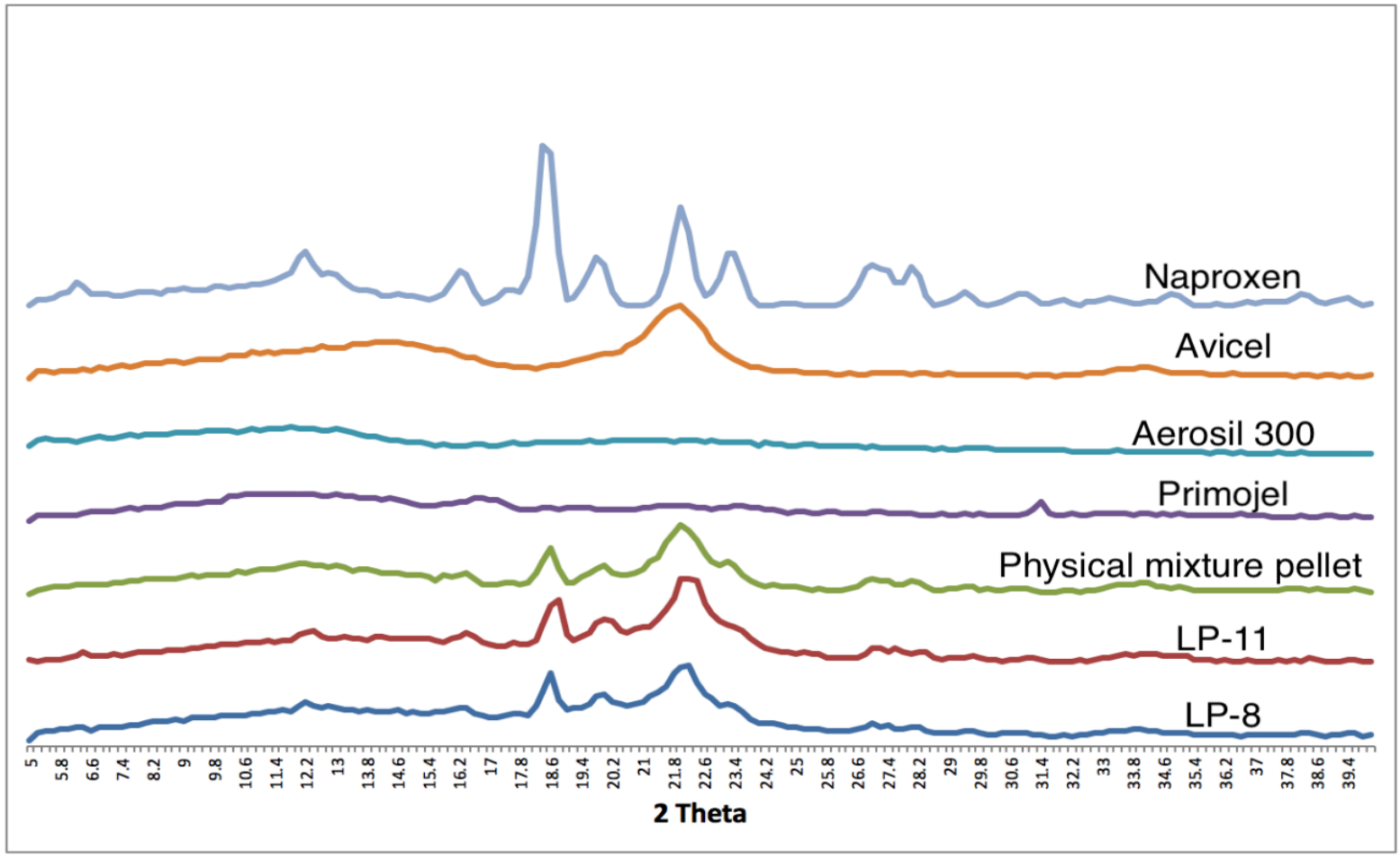


Figure 3.9. Diffractograms of naproxen, avicel, aerosil, primojel, physical mixture pellet, LP-8 and LP-1

Table 3.7. % relative crystallinity via integrated peak area and peak height method

Formulation	% relative crystallinity via integrated peak area method	% relative crystallinity via peak height method
Physical mixture	23.26	39.54
LP-8	17.57	36.30
LP-11	22.36	48.73

3.5 Conclusion

It is confirmed that optimized liqui-pellet is capable of enhanced drug release when the propensity for disintegration is improved. Although avicel is known to be non-disintegrating, when the water content is reduced during liqui-pellet production, the pellet is capable of fast and even explosive disintegration. The major drawback of classical liquisolid formulation having poor flowability has been overcome by replacing it with the new liqui-pellet dosage form. All liqui-pellet formulation maintained excellent-good flow properties even with an extremely high liquid load factor of 1.52, where 38% of total pellet mass is co-solvent. Solid state analysis via DSC and XRPD results show a reduction in crystallinity, which displays improvement in drug release. In conclusion, it is reasonable to postulate that liqui-pellet is highly commercially feasible without having the advantages of liquisolid formulation compromised. Furthermore, there is potential for further optimization of this novel delivery system as the parameters have yet to be optimized.

Chapter 4: The crucial effect of water and co-solvent on liqui-pellet

4.1 Abstract

Liqui-pellet is considered to be the next generation oral dosage form. It is highly commercially feasible unlike its predecessor, liquisolid formulation. Liqui-pellet uses liquid-mass system, allowing the formulation to overcome critical drawbacks, which were apparent in liquisolid technology such as, poor flowability, poor compressibility and inability for high dose without the product being too heavy and bulky for swallowing. However, to make this novel oral delivery system a commercial product, it is prudent to further understand the parameters affecting its drug release rate. Two major parameters affecting the drug dissolution rate that is investigated are water and co-solvent (tween 80) content. It is found out that reducing water content and increasing tween 80 concentration in naproxen liqui-pellet results to an increase in drug release rate; however, there is a limit of how much water and tween 80 can be adjusted. Outside of this range limit, the formulation would fail to produce liqui-pellet due to agglomeration. In the successful formulation where liqui-pellets are formed, the excellent-good flow properties, resistant to friability and narrow size distribution makes it ideal for commercial production. SEM of the liqui-pellet shows a smooth surface which is ideal for coating. The solid state analysis via XRD and DSC indicated reduced crystallinity of the drug which is expected.

4.2 Introduction

The key introductory points are covered in chapter 2 section 2.2 and 3.2; however, further background relating to this chapter will be covered here.

In studies by the author, liqui-pellet has shown remarkable potential for increasing drug dissolution rate, whilst overcoming the drawbacks of the classical liquisolid technology. The key drawbacks of the classical liquisolid formulation are poor flowability, poor compactability and inability to produce high dose drug without being too bulky and heavy for real life use [1,4]. The liqui-pellet can achieve excellent-good flow properties with high liquid load factor without compromising the inherent advantages of liquisolid technology as shown in the authors previous investigation (chapter 2 and 3). The key advantages are rapid drug release, simplicity and cost-effectiveness in production [1,4]. The incorporation of high amounts of liquid medication whilst having the ability to achieve

excellent flowability and the versatility for further modification makes liqui-pellet an exciting and interesting dosage form. The high liquid load factor can potentially make high dose liqui-pellet formulation without being too bulky. It is in fact highly commercially feasible unlike its predecessor (liquisolid formulation).

Among the pelletization technique, extrusion-spheronization is the chosen technique for this study. This is because it has a major advantage in that it is capable of having high loading of API without producing very large particles [73,75]. The API is integrated within the pellet structure unlike some pelletization technique where the API is only present at the surface of the pellet. In addition, extrusion-spheronization technique can produce pellets with uniform size, good flowability, narrow size distribution and smooth surface [73]. All is important in terms of manufacturing and quality control.

From the previous investigation, it is known that naproxen liqui-pellet is able to achieve excellent flow properties (in accordance to Carr's compressibility index and angle of repose) with a very high liquid load factor of 1.52, where 38% of total pellet mass is co-solvent (chapter 3). Initially, in the early studies, naproxen liqui-pellet has high liquid load factor and excellent flowability but the drug release rate is slow (~17 % release after 2 hours at pH1.2). This is due to the use of microcrystalline cellulose (MCC) carrier; MCC-based pellet produced from extrusion spheronization are known to form a strong bond, which made it virtually unable to disintegrate [127,203]. It is later found that this inability to disintegrate is the drug release rate limiting step in liqui-pellet. Modifications of the formulation are later carried out and it is found that water content incorporated in extrusion-spheronization process is the key factor in determining liqui-pellet propensity to disintegrate. In addition, the amount of co-solvent used in the formulation was observed to have an impact in disintegration and drug release rate; thus, it seems prudent to investigate the water and co-solvent content parameters.

Water content is a crucial factor in formulation containing MCC; this is to achieve good rheological properties for a successful pellet production via extrusion-spheronization [99]. Good rheological properties refer to being plastic enough to be moulded but cohesive enough to retain moulded shape. Moisture content affects the internal porosity, friability, mechanical strength/cohesiveness, particle size distribution, shape and size of the pellets [74,95]. In studies by Otsuka *et al*, an increase in water content results to increase in hardness, which effectively reduces friability due to a decrease of internal porosity of pellets [130]. Non-volatile co-solvent such as tween 80 has plasticizing effect [206], which can results in pellets

with the better plastic property because of the polymer transit from glassy to rubbery state [151].

In this study, the key objective is to observe the drug release profile of liqui-pellet formulation made from varying water and co-solvent content. The study begins with investigating the most suitable co-solvent among tween 20, tween 80 and tween 85. Afterward the water content will be varied in different formulation to observe its effect on the drug release profile. Then specific effect of varying water and co-solvent content will be investigated. With further understanding of the effect of drug release of the mentioned parameters, it is possible to control and tailor the dissolution behavior of liqui-pellet.

4.3 Materials and methods

4.3.1 Material

Naproxen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel), (DFE Pharma, Goch, Germany); polysorbate 20 (tween 20), (Acros, Netherlands); polysorbate 80 (tween 80), (Acros, Netherlands) and polysorbate 85 (tween 85), (Acros, Netherlands). All other reagents and solvent were of analytical grades.

4.3.2 Saturation solubility studies

Saturation solubility studies were carried out in a similar manner as in chapter 2 section 2.3.2, however, only 3 liquid vehicles were used (tween 20, tween 80 and tween 85). Also, the duration of time sample was left in the bath shaker was longer (72 h).

4.3.3 Preparation of naproxen liqui-pellet with different tween co-solvent

The naproxen liqui-pellet formulations were prepared in the same manner as in chapter 2 section 2.3.3; however, there are variations in parameters such as type of liquid vehicle; water content; amount of liquid vehicle and the presence of primojel 5% w/w (Table 4.1)

Table 4.1. Key formulation characteristics of the investigate liqui-pellet in capsule with different liquid vehicle

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Amount of liquid vehicle (% w/w)	Type of liquid vehicle	Liquid load factor	Mass of carrier (mg)	Mass of coating material (mg)	Successfully spheronize into pellets? (Yes/No)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet	6.01				58.15	2.90	Yes	90.58
LP-1	8.62	28	Tween 20	1	62.41	3.11	Yes	132.70
LP-2	8.62	28	Tween 80	1	62.41	3.11	Yes	132.70
LP-3	8.62	28	Tween 85	1	62.41	3.11	Yes	132.70

Note that all formulation contained 25mg of naproxen, primojel 5% w/w and the carrier to coating ratio of 20:1 respectively

4.3.4 Preparation of naproxen liqui-pellet with varying water content and co-solvent concentration

The naproxen liqui-pellet formulations were prepared in a same manner as in chapter 2 section 2.3.3; however, there are variation in parameters such as: type of liquid vehicle; water content; amount of liquid vehicle and the present of primojel 5% w/w (Table 4.2).

Table 4.2. Key formulation characteristics of the investigate liqui-pellet in capsule with varying water and liquid vehicle concentration

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Amount liquid vehicle (% w/w)	Type of liquid vehicle	Liquid load factor	Mass of carrier (mg)	Mass of coating material (mg)	Successfully spheronize into pellets? (Yes/No)	Total weight of 25mg naproxen liqui-pellet (mg)
LP-4	8.57	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-5	8.57	36	Tween 80	1.38	52.77	2.64	No	132.70
LP-6	8.57	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-7	8.57	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-8	4.76	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-9	4.76	36	Tween 80	1.38	52.77	2.64	Yes	132.70
LP-10	4.76	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-11	4.76	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-12	1.90	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-13	1.90	36	Tween 80	1.38	52.77	2.64	Yes	132.70
LP-14	1.90	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-15	1.90	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-16	0.95	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-17	0.95	36	Tween 80	1.38	52.77	2.64	No	132.70
LP-18	0.95	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-19	0.95	44	Tween 80	1.94	43.16	2.16	No	132.70

Note that all formulation contained 25mg of naproxen, primojel 5% w/w and the carrier to coating ratio is 20:1 respectively

4.3.5 Flowability test on formulated liqui-pellet

Carried out in same manner as described in chapter 1 section 2.3.5.

4.3.6 Friability test on formulated liqui-pellet

Carried out in same manner as described in chapter 2 section 2.3.6.

4.3.7 Particle size analysis via sieve method

Carried out in same manner as described in chapter 2 section 2.3.7.

4.3.8 Scanning electron microscopy (SEM) analysis

Carried out in same manner as described in chapter 2 section 2.3.9; however, only magnification of x80 and x800 were used.

4.3.9 In-vitro dissolution test

Carried out in same manner as described in chapter 2 section 2.3.10.

4.3.10 Kinetic model analysis of drug release

Carried out in same manner as described in chapter 2 section 2.3.11.

4.3.11 Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD)

DSC carried out in same manner as described in chapter 2 section 2.3.12; and XRPD carried out in same manner as described in chapter 2 section 2.3.13, however, the scan rate for XRPD was 0.02°/s.

4.3.12 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.3.14.

4.4 Results and discussion

4.4.1 Saturation solubility studies

Results from the saturation solubility studies (Table 4.3) show naproxen is sparingly soluble in tween 20, tween 80 and tween 85. Among the mentioned co-solvents, which are non-ionic surfactant derived from sorbitan ester [207], naproxen has the highest solubility in tween 80 (21.85mg/ml) and least soluble in tween 85 (14.27mg/ml). This is reflected in the dissolution studies (Figure 4.3) where tween 80 has the fastest drug release rate and

tween 85 is the slowest. This fit into the general assumption that formulation containing the liquid vehicle, which the API have the highest solubility in, would have the fastest drug release rate. This is due to increase of drug in solubilized or in molecularly dispersed state; thus, increasing the surface area for dissolution [3].

The differences in the solubility in various tweens are due to their different properties; however, the detailed explanation remains unclear. On comparing the HLB (hydrophilic-lipophilic balance), tween 20 (HLB = 16.7) have the highest HLB followed by tween 80 (HLB = 15.0) then tween 85 (HLB = 11.0) [207] ; however, these HLB value does not seem to show clear correlation with the solubility data or drug release rate. This reinstates how predicting solubility is complex and require consideration of additional factors such as viscosity, polarity, chemical structure and molecular mass may affect drug release [1].

It is interesting to note that the 42h saturation solubility test from previous studies (chapter 2 section 2.4.1) showed that tween 80 is only slightly soluble (2.99mg/ml), which is rather different from this 72 h saturation solubility test results (14.27mg/ml).

Table 4.3. Solubility of naproxen liqui-pellet in tween 20, 80 and 85 at 37°C (n=3)

Non-volatile solvent	Mean concentration (mg/ml) ± SD[a]	Inference
Tween 20	17.98 ± 3.09	Sparingly soluble
Tween 80	21.85 ± 1.88	Sparingly soluble
Tween 85	14.27 ± 1.58	Sparingly soluble

[a] SD, standard deviation from the mean

4.4.2 Success of spheronizing formulation

Not all formulations were successfully spheronized into pellets. Table 4.1 and Table 4.2 show which formulations were successful and which failed in producing pellets. In general, there seems to be a limit of how much water and co-solvent can be added until the formulation is prone to agglomeration, leading to failure in liqui-pellet production.

Within the spectrum of water content used in this investigation, 8.57ml of water per 20g of admixture is considered high water content. At this water content, only the lowest spectrum of co-solvent (32% w/w) was able to successfully produce liqui-pellet. By increasing the co-solvent above 32% w/w with this high water content formulation, the

extrudates produced have sticky surface and highly plastic property, which lead to agglomeration during spheronization process. It seems like there is a synergistic effect of water and tween 80 in enhancing extrudate plastic properties. The non-ionic surfactant tween 80 have plasticizing effect [206] contributing to the rheology of the wet mass and extrudates. Care must be taken into consideration so that the extrudates are plastic enough to form spherical pellet when spheronized but not to the extent that would result to agglomeration.

At the mid spectrum of water content (4.76ml and 1.9ml per 20g admixture), it is possible to make liqui-pellet with higher tween 80 content (36% w/w). The reason why the co-solvent could be increased is because the water content is reduced; thus, the overall plasticity of the extrudates do not go over the limit that can cause agglomeration. At this mid-range of water content, tween 80 above 36% w/w all agglomerated during spheronization process. Despite some of the extrudates appearing ideal for pellet production (i.e. short and brittle enough to break), the increased in co-solvent made the extrudate surface too cohesive that agglomeration could not be avoided.

Similar to the high spectrum of water content, the lowest spectrum of water content (0.95ml per 20g admixture) could only produce liqui-pellet successfully at low co-solvent concentration (32% w/w). The lack in water, affects the rheological properties of the extrudate in such that concentration of tween 80 at 36% w/w and higher were too soft and cohesive to spheronize into pellets. Overall it can be seen clearly that understanding the water and co-solvent limits in liqui-pellet production is prudent for the success of the formulation.

4.4.3 Flow properties

All successfully made formulations have shown excellent, excellent-good or good flowability (Table 4.4). The results from the author's previous work also show similar results, indicating clearly that liqui-pellet can overcome its' predecessor's (liquisolid technology) drawback of poor flow properties. This is a major step forward in bringing concept from liquisolid technology towards commercial production.

Tween 80 that is used in the formulations has been classified as a surfactant according to 'Handbook of Pharmaceutical Excipients' [207]. Surfactant that has high HLB value tends to reduce sharkskinning of extrudate, which is the result from decreased

frictional force at the die wall of extrusion screen. This helps to produce pellets with higher sphericity [142]. The high degree sphericity contributes to the desirable flow properties that are seen in Table 4.4.

It is noteworthy to mention that some of the formulations have liquid load factor as high as 1.38, where total mass of pellet contains 55% liquid medication. Furthermore, since flow properties and compressibility are no longer a major issue in the emerging liqui-pellet, the production is simplified by not having to rely on the liquisolid mathematical model that was introduced by Spireas.

Table 4.4. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulation (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	10.72 ± 0.33	19.96 ±1.43	11.11 ± 0.62	Excellent flowability	Good flowability
LP-1	8.77 ± 0.16	23.81 ± 0.74	10.08 ± 0.55	Excellent flowability	Excellent-good flowability
LP-2	8.22 ± 0.29	23.51 ± 0.19	12.11 ± 0.64	Excellent flowability	Good flowability
LP-3	8.08 ± 0.07	23.95 ± 0.21	12.73 ± 0.00	Excellent flowability	Good flowability
LP-4	6.74 ± 0.08	28.7 ± 0.20	11.05 ± 1.36	Excellent flowability	Good flowability
LP-8	7.17 ± 0.10	27.63 ± 0.31	10.17 ± 0.63	Excellent flowability	Excellent-good flowability
LP-9	7.07 ± 0.11	27.65 ± 1.00	6.31 ± 0.70	Excellent flowability	Excellent flowability
LP-12	6.12 ± 0.18	31.02 ± 0.66	7.33 ± 0.00	Good flowability	Excellent flowability
LP-13	6.4 ± 0.19	29.52 ± 0.85	3.96 ± 0.00	Excellent flowability	Excellent flowability
LP-16	5.57 ± 0.25	30.87± 0.55	5.80 ± 0.74	Excellent-good flowability	Excellent flowability

[a] For the composition of each formulation refer to Table 4.1 and Table 4.2
[b] SD, standard deviation from the mean

4.4.4 Friability test

All of the successfully produced formulations have weight loss of less than 1% (Table 4.5), which is the limit of weight loss considered acceptable for tablet according to the USP. Liqui-pellet from the author's previous studies also have weight loss of less than 1%. Currently there is no standard for friability test for pellets; however, it seems reasonable to say that liqui-pellet is robust enough for commercial use.

These liqui-pellets contain MCC as carrier, which have strong bonding within its structure when water is added; in addition, the tween 80 gives the formulation its plastic properties. Both of these enhance liqui-pellet resistant to friability which is supported in Table 4.5.

Table 4.5. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.14
LP-1	0.05
LP-2	0.12
LP-3	0.20
LP-4	0.29
LP-8	0.10
LP-9	0.09
LP-12	0.11
LP-13	0.29
LP-16	0.53

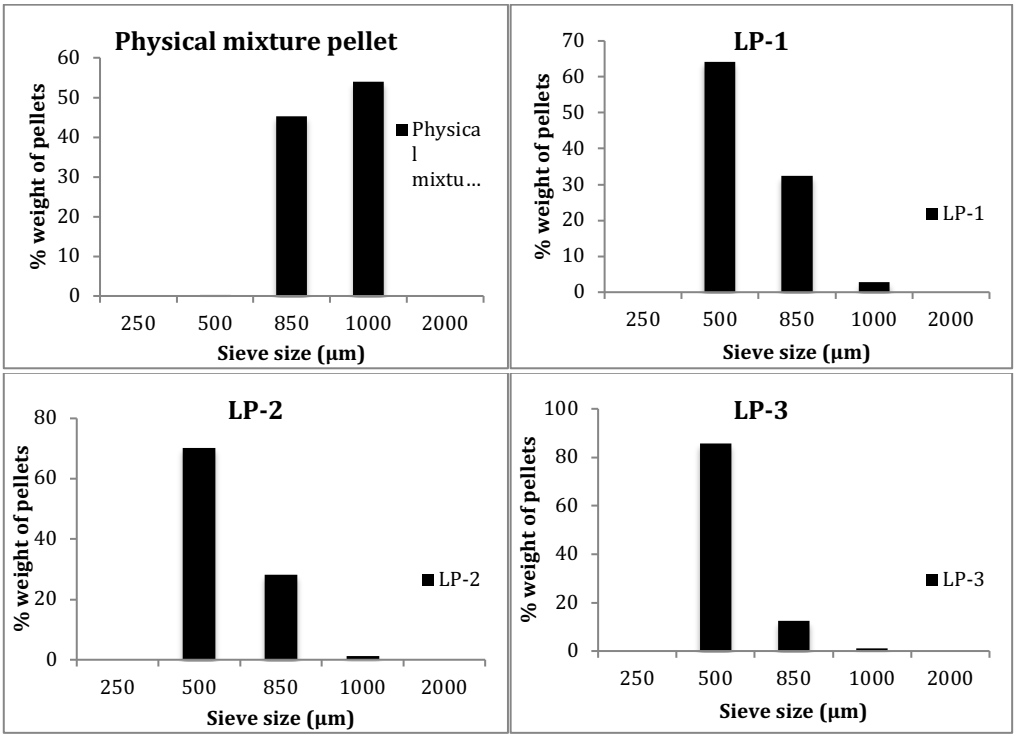
4.4.5 Particle size of formulated liqui-pellet via sieve method

Results obtained from the particle size analysis (Figure 4.1), clearly show narrow size distribution from all formulations apart from physical mixture pellet. Physical mixture pellets have relatively wider size distribution than the rest of the formulations (~53.95% within 1mm and 45.21% within 0.85mm). This could be due to the absence of tween 80 in physical mixture pellet. Without tween 80 the wet mass and extrudates would have less plastic properties, which could result into rougher extrudates, leading to poorer pellet quality with wider size distribution.

The formulations that have exceptional narrow size distribution are LP-4 (99.09% within 1mm), LP-8 (94.47% within 1mm), LP-9 (99.08% within 1mm), LP-12 (98.22% within 1mm), LP-13 (97.71% within 1mm) and LP-16 (97.92% within 1mm). These narrow size distributions are ideal for commercial manufacturing, particularly when considering the uniformity of drug content during the filling process into capsule.

It is interesting how the changes in water content and tween 80 concentration did not have significant influence on the liqui-pellet size distribution. Formulation containing 8.57ml of water per 20g of liqui-mass admixture (LP-4) and 0.95ml of water per 20g of liqui-mass admixture (LP-16) are 99.09% and 97.92% within 1mm respectively. It seems like the tween 80 could be contributing to the reduce variability in plastic properties, consequently reducing variability of size distribution among the formulation.

It should be noted that there are many parameters that can affect the pellet size produced from extrusion-spheronization. In brief, these key parameters include moisture content [74,95]; type and amount of granulating liquid [130]; spheronization speed, load & duration; and drying method [80]. Thus, it is actually rather difficult to be certain if parameters such as amount of water or co-solvent are actually influencing the pellet size. Nonetheless, it is clear that it is possible to produce liqui-pellet with narrow size distribution and within size that would allow it to have short transit time in the stomach (<2mm).



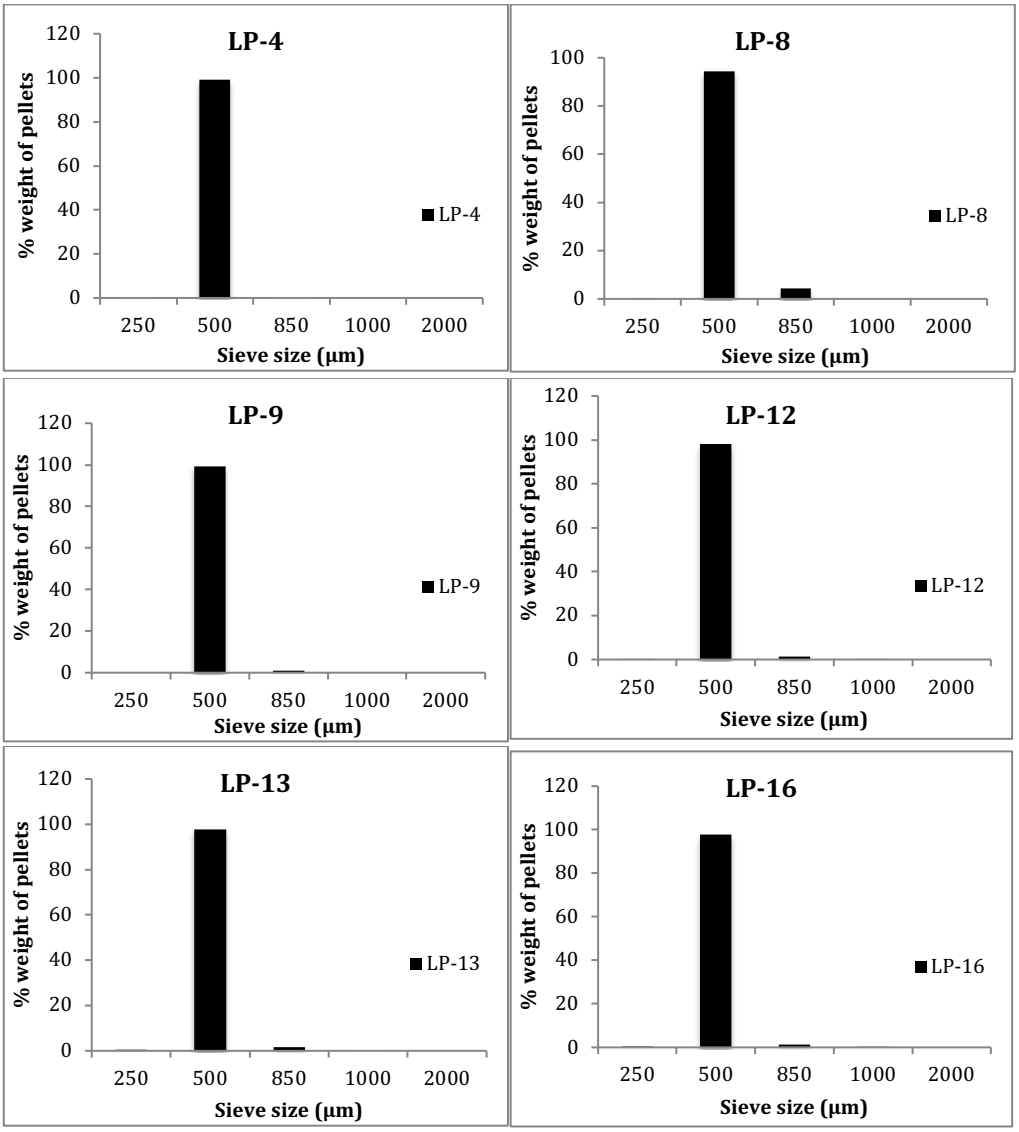


Figure 4.1. Particle size distribution of physical mixture pellet and all other successfully formulated liqui-pellets

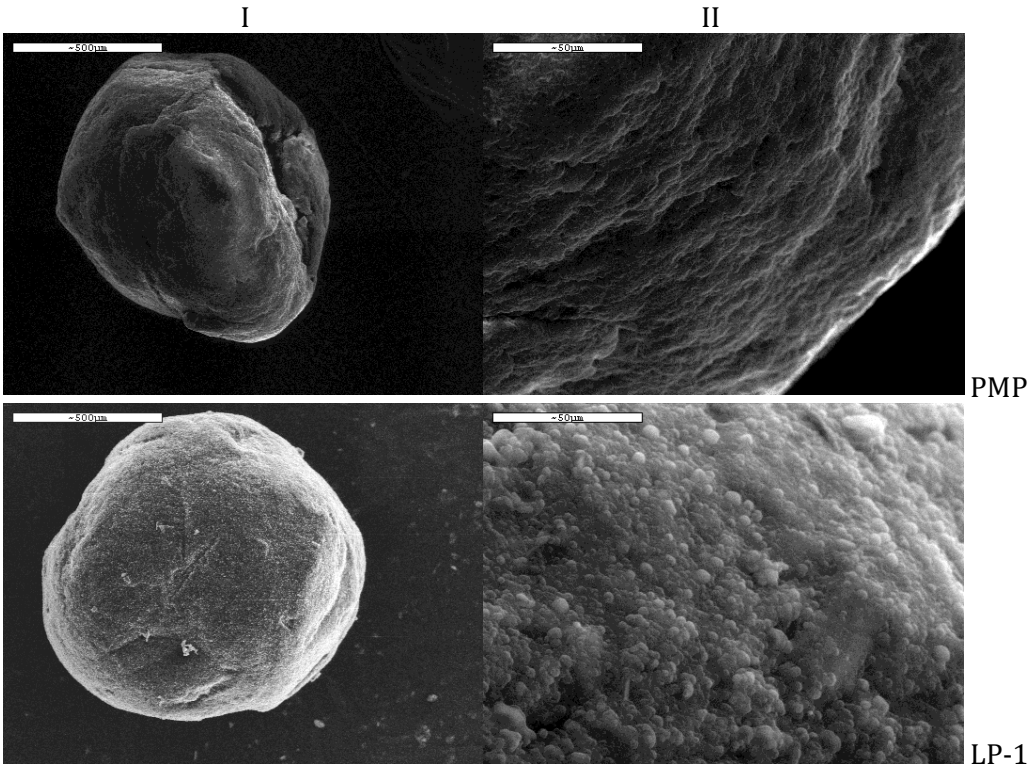
4.4.6 Studies of surface structure via SEM

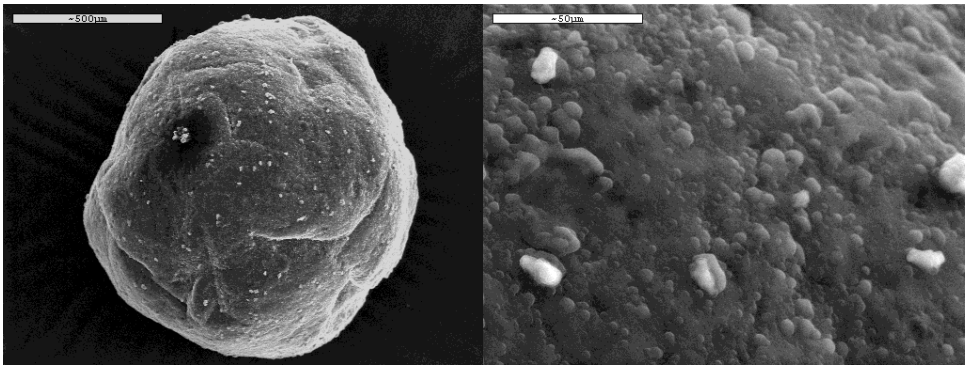
There is a clear difference in surface structure of liqui-pellet formulations and physical mixture pellet (Figure 4.2). The surface of all of the liqui-pellet formulations have smooth round pebble like appearance, which is not present in the physical mixture pellet (PMP). Among the different type of tween co-solvents, tween 20 (LP-1) show the smallest bump size on the surface, which could suggest that different tweens may influence surface morphology. The rest of the formulations' surface structure looks similar to one another, with the exception of intricate variation in bump size. It appears like LP-16 has slightly larger bumps, which protrude more than the rest of the formulations. It should be noted that the priority focus of the study is to see if it is possible to produce liqui-pellet with

different amount of water and tween 80 content; thus, in order to achieve this the spheronization duration and speed were varied for optimal success rate. This may have an impact on the surface structure of the liqui-pellet formulations.

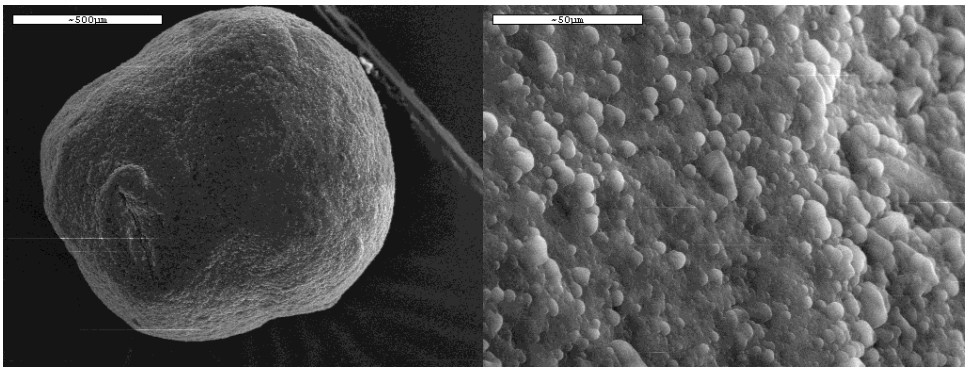
It is interesting to point out that in the previous study, the formulation that contained ~29% w/w tween 80 did not have the smooth pebble-like appearance (chapter 2 section 2.4.8). The pebble-like appearance seems to appear when the amount of tween 80 is increased as shown in this study, where only 32% w/w and above of tween 80 were used.

All of the liqui-pellet formulations have a relatively smooth surface structure which is an important factor for successful coating [73]. The coating of these pellets is an important consideration when making sustained and controlled release liqui-pellet formulation via polymeric coating. In addition, smooth surface and spherical shape of the liqui-pellet would make it easier to apply taste masking polymer [120–123], which may have benefits in pediatric formulations.

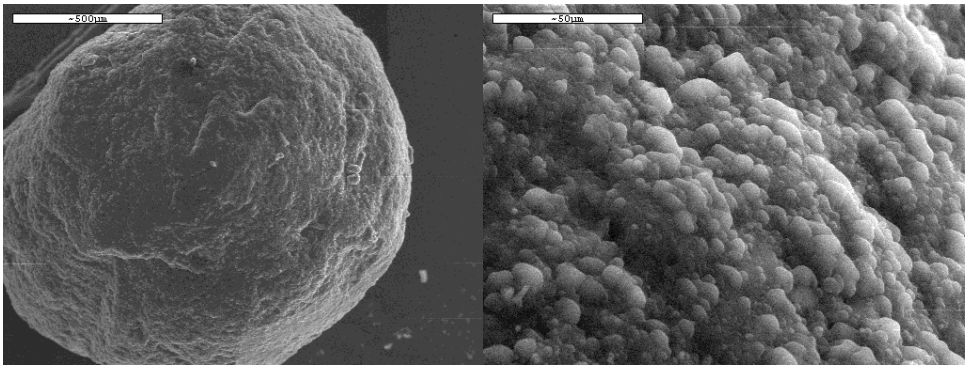




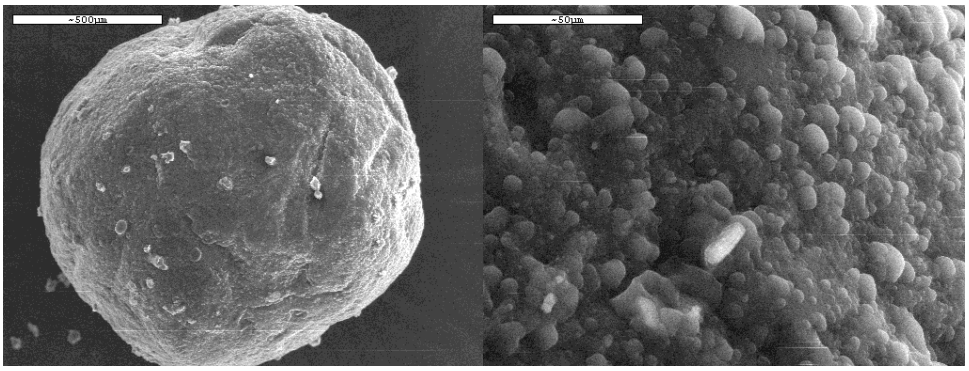
LP-2



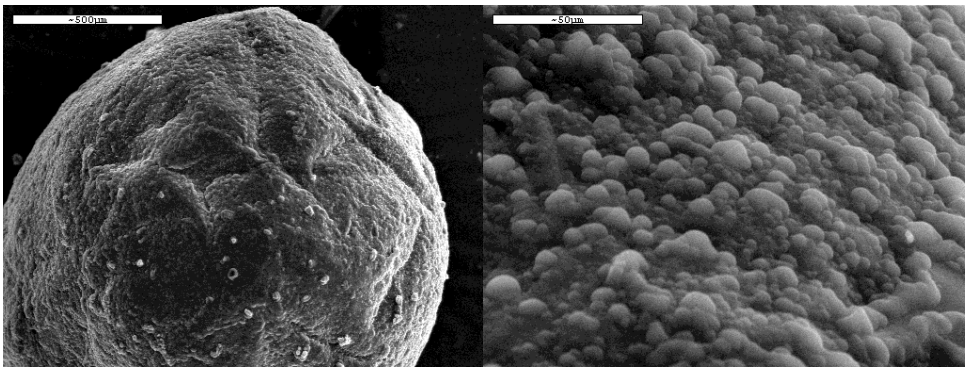
LP-3



LP-4



LP-8



LP-9

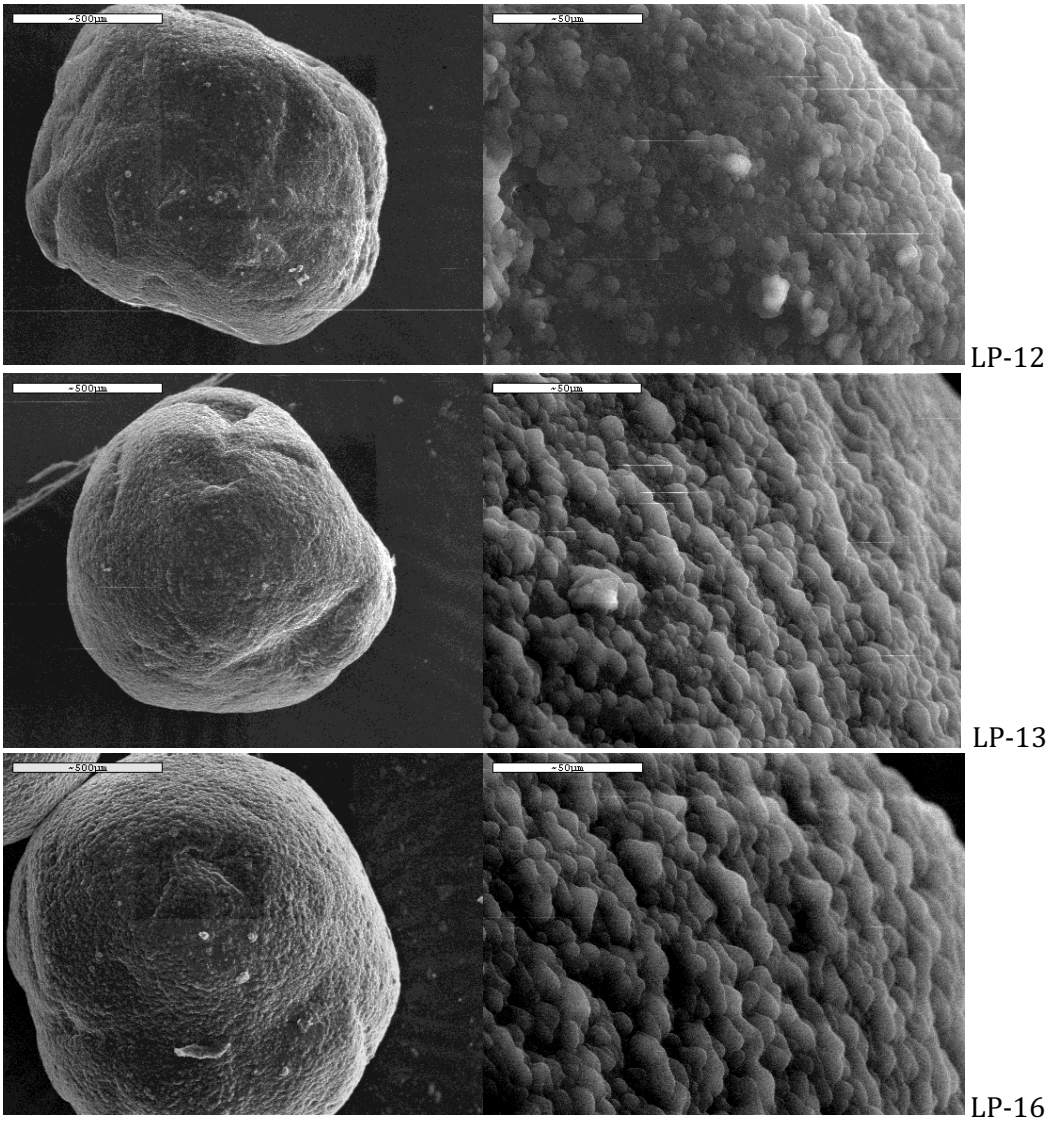


Figure 4.2. SEM images of physical mixture pellet and all successful formulation; I. x 80 magnification and II. x 800 magnification

4.4.7 Dissolution studies

The results from the dissolution studies on the different co-solvent show formulation with tween 80 having the fastest drug release rate, and tween 85 being the slowest (Figure 4.3). The results correspond well to the saturation solubility studies (Table 4.3) in which naproxen is most soluble in tween 80 and least soluble in tween 85.

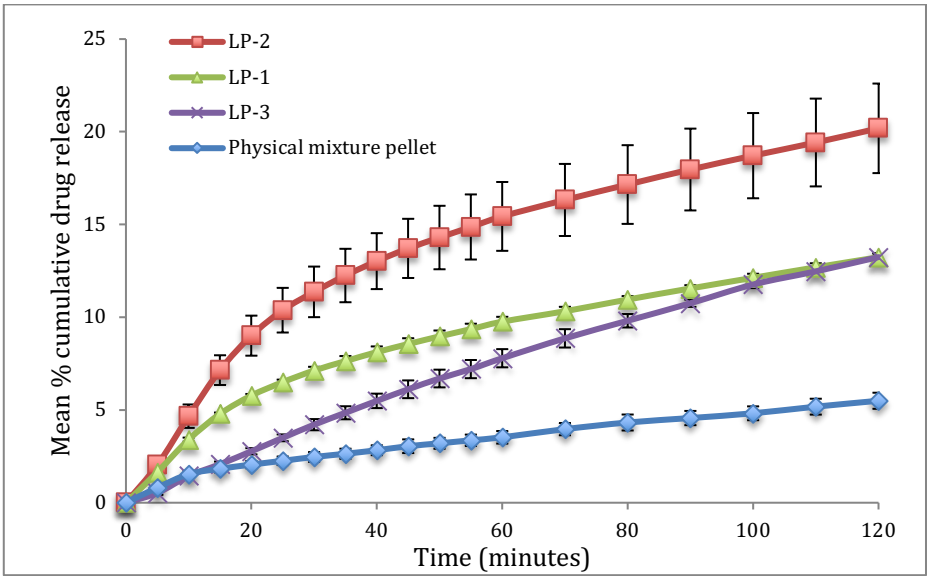


Figure 4.3. Dissolution profile of 25mg of naproxen liqui-pellet in capsule with different liquid vehicle (tween 20, tween 80 and tween 85) and physical mixture pellet (pH 1.2) (n = 3)

Results from Figure 4.4 show the dissolution profile of all successful formulations at acidic pH of 1.2, which mimics the pH in the stomach. It is clearly shown that the amount of water content and co-solvent concentration have a crucial effect on the drug release rate on liqui-pellet. In general, reduced water content increases drug release rate, and increased in tween 80 concentration increases drug release rate.

Using mathematical analysis, it can be seen that decreasing of water content has an impact on drug release rate. Formulation LP-8 (4.76ml of water per 20g of liqui-mass admixture) has an increase of ~4% of drug release after 2 h compared to LP-4 (8.57ml of water per 20g of liqui-mass admixture) with f_1=14.54 and f_2=79.07. Even though the f_1 and f_2 values do not show a significant difference, as the water content further decreases, it is possible to see influences of water content on dissolution rate (Figure 4.4). For example, when water content is further decreased from 8.57ml of water per 20g of liqui-mass admixture (LP-4) to 1.9ml of water per 20g of liqui-mass admixture (LP-12), the drug release rate increased by ~13% after 2 h with f_1=33.87 and f_2=55.76. This f_1 value shows that the drug dissolution rate of both of these formulations is different; LP-12 drug release rate is faster than LP-4. Furthermore, when water content is again further decreased from 8.57ml of water per 20g of liqui-mass admixture (LP-4) to 0.95ml of water per 20g of liqui-mass admixture (LP-16), the drug release rate increased by ~16% with f_1=39.22 and f_2=50.34. It is clear that f_1 value is increasing and f_2 value is decreasing with decreasing water content, indicating that the drug release rate is becoming more different with changes of water content. The f_1 of 39.22 signifies the difference in drug dissolution rate of LP-16

and LP-4. It should be pointed out that the f_1 value seems to show differences in dissolution profile but not the f_2 value. It is worth stating that there seems to be no well define basis for the equivalence threshold of f_2=50 [195].

The enhanced drug release rate with decreased water content in the formulation can be explained in terms of MCC aggregates subunit. Sarkar and Liew state that MCC is made up of aggregates of small subunits, which are held together via hydrogen bond [131]. In order for de-aggregation of MCC subunit to occur, these hydrogen bond must be broken [131]. By taking Sarkar and Liew statement into account, when less amount of water is used during the mixing stage, there is less polar granulating liquid to cause de-aggregation. This would lead to MCC with larger particle size. During granulation and extrusion process of this larger MCC particle size along with less moistening liquid results to less surface tension and van der Waal force; the wet mass and extrudate have reduced cohesive strength. Essentially this would produce pellets with weaker cohesive strength; thus, better propensity for disintegration, which results in faster drug release rate as disintegration is the drug release rate-limiting step for MCC-based liqui-pellet.

The effect of co-solvent content can be seen in formulation LP-12 (32% tween 80) and LP-13 (36% tween 80). Despite both having the same water content of 1.9ml per 20g of liqui-mass admixture, the difference of ~3.5% drug dissolution rate after 2 hours is due to the different concentration of tween 80. The f_1=26.75 and f_2=54.24; f_1 value indicates that LP-12 and LP-13 have different drug dissolution rate; LP-13 having faster drug release rate than LP-12. Hence, tween 80 content in formulation does influence the drug release rate. However, the significant f_1 and f_2 values are not seen for LP-8 (32% tween 80) and LP-9 (36% tween 80) where 4.76ml of water per 20g of liqui-mass admixture is used (f_1=7.64 and f_2=87.94). It seems that tween 80 has a greater impact on drug dissolution rate when the water content is lower.

The increase in drug release rate with increasing co-solvent is due to more drugs being solubilized or in a molecularly dispersed state, which results to an increased in surface area available for dissolution [3]. This can also be explained using the Noyes-Whitney equation, where surface area available for dissolution is directly proportional to dissolution rate [40]. In addition to the increase in the area available for dissolution, tween 80 reduces surface tension or cohesive force, which improves propensity for disintegration; thus, further enhancing drug release rate. A similar finding in terms of tween 80 improving disintegration of MCC-based pellet was observed by Chamsai and Sriamornsak [127].

When comparing formulation LP-4 with LP-13, the combined effect of decreased water content and increased tween 80 showed a significant increase in drug release by ~25% after 2 h with f_1=51.56 and f_2=40.10. In summary, water and tween 80 (or liquid vehicle) are crucial parameters influencing the drug release rate from liqui-pellet. Reduced water content and increased tween 80 improves drug release rate of liqui-pellet. At lower spectrum of water content, tween 80 have a more prominent effect on drug release rate than at higher spectrum of water content. Nonetheless, there are limits of how much water can be reduced and how much tween 80 can be increased. Table 4.2 shows which formulation failed to form liqui-pellets and at particular water content and tween 80 concentration, indicating the limits.

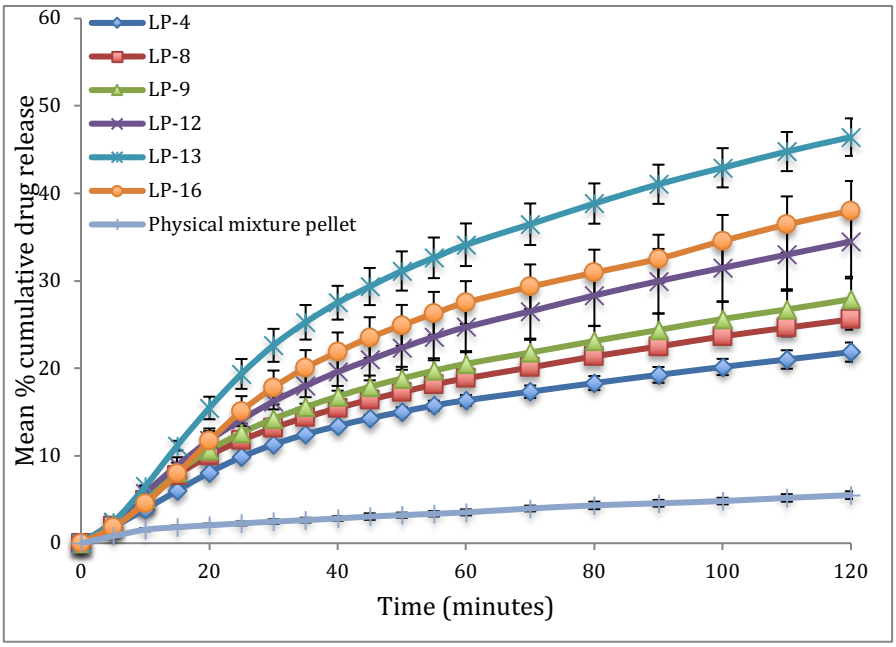


Figure 4.4. Dissolution profile of 25 mg of naproxen liqui-pellets in capsule with different water and co-solvent content (pH 1.2) (n = 3)

Dissolution studies at pH 7.4 (Figure 4.5) shows fast drug release rate to all successfully made liqui-pellet formulations, which plateau at ~20 min. The fast drug release rate is expected because the naproxen is a weakly acidic drug which is more soluble in alkaline pH than acidic pH environment.

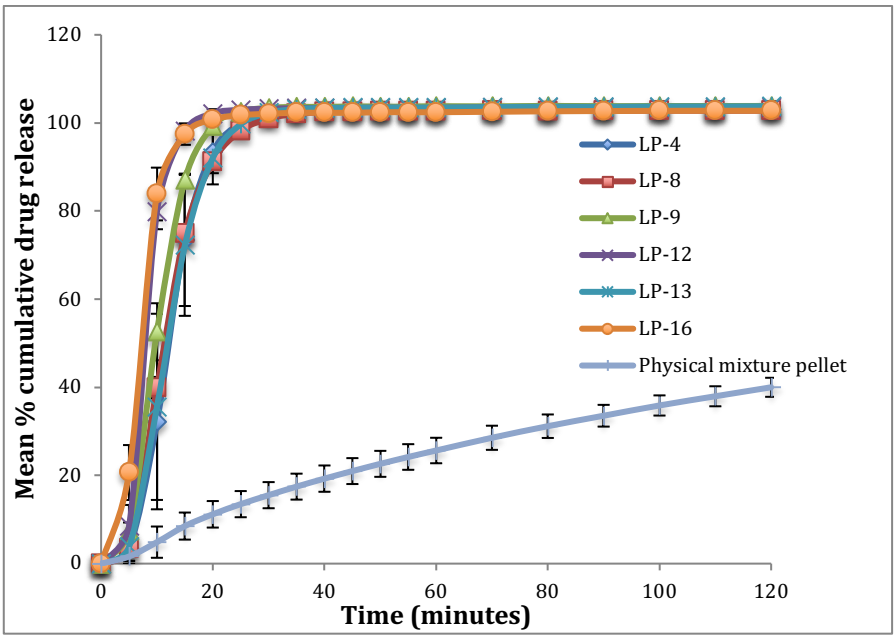


Figure 4.5. Dissolution profile of 25 mg of naproxen liqui-pellets in capsule with different water and co-solvent content (pH 7.4) (n = 3)

4.4.8 Kinetic model analysis of drug release

Table 4.6 shows that the two best formulations (LP-13 and LP-16) under pH 1.2 best fit the Higuchi's release kinetic model. Such results have been consistent in chapter 2 and 3 as well. Under pH 7.4, the release kinetic model for these two formulations are best described under zero order release model (Table 4.7).

Table 4.6. Release parameters of naproxen formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.952	0.955	0.993
LP-13	0.906	0.950	0.977
LP-16	0.912	0.945	0.975

Table 4.7. Release parameters of naproxen formulations at pH 7.4

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.966	0.988	0.980
LP-13	0.912	0.848	0.701
LP-16	0.935	0.918	0.847

4.4.9 XRPD studies

The diffractogram in Figure 4.6 shows that naproxen peak at 2θ values of 6.4, 12.28, 12.96, 16.32, 18.72, 19.88, 22.16, 23.40, 26.96 and 28.04, which is very similar to the naproxen peak from previous studies. The peak in physical mixture only corresponds to naproxen and avicel, indicating that there is no interaction between API and the excipients.

The relative crystallinity measured is in respect to AUC at 18.9 ◦ peak (Table 4.8). Note that the data does not represent the whole percentage of crystallinity of each formulation as only one crystalline peak is used for the analysis. The purpose of this study is to observe if the API crystallinity differs among each other; thus, using the AUC at 18.9 ◦ peak seems sufficient for the task. The results from integrated peak area method show that all the liqui-pellet formulations (LP-4, LP-8, LP-9, LP-12, LP-13 and LP-16) have reduced crystallinity in comparison to physical mixture pellet. This is expected as API are solubilized or held in molecularly dispersed state in liqui-pellet formulation; hence, the crystallinity of API is reduced as indicated in the results. The results from peak height method also show similar trend except for formulation LP-12, where LP-12 seems to be less crystalline than a physical mixture. It should be noted that there are quite a few methods of measuring crystallinity via XRPD. This reflects the intricacy in obtaining accurate results.

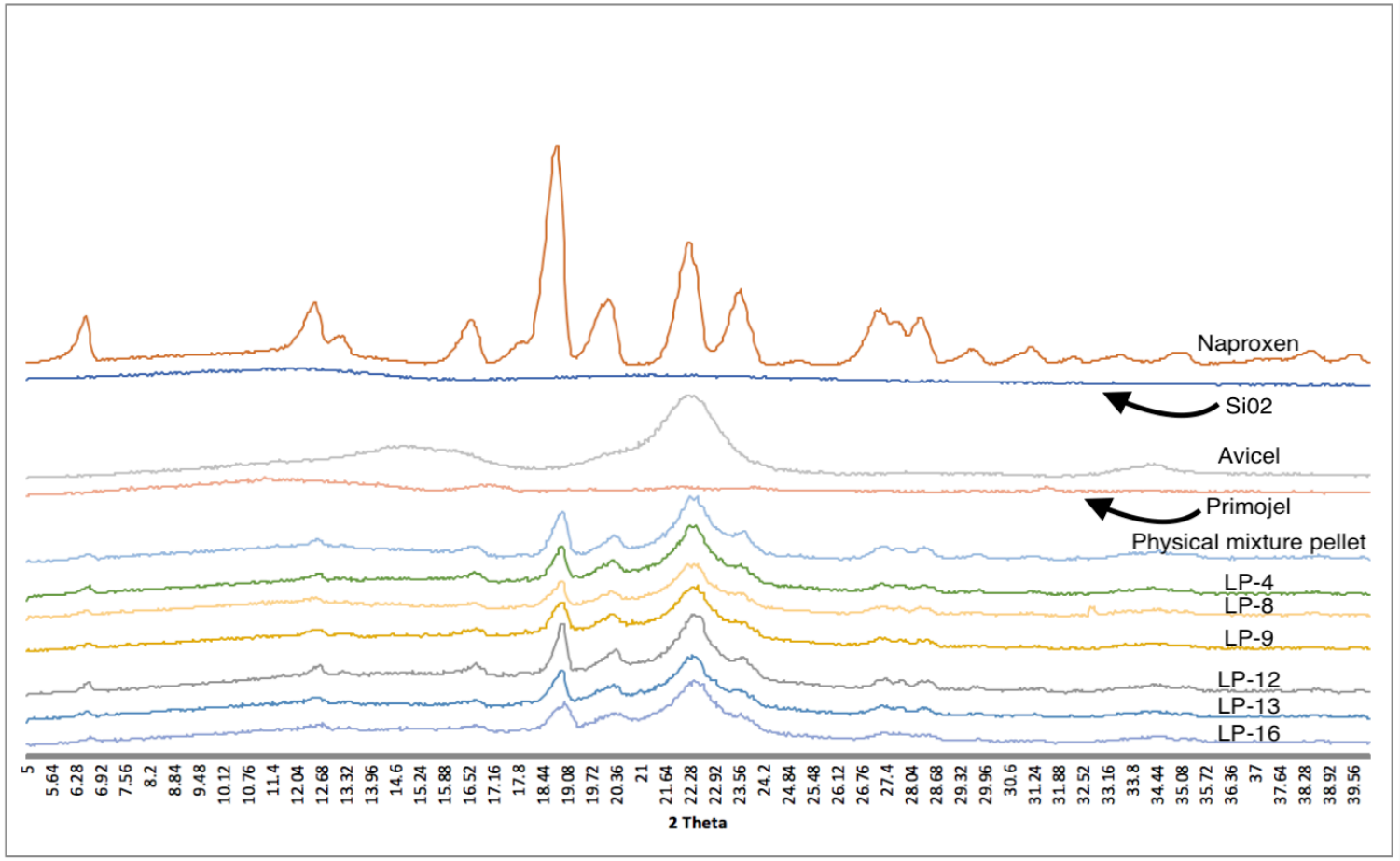


Figure 4.6. Diffraction peaks of naproxen, avicel, aerosil, primojel, physical mixture pellet and all of the successful formulation

Table 4.8. Relative crystallinity in respect to AUC at 18.9 ° peak among physical mixture pellet, LP-4, LP-8, LP-9, LP-12, LP-13 and LP-16

Formulation	% relative crystallinity via integrated peak area method	% relative crystallinity via peak height method
Physical mixture	12.92	20.27
LP-4	7.56	15.60
LP-8	4.83	11.80
LP-9	9.69	13.65
LP-12	11.54	22.17
LP-13	6.31	14.85
LP-16	6.21	12.18

4.4.10 DSC studies

The naproxen crystalline state is presented as a sharp endothermic peak (T_m = 160.45°C and ΔH = 64.23J/g), which is shown in Figure 4.7. The DSC traces of excipients are shown in Figure 4.8; they display broad peaks for avicel (T_m = 76.36°C and ΔH = 80.73J/g) and primojel (T_m = 79.76°C and ΔH = 257.79J/g), which could be due to water evaporation within these hygroscopic excipients. Similar observations are seen from the author's previous publications and in Tiong *et al* work [15]. As for aerosil, there is no definitive peak, which is to be expected from this amorphous material.

When comparing the naproxen and physical mixture pellet thermograms (Figure 4.7 and Figure 4.9), it can be seen that there is a small shift of peak from 160.45°C to 154.50°C respectively. This could be due to avicel influencing the overall peak of naproxen in the physical mixture pellets. Nonetheless, the crystalline state of naproxen is still present in the physical mixture pellet. This peak that indicates crystalline state of naproxen become less prominent in the rest of the successful liqui-pellet formulations, implying that the liqui-pellet formulations crystallinity is reduced. This reduced crystallinity is due to naproxen in solubilized or molecularly dispersed state, which is evident by the enhanced drug dissolution rate of liqui-pellet formulations compared to physical mixture pellet.

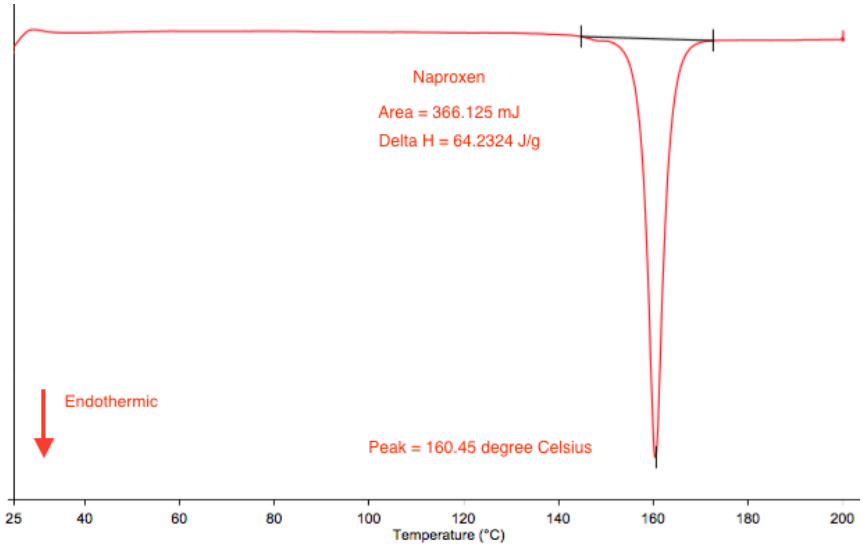


Figure 4.7. DSC thermograms of naproxen

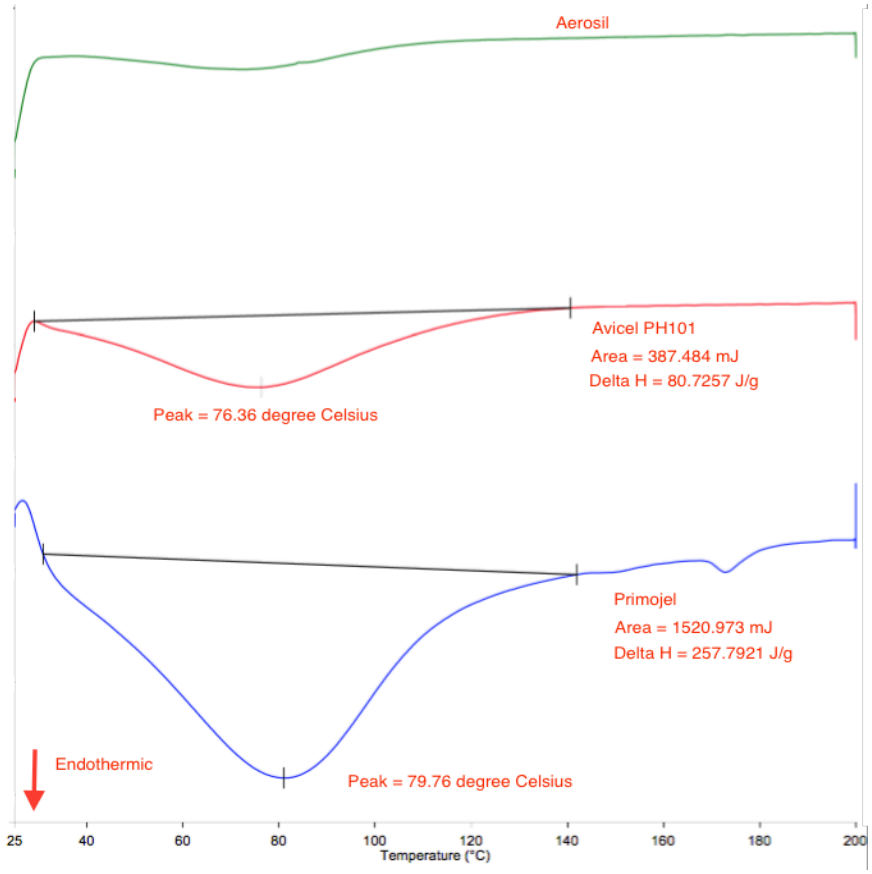


Figure 4.8. DSC thermograms of excipients (aerosil, avicel PH101 and primojel)

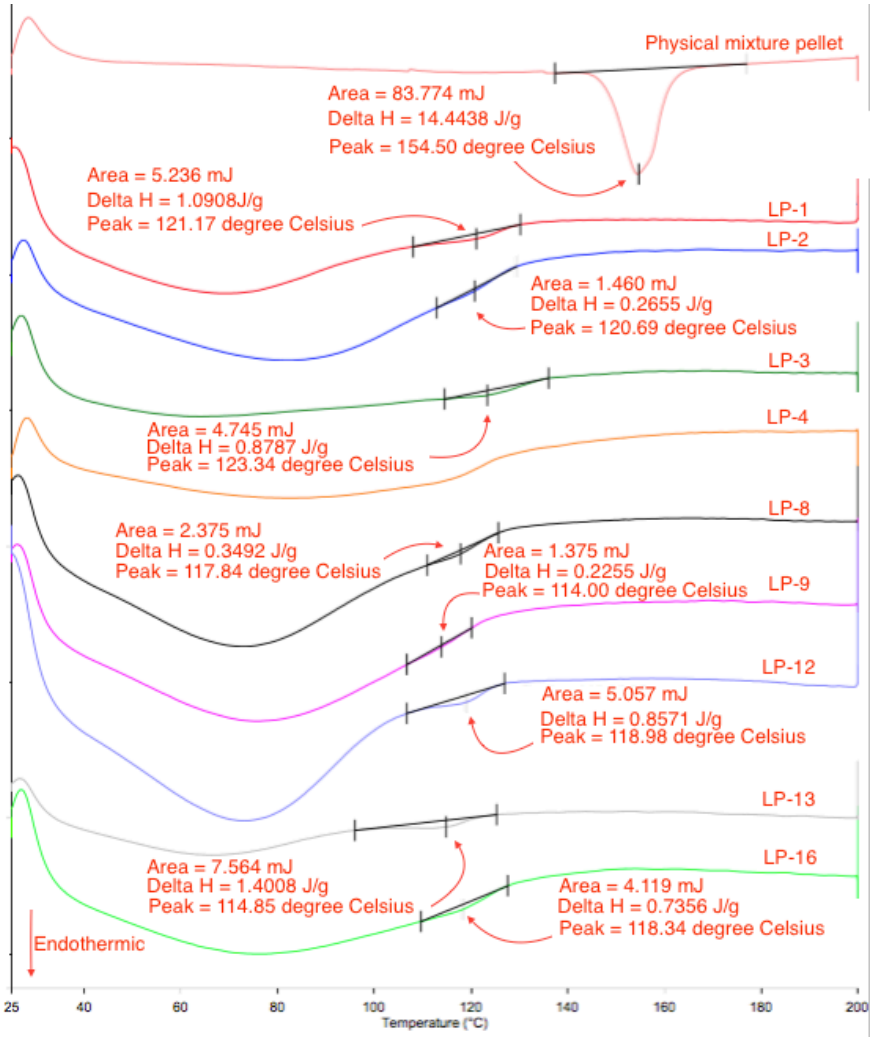


Figure 4.9. DSC thermograms of physical mixture and all successful formulation

4.5 Conclusion

The amount of water and tween 80 in liqui-pellet formulations are important parameters, which influences the drug release rate. This is seen when comparing formulation LP-4 with LP-13; the combined effect of decreased water content and increased tween 80 in LP-13 shows a significant increase drug release by ~25% after 2 h compared to LP-4. The reduction of water content effectively reduces cohesive strength of the liqui-pellet, improving its disintegrating properties; thus, enhancing drug release rate. The increase in tween 80 concentration increases the proportion of drug being in solubilized or molecularly dispersed state, which increases surface available for dissolution. Also, tween 80 reduces surface tension or cohesive force, improving propensity for disintegration; hence, enhancing drug release rate.

Despite reducing water and increasing tween 80 content, which results in faster drug release rate, there is a limit of how much water can be reduced and how much tween 80 can be increased. Outside of this limit, the liqui-pellet formulation is likely to fail due to agglomeration.

In conclusion, it can be seen that water and tween 80 (co-solvent) parameters can be optimized to further enhance drug release rate of liqui-pellet. The fact that liqui-pellet drug release rate can be modified or tailored by adjusting the mentioned parameters whilst maintaining excellent flow properties with a narrow size distribution makes it a very valuable oral drug delivery system.

Chapter 5: A novel application of effervescent agent in naproxen liqui-pellet for enhanced drug release

5.1 Abstract

Recently there has been an emerging novel oral dosage form called liqui-pellet. Liqui-pellet stems from combining the liquisolid concept with pelletization technology. Recent studies have shown liqui-pellet to be a promising next generation oral dosage form. Liqui-pellet maintains the inherent advantages of liquisolid formulation, whilst overcoming its drawbacks. This gives rise to a potentially commercially feasible and promising product. Since liqui-pellet is still in its infancy, an investigation to incorporate effervescent agent (sodium bicarbonate) into the liqui-pellet formulation was carried out for the first time to further explore its potential. Naproxen liqui-pellet formulations containing 5, 12, 22, 32 and 42% w/w of sodium bicarbonate were successfully produced and its physicochemical properties were investigated. Note that incorporation of such a large amount of functional excipient is impossible or near impossible in the classical liquisolid formulation due to the weight and size issue, particularly for high dose drug. The drug release data obtained shows sodium bicarbonate is an effective functional excipient to enhance drug release rate. In general, faster drug release rate was observed with increasing sodium bicarbonate concentration. However, there is a limit in this effect; above this limit the increasing sodium bicarbonate influence on drug dissolution rate lessen. Flowability test shows that all formulations have excellent, excellent-good or good flow property. All formulations show good robustness from friability test and narrow size distribution from particle size analysis. Overall, the studies demonstrate the flexibility of liqui-pellet in terms of formulation design, which in turn further support liqui-pellet potential as the next generation oral dosage form.

5.2 Introduction

The key introductory points are covered in chapter 2 section 2.2, 3.2 and 4.2; however, further background relating to this chapter will be covered here.

In general, liqui-pellet stems from combining the concept similar to powdered solution or liquisolid technology with pelletization technology. Liqui-pellet differs from liquisolid formulation in that it uses the more versatile liqui-mass system as oppose to liquisolid system. Liquisolid system by definition is powdered form of liquid medications formulated by transforming liquid lipophilic drugs, or drug suspensions or solutions of

water-insoluble drugs in an appropriate non-volatile liquid vehicle into dry looking nonadherent, free flowing and readily compressible powder admixtures by incorporating specific carriers and coating materials [5]. Notice that liquisolid system is limited to free-flowing powder admixture, whereas liqui-mass system encompasses wet none-flowable mass as well as free-flowing powder. In liqui-pellet, the admixture becomes free-flowing once it undergoes pelletization process. This fundamental difference gives greater potential and versatility to liqui-pellet compared to liquisolid formulation as more liquid vehicle and additional excipient can be incorporated into the formulation whilst still achieving commercially acceptable flowability and dosage form size. In addition, liqui-pellet is not restricted to mathematical equation developed by Spireas for liquisolid formulation because flow property is not a major issue as it is in liquisolid formulation.

Liqui-pellet has demonstrated excellent flow property whilst having a high amount of liquid vehicle in the formulation. Previous studies on liqui-pellet have proven it to be robust, capable of smooth surface (potential for application of coating technology) and have narrow size distribution. Furthermore, the method of manufacturing is simple, cost-effective, capable of green technology, capable of versatile modification (i.e. apply coating technology, incorporation of functional excipients and inherent versatility of being a multi-unit dosage form), potential for easy upscale of production and the excipients used are common and easily obtainable. Hence, liqui-pellet is considered commercially attractive for industrial production.

So far in studies by the author of this thesis, microcrystalline cellulose is the only carrier material used for making liqui-pellet. This is because extrusion and spheronization is the choice of method used in the pelletization process. In extrusion and spheronization technique, MCC is the gold standard carrier, which is explained in the previous introduction section. However, it should be noted that liqui-pellet carrier composition is not restricted to MCC only.

In the investigation, sodium bicarbonate ($NaHCO_3$) will be applied to naproxen liqui-pellet formulations for the first time as a functional excipient to enhance drug release rate. Sodium bicarbonate is considered an effervescent agent when in contact with acid [207]. Its function is to enhance liqui-pellet drug release rate through promoting disintegration and disruption of the diffusion boundary layer when in contact with the acidic gastric fluid [207]. Increased in drug dissolution rate via promoting disintegration and disruption of diffusion boundary layer diffusion layer can be explained using Noye's Whitney equation [40].

According to the equation, enhanced disintegration increases surface area for drug release, which is proportional to dissolution rate; and thickness of the stagnant layer is inversely proportional to dissolution rate [40]. Thus, the greater surface area from disintegration and reduce thickness of the stagnant layer, due to the formation of CO_2 gas, results in an increase in drug release rate [210]. In addition to enhanced dissolution rate, $NaHCO_3$ is able to reduce gastric irritation of weakly acidic drug and is generally regarded as an essentially non-toxic and non-irritant material [207].

5.3 Materials and methods

5.3.1 Materials

Naproxen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel), (DFE Pharma, Goch, Germany), sodium bicarbonate, (Acros, New Jersey, USA); synthetic magnesium alumino-metasilicate (Neusilin US2), (Fuji Chemicals, Japan) and polysorbate 80 (tween 80), (Acros, Netherlands). All other reagents and solvent were of analytical grades.

5.3.2 Preparation of naproxen effervescent liqui-pellet

The liquid medication was prepared by mixing naproxen with tween 80 using the pestle and mortar method. Note that tween 80 was chosen as the co-solvent (also known as liquid vehicle) as it was the most suitable co-solvent for naproxen according to the author's previous studies (chapter 2 and chapter 4). The liquid medication was then incorporated into avicel PH-101 (carrier) along with specified amount of $NaHCO_3$ (effervescent agent) and primojel (superdisintegrant), which was mixed for 2 min at a constant rate of 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). Notice that the superdisintegrant was added intragranularly as previous studies showed this was better at promoting disintegration than extragranular incorporation. A specified amount of deionized water, which was the granulating liquid, was then incorporated into the admixture bit by bit to achieve reasonable plastic property for extrusion (Caleva Multitab, Caleva Process Solutions Ltd, UK). The duration of mixing of the admixture with granulating liquid was 5 min. Aerosil 300 (coating material) was then added into the admixture and further mixed for 5 min before extrusion. Once the sample was extruded, the extrudate was spheronized at an

almost constant rotation at 4000rpm (decrease to 2000 rpm if agglomeration seems likely). The spheronization time varied depending on the extrudate's plastic property to avoid agglomeration. The spheroids were then placed in an oven under a constant temperature of 40°C overnight to remove water content. Table 5.1 shows the physical mixture pellet and liqui-pellet formulations with different concentration of $NaHCO_3$. Apart from the different concentration of $NaHCO_3$ and water content, all other compositions were kept constant for all formulations, and the carrier to coating ratio was kept constant at 20:1 respectively.

Table 5.1. Key formulation characteristics of the investigate liqui-pellet in capsule

Formulation	Amount of sodium bicarbonate (%w/w)	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Mass of carrier (mg)	Mass of coating material (mg)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet		12	58.15	2.90	90.58
F-1	5	5.59	62.54	3.15	141.20
F-2	12	5.18	62.54	3.15	152.20
F-3	22	4.59	62.54	3.15	172.90
F-4	32	5.60	62.54	3.15	197.20
F-5	42	4.78	62.54	3.15	231.10

Note all liqui-pellet formulation contains 25mg of naproxen; primojel 4.4 %w/w; liquid vehicle 27.96% w/w and carrier to coating material ratio is 20:1 respectively. Note the concentration of primojel and liquid vehicle were calculated using total mass of admixture of API and excipients excluding $NaHCO_3$

5.3.3 Flowability test on formulated effervescent liqui-pellet

Carried out in the same manner as described in chapter 1 section 2.3.5.

5.3.4 Particle size analysis (sieve method)

Carried out in the same manner as described in chapter 2 section 2.3.7.

5.3.5 Friability test on formulated effervescent liqui-pellet

Carried out in the same manner as described in chapter 2 section 2.3.6.

5.3.6 In-vitro drug release test

Carried out in the same manner as described in chapter 2 section 2.3.10.

5.3.7 Kinetic model analysis of drug release

Carried out in the same manner as described in chapter 2 section 2.3.11.

5.3.8 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.3.14.

5.4 Results and discussion

5.4.1 Preparation of naproxen effervescent liqui-pellet

All formulations were successfully made into pellet form. It is observed that liqui-pellet formulations F-4 and F-5 required more granulating liquid than the other formulations to produce liqui-pellet. This is because these two formulations have the two highest amount of $NaHCO_3$ content, consequently larger amount of total powder admixture; thus, more granulating liquid is required to obtain reasonable plastic property of wet mass for extrusion. The plastic property is essential to allow shaping and retaining desired shape of extrudate. This plastic property is primarily due to moisture in the powder admixture which has been subjected to much research [95–100].

The fact that liqui-pellet can contain 42% of $NaHCO_3$ in the dosage form total weight is very interesting. Such a large amount of addition of functional excipient whilst maintaining good dosage size and weight for swallowing would have been difficult or impossible for liquisolid formulation. This is because liquisolid formulation requires a large amount of carrier and coating material when L_f is high as 1. Yet liqui-pellet formulation F-5 contain 42% of $NaHCO_3$ and the dosage weight is only 231mg; thus, displaying the promising commercial potential of liqui-pellet.

5.4.2 Flowability studies

All formulations show excellent, excellent-good or good flow properties (Table 5.2). Similar results are also observed in previous flowability studies in previous chapters, verifying that flowability is not a major issue for liqui-pellet as it is for liquisolid formulation.

Table 5.2. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulations (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	10.72 ± 0.33	19.96 ±1.43	11.11 ± 0.62	Excellent flowability	Good flowability
F-1	6.77 ± 0.49	28.95 ± 1.62	10.82 ± 1.33	Excellent flowability	Excellent-good flowability
F-2	7.55 ± 0.21	26.98 ± 0.37	9.85 ± 0.00	Excellent flowability	Excellent flowability
F-3	8.35 ± 0.25	25.37 ± 0.68	11.32 ± 0.65	Excellent flowability	Good flowability
F-4	8.10 ± 0.17	26.71 ± 0.20	10.23 ± 0.00	Excellent flowability	Excellent-good flowability
F-5	8.08 ± 0.19	27.84 ± 0.05	10.01 ± 0.00	Excellent flowability	Excellent-good flowability

[a] For the composition of each formulation refer to Table 5.1
[b] SD, standard deviation from the mean

5.4.3 Particle size studies

All liqui-pellet have narrow size distribution which falls under 500 μm in size (Figure 5.1). This suggests that increasing the $NaHCO_3$ content in liqui-pellet formulation does not seem to have an effect on its size. The small liqui-pellet size would allow fast gastric emptying similar to liquid [115], which would expose the weakly acidic naproxen to the more alkaline small intestine quicker. Note that weakly acidic drug tends to be more soluble in alkaline condition; hence, dissolution rate can be increased.

The narrow size distribution of liqui-pellet formulation is ideal for manufacturing, particularly in an industrial scale. This is due to reduced risk of failing uniformity of content quality control test. The probability of none uniform filling of capsule due to liqui-pellet size variation is reduced.

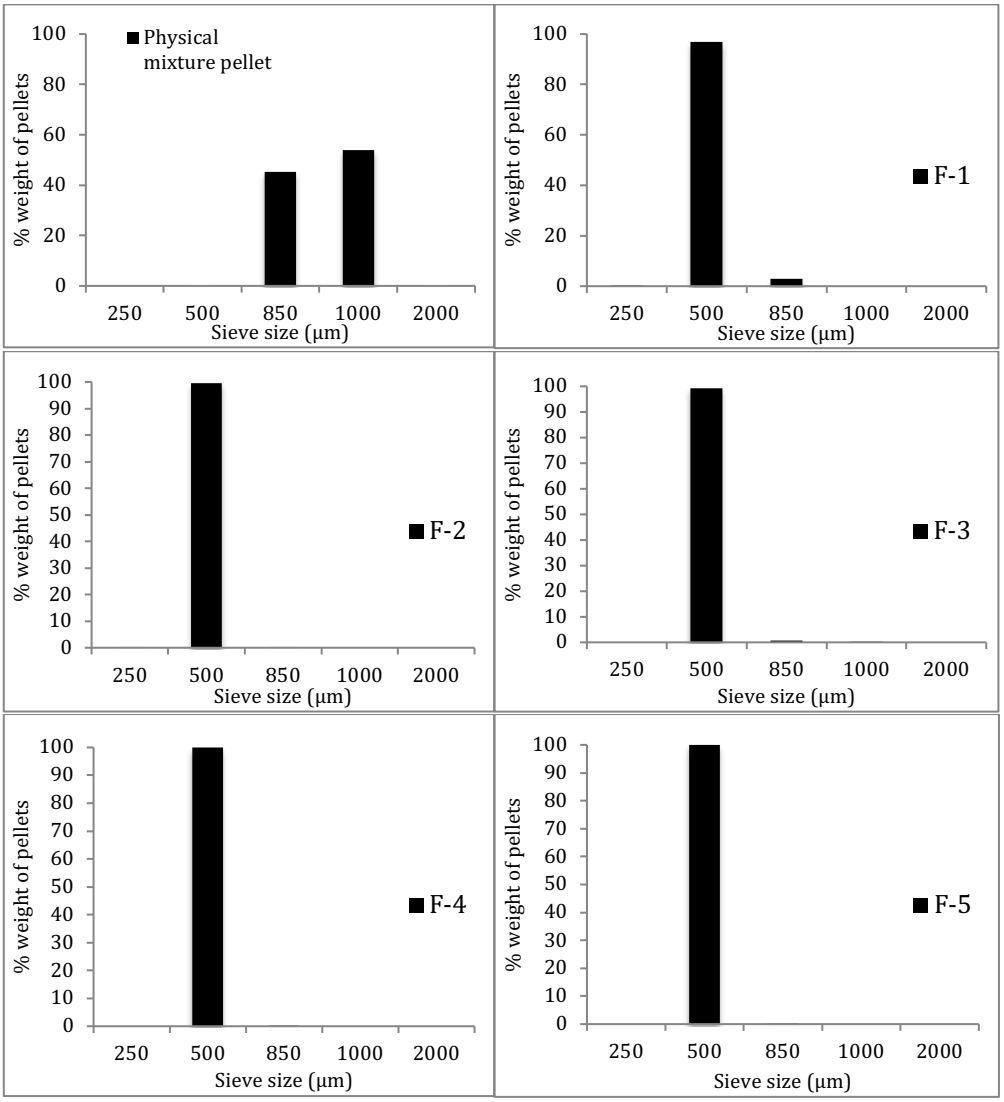


Figure 5.1. Graphs showing particle size distribution of all formulations via sieve method

5.4.4 Friability studies

The friability test results (Table 5.3) show that all formulations display a good level of robustness. All formulations have less than 1% weight loss after being treated in the friabilator. This is considered acceptable weight loss for tablets under USP standard. Note that at current time of the investigation, there is no USP standard for friability test for pellets, thus the tablet standard is adopted.

The liqui-pellet in this study uses MCC as the carrier material, which has strong bonding within its structure when water is added. This and along with the plastic property, which tween 80 contributes to liqui-pellet, makes liqui-pellet resistant to friability. The resistance to friability is ideal in terms of commercial production.

Table 5.3. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.14
F-1	0.21
F-2	0.05
F-3	0.24
F-4	0.13
F-5	0.14

5.4.5 Dissolution studies

Results from the dissolution studies at pH 1.2 (Figure 5.2) show marked increase of drug release rate for formulation F-4 ($NaHCO_3$ 32% w/w) and F-5 ($NaHCO_3$ 42% w/w) in comparison to physical mixture pellet. The cumulative drug dissolution rate of F-4 after 2 h is ~64% higher than the physical mixture pellet and F-5 is ~71% higher than physical mixture pellet. This shows that $NaHCO_3$ is an effective functional excipient in naproxen liqui-pellet for enhanced drug release.

The dissolution profiles in Figure 5.2 show a general trend that an increase in $NaHCO_3$ concentration increases drug release rate quite markedly, which is mathematically supported by the difference and similarity factor in Table 5.4. When comparing the dissolution profile each time $NaHCO_3$ concentration is increased, the f_1 and f_2 results show a significant difference in the dissolution profile due to marked increase in drug release rate. However, formulation F-4 (32% $NaHCO_3$) and F-5 (42% $NaHCO_3$) did not show a significant difference in dissolution profile according to f_1 (7.59) and f_2 (63.76) value despite F-5 containing 10% more $NaHCO_3$ than F-4. This suggests that there is a limit of $NaHCO_3$ concentration that can cause noticeable improvement of drug release rate; above this limit, $NaHCO_3$ have less influence on liqui-pellet drug dissolution rate. Even though F-5 show slightly higher dissolution rate than F-4, the difference is not significant according to f_1 and f_2; hence, this 10% increase in $NaHCO_3$ does not seem worthwhile and 32% $NaHCO_3$ seems sufficient for drug release enhancement.

When comparing the drug dissolution profile of naproxen effervescent liqui-pellet in this study to previous studies on naproxen liqui-pellet, it can be seen how incorporation of $NaHCO_3$ can noticeably improve drug release rate, particularly for F-4 and F-5, where its

drug release rate is more superior than earlier naproxen liqui-pellet formulations. Although F-4 and F-5 have the fastest drug release rate in acidic pH, it is noteworthy to point out that F-4 and F-5 formulation have yet to be further optimized by taking parameters such as water content and co-solvent content into account. Previous studies by the author have already shown how these parameters can significantly affect the drug release rate. Hence, despite already obtaining an impressive enhancement of drug release rate, the potential of effervescent liqui-pellet is yet to be realized.

The $NaHCO_3$ has three key mechanisms that promotes drug release in naproxen liqui-pellet. It is well known that $NaHCO_3$ produces CO_2 gas when in contact with the acidic environment such as the stomach [207,211]. The first drug release enhancement mechanism is due to promotion of disintegration of liqui-pellet owed to formation of CO_2 gas. Since naproxen liqui-pellet in this study uses MCC as a carrier, the MCC is known to form virtually none disintegrating pellet via extrusion and spheronization technique due to strong bond within its structure [80,94,127,203,212–214]. Hence, the CO_2 gas serves as a mechanical force within the liqui-pellet to aid disintegration, which consequently results to larger surface area for dissolution.

The second mechanism of how $NaHCO_3$ increase dissolution rate is the disruption of the diffusion boundary layer due to CO_2 gas formation. By using the Noye's Whitney equation [40], it can be seen that the thickness of the dissolution boundary layer is inversely proportional to dissolution rate [40].

The third mechanism is that $NaHCO_3$ is an alkalizing agent [207]. Since naproxen is a weakly acidic drug, $NaHCO_3$ can make the pH at the microenvironment more alkaline; thus, improving naproxen solubility which in turn improves drug release rate.

The dissolution test on all formulations was also tested under pH 7.4 (Figure 5.3). Data shows that all formulations' dissolution profile rapidly nearing 100% after 20 min, which is expected as naproxen is very soluble at pH 7.4.

Overall, this study proves that liqui-pellet is indeed a versatile formulation with the ability for flexible modification such as the addition of effervescent functional excipient. The addition of functional excipient has proven to be effective in the enhancement of drug release rate as shown in the results. Liqui-pellet is capable of such addition of functional excipient because it is capable of achieving high liquid load factor or high amount of liquid

vehicle whilst maintaining excellent/good flow properties. This means there is no need to increase the amount of carrier and coating material to achieve acceptable flow properties, which in turns gives the option for the addition of functional excipients without making the dosage form too heavy and big for swallowing.

To appreciate the capability of additional functional excipient/s, it is noteworthy to point out that such flexibility in formulation design is difficult or impossible to achieve using liquisolid technology. This is because flowability is a major issue in liquisolid formulation and in order to achieve high liquid load factor whilst maintaining reasonable flow property, the carrier and coating material need to be increased, which more than often results to final dosage form being too bulky and heavy for real life use, particularly for high dose drug.

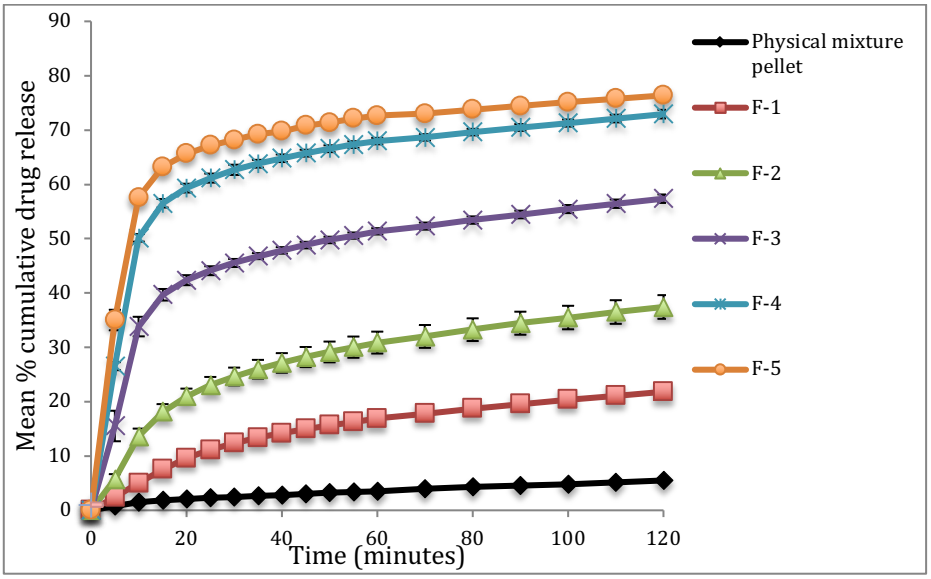


Figure 5.2. Dissolution profile of physical mixture pellet in capsule and all liqui-pellet formulations in capsule at pH 1.2. Each formulation contains 25mg of naproxen (n = 3)

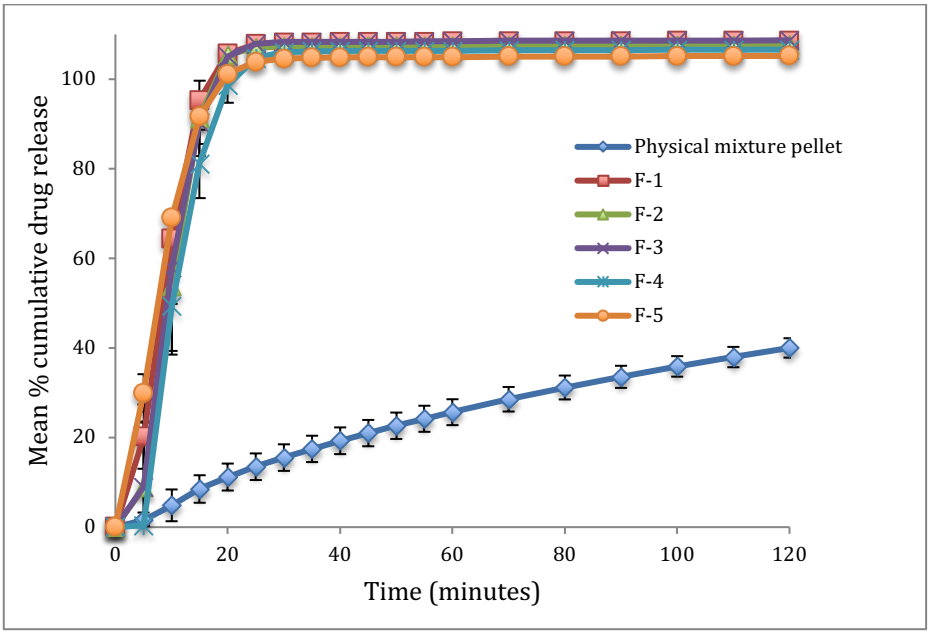


Figure 5.3. Dissolution profile of physical mixture pellet in capsule and all liqui-pellet formulations in capsule at pH 7.4. Each formulation contains 25mg of naproxen (n = 3)

Table 5.4. Difference factor (f_1) and similarity factor (f_2) of the compared formulations

Formulation in comparison	f_1	f_2
Physical mixture & F-1	77.59	46.74
F-1 & F-2	88.22	44.82
F-2 & F-3	42.46	35.40
F-3 & F-4	34.35	39.97
F-4 & F-5	7.59	63.76

5.4.6 Kinetic model analysis of drug release

Table 5.5 shows liqui-pellet formulations with different concentration of effervescent agent under pH 1.2, follow either Higuchi or first order drug release kinetic model. The concentration of effervescent agent may influence the release kinetic model however, there is no clear trend observed. Under pH 7.4 (Table 5.6), all liqui-pellet formulation is best described by zero order kinetic model, where drug release is independent from concentration. zero order release kinetic is particularly useful in sustained release formualtion which may be vital in future work on sustain release liqui-pellet formulation.

Table 5.5. Release parameters of naproxen formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.952	0.955	0.993
F-1	0.861	0.885	0.978
F-2	0.991	0.992	0.921
F-3	0.964	0.975	0.952
F-4	0.726	0.809	0.921
F-5	0.912	0.960	0.988

Table 5.6. Release parameters of naproxen formulations at pH 7.4

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.966	0.988	0.980
LP-1	0.982	0.857	0.855
LP-2	0.944	0.836	0.761
LP-3	0.945	0.865	0.772
LP-4	0.941	0.817	0.789
LP-5	0.991	0.937	0.929

5.5 Conclusion

The studies have proven that it is possible to incorporate effervescent agent into liqui-pellet formulation, whilst achieving excellent or good flowability and yet maintaining the overall dosage form small and light enough for swallowing. With 42% w/w $NaHCO_3$ in the total liqui-pellet mass, the total liqui-pellet weight in the capsule was only 231mg. This would have been very difficult or near impossible to achieve with liquisolid technology, particularly in high dose drug, where high liquid load factor would result to heavy and bulky formulation due to increase carrier and coating material being required, let alone the addition of functional excipient/s.

The dissolution test results showed a remarkable increase in drug release rate with $NaHCO_3$. When $NaHCO_3$ concentration increase, so does the drug release rate. However, there is a limit of how much $NaHCO_3$ can be increased before its influence on drug release rate lessens. Thus, it is prudent to know this limit in order to balance the weight of dosage form and drug release performance into an ideal dosage form.

The data from this investigation verifies that effervescent liqui-pellet can achieve good robustness and excellent or good flow properties with narrow size distribution.

Overall, liqui-pellet shows promising potential as a commercially feasible next generation oral dosage form with capability for versatile formulation manipulation such as the addition of functional excipients.

Chapter 6: Producing exploding naproxen liqui-pellet for rapid drug release using optimized formulation with effervescent agent and the large specific surface area carrier, neusilin US2

6.1 Abstract

Liqui-pellet is a novel oral dosage form and has been showing promising advantages in terms of commercial production and formulation manipulation. This study attempts to further explore the potential of liqui-pellet enhanced drug release formulation by optimizing naproxen effervescent liqui-pellet formulation. Parameters include tween 80 concentration, water content and present/absent of neusilin US2, which is part of a binary carrier. It was found that the success of liqui-pellet production is determined by the amount of tween 80 and water used; above the upper limit, agglomeration occurs and formulation fails. Physicochemical analysis showed the liqui-pellet formulation generally have excellent flow property, narrow size distribution and is robust enough to pass friability test. The key finding in the investigation is that the liqui-pellet is capable of remarkable drug release rate; 100% drug release was achieved within 20 min at pH 1.2, where naproxen is known to be practically insoluble in such pH. This display the potential of liqui-pellet enhanced release formulation. Furthermore, the accelerated stability test showed acceptable drug stability and the dissolution behaviour.

6.2 Introduction

The key introductory points are covered in chapter 2 section 2.2, 3.2, 4.2 and 5.2; however, further background relating to this chapter will be covered here.

In the author's previous studies, liqui-pellet demonstrated that high liquid load factor whilst maintaining excellent flow property and achieving dosage form with size and weight that is reasonable for swallowing is possible. This however, is a challenge to achieve in liquisolid technology. This is the key reason why liqui-pellet is claimed to be commercially feasible, unlike liquisolid formulation. Also, since high liquid load factor is not a major issue in liqui-pellet as it is for liquisolid formulation, it is possible to reduce the carrier and coating material required; thus, giving the potential for the addition of functional excipients without making the dosage form too heavy and bulky for swallowing. This is demonstrated in the author's previous studies (chapter 5) where sodium

bicarbonate ($NaHCO_3$) of up to 42% w/w, is added into liqui-pellet formulation to enhance drug release rate via producing carbon dioxide, which promotes disintegration and disrupts the diffusion stagnant layer [207], whilst maintaining good dosage form size for swallowing. Furthermore, $NaHCO_3$ is an alkalizing agent, which may promote weakly acidic drug solubility, such as naproxen, in the microenvironment, hence improving the drug bioavailability.

The investigation in this study is an extension of the previous work in chapter 5. In the previous work, $NaHCO_3$, which is an effervescent agent, was incorporated into the liqui-pellet formulation to increase drug release rate. The effervescent agent promotes disintegration of the MCC-based liqui-pellet. The reason why promotion of disintegration is targeted is due to MCC-based pellet being virtually non-disintegrating due to strong bonding within its structure [127,203].

In this study, an attempt is made to further improve the drug release rate by taking into account of various parameters investigated from previous work, which include: using suitable amount of effervescent agent where dosage form size and performance is taken into account; increase of co-solvent content to maximum limit to increase API in solubilize state and reducing water content to minimum limit in order to reduce pellet bonding force, which will promote pellet disintegration. In addition, neusilin US2, which is a material with large specific surface area (SSA), is used in combination with MCC as a carrier material to see its effect on liqui-pellet physicochemical properties.

6.3 Materials and methods

6.3.1 Materials

Naproxen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel), (DFE Pharma, Goch, Germany), sodium bicarbonate, (Acros, New Jersey, USA); synthetic magnesium alumino-metasilicate (Neusilin US2), (Fuji Chemicals, Japan) and polysorbate 80 (tween 80), (Acros, Netherlands). All other reagents and solvent were of analytical grades.

6.3.2 Preparation of naproxen effervescent liqui-pellet

All liqui-pellet formulations were prepared in a similar manner except for the variation in parameters such as carrier composition; tween 80 concentration, water content and liquid load factor (Table 6.1). The liquid medication was prepared by adding a specified amount of naproxen (API) and tween 80 (liquid vehicle) into a mortar then mixing it with a pestle. The liquid medication was then incorporated into specified carrier material (avicel PH101 or a binary mixture of avicel PH101 and neusilin US2) where 32% w/w $NaHCO_3$ (effervescent agent) and specified amount of primojel (superdisintegrant) was added. Note that 32% w/w $NaHCO_3$ was used as previous studies showed this was the most suitable concentration when considering dosage form weight and drug releasing performance. The admixture was mixed 2 min at a constant rate of 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). The primojel was added intragranularly as previous studies showed this was better at promoting disintegration than extragranular incorporation. A specified amount of granulating liquid (deionized water) was added bit by bit to achieve reasonable plastic property for extrusion (Caleva Multitab, Caleva Process Solutions Ltd, UK). The duration of mixing of the admixture with granulating liquid was 5 min. Aerosil 300 (coating material) was then added into the admixture and further mixed for 5 min before extrusion. Once the sample was extruded, the extrudate was spheronized at an almost constant rotation at 4000rpm (decrease to 2000 rpm if agglomeration seems likely). The spheronization time varied depending on the extrudate's plastic property to avoid agglomeration. The pellets were then placed in an oven under a constant temperature of 40^{o}C overnight to remove water content.

Also note that physical mixture pellet was prepared in a similar manner as above including 32% w/w $NaHCO_3$, but without liquid vehicle incorporated. All formulations' carrier to coating material ration were kept constant at 20:1 respectively.

Table 6.1. Key characteristics of the investigated formulation

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Liquid vehicle concentration (% w/w)	Liquid load factor	Promojel (mg)
Physical mixture pellet	7.00			5.91
F-1	5.60	19	1	5.92
F-2	3.21	21	1.14	5.91
F-3	3.12	23	1.23	7.69
F-4	1.60	27	1.65	5.92
F-5	6.40	19	1	5.92
F-6	3.20	19	1	5.92
F-7	3.20	23	1.23	5.92

Formulation	Carrier type	Mass of carrier (mg)	Mass of coating material (mg)	Successfully spheronized into pellet? (Yes/ No)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet	100% avicel PH101	58.06	2.90	Yes	135.25
F-1	100% avicel PH101	62.54	3.15	Yes	197.20
F-2	100% avicel PH101	58.06	2.90	Yes	196.41
F-3	100% avicel PH101	55.06	2.75	Yes	197.20
F-4	100% avicel PH101	47.55	2.37	No	197.20
F-5	100% avicel PH101	62.54	3.15	No	197.20
F-6	50% avicel PH101 & 50% neusilin US2	62.54	3.15	Yes	197.20
F-7	50% avicel PH101 & 50% neusilin US2	55.06	2.75	Yes	197.20

Note all formulation contain 25mg of naproxen, 32% w/w $NaHCO_3$ and the carrier to coating material is at a ratio of 20:1

6.3.3 Flowability test on formulation

Carried out in the same manner as described in chapter 1 section 2.3.5.

6.3.4 Particle size analysis (sieve method)

Carried out in the same manner as described in chapter 2 section 2.3.7.

6.3.5 Friability test on formulated pellet

Carried out in the same manner as described in chapter 2 section 2.3.6.

6.3.6 In-vitro drug release test

Carried out in the same manner as described in chapter 2 section 2.3.10.

6.3.7 Accelerated stability test

Accelerated stability test were conducted on formulation F-6 and F-7, which had the fastest drug dissolution rate. Storage condition was set at 40 °C with relative humidity of 75% for a period of 3 months. Drug dissolution profiles were recorded each month for 3 months.

6.3.8 Kinetic model analysis of drug release

Carried out in the same manner as described in chapter 2 section 2.3.11.

6.3.9 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.3.14.

6.4 Results and discussion

6.4.1 Preparation of naproxen effervescent liqui-pellet

All liqui-pellet formulations were successfully produced except for F-4 and F-5. Formulation F-4 has the highest amount of tween 80 of 27% w/w and F-5 has the highest amount of water of 6.4ml per 20g of liqui-mass composition. Tween 80 and water content increases the extrudate's plastic property [6]. Formulations F-4 and F-5 extrudate's plastic property increased beyond the acceptable limit, causing agglomeration during spheronization process, hence, leading to formulation failure. This reflects the importance of understanding the ideal extrudate's plastic property and the parameters that affect it. It is already stated by the author's previous studies that water and co-solvent content have a major influence in extrudate's plastic property, which in turns determine the success of liqui-pellet production.

6.4.2 Flowability studies

According to flowability studies (Table 6.2), all formulations obtain excellent, excellent to good or good flow properties. This is expected because previous studies on liqui-pellet have

consistently shown flowability is not an issue in this technology unlike in liquisolid technology. The smooth flow of liqui-pellet is one of the key features that makes it a suitable commercial product. Liqui-pellet can achieve high liquid load factor and yet have excellent flow properties without requiring considerable addition of carrier and coating materials. Such a feature allows liqui-pellet to outperform liquisolid formulation in terms of enhanced drug dissolution rate, flow properties and versatility in formulation modification such as addition of functional excipients.

Table 6.2. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulations (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	8.75 ± 0.19	24.39 ± 0.56	13.32 ± 0.00	Excellent flowability	Good flowability
F-1	8.10 ± 0.17	26.71 ± 0.20	10.23 ± 0.00	Excellent flowability	Excellent to good flowability
F-2	8.12 ± 0.27	27.32 ± 0.44	10.33 ± 0.57	Excellent flowability	Excellent to good flowability
F-3	7.81 ± 0.28	28.92 ± 0.49	10.33 ± 1.14	Excellent flowability	Excellent to good flowability
F-6	7.86 ± 0.19	28.58 ± 1.00	11.17 ± 0.00	Excellent flowability	Good flowability
F-7	8.37 ± 0.11	26.83 ± 0.79	10.23 ± 0.00	Excellent flowability	Excellent to good flowability

[a] For the composition of each formulation refer to Table 6.1
[b] SD, standard deviation from the mean.

6.4.3 Particle size studies

Particle size distribution of all formulations is shown in Figure 6.1, where all formulations show narrow size distribution. Apart from physical mixture pellet, all formulations mainly fall into the size of 500 µm. This narrow size distribution is also observed rather consistently by previous studies on liqui-pellet, indicating that the use of extrusion and spheronization technology for liqui-pellet production is commercially practical. Narrow size distribution would make handling these liqui-pellets more ideal, for example, capsule filling and reduce risk of failing dosage form uniformity of content quality control test. It has also been stated that extrusion-spheronization method of pelletization is able to produce

uniform size and narrow size distribution pellets [73], which is evident in the data shown in Figure 6.1.

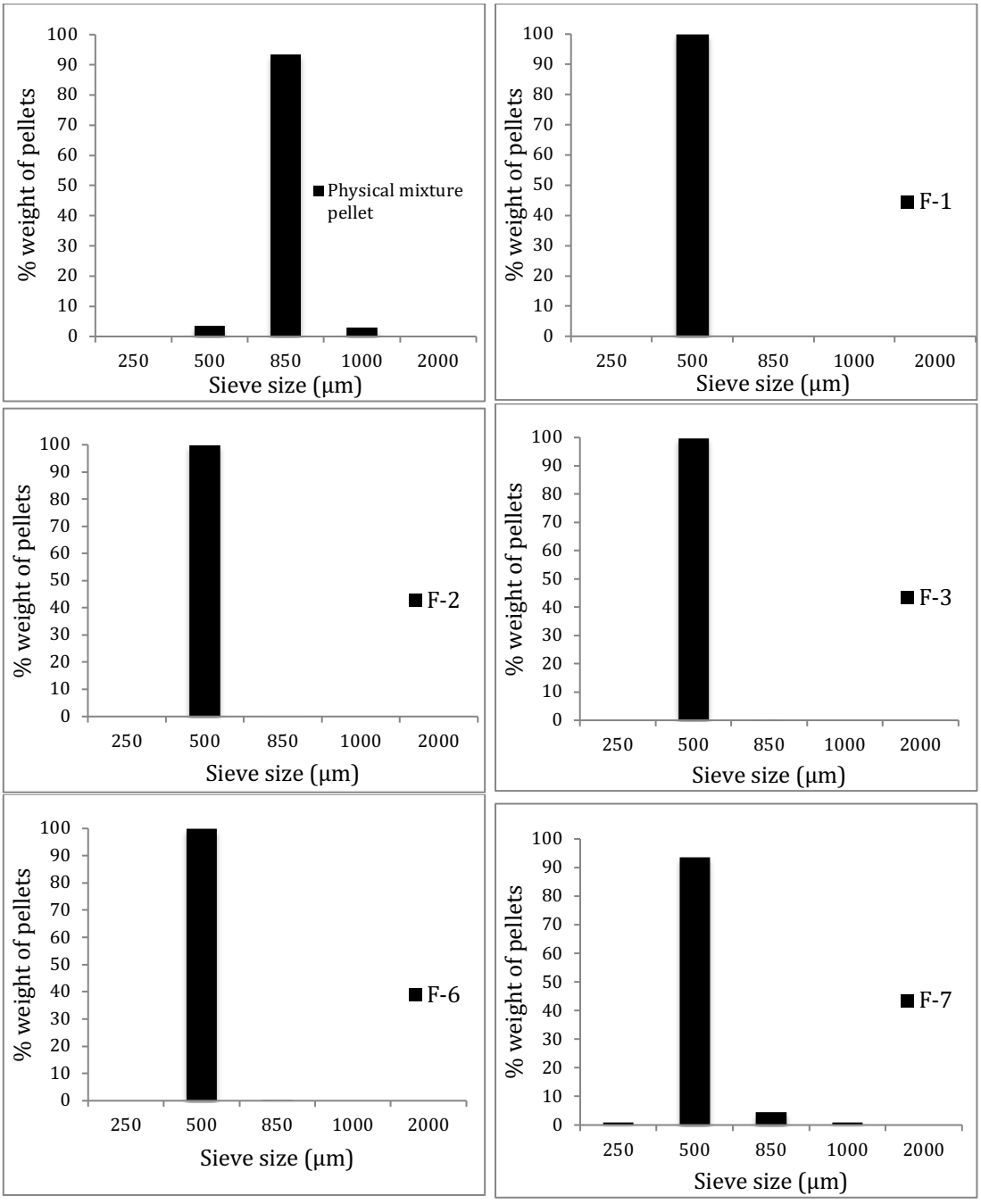


Figure 6.1. Graphs showing particle size distribution of all formulations via sieve method

6.4.4 Friability studies

The percentage weight loss of all formulations after being treated in the friabilator are all below 1% (Table 6.3). Since there is no standard for friability test on pellets, USP standards for friability test on tablet was adapted, which mean weight loss of less than 1% is acceptable.

Although F-3 and F-7 pass the friability test, it can be seen that they have the highest amount of weight loss, which indicates they are less robust than the other formulations. This is most likely due to F-3 and F-7 having the highest amount of tween 80 possible for a successful production of this particular liqui-pellet, which is 23% w/w. With high amount of tween 80, less water is required in the formulation for successful extrusion and spheronization. The reduction in water leads to decrease in cohesive force within F-3 and F-7; thus, they are less robust. Water content seems to be an important factor affecting MCC-base pellet as stated in various literature [74,95,130]. Nonetheless, all formulations passed the friability test; and there is more room for formulation optimization for improvement of effervescent liqui-pellet robustness.

Table 6.3. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.18
F-1	0.61
F-2	0.5
F-3	0.94
F-6	0.16
F-7	0.98

6.4.5 Drug release studies

The optimized naproxen effervescent liqui-pellet formulations F-7 and F-6 have shown a remarkable enhanced drug release profile at pH 1.2 (Figure 6.2), where naproxen is practically insoluble in such acidic pH (solubility of 27mg/L [189]). Formulation F-7 drug release rate was extremely fast and was nearing 100% at 10 min under pH 1.2, which is similar to its drug dissolution profile at pH 7.4 as shown in Figure 6.3, where naproxen is freely soluble at this pH (solubility of 3347mg/L [189]).

Formulation F-7 has been optimized by using the upper limit of tween 80 concentration (23% w/w) and lower limit of water content (3.21ml per 20g of liqui-mass admixture). These two parameters have been proven to effect liqui-pellet drug release profile substantially in the author's previous studies. Although tween 80 and water content are optimized, the single most significant factor resulting to F-7 remarkable rapid and explosive drug release other than $NaHCO_3$, is the use of neusilin US2 in the formulation.

Neusilin is considered as a multifunctional excipient and is known as an excellent absorbent material [215] with disintegrant and suspending properties [207]. Perhaps such properties promote fast disintegration in F-6 and F-7, leading to rapid drug release rate.

Despite F-7 having lower concentration of $NaHCO_3$ (32% w/w) than a naproxen effervescent formulation from previous studies, where $NaHCO_3$ concentration of 42% w/w was used, F-7 interestingly has a significantly faster drug release rate under acidic condition of pH 1.2 (f_1= 79.26 and f_2= 26.16). This indicates that although $NaHCO_3$ concentration is 10% w/w lower for F-7, the neusilin, which is present in F-7, resulted to a remarkable enhancement of drug release that even surpasses a similar formulation with 10% more $NaHCO_3$ but without neusilin US2.

To further appreciate such improvement in enhanced drug release of F-7, it is noteworthy to compare this naproxen effervescent liqui-pellet with current naproxen liquisolid formulation. In Tiong studies, the best naproxen liquisolid tablet formulation obtained ~60% drug release in 1 h [15], whereas F-7 neared 100% in 10 min. Such drug dissolution profile along with excellent flowability (Table 6.2), narrow size distribution (Figure 6.1) and acceptable size and weight for swallowing, indicates liqui-pellet potential as a promising next generation oral dosage form with capability for rapid drug release. Even when comparing F-7 liqui-pellet performance with other promising technology such as solid dispersion, the liqui-pellet displays a superior enhanced drug release. Naproxen (20mg) solid dispersion formulation in Adibkia, Barzegar-Jalali, *et al* studies [216], reached 100% drug release rate at about 2 h even though the dissolution test were at pH 3 where naproxen is more soluble than in pH 1.2, which was used for liqui-pellet.

Formulation F-6 also shows a very fast drug dissolution profile similar to F-7 (f_1= 5.05 and f_2= 72.3) as shown in Figure 6.2. Despite F-6 having lower tween 80 concentration (19% w/w) than F-7 (23% w/w), F-6 achieved fast dissolution rate similar to F-7 due to neusilin US2 in the formulation. Neusilin US2 seems to be a major factor influencing drug release.

It is observed that an increase in tween 80 and reduction of water content increases the drug release rate. This is shown in Figure 6.2 where F-2 (containing 21% w/w tween 80 and 3.2ml of water per 20g of liqui-mass admixture) shows faster dissolution rate than F-1 (containing 19% w/w tween 80 and 5.6ml of water per 20g of liqui-mass admixture) by ~15 % after 2 h (f_1= 21.22 and f_2=38.95). However, as tween 80 concentration further

increases and water content further decreases, their influence on drug dissolution rate diminishes. This can be seen in F-3 (containing 23% w/w tween 80 and 3.12ml of water per 20g of liqui-mass admixture) and F-2 (containing 21% w/w tween 80 and 3.21ml of water per 20g of liqui-mass admixture), where their dissolution profile is very similar (f_1= 0.64 and f_2= 96.78), despite the difference in tween 80 concentration and water content.

Dissolution test results under pH 7.4 (Figure 6.3) show that F-6 and F-7 have the fastest drug release rate. The drug release rate improves with increasing tween 80, for example, F-3 (23% w/w tween 80) is better than F-2 (21% w/w tween 80), and F-2 is better than F-1 (19% w/w tween 80). It is interesting to see physical mixture pellet having slightly better enhanced dissolution profile than F-1, F-2 and F-3. This is due to naproxen being freely soluble in pH7.4 and the $NaHCO_3$ may further enhance the alkaline pH; thus, liquid vehicle plays a less vital role in drug dissolution as naproxen is already freely soluble in this environment.

Overall, the optimized naproxen effervescent liqui-pellet is capable of remarkable drug release enhancement, with $NaHCO_3$ and neusilin US2 being a major contribution to this. Such optimized liqui-pellet formulation shows more superior drug dissolution enhancement than the liquisolid formulation and even other promising technology such as solid dispersion.

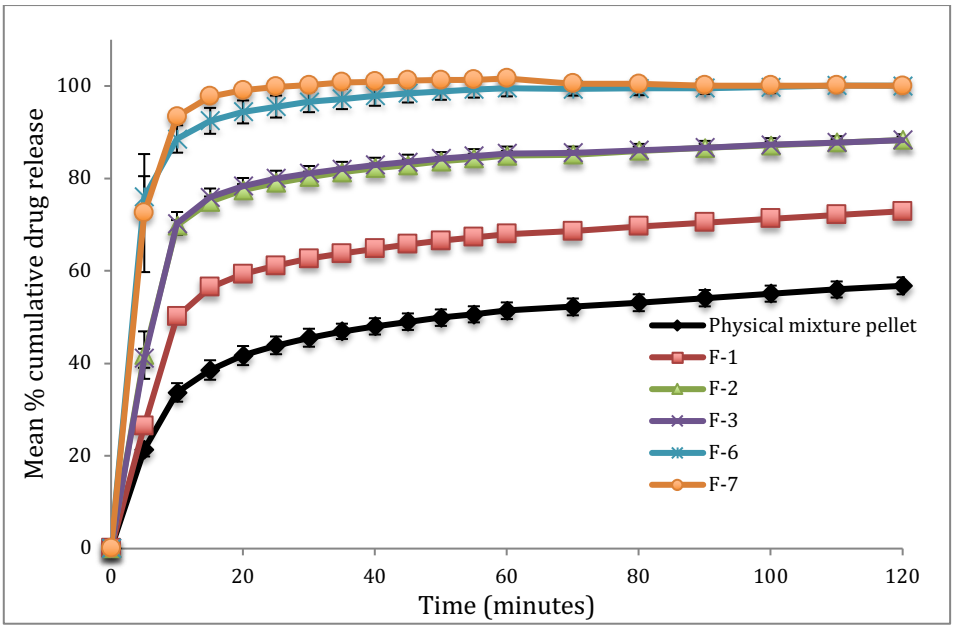


Figure 6.2. Dissolution profile of physical mixture pellet capsule and all successful liqui-pellet formulations capsule at pH 1.2 (n = 3)

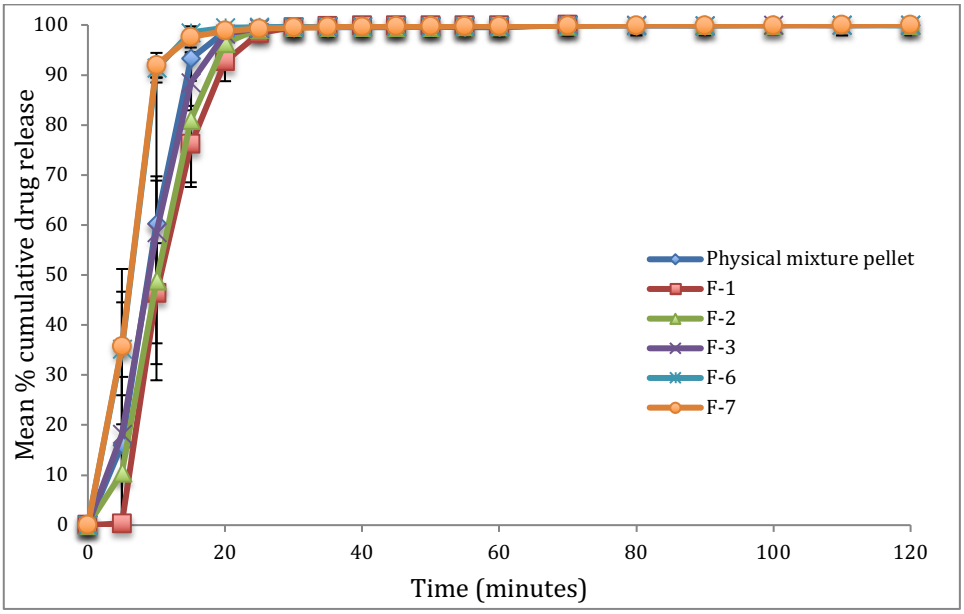


Figure 6.3. Dissolution profile of physical mixture pellet capsule and all successful liqui-pellet formulations capsule at pH 7.4 (n = 3)

6.4.6 Accelerated stability test

The drug dissolution profile of formulations F-6 and F-7 (shown in Figure 6.4 and Figure 6.5 respectively) were investigated to observe if the stressed condition of the accelerated stability test affects drug release rate. In comparing F-6 dissolution profile at month 0 and a month afterward (month 1), there is a difference in the dissolution profile (f_1 = 27.93 and f_2 = 34.66), indicating some degree of decrease in drug release. This difference in dissolution profile may be due to changes in the formulation over storage time such as pellet became harder over time. The reduction in drug release becomes less apparent after this first month where F-6 dissolution profile in month 1 and month 2 gives f_1 = 2.44 and f_2 = 83.66. This indicates no significant difference in the dissolution profile. A similar observation is made between month 2 and month 3 where f_1 = 3.23 and f_2 = 73.60.

The stability test for formulation F-7 as shown in Figure 6.5, shows no significant difference of the dissolution profile between month 0 to month 1 (f_1 = 6.94 and f_2 = 60.96), month 1 to month 2 (f_1 = 2.44 and f_2 = 83.66) and month 2 to month 3 (f_1 = 3.23 and f_2 = 73.60).

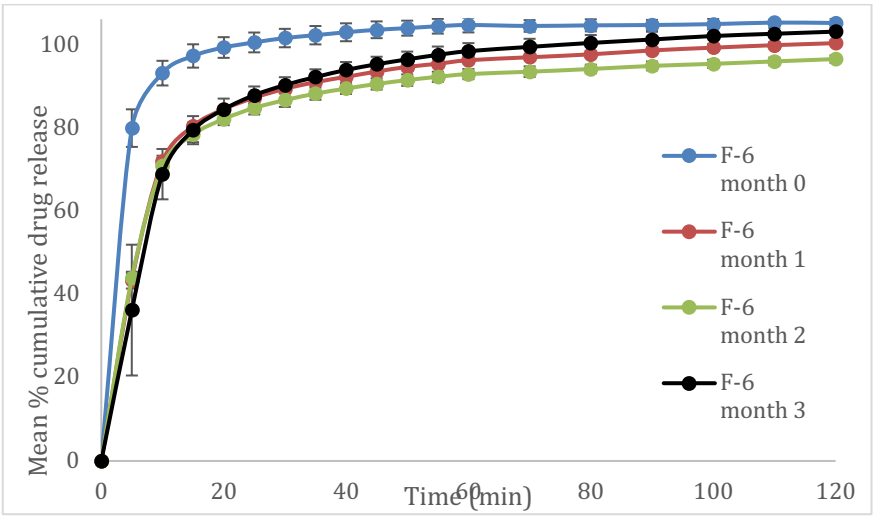


Figure 6.4. Stability test of formulation F-6 represented through dissolution profile taken each month over the period of 3 months under pH 1.2 (n = 3)

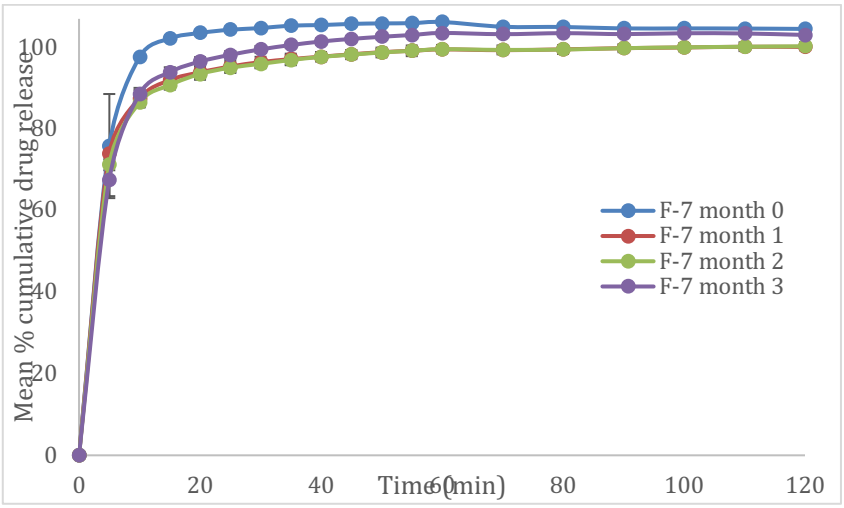


Figure 6.5. Stability test of formulation F-7 represented through dissolution profile taken each month over the period of 3 months under pH 1.2 (n = 3)

6.4.7 Kinetic model analysis of drug release

Table 6.4 show formulations of liqui-pellet correlation coefficients (R^2) in regards to zero order, first order and Higuchi's model under pH 1.2. Formulations F-2, F-3 and F-7 is best fit under the first order release kinetic, whereas F-1 and F-6 best described by Higuchi's model. Formulations F-2, F-3 and F-7 contain higher amount of liquid vehicle and lower amount of water compared to whereas F-1 and F-6, which may contribute to the different kinetic release model. In addition, Table 6.4 contain data of kinetic release model for F-6 and F-7 over a period of time under accelerated stability test condition. It is found that release kinetic for these formulations may change over time under accelerated stability

condition. Under pH 7.4 (Table 6.5), all formulation best fit under zero order drug release kinetic model.

Table 6.4. Release parameters of naproxen formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.923	0.952	0.994
F-1	0.943	0.970	0.975
F-2	0.987	0.997	0.985
F-3	0.990	0.995	0.981
F-6	0.854	0.968	0.975
F-6 (After 1 month under 40 °C with relative humidity of 75%)	0.986	0.997	0.987
F-6 (After 2 month under 40 °C with relative humidity of 75%)	0.981	0.999	0.991
F-6 (After 3 month under 40 °C with relative humidity of 75%)	0.999	0.983	0.959
F-7	0.907	0.999	0.994
F-7 (After 1 month under 40 °C with relative humidity of 75%)	0.842	0.939	0.970
F-7 (After 2 month under 40 °C with relative humidity of 75%)	0.878	0.980	0.985
F-7 (After 3 month under 40 °C with relative humidity of 75%)	0.916	1.00	0.996

Table 6.5. Release parameters of naproxen formulations at pH 7.4

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.972	0.857	0.825
F-1	0.941	0.904	0.789
F-2	0.971	0.883	0.848
F-3	0.967	0.901	0.895
F-6	0.983	0.878	0.872
F-7	0.984	0.877	0.874

6.5 Conclusion

This study has proven liqui-pellet is capable of explosive and rapid drug release. The data from the dissolution test shows naproxen liqui-pellet can achieve 100% drug release within 20 min at an acidic pH of 1.2, which naproxen is known to be practically insoluble in. Such results are more superior than naproxen liquisolid formulation or even other promising and competitive formulation such as naproxen solid dispersion.

It seems like the key factor contributing to this remarkable drug release profile is the use of an effervescent agent ($NaHCO_3$) and neusilin US2 in the liqui-pellet formulation. Furthermore, the accelerated stability test shows some of the formulations maintained their original dissolution behaviour over the 3 months. This clearly displays the potential of liqui-pellet being a valuable next generation dosage form for the future.

Chapter 7: Using liqui-pellet technique to enhance dissolution rate of poorly water-soluble hydrochlorothiazide

7.1 Abstract

Liqui-pellet is a new and promising oral dosage form that has recently shown potential for rapid drug release rate of a poorly water-soluble drug. So far, only naproxen liqui-pellets are produced. In this study, the aim is to explore liqui-pellet as a dosage form with another poorly water-soluble API, namely hydrochlorothiazide (HCTZ). The technology is still in its infancy; thus, it is prudent to explore its potential. HCTZ liqui-pellet with different liquid vehicle, which includes tween 80, PG, kolliphor EL and PEG 200, were investigated. Saturation solubility studies showed HCTZ was most soluble in PEG 200, which explains the reason for HCTZ liqui-pellet containing PEG 200 having the best enhanced release drug release profile. The formulation was then optimized through incorporating effervescent agent (sodium bicarbonate) and binary carrier (1:1 ratio of avicel PH101 and neusilin US2). In-vitro dissolution test showed the fastest optimized formulation achieving a remarkably rapid drug release of 100% within 15 min. Such drug release performance of a simple and cost-effective technology reveals the potential of liqui-pellet. All formulations obtained narrow size distribution, passed friability test and show no issue with flow properties. Thus, supporting liqui-pellet potential as a promising next generation oral dosage form.

7.2 Introduction

The key introductory points are covered in chapter 2 section 2.2, 3.2, 4.2, 5.2 and 6.2; however, further background relating to this chapter will be covered here.

In this study, hydrochlorothiazide (HCTZ), which is a poorly water-soluble drug, is the drug candidate for liqui-pellet enhanced release dosage form. HCTZ is a thiazide diuretic and is used in the treatment of oedema, chronic heart failure and high blood pressure [217]. According to studies by Baka, Comer, *et al* [218], HCTZ solubility is around 0.556 mg/ml at pH 6, which is considered to be very slightly soluble. Hence, HCTZ is a suitable drug candidate for liqui-pellet enhanced drug release formulation.

Previous studies by the author have shown that naproxen liqui-pellet has the potential for remarkable enhanced drug release, which is more superior than liquisolid

formulation and even other promising formulation such as solid dispersion. Naproxen is a weakly acidic water insoluble drug; however, by using liqui-pellet technology, it is able to achieve 100% drug release within 20 min under pH 1.2, which is a pH it is practically insoluble in. This display the potential of liqui-pellet dosage form.

Liqui-pellet has proven itself capable of overcoming the major drawbacks of liquisolid formulation such as poor flowability and inability to achieve reasonable size and weight dosage form for swallowing particularly high dose drug [1,4]. In this study, the aim is to see the feasibility of liqui-pellet using other API other than naproxen; and to see if the key advantages and rapid drug release can be maintained in HCTZ liqui-pellet.

7.3 Materials and methods

7.3.1 Materials

Hydrochlorothiazide was obtained from Spectrum Chemical MFG Corp (USA). Other excipients used to prepare the liqui-pellet included microcrystalline cellulose (avicel PH-101), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel), (DFE Pharma, Goch, Germany); sodium bicarbonate, (Acros, New Jersey, USA); synthetic magnesium alumino-metasilicate (Neusilin US2), (Fuji Chemicals, Japan); polysorbate 80 (tween 80), (Acros, Netherlands); propylene glycol (SAFC, Spain); polyethylene glycol 200 (PEG 200), (Fisher Scientific, Leicester, UK) and macrogolglycerol ricinoleate 35 (Kolliphor EL), (BASF SE, Ludwigshafen, Germany). All other reagents and solvent were of analytical grades.

7.3.2 Solubility studies

Saturation solubility studies were carried out in a similar manner as in chapter 2 section 2.3.2, however, the liquid vehicles that were used were: tween 80; propylene glycol (PG); kolliphor EL and polyethylene glycol 200 (PEG 200). Also, the duration of time the samples were left in the bath shaker was longer (96 h).

7.3.3 Preparation of HCTZ 12.5mg liqui-pellet

All liqui-pellet formulations were prepared in a similar manner except for the variation in parameters such as carrier composition; types of liquid vehicle; presence/ absence of

effervescent agent and water content (Table 7.1). The liquid medication was prepared by mixing a specified amount of HCTZ with specified liquid vehicle of a specified amount using a mortar and pestle. The liquid medication was then incorporated into a specified carrier of specified amount. Effervescent agent may be incorporated at this stage. Carrier could be could be 100% avicel PH101, 100% avicel PH102 or a mixture of 50% avicel PH102 and 50% neusilin US2. All formulations made had around 5% w/w primojel (superdisintegrant) and carrier to coating ratio of 20:1 respectively. The coating material used was aerosil 300.

The liquid medication along with carrier and primojel were mixed 2 min at a constant rate of 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). The primojel was added intragranularly as previous studies showed this was better at promoting disintegration than extragranular incorporation. A specified amount of granulating liquid (deionized water) was added bit by bit to achieve reasonable plastic property for extrusion (Caleva Multitab, Caleva Process Solutions Ltd, UK). The duration of mixing of the admixture with granulation liquid was 5 min. Aerosil 300 was then added into the admixture and further mixed for 5 min before extrusion. Once a sample was extruded, the extrudates were spheronized at an almost constant rotation at 4000rpm (decrease to 2000 rpm if agglomeration seems likely). The spheronization time varied depending on the extrudate's plastic property to avoid agglomeration. The liqui-pellets were then placed in an oven under a constant temperature of 40^{o}C overnight to remove water content.

Note that from F-1 to F-2 was made to compare the effect of different grade of avicel (PH101 and PH102). Formulations F-2 to F-5 was made to determined the most suitable liquid vehicle. Formulations after F-5 was made made to optimized and study parameters such as water, effervescent agent and neusilin US2.

Table 7.1. Key formulation characteristics of the investigate liqui-pellet in capsule

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Liquid vehicle	Amount of liquid vehicle (% w/w)	Liquid load factor	Amount of $NaHCO_3$ (%w/w)
Physical mixture pellet	22.50				
F-1	2.46	Tween 80	34	0.79	
F-2	2.46	Tween 80	34	0.79	
F-3	2.46	PG	34	0.79	
F-4	2.46	Kolliphor EL	34	0.79	
F-5	2.46	PEG 200	34	0.79	
F-6	7.39	Tween 80	34	0.79	
F-7	7.39	Kolliphor EL	34	0.79	
F-8	12.32	PEG 200	34	0.79	
F-9	3.37	Tween 80	28.29	1.03	31.80
F-10	3.37	Kolliphor EL	28.29	1.03	31.80
F-11	5.24	PEG 200	28.29	1.03	31.80

Formulation	Carrier composition	Mass of carrier (mg)	Mass of coating material (mg)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture pellet	100% avicel PH 102	104.37	5.22	133.34
F-1	100% avicel PH 102	104.37	5.22	202.84
F-2	100% avicel PH 101	104.37	5.22	202.84
F-3	100% avicel PH 102	104.37	5.22	202.84
F-4	100% avicel PH 102	104.37	5.22	202.84
F-5	50% avicel PH101 & 50% neusilin US2	104.37	5.22	202.84
F-6	50% avicel PH101 & 50% neusilin US2	104.37	5.22	202.84
F-7	50% avicel PH101 & 50% neusilin US2	104.37	5.22	202.84
F-8	50% avicel PH101 & 50% neusilin US2	104.37	5.22	202.84
F-9	50% avicel PH101 & 50% neusilin US2	104.37	5.22	334.09

F-10	50% avicel PH101 & 50% neusilin US2	104.37	5.22	334.09
F-11	50% avicel PH101 & 50% neusilin US2	104.37	5.22	334.09

Note all liqui-pellet formulation contains 12.5mg of HCTZ, primojel ~5%w/w and carrier to coating material is at a ratio of 20:1.

7.3.4 Flowability test on HCTZ liqui-pellet and physical mixture pellet

Carried out in the same manner as described in chapter 1 section 2.3.5.

7.3.5 Friability studies on HCTZ liqui-pellet and physical mixture pellet

Carried out in the same manner as described in chapter 2 section 2.3.6.

7.3.6 Particle size analysis (sieve method) on HCTZ liqui-pellet and physical mixture pellet

Carried out in the same manner as described in chapter 2 section 2.3.7.

7.3.7 In-vitro drug dissolution test

All formulations underwent dissolution test using USP dissolution apparatus II (708-DS Dissolution Apparatus & Cary 60 UV-Vis, Agilent Technologies, USA). The formulations were in a form of liqui-pellet filled in hard shell capsule. Each capsule contained physical mixture pellet or specified liqui-pellet formulation equivalent to 12.5mg of HCTZ. The dissolution test was set under the constant condition of 900 ml of dissolution medium, the temperature of 37.3 ± 0.5^{o}C and paddle agitation of 50rpm. HCl buffer solution with pH of 1.2 without enzymes was used as dissolution medium to mimic pH in gastric fluid. The absorbance reading was taken at 272 nm at time intervals of 5 min for an hour then time interval of 10 min for another hour.

Beers Lambert calibration curve obtained from preliminary work (Figure 7.1) was used to calculate the concentration of HCTZ in the dissolution test. Note that HCTZ dissolution rate is not significantly affected by the change in pH in the stomach (~1.2) to the

small intestine (~7.4); hence, it was considered sufficient to only carry out the dissolution test under pH 1.2 at wavelength 272 nm.

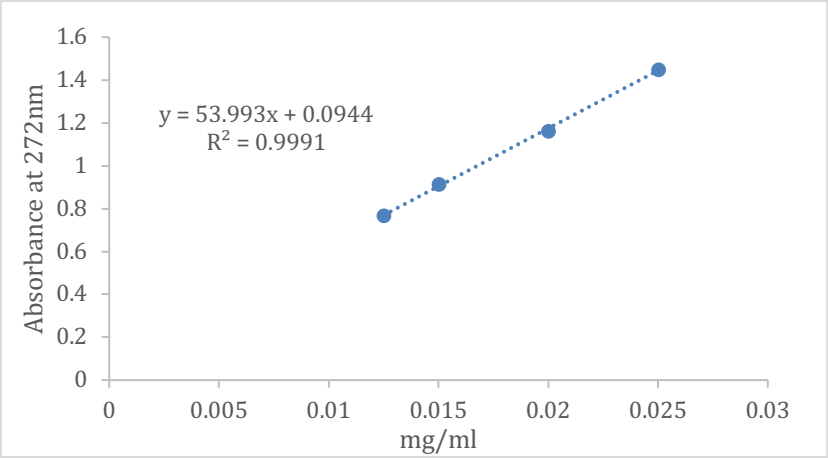


Figure 7.1. Beers Lambert calibration curve of HCTZ under pH 1.2

7.3.8 Kinetic model analysis of drug release

Carried out in the same manner as described in chapter 2 section 2.3.11.

7.3.9 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.4.14.

7.4 Results and discussion

7.4.1 Solubility measurement

The saturation solubility test shows that HCTZ is most soluble in PEG 200 compared to the other liquid vehicles (Table 7.2). In fact, the solubility data suggests that HCTZ is freely soluble in PEG 200, making it the most suitable liquid vehicle candidate for HCTZ liqui-pellet. This is because it is generally considered that the liquid vehicle in which an API is most soluble in would exhibit the fastest drug release rate. This is due to reduced API in crystalline form and more API are in solubilized or in molecularly dispersed state in the carrier; hence, increasing surface area for drug release [3].

After PEG 200, the next liquid vehicle which HCTZ is most soluble in is Kolliphor EL, then tween 80, and finally least soluble in PG. Despite the solubility test results, formulations F-1 (tween 80) and F-4 (kolliphor EL) have a very similar drug dissolution

profile even though HCTZ is more soluble in kolliphor EL than tween 80 (Figure 7.3). Hence, it should be reminded that API solubility is not the only factor that can influence the drug dissolution rate. Other physicochemical characteristics of liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure and molecular mass may affect drug release [1]. Nevertheless, drug solubility in a liquid vehicle is a major factor that could greatly influence drug release profile.

Table 7.2. Solubility of HCTZ in various liquid vehicles at 37°C (n=3)

Non-volatile solvent	Mean concentration (mg/ml) ± SD[a]	Inference
Tween 80	27.46 ± 1.31	Sparingly soluble
PG	11.35 ± 4.94	Sparingly soluble
Kolliphor EL	95.93 ± 5.81	Soluble
PEG 200	155.92 ± 6.33	Freely soluble

[a] SD, standard deviation

7.4.2 Flowability studies

According to the angle of repose, all formulations have excellent flow properties as shown in Table 7.3. As for CI, the flow properties are slightly more dispersed; there are excellent, good and good-fair flow properties. In general, the flow properties of all of the formulations do not pose a major issue, which is also observed in the author's previous studies.

Table 7.3. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulations (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	7.73 ± 0.21	24.38 ± 0.73	11.62 ± 0.00	Excellent	Good
F-1	6.93 ± 0.10	27.57 ± 1.00	8.83 ± 0.00	Excellent	Excellent
F-2	6.28 ± 0.61	28.19 ± 0.84	11.71 ± 1.56	Excellent	Good
F-3	6.33 ± 0.19	26.38 ± 0.77	15.16 ± 0.00	Excellent	Good-fair
F-4	6.31 ± 0.33	28.86 ± 0.60	11.12 ± 0.00	Excellent	Good
F-5	6.00 ± 0.18	27.96 ± 0.46	9.80 ± 1.70	Excellent	Excellent
F-6	6.78 ± 0.25	24.95 ± 0.73	12.29 ± 1.52	Excellent	Good
F-7	6.28 ± 0.61	28.19 ± 0.84	11.71 ± 1.56	Excellent	Good
F-8	7.63 ± 0.20	23.41 ± 0.43	11.77 ± 0.00	Excellent	Good
F-9	8.18 ± 0.08	26.18 ± 0.90	8.33 ± 0.00	Excellent	Excellent
F-10	8.24 ± 0.06	26.16 ± 0.34	12.82 ± 0.00	Excellent	Good
F-11	9.59 ± 0.04	24.03 ± 0.35	11.12 ± 0.00	Excellent	Good

[a] Refer to Table 7.1 for the composition of each formulation
[b] SD, standard deviation

7.4.3 Friability studies

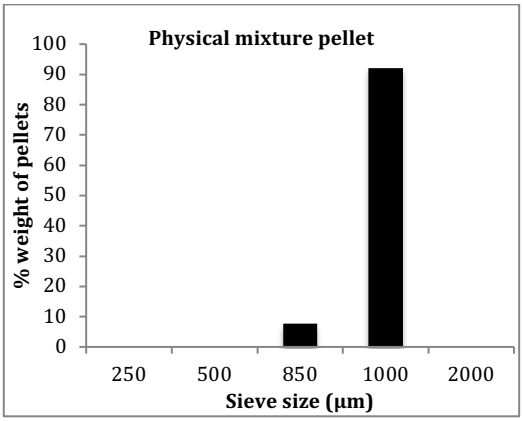
All formulations pass the friability test as the percentage weight loss is below 1% (Table 7.4). This indicates that all formulations have acceptable robustness. It is known that due to shape and size of pellet form, they are more resistant to friability [219]. It is noticed that liqui-pellets are more robust than the physical mixture pellet; perhaps the liquid vehicle in liqui-pellet made them more robust due to the increase in plasticity.

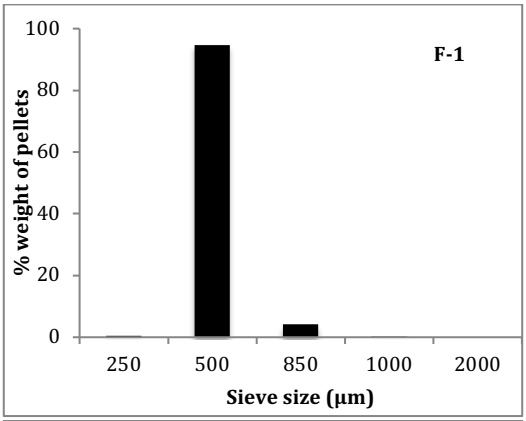
Table 7.4. Weight loss of 3g of each formulation under rotational speed of 25rpm for 4 min

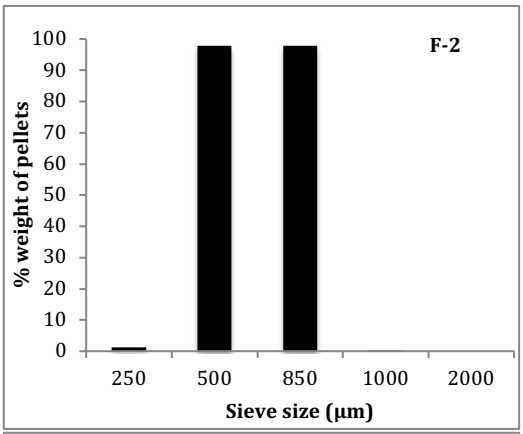
Formulation	% Weight loss
Physical mixture pellet	0.91
F-1	0.10
F-2	0.02
F-3	0.60
F-4	0.20
F-5	0.81
F-6	0.12
F-7	0.00
F-8	0.14
F-9	0.01
F-10	0.16
F-11	0.01

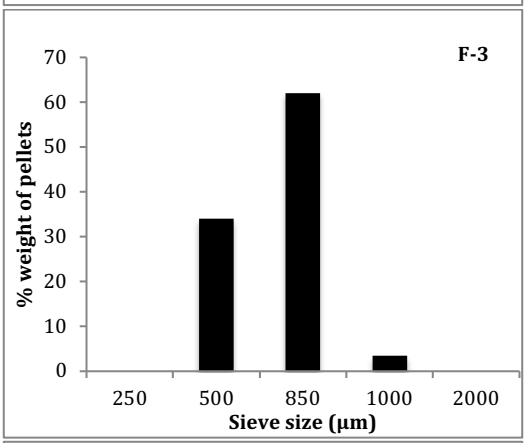
7.4.4 Particle size studies

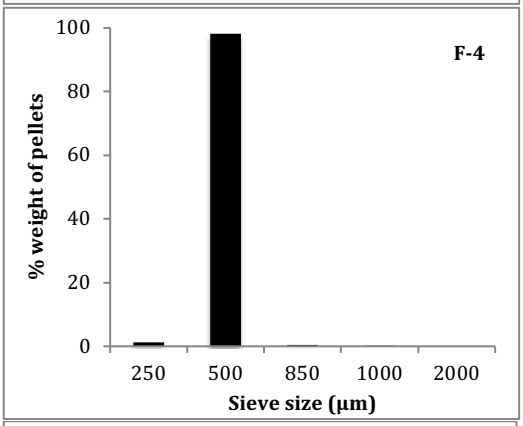
Almost all the HCTZ formulations (except F-2 and F-3) appear to have a very narrow size distribution as shown in Figure 7.2. Narrow size distribution is ideal for manufacturing as it will reduce weight and content variation when filled into a capsule or a hopper for tablet production. Interestingly all liqui-pellet formulations containing neusilin US2 (from F-5 to F-11) are mostly within 500 μm in size. It is postulated that neusilin US2 may have a contribution to the consistency of small pellet size of all the liqui-pellet formulations. It is claimed that API and excipients size can affect the pellet size [87,90,100,107,150,220]. Neusilin US2 is considered as fine ultra-light granules of magnesium aluminometasilicate, with a mean agglomerated particle size of 60-120 μm [221]. Hence, it is assumed that such characteristic of the carrier material can influence particle size. The physical mixture pellet, which does not contain neusilin US2, is mostly 1000 μm in size. This is twice the size of all of the liqui-pellet formulations. Nonetheless it should be pointed out that size and size distribution of pellets is rather difficult to control. It has been stated in literature that there are numerous factors that can influence pellet size prepared by extrusion-spheronization, which includes: API and excipients size [87,90,100,107,150,220]; extruder types; extrusion speed; properties of extrusion screen; spheronization speed [80]; spheronization time [98,103,140,145] and spheronization load [103,104,140]. Overall, all of the pellet size is within the range that is expected and most formulation achieved narrow size distribution.

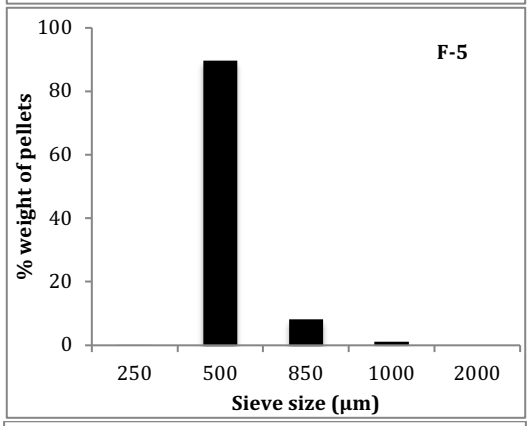

Physical mixture pellet
% weight of pellets
100
90
80
70
60
50
40
30
20
10
0
250
500
850
1000
2000
Sieve size (µm)

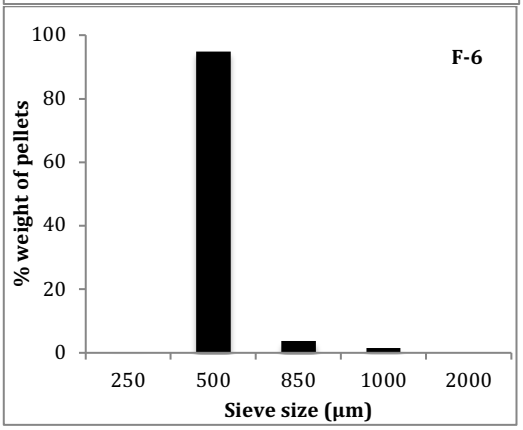

F-1
% weight of pellets
100
80
60
40
20
0
250
500
850
1000
2000
Sieve size (µm)

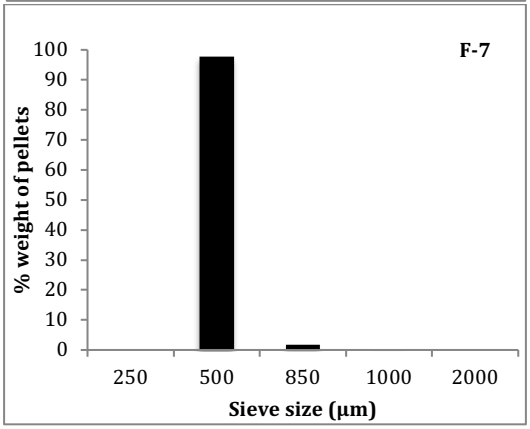

F-2
% weight of pellets
100
90
80
70
60
50
40
30
20
10
0
250
500
850
1000
2000
Sieve size (µm)


F-3
% weight of pellets
70
60
50
40
30
20
10
0
250
500
850
1000
2000
Sieve size (µm)


F-4
% weight of pellets
100
80
60
40
20
0
250
500
850
1000
2000
Sieve size (µm)


F-5
% weight of pellets
100
80
60
40
20
0
250
500
850
1000
2000
Sieve size (µm)


F-6
% weight of pellets
100
80
60
40
20
0
250
500
850
1000
2000
Sieve size (µm)


F-7
% weight of pellets
100
90
80
70
60
50
40
30
20
10
0
250
500
850
1000
2000
Sieve size (µm)

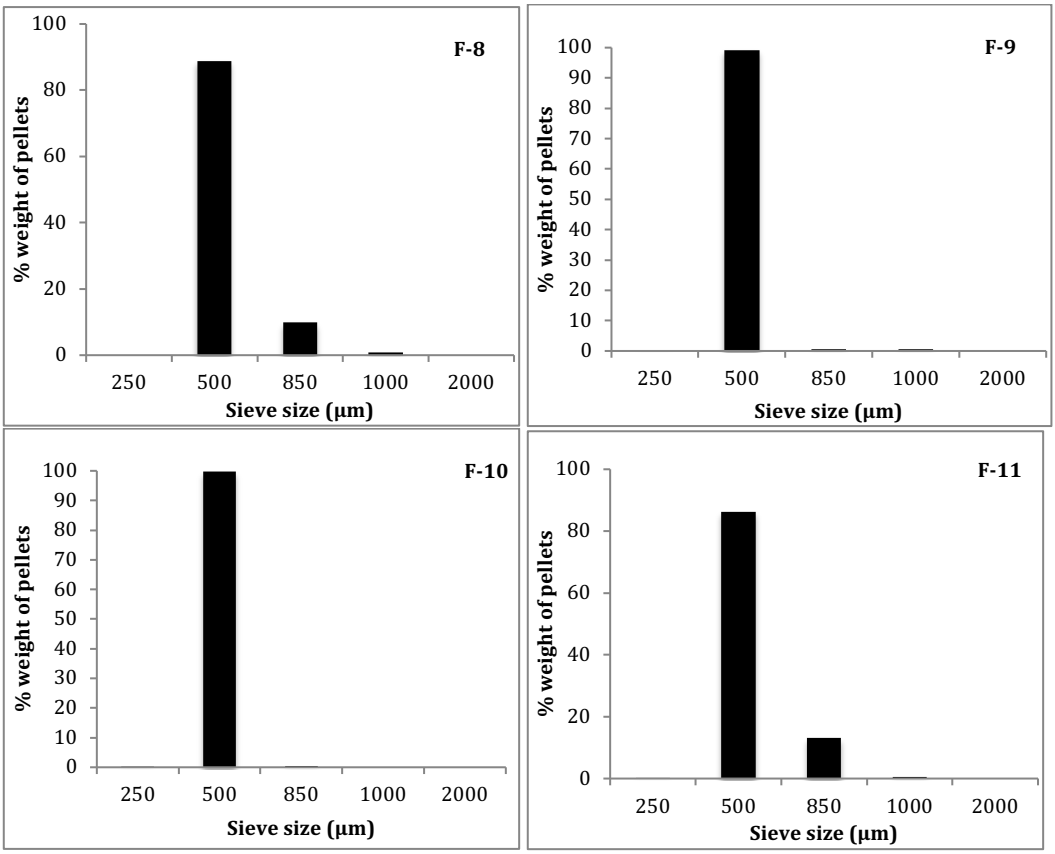


Figure 7.2. Graphs showing particle size distribution of all formulations

7.4.5 In-vitro dissolution test

It can clearly be seen in Figure 7.3 that the optimized formulation F-11 has a remarkably fast drug release rate, where 100% HCTZ release rate is achieved within 15 min. This is considered extremely fast in comparison to other technologies, which also aims to achieve fast drug dissolution rate. To put this into perspective, it is important to refer the drug release profile of other technologies for comparison. In Khan, Iqbal, *et al* studies, HCTZ liquisolid compact achieved ~95% drug release in ~48 min, and HCTZ solid dispersion achieved ~88% drug release in ~48 min [14]. In Sultan, El-Gizawy, *et al* studies, HCTZ solid self-dispersing mixed micelle forming system achieved 100% drug release in 20 min [222]. It is clear that the explosive and rapid drug releasing HCTZ liqui-pellet is more superior than the mention HCTZ liquisolid compact, solid dispersion and solid self-dispersing mixed micelle forming system in terms of drug release. In general, the dissolution test results along with results from other physicochemical analysis, makes liqui-pellet a potentially exciting endeavour for a pharmaceutical company, particularly in terms of drug release performance, simplistic approach, cost-effectiveness and commercial feasibility. It should be noted that this is not the first time such rapid dissolution rate is observed in liqui-pellet

formulation. In the previous studies in chapter 6, effervescent naproxen liqui-pellet also achieved rapid dissolution rate that is faster than naproxen liquisolid compact and solid dispersion formulation [15,216].

Formulations F-2 to F-5 serves to determine the most appropriate liquid vehicle for HCTZ liqui-pellet; and formulations F-1 and F-2 serves to determine if different grade of avicel (avicel PH101 and PH102) have an affect on drug release rate. As shown in the results (F-2 to F-5), PEG 200 (F-5) is the most appropriate liquid vehicle for HCTZ liqui-pellet as it shows the fastest drug release compared to other liquid vehicles, which agrees with the results from solubility studies (Table 7.2) Also, drug release data indicate that there is no observable effect of switching from avicel PH102 to avicel PH101 (f_1= 1.89 and f_2= 90.53).

Formulations F-6 to F-8 are made identically except different liquid vehicles were incorporated. The results again support that PEG 200 (F-8) is the most suitable liquid vehicle. It is interesting how formulation F-8 shows a slower drug dissolution profile than F-5 (f_1= 38.95 and f_2= 37.25). Formulation F-8 contains neusilin US2 and avicel PH102 as part of the carrier material. It has been observed in the author's previous work that neusilin US2 significantly improves the dissolution rate of naproxen effervescent liqui-pellet. However, nesusilin US2 does not seem to have the same effect with the HCTZ liqui-pellet in this study. It should be noted that F-8 contains 5 times the amount of water content than F-5, which could be the reason for the slower drug dissolution rate. From the author's previous studies, it is already established that water content has a crucial effect on liqui-pellet physicochemical properties, particularly drug release rate. In brief, a reduction of water content effectively reduces cohesive strength of the liqui-pellet, improving its disintegrating properties; thus, enhancing drug release rate.

Although F-5 shows faster drug release rate than F-8, formulation F-8 is more robust than F-5 as shown in results from friability test (Table 7.4). This suggests that formulation scientist will need to adjust water content in liqui-pellet production to compromise between drug release performance and the robustness of the dosage form.

Formulations F-9, F-10 and F-10 all contain effervescent agent but have a lower concentration of co-solvent than formulations F-6, F-7 and F-8 (~28% w/w and ~34% w/w respectively). The composition in F-9, F-10 and F-11 are the same except for the type of liquid vehicle and amount of water used. The amount of water used is determined by the likelihood of successful liqui-pellet production. It is found that although F-9, F-10 and F-11

have lower concentration of co-solvent than the other formulations, their dissolution profile shows markedly faster drug release rate. This is due to the presence of an effervescent agent promoting disintegration and disrupting the diffusion boundary layer. Effervescent agent indeed is an effective excipient in liqui-pellet for enhanced drug release.

Among these effervescent liqui-pellet formulations, it is not surprising that F-11 has the fastest dissolution rate (100% drug release in 15 min) as it contains PEG 200, which HCTZ is most soluble in among the other liquid vehicles used in the study. The combined effect of effervescent agent and suitable liquid vehicle have marked impact in enhancing the drug release. Overall, the study shows liqui-pellet is capable of achieving rapid drug release, reflecting the potential of this novel oral drug delivery dosage form.

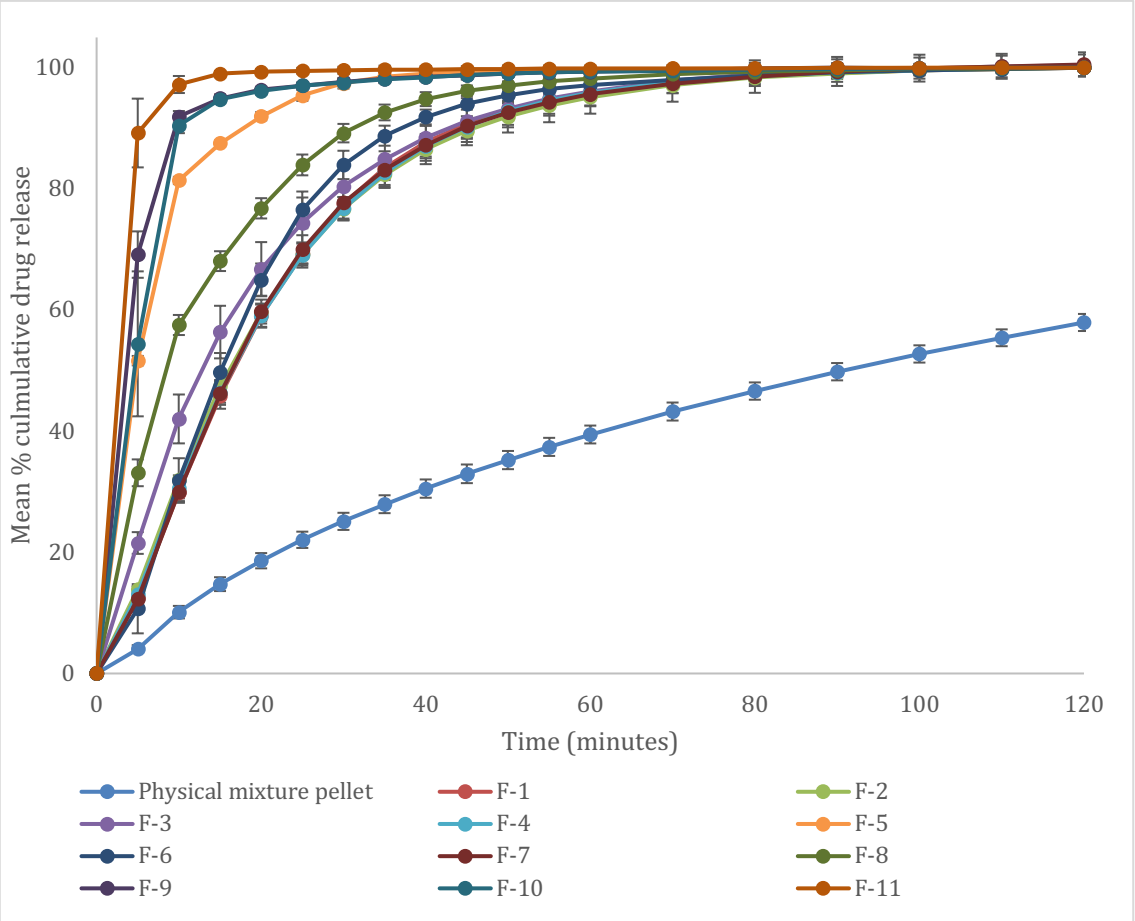


Figure 7.3. Dissolution profile of physical mixture pellet capsule and formulation F-1 to F-11 at pH 1.2 (n = 3)

7.4.6 Kinetic model analysis of drug release

The information about the correlation coefficients (R^2) of formulations are shown in Table 7.5 using kinetic release models such as, zero order, first order and Higuchi model. Most HCTZ liqui-pellet formulations is best described by first order release kinetic model where drug release is dependent on concentration. It is worth pointing out that the formulation containing the lower amount of water tends to be best described by first order kinetic model, which was also seen in chapter 6 section 6.4.7.

Table 7.5. Release parameters of HCTZ formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture pellet	0.949	0.989	0.989
F-1	0.988	0.989	0.934
F-2	0.982	0.994	0.947
F-3	0.948	0.999	0.980
F-4	0.975	0.993	0.951
F-5	0.976	0.994	0.994
F-6	0.992	0.974	0.900
F-7	0.994	0.986	0.917
F-8	0.905	0.995	0.991
F-9	0.922	0.999	0.998
F-10	0.986	0.965	0.986
F-11	0.811	0.981	0.955

7.5 Conclusion

The study has shown HCTZ liqui-pellet is able to achieve remarkably rapid enhanced drug release when the formulation is optimized. The liqui-pellet formulation with the fastest drug release rate achieved 100% drug release within 15 min. It was found that the combination of suitable liquid vehicle and effervescent agent are responsible for the rapid drug release. In general, the effervescent agent improves liqui-pellet drug release rate through promoting disintegration and disrupting the diffusion boundary layer.

In conclusion, liqui-pellet is capable of rapid drug release of poorly water-soluble drugs, which can surpass current technologies such as, liquisolid, solid dispersion and even solid self-dispersing micelle, whilst remaining simple and cost-effective. Such feature reflects liqui-pellet potential as commercially feasible dosage form. Furthermore, all liqui-pellet formulations have a narrow size distribution, passed friability test and show no issue in terms of flow properties.

Chapter 8: Producing naproxen liqui-tablet, the emerging new dosage form stemming from liqui-pellet

8.1 Abstract

In this study, an attempt is made to produce liqui-tablet for the first time. This is carried out through compacting naproxen liqui-pellets. The incentive to convert the emerging liqui-pellet into liqui-tablet is due to the array of inherent advantages the popular and preferred tablet dosage form has. The study shows that naproxen liqui-tablet can be successfully produced and the rapid drug release rate can be achieved under pH 1.2, where naproxen is supposed to be insoluble in. It is shown that different pH of the dissolution medium affects the trend of drug release of formulations of varying amount of liquid vehicle. The order of fastest drug releasing formulations is different depending on the pH. The present of neusilin US2 have shown to significantly enhance drug release rate as well as improving liqui-tablet robustness and hardness. Furthermore, accelerated stability studies have shown acceptable stability.

8.2 Introduction

The key introductory points are covered in chapter 2 section 2.2, 3.2, 4.2, 5.2, 6.2, and 7.2; however, further background relating to this chapter will be covered here.

Liqui-tablet is an emerging dosage form which stems from the novel liqui-pellet. Liqui-tablet is essentially compacted liqui-pellet; thus, it is also under liqui-mass system like liqui-pellet. Note that in previous studies regarding liqui-pellet, the final dosage form is in a form of liqui-pellet filled into a hard-shell capsule. It is a well-known fact that tablet dosage form is a more commercially favorable dosage form than capsule in terms of cost-effectiveness. Producing tablet have lower production cost and higher production rate compared to capsule [164], and costly control steps to ensure capsule integrity are eliminated [77,165]. Other advantages of tablet over capsule includes: lower tendency of dosage form adhering to esophagus during ingestion [166]; ability to administer higher dose strength than capsule [167]; reduces risk of dosage form being tampered with [164]; improves patient compliance, particularly for those who prefer not to ingest gelatin capsule [110]. It is also worth mentioning that the issues with gelatin capsules are not just individual preference, but extend to chemical instability [168], varying dissolution rate of capsule due to varying structure and composition of gelatin [169], and questionable source, particularly from waste

leather which may have been treated with harmful substance [170]. Hence, there is an incentive to explore the feasibility of liqui-tablet.

Studies by the author on naproxen liqui-pellet and hydrochlorothiazide liqui-pellet, which are both poorly water-soluble drug, have demonstrated that liqui-pellet can achieve remarkably fast drug release rate; ~100% drug release rate in 15 min for both liqui-pellet formulations. The dissolution test results from these two liqui-pellet formulations are in fact more superior than solid dispersion, liquisolid compact and solid self-dispersing mixed micelle forming system (chapter 6 and 7). Since liqui-tablet is essentially compacted liqui-pellet, it has the same advantages of liqui-pellet and arguably more as capsule filling process can be eliminated.

The compaction of pellets into tablet is a challenging field of research, however, if successfully made, it holds the key advantages of MUPS when that tablet reverts back to MUPS [102,154]. Nonetheless, compaction process could lead to pellets fusing to each other to form a non-disintegrating matrix, preventing it from reverting back into individual pellets in the GIT, which would eliminate the inherent advantages of MUPS [102]. Also, compaction process poses a major challenge for film coated pellet, where functional polymeric coating is prone to damage/rupture during compression process, resulting to unintended changes of drug release profile [102,154,167,223].

In this investigation, for the first time ever, an attempt will be made to study the feasibility of compacting liqui-pellet into liqui-tablet. Also, the key objective is to see if liqui-tablet can also achieve rapid drug release like liqui-pellet. Fortunately, the liqui-pellet used are not film coated so issue of coating material rupturing will not be present; however, there are numerous reason polymeric coating will become relevant to liqui-tablet in the near future. There are many reason for film coating to be applied to compacted pellets which includes: modified release; taste masking; improved appearance; improved stability and improved mechanical integrity [102].

8.3 Materials and methods

8.3.1 Materials

The materials used are the same as in the materials mention in chapter 6 section 6.3.1.

8.3.2 Preparation of naproxen liqui-tablet

The liqui-tablet formulations were prepared via compacting liqui-pellets under specified compression force using a manual tablet press machine (Compaction model MTCM-I, Globe pharma, UK). The liqui-pellets were prepared in the same manner as in chapter 6 section 6.3.2. Table 9.1 contains detail of the parameters of each formulation.

Table 8.1. Key formulation characteristics of the investigate liqui-tablet

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Liquid vehicle concentration (% w/w)	Liquid load factor	Primojel (mg)
Physical mixture 1	7.00			5.91
Physical mixture 2	7.00			5.91
F-1	5.60	19	1	5.92
F-2	3.12	23	1.23	7.69
F-3	3.20	19	1	5.92
F-4	3.20	23	1.23	5.92
F-5	3.20	23	1.23	5.92
F-6	3.20	23	1.23	5.92
F-7	5.60	19	1	5.92
F-8	3.12	23	1.23	7.69

Formulation	Carrier type	Mass of carrier (mg)	Mass of coating material (mg)	Compression force (PSI)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture 1	100% avicel PH101	58.06	2.90	400	135.25
Physical mixture 2	100% avicel PH101	58.06	2.90	800	135.25
F-1	100% avicel PH101	62.54	3.15	400	197.20
F-2	100% avicel PH101	55.06	2.75	400	197.20
F-3	50% avicel PH101 & 50% neusilin US2	62.54	3.15	400	197.20
F-4	50% avicel PH101 & 50% neusilin US2	55.06	2.75	400	197.20
F-5	50% avicel PH101 & 50% neusilin US2	55.06	2.75	600	197.20
F-6	50% avicel PH101 & 50% neusilin US2	55.06	2.75	800	197.20
F-7	100% avicel PH101	62.54	3.15	800	197.20
F-8	100% avicel PH101	55.06	2.75	800	197.20

Note all formulation contain 25mg of naproxen, 32% w/w $NaHCO_3$ and the carrier to coating material is at a ratio of 20:1

8.3.3 Pre-compacted flowability test

Carried out in the same manner as described in chapter 1 section 2.3.5.

8.3.4 Friability test on formulated liqui-tablet

All formulations were subjected to friability test, where 10 liqui-tablet of each formulation was placed in a friabiliator chamber (D-63150, Erweka, Germany) and set under constant rotation of 25 rpm for 4 min. The % weight loss of samples was calculated using the weight of samples before and after the friability test.

8.3.5 Tablet hardness test

All liqui-tablet formulations were subjected to tablet hardness test except for formulations F-2 and F-8, which were too soft for tablet hardness test. For each formulation, liqui-tablets were placed in a tablet hardness tester (TBH 125, Erweka, Germany) where the diameter and thickness of each tablet were measured. The tablet hardness tester then measured the amount of force in N requires to fracture the tablet. This was repeated 5 times for each formulation and an average mean was calculated.

8.3.6 In-vitro drug release test

Carried out in the same manner as described in chapter 7 section 7.3.7.

8.3.7 Accelerated stability test

Stability test was conducted on formulation F-5 which is considered one of the best optimized formulation in this investigation. The storage temperature of the accelerated stability test was kept at 40 °C with relative humidity of 75% for a period of 3 months. Observation of physical changes was recorded and in-vitro drug release studies were carried out each month for 3 months.

8.3.8 Kinetic model analysis of drug release

Carried out in the same manner as described in chapter 2 section 2.3.11.

8.3.9 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.3.13.

8.4 Results and discussion

8.4.1 Pre-compression flowability studies on liqui-tablet

According to flowability results in Table 8.2, there are no issues in terms of flow properties for all formulations. The inference from the angle of repose method shows that all formulations achieve excellent flow property. There is more variation from the CI, however, there is no issue in flowability as the results ranged from excellent to good flowability. Such results are typical of liqui-pellet formulations and further support the claim that liqui-pellets have overcome the issue of poor flowability that was prevalent in the classical liquisolid technology.

Table 8.2. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulations (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture 1	8.75 ± 0.19	24.39 ± 0.56	13.32 ± 0.00	Excellent flowability	Good flowability
Physical mixture 2	8.75 ± 0.19	24.39 ± 0.56	13.32 ± 0.00	Excellent flowability	Good flowability
F-1	8.10 ± 0.17	26.71 ± 0.20	10.23 ± 0.00	Excellent flowability	Excellent-good flowability
F-2	7.81 ± 0.28	28.92 ± 0.49	10.33 ± 1.14	Excellent flowability	Excellent to good flowability
F-3	7.86 ± 0.19	28.58 ± 1.00	11.17 ± 0.00	Excellent flowability	Good flowability
F-4	8.37 ± 0.11	26.83 ± 0.79	10.23 ± 0.00	Excellent flowability	Excellent to good flowability
F-5	8.37 ± 0.11	26.83 ± 0.79	10.23 ± 0.00	Excellent flowability	Excellent to good flowability
F-6	8.37 ± 0.11	26.83 ± 0.79	10.23 ± 0.00	Excellent flowability	Excellent to good flowability
F-7	8.10 ± 0.17	26.71 ± 0.20	10.23 ± 0.00	Excellent flowability	Excellent-good flowability
F-8	7.81 ± 0.28	28.92 ± 0.49	10.33 ± 1.14	Excellent flowability	Excellent to good flowability

[a] For the composition of each formulation refer to Table 8.1
[b] SD, standard deviation from the mean.

8.4.2 Friability studies

The compaction of liqui-pellets into liqui-tablet was successful, however, not all formulations passed the friability test, which suggests that some formulations are not robust enough (Table 8.3). Physical mixture 1 and formulations F-1, F-2, F-7 and F-8 all failed the friability test due to fracturing. It is interesting to note that all of those failed formulations did not contain neusilin US2, and all of the formulations that passed the friability test contain neusilin US2. Hence, it seems that carrier composition is an important factor to consider in liqui-tablet production. It is speculated that the extremely large specific surface area of neusilin US2, which is 300 m^2/g [224], may have contributed to the sufficient

bonding strength upon compaction of the liqui-pellets; hence, liqui-tablets containing neusilin US2 were robust enough to pass the friability test. In addition, tablet hardness test results (Table 8.4) show that formulations containing neusilin US2 have increased hardness.

Both physical mixture 1 and 2 have the exact same composition; the only difference is that different compression forces were applied; 400 PSI and 800 PSI respectively. Physical mixture 1, which underwent lower compression force, failed the friability test, whereas physical mixture 2, which compressed at higher force, passed the test. This suggests that compaction force influences the physical property of physical mixture tablet and that higher compaction force seems to result to a more robust liqui-tablet.

All liqui-tablets which contain neusilin US2 passed the friability test despite the differences in liquid vehicle concentration and compression force. Thus, neusilin US2 seems to be the single most important factor in liqui-tablet that influences the dosage form robustness. Note that these liqui-tablet formulations have 0% weight loss after being subjected to the friabilator, which is due to the plastic property of the formulations. This plastic property makes the tablet resistant to friability.

Although some formulations failed the friability test due to the fracturing of the liqui-tablet, it should be noted that there are simple approaches to overcome this issue such as incorporating binding excipient, manipulating the liqui-pellet physical properties or incorporating a mixture of excipient-based pellet with the liqui-pellet. Such modifications will be carried forward in future work regarding liqui-tablet.

Table 8.3. Friability test results of all formulations

Formulation[a]	% weight loss	Fractured (Yes/No)	Pass/Fail
Physical mixture 1	na	Yes	Fail
Physical mixture 2	0.15	No	Pass
F-1	na	Yes	Fail
F-2	na	Yes	Fail
F-3	0.00	No	Pass
F-4	0.00	No	Pass
F-5	0.00	No	Pass
F-6	0.00	na	Pass
F-7	na	Yes	Fail
F-8	na	Yes	Fail

[a] For the composition of each formulation refer to Table 8.1

8.4.3 Tablet hardness test

The tablet hardness test results (Table 8.4) show that compression force has major influences on the hardness of physical mixture tablet, but hardly any influences on liqui-tablet formulations. Physical mixture 1 and 2 have the exact same composition, but physical mixture 2 was compressed with double the amount of force compared to physical mixture 1 (800 PSI and 400 PSI respectively), which results to physical mixture 2 having around double the hardness of physical mixture 1 (56.8 N and 102.6 N respectively). However, in the case for liqui-tablet, the compression force seems to have hardly any effect on tablet hardness. This can be seen in formulation F-1 and F-7, where both formulations have the same composition (Table 9.1) but F-7 was compressed with twice as much force than F-1 (800 PSI and 400 PSI respectively). Despite the difference in compression force, both F-1 and F-7 hardness are not very much different (85.2 N and 73.6 N respectively). A similar observation was made for formulation F-4, F-5 and F-6 where their composition is the same but compression force differs (400 PSI, 600 PSI and 800 PSI respectively), but their hardnesses are similar (54.6 N, 60.6 N and 52.4 N respectively).

It is observed that liquid vehicle concentration has major influences on liqui-tablet hardness. When liquid vehicle concentration is increased the hardness of liqui-tablet is reduced. This is shown in formulations F-3 and F-4 where both compositions are the same except for the amount of liquid vehicle (concentration of tween 80 of 19% w/w and 23% w/w respectively). With the higher concentration of tween 80 in F-4 in comparison to F-3, the tablet hardness is reduced considerably (54.6 N and 90.4 N respectively). The influences of the liquid vehicle are also shown in F-1 and F-2, where both formulations are identical except that F-2 has higher concentration of tween 80 than F-1, which results to F-2 being too soft for the tablet hardness test. A similar observation is made for F-7 and F-8 where F-8 having the higher amount of tween 80, is too soft for tablet hardness test to be carried out. Hence, liquid vehicle concentration is one of the major parameters that determines liqui-tablet hardness.

Another observed parameter that has major influences on tablet hardness is the carrier composition. Formulations containing neusilin US2 increase liqui-tablet hardness. This is shown in F-2 and F-4 where both have the same high concentration of tween 80 (23% w/w) and compressed at the same force (400 PSI); however, only F-2, which is absent of neusilin US2, is too soft to be subjected to the tablet hardness test. The same observation

is made in F-8 and F-6, where F-8, which does not contain neusilin US2, is too soft to be tested by the tablet hardness tester.

Overall, liquid vehicle concentration and carrier composition are important factors to consider in terms of liqui-tablet hardness. As for compression force, it does not seem to have any observable effect on liqui-tablet hardness.

Table 8.4. Tablet harness test results of all formulations

Formulation[a]	Mean thickness ± SD[b] (mm)	Mean diameter ± SD[b] (mm)	Mean hardness ± SD[b] (N)
Physical mixture 1	5.98 ± 0.05	5.23 ± 0.02	56.80 ± 10.94
Physical mixture 2	5.60 ± 0.01	5.25 ± 0.01	102.60 ± 13.03
F-1	7.92 ± 0.05	5.25 ± 0.01	85.20 ± 8.11
F-3	7.55 ± 0.02	5.26 ± 0.01	90.40 ± 2.70
F-4	7.66 ± 0.02	5.26 ± 0.00	54.60 ± 3.13
F-5	7.61 ± 0.03	5.25 ± 0.00	60.60 ± 5.27
F-6	7.60 ± 0.02	5.27 ± 0.01	52.40 ± 2.51
F-7	7.87 ± 0.02	5.26 ± 0.01	73.60 ± 5.59

[a] For the composition of each formulation refer to Table 8.1
[b] SD, standard deviation from the mean

8.4.4 In-vitro dissolution test

The dissolution test results of all formulations at acidic condition (pH1.2), which is used to mimic the stomach condition, are shown in Figure 8.1. The results show a general trend that increasing liquid vehicle concentration results to increase of drug release rate. This is shown when comparing similar formulations with different liquid vehicle concentration such as: F-1 (tween 80 19% w/w) and F-2 (tween 80 23% w/w), where F-2 have ~17% more drug release after 2 hours than F-1 (f_1= 23.61 and f_2= 38.89); F-7 (tween 80 19% w/w) and F-8 (tween 80 23% w/w), where F-8 have ~17% more drug release after 2 hours than F-7 (f_1= 24.55 and f_2= 38.03); F-3 (tween 80 19% w/w) and F-4 (tween 80 23% w/w), where F-4 have ~4% more drug release after 2 hours than F-3 (f_1= 8.71 and f_2= 47.52). Such observation is in agreement with the author's previous studies on the crucial effect of co-solvent in liqui-pellet. The increase in co-solvent/ liquid vehicle increases the proportion of API being solubilized or in a molecularly dispersed state, which results to an increased in surface area available for dissolution [3]. In accordance to Noyes-Whitney equation, surface area available for dissolution is directly proportional to dissolution rate; hence, more liquid vehicle would result in a faster drug release rate [40]. Also, since tween 80 reduces surface tension/ cohesive force, the higher the amount of tween 80 the greater the extent of

disintegration; thus, further enhancing the drug release. A similar finding in terms of tween 80 improving propensity of the disintegration of MCC-based pellet was observed by Chamsai and Sriamornsak [127].

When comparing formulations with identical composition but under different compression force, there is no observable effect on drug release rate. This can be seen when comparing F-1 and F-2/ F-7 and F-8/ F-4/ F-5 and F-6. Unlike compressed powdered tablet, where compression force can significantly influence propensity of disintegration and consequently drug release rate, the liqui-tablet reverts back to pellet form under a minute; hence, there is less variation in disintegration and drug dissolution rate for liqui-tablet made under different compression force.

Formulations with neusilin US2 have significantly faster drug release rate than formulations absent of neusilin US2. This is shown when comparing formulation F-1 and F-3, where both have same liquid vehicle concentration and compression force, but F-3 has significantly faster drug release rate due to the presence of neusilin US2. Formulation F-3 reached 100% drug release after ~45 min, whereas F-1 only reached ~71% drug release after 2 h (f_1= 41.17 and f_2= 21.51). A similar observation is made in formulations F-2 and F-4, where F-4 drug release rate is considerably faster due to the presence of neusilin US2. Formulation F-4 start plateauing at 100% drug release at around 25 min, whereas F-2 only reached 86% drug release after 2 h (f_1= 27.18 and f_2= 28.33).

On comparing dissolution profile of formulation F6, which displayed one of the fastest drug release rate in this study, with the fastest drug releasing naproxen liqui-pellet from the author's previous work, liqui-tablet drug release is only slightly slower than liqui-pellet. The naproxen liqui-pellet from previous studies plateau at around 20 min, whereas F-4 plateau at around 25 min. Nonetheless, both drug release rate is very similar.

The dissolution test results at alkaline condition (pH7.4) mimics the small intestine pH condition where naproxen is soluble in are shown in Figure 8.2. It is surprising to see that the physical mixture tablet 1 and 2 had a faster drug release rate than the liqui-tablet formulations. It is postulated that since the API is soluble at this alkaline pH, the rate limiting step for drug release is the disintegration rate and surface area available for drug release. If that is the case, then perhaps the liquid vehicle in liqui-tablet is reducing the propensity of disintegration as it could be acting as a binding material; hence, displaying slower drug release. The results from Figure 8.2 also show that compression force does not have major

effect on liqui-tablet drug release rate as seen in formulations F-4, F-5 and F-6, where all of these formulations' composition are the same but the compression force applied to them are different (400 PSI, 600 PSI and 800 PSI respectively).

Overall, varying compaction force does not seem to have any influences on liqui-tablet drug release rate; however, on comparing liqui-tablet with previous liqui-pellet dosage form, liqui-tablet has a slightly slower drug release rate. Nonetheless, naproxen liqui-tablet drug release at acidic pH is still considered very fast (F-6 starting to plateau at 20 min) and more superior than naproxen solid dispersion [216] and naproxen liquisolid compact [15].

The concentration of liquid vehicle and the presence of neusilin US2 have major influences on drug release rate at acidic pH. As expected, the increase in liquid vehicle concentration improves the enhancement of drug release at pH 1.2. It is interesting to observe that at pH 7.4, the liquid vehicle in liqui-tablet could be responsible for slowing down the drug release rate possibly due to binding action, which reduces the propensity for disintegration. The presence of neusilin US2, which is part of the carrier material, improves the drug release rate considerably. Not only does neusilin US2 improves drug release rate but it also improves the robustness and hardness of liqui-tablet (Table 8.3 and 8.4), making it a valuable excipient in liqui-tablet. Future studies will include investigating different excipients that may improve liqui-tablet quality and drug release performance.

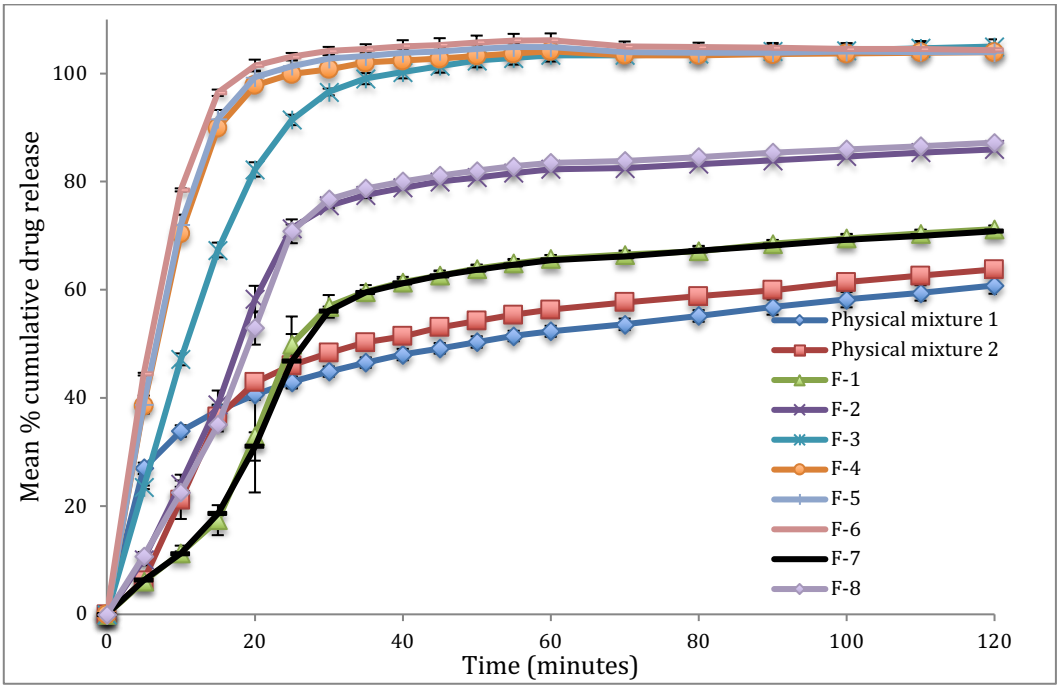


Figure 8.1. Dissolution profile of all formulations at pH 1.2 (n = 3)

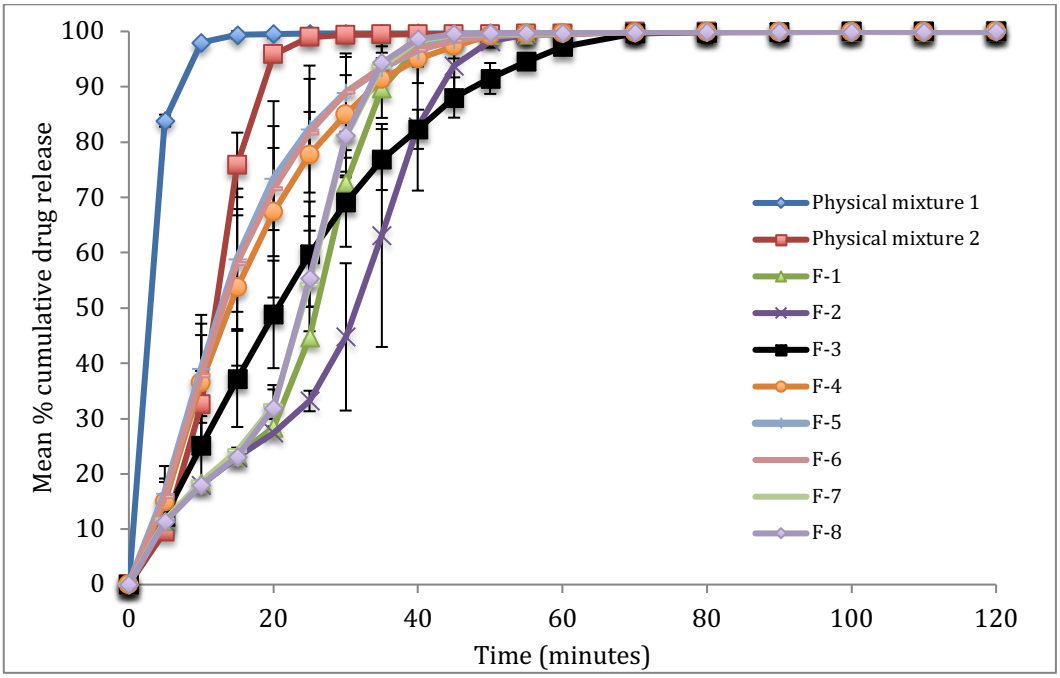


Figure 8.2. Dissolution profile of all formulations at pH 7.4 (n = 3)

8.4.5 Accelerated stability studies

The drug release rate of formulation F-5 (Figure 8.3) was investigated under stress condition specified under the accelerated stability test over 3 months. In comparing F-5 drug dissolution profile at month 0 and a month after it (month 1), there is a difference in the dissolution profile (f_1 = 22.52 and f_2 = 42.61), indicating some degree of decrease in drug release. This difference in dissolution profile may be due to changes in the formulation over

storage time such as pellet became harder over time. The decrease in drug release becomes less apparent after the first month where F-5 drug dissolution profile in month 1 and month 2 show f_1 = 3.03 and f_2 = 80.61. A similar observation is made between month 2 and month 3 where f_1 = 5.01 and f_2 = 72.46.

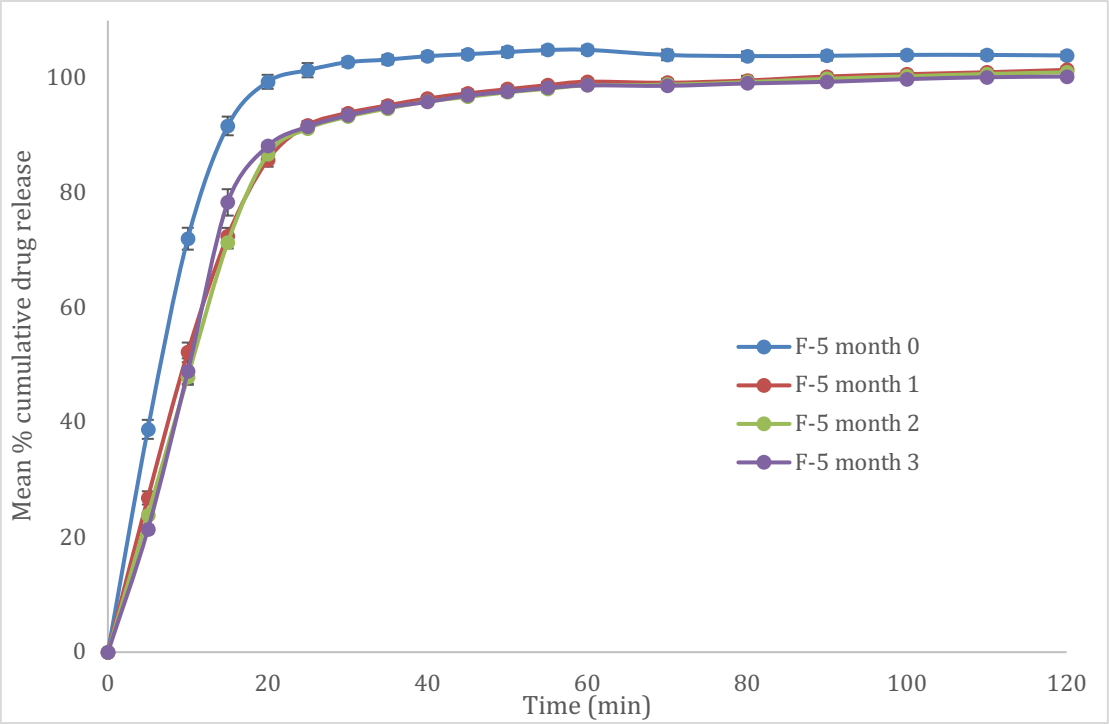


Figure 8.3. Stability test of formulation F-5 represented through dissolution profile taken each month over the period of 3 months under pH 1.2 (n = 3)

8.4.6 Kinetic model analysis of drug release

Correlation coefficients value (R^2) for each formulation in relation to zero order, first order and Higuchi's drug release kinetic model is shown in Table 8.5. Most naproxen liqui-tablet formulation is best described by zero order kinetic model under pH 1.2. This is interesting as data from previous chapters show naproxen liqui-pellet tends to fall under first order or Higuchi's kinetic model under pH 1.2. Kinetics studies for F-5 under accelerated stability test condition show that the drug release kinetic remains to best fit zero order kinetic, hence showing drug release kinetic of the liqui-tablet does not change over the investigated time (Table 8.6).

Table 8.5. Release parameters of naproxen liqui-tablet formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture 1	0.895	0.917	0.991
Physical mixture 2	0.970	0.952	0.809
F-1	0.956	0.919	0.789
F-2	0.993	0.949	0.865
F-3	0.977	0.971	0.959
F-4	0.980	0.970	0.974
F-5	0.980	0.963	0.972
F-6	0.967	0.940	0.983
F-7	0.965	0.925	0.800
F-8	0.987	0.922	0.850

Table 8.6. Release parameters of naproxen liqui-tablet formulations that was used in the accelerated stability test at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
F-5 (after 0 month)	0.980	0.963	0.972
F-5 (after 1 month)	0.984	0.980	0.960
F-5 (after 2 month)	0.994	0.960	0.938
F-5 (after 3 month)	0.995	0.928	0.883

8.5 Conclusion

The first ever liqui-tablet formulation has been successfully made using naproxen as the drug model. On comparison to the rapid drug release naproxen liqui-pellet from previous studies, it can be concluded that the rapid drug release is maintained in liqui-tablet dosage form; however, a slight reduction in drug dissolution rate was observed. Nonetheless, when comparing the dissolution profile of the best naproxen liqui-tablet with other studies concerning naproxen solid dispersion and liquisolid compact, the drug release rate of liqui-tablet is more superior.

It is interesting how the liquid vehicle in naproxen liqui-tablet under pH 7.4 actually slows down the drug release rate. This is possibly due to liquid vehicle binding effect within the liqui-tablet, which reduces the propensity for disintegration. The disintegration step seems to be the rate-determining step at this pH as API solubility is no longer an issue.

The studies also confirm that compaction force during tableting has no significant effect on liqui-tablet drug release. The presence of neusilin US2 in liqui-tablet formulations have shown to be an important factor to achieve ideal liqui-tablet physical properties such

as, robustness and hardness, as well as allowing faster drug release rate to be achieved. Furthermore, accelerated stability studies have shown that although, the stored formulation dissolved a bit slower than month 0, still they can release the whole drug within the formulation in 2 hours with a good dissolution stability over 3 months.

Chapter 9: Producing 100mg ketoprofen liqui-tablet

9.1 Abstract

Liqui-tablet in the most simplistic form is compressed liqui-pellet. Liqui-pellet comes from combining concepts from liquisolid technology with pelletization technology, which has proven to be a promising approach to improve drug dissolution rate and consequently bioavailability of poorly water-soluble drug. Previous studies have shown that liqui-tablet is feasible for low dose drug. In this study, an attempt is made to produce high dose liqui-tablet (100mg ketoprofen). The purpose is to bring forward the unique intrinsic advantages of liquisolid concept to high dose drug, whilst maintaining ideal physicochemical properties for commercial manufacturing. This has never been achieved before in liquisolid technology. Liqui-tablet containing 100mg of ketoprofen were successfully produced using various liquid vehicle including span 80, PEG 200, PG, kolliphor EL and tween 85. The weight of these liqui-tablets was acceptable for swallowing (483.8mg) and the saturation solubility test show PEG 200 to be the most suitable liquid vehicle. Tests investigating physicochemical properties such as flowability, particle size distribution, friability and tablet harness show no issue concerning quality control requirement and manufacturing. Drug release test of the best formulation shows extremely rapid drug release at pH 7.4 (100% after 5 min), which is much more superior than liquisolid compact. At pH 1.2 the drug release is reasonable considering the formulation is yet to be optimized. Overall, the study further supports the potential to diversify the technology due to the promising results concerning performance and feasibility for commercial manufacturing.

9.2 Introduction

The key introductory points are covered in chapter 2 section 2.2, 3.2, 4.2, 5.2, 6.2, 7.2, and 8.2; however, further background relating to this chapter will be covered here.

Ketoprofen is a weakly acidic nonsteroidal anti-inflammatory (NSAID) drug with analgesic and antipyretic action, which is widely used for rheumatoid arthritis, cancer and postoperative pain. It is poorly water-soluble and belongs to class II according to biopharmaceutics classification system (BSC). It works by inhibitory effect on peripheral COX-1 and COX-2, which in turn reduces the synthesis of prostaglandin and thromboxane precursor [225]. Ketoprofen poor water-solubility makes it a suitable drug candidate to be

made into liqui-tablet dosage form, due to liqui-tablet enhanced drug release in an aqueous medium.

In compaction of uncoated pellets, it has been suggested that there are four stages involved. They are: 1) rearrangement of pellets, 2) surface deformation, 3) bulk deformation and 4) cessation of volume reduction [102,156]. During the low compression force of rearrangement of pellet, the pellets fill the inter-particle void, reducing the volume [102,156]. At moderate compaction force, the reduction of volume is caused by local surface deformation, where surface of pellets is flattened [102,156]. At high compaction force, bulk deformation of pellets occurs, which mean the change in pellet dimension is in parallel to densification of pellet [102,156]. Still under high compaction force, however, there is no further volume reduction due to low inter-granular and intra-granular porosity at the fourth stage.

In spite of the array of advantages in pellet-based tablet (provided that it reverts back to MUPS), the manufacturing of such dosage form is an extremely challenging area of study. The content uniformity of compacted pellet can be influenced by the size of the pellets, pellet size distribution and the size of additional excipients. In general, compaction of pellets together with excipient of smaller particle size, results in high variation in mass and size due to a segregation phenomenon [171]. The main challenge however, concerns with coated pellet. The induced damage of functional polymeric coating due to compression process poses a major issue in pellet-based tablet. Fortunately, the liqui-pellet used are not film coated so the issue of coating material rupturing is not of concern.

Ideally, the compacted pellet should rapidly revert back to MUPS with the same drug release profile as the uncompressed MUPS [102,154]. The pellet core should be soft enough to deform under the compression force without brittle fracture, but hard enough to resist compression force to prevent permanent fusion of the pellets [102,154]. In other words, the major mechanism during compaction of pellet should be elastic deformation as oppose to plastic deformation [155].

Since MCC-based pellet is used in this investigation, it is noteworthy to point out some of the observations in studies relating to compression of MCC-base pellet by Johansson *et al* [156,157]. They observed that MCC-based pellet compressed by deformation and the incidence of pellet fragmentation is very low or non-existence. It is also stated that MCC-based pellet is inappropriate for enhanced drug release formulation as it does not

disintegrate quickly [154]. However, in the author of this thesis previous studies, rapid drug release can be achieved in liqui-pellet which contain MCC as the main bulking agent.

In this investigation, the aim is to further explore the potential of liqui-tablet (and effectively liqui-pellet too); to see the feasibility of producing high dose liqui-tablet (100mg ketoprofen) whilst maintaining suitable size and weight for swallowing. The intention is to diversify the technology, allowing high dose liqui-tablet or liqui-pellet to be produced in a commercially acceptable manner, which is not possible in liquisolid formulation.

9.3 Materials and methods

9.3.1 Materials

Ketoprofen was obtained from Tokyo Chemical Industry Co (Japan). Other excipients used to prepare the liqui-tablet included microcrystalline cellulose (avicel PH-102), (FMC corp., UK); colloidal silicon dioxide (aerosil 300), (Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (primojel); polyethylene glycol 200 (Fisher Scientific, Leicester, UK); propylene glycol (SAFC, Spain); polysorbate 85 (Tween 85), (Acros, Netherlands); sorbitan laurate (Span 20), (Gattefosse, Saint Priest, France) and macrogolglycerol ricinoleate 35 (Kolliphor EL), (BASF SE, Ludwigshafen, Germany). All other reagents and solvent were of analytical grades.

9.3.2 Saturation solubility test

Saturated solubility test of ketoprofen in five different liquid vehicles was performed. The liquid vehicles used were: span 80, polyethylene glycol 200 (PEG 200), propylene glycol (PG), kolliphor EL and tween 85. Saturated solutions were prepared by adding excess ketoprofen in a small vial containing 10ml of specified liquid vehicle. The samples were then left in a bath shaker (OLS Aqua Pro, Grant Instruments Ltd, UK) for 24 h under a constant temperature of 37^{o}C and shaking speed of 60rpm. The supernatant was then filtered through a pre-heated filter (pore size 0.22 μm, Millex GP, Merck Millipore Ltd, Ireland), and diluted with phosphate buffer solution (pH 7.4). This was then analyzed via UV/vis spectrophotometer (Biowave II, Biochrom Ltd, UK) to determine the concentration of ketoprofen in each sample. Each test was carried out in triplicates.

9.3.3 Preparation of Ketoprofen liqui-tablet

The liqui-tablet formulations were prepared via compacting liqui-pellets under a compression force of 800PSI using a manual tablet press machine (Compaction model MTCM-I, Globe pharma, UK). All liqui-pellet formulations were produced in a similar manner except for the variation in parameters such as types of liquid vehicle and water content as shown in Table 9.1. The liquid medication was prepared by mixing ketoprofen and specified liquid vehicle using pestle and mortar. This mixture was then incorporated into a specified carrier material alongside primojel ~5% w/w (primojel added intragranularly). The admixture was mixed for 2 min at a constant rate of 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). A specified amount of deionized water (granulating liquid) was added bit by bit to achieve reasonable plastic property for extrusion (Caleva Multitab, Caleva Process Solutions Ltd, UK). The admixture with water was mixed for 5 min, then Aerosil 300 (coating material) was added and further mixed for another 5 min before extrusion. Once the sample was extruded, the extrudates were spheronized at an almost constant rotation at 4000rpm (decrease to 2000 rpm if agglomeration seemed likely). The spheronization time varied depending on the extrudates' plastic property to avoid agglomeration. The pellets were then placed in an oven under a constant temperature of 40^{o}C overnight to remove the water content.

Also note that physical mixture pellet was prepared in a similar manner as above, but without liquid vehicle incorporated. All formulations' carrier to coating material ratio were kept constant at 20:1 respectively. The final weight of all liqui-tablet formulations was 483.8mg and physical mixture tablet was 353.8mg.

Table 9.1. Key formulation characteristics of the investigate liqui-tablet

Formulation	Water content during extrusion-spheronization (ml) per 20g of admixture of API and excipient	Liquid vehicle	Amount of liquid vehicle (% w/w)	Mass of carrier (mg)	Mass of coating material (mg)	Total weight of 25mg naproxen liqui-pellet (mg)
Physical mixture	19.79			225	11.25	353.75
F-1	3.10	Span 80	25.84	225	11.25	483.75
F-2	3.10	PEG 200	25.84	225	11.25	483.75
F-3	3.10	PG	25.84	225	11.25	483.75
F-4	3.10	Kolliphor EL	25.84	225	11.25	483.75
F-5	3.10	Tween 85	25.84	225	11.25	483.75

Note all liqui-tablet formulations contain 100mg ketoprofen, primojel ~5%w/w, subjected to a compression force of 800 PSI, liquid load factor of 1 and the carrier to coating material is at a ratio of 20:1

9.3.4 Flowability test on pre-compressed formulation

Carried out in the same manner as described in chapter 1 section 2.3.5.

9.3.5 Particle size analysis on pre-compressed formulation

Carried out in the same manner as described in chapter 2 section 2.3.7.

9.3.6 Friability test

Carried out in the same manner as described in chapter 8 section 9.3.4.

9.3.7 Tablet hardness test

Carried out in the same manner as described in chapter 8 section 8.3.5.

9.3.8 In-vitro drug release test

All formulations were subjected to dissolution test in accordance to the USP paddle method (708-DS Dissolution Apparatus & Cary 60 UV-Vis, Agilent Technologies, USA). Each tablet contained 100mg of ketoprofen. The dissolution tests were carried out under the constant condition of 900 ml dissolution medium, temperature of 37.3 ± 0.5°C and paddle agitation of 50rpm. Dissolution medium used were either HCl buffer solution of pH 1.2 or phosphate buffer solution of pH 7.4 to simulate gastric fluid and intestinal fluid respectively in absence

of enzymes. Under acidic condition, the absorbance readings were taken at 260 nm at time intervals of 5 min for an hour then time interval of 10 min for another hour. Under alkaline condition, the readings were taken in the same manner as for acidic condition except readings were taken at 262nm. The chosen absorbance wavelength was according to Clarke's analysis of drug and poison [226].

9.3.9 Mathematical analysis

The similarity factor and difference factor were used for mathematical analysis. For details of the calculation refer to chapter 2 section 2.3.13.

9.3.10 Accelerated stability test

Stability test was conducted on formulation F-2, which had the fastest dissolution rate under pH 1.2. Storage condition was set at 40 °C with relative humidity of 75% for a period of 3 months. Dissolution profiles were recorded each month for 3 months.

9.3.11 Kinetic model analysis of drug release

Carried out in the same manner as described in chapter 2 section 2.3.11.

9.4 Results and discussion

9.4.1 Weight of liqui-tablet

Although all liqui-tablet contained 100mg of ketoprofen, the weight of all liqui-tablets is 483.8mg, which is considered acceptable for swallowing. In liquisolid formulation, such high dose API would have been near impossible to achieve with ideal flow properties. With poor flow property, commercial manufacturing would not be ideal. The high dose API would require an increase in carrier and coating material, rendering the liquisolid compact above 1g in weight [4]. However, liqui-tablets have proven itself capable of high dose API with acceptable weight, acceptable size and excellent pre-compression flow properties. With the capability of high dose drug in liqui-tablet, more variety of drugs will be suitable for this emerging dosage form.

Since high dose drug in liqui-tablet does not pose a major issue as it does in liquisolid formulations, there is potential for incorporation of functional excipients, bringing more flexibility and function in formulation design. 22

9.4.2 Saturation solubility test

The saturation solubility test results are shown in Table 9.2. According to the test results, it is clear that ketoprofen is most soluble in PEG 200 (~493mg/ml) followed by tween 85 (~295mg/ml), PG (~258mg/ml), kolliphor EL (~169mg/ml) then span 80 (~20mg/ml). This indicates that ketoprofen is freely soluble in PEG 200 and is the most likely suitable liquid vehicle candidate for ketoptofen enhanced drug release liqui-tablet.

In general, the solubility test results usually correspond to the dissolution test results, which mean greater solubility would lead to faster drug release. Although this agrees with the general trend, there are some discrepancies according to dissolution test results in Figure 9.2 and Figure 9.3. Furthermore, the dissolution profile trend differs in acidic and alkaline condition. Hence, it should be reminded that API solubility is not the only factor that can influence the drug dissolution rate. Other physicochemical characteristics of liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure and molecular mass may affect drug release [1]. Nevertheless, drug solubility in a liquid vehicle is a major factor that could greatly influence the drug release profile.

Table 9.2. Solubility of ketoprofen in various liquid vehicles at 37°C (n=3)

Non-volatile solvent	Mean concentration (mg/ml) ± SD[a]	Inference
Span 80	19.83 ± 2.85	Sparingly soluble
PEG 200	492.53 ± 2.26	Freely soluble
PG	257.64 ± 7.13	Freely soluble
Kolliphor EL	168.67 ± 0.39	Freely soluble
Tween 85	294.59 ± 6.54	Freely soluble

[a] SD, standard deviation

9.4.3 Pre-compression flowability test

Flow properties of pre-compressed formulations are shown in Table 9.3, where according to the angle of repose, all have excellent flowability. According to CI results, formulations range from excellent to good flowability. These flowability results are typical of liqui-pellet as observed in many studies relating to liqui-pellet, which further supports the claim that flow property is not a major issue in liqui-pellets as it is for liquisolid formulation.

Table 9.3. Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulations (n=3)

Formulation[a]	Flow Rate (g/sec) ± SD[b]	Angle of repose ± SD[b]	CI% ± SD[b]	Inference according to Angle of repose	Inference according to CI%
Physical mixture pellet	9.4 ± 0.36	20.52 ± 3.18	10.56 ± 0.00	Excellent flowability	Excellent-good flowability
F-1	7.20 ± 0.21	26.66 ± 0.95	10.92 ± 1.63	Excellent flowability	Excellent-good flowability
F-2	6.26 ± 0.12	27.59 ± 1.31	11.77 ± 0.00	Excellent flowability	Good flowability
F-3	7.42 ± 0.32	23.66 ± 2.13	12.5 ± 0.00	Excellent flowability	Good flowability
F-4	7.47 ± 0.42	24.63 ± 0.55	9.82 ± 1.70	Excellent flowability	Excellent flowability
F-5	7.20 ± 0.30	25.74 ± 0.60	11.36 ± 0.00	Excellent flowability	Good flowability

[a] For the composition of each formulation refer to Table 9.1
[b] SD, standard deviation from the mean.

9.4.4 Particle size analysis

All pre-compressed liqui-tablet formulations generally show narrow size distribution as shown in Figure 9.1. Narrow size distribution is ideal for manufacturing as it will reduce weight and content variation when filled into a capsule or a hopper for tablet production. The physical mixture pellets seem to have a wider size distribution than the pre-compressed liqui-tablet (or liqui-pellet), which suggest that liqui-vehicle influences size distribution.

It is noteworthy to state that size distribution of pellets is rather complex to control. There are numerous factors that can influence pellet size during the extrusion-spheronization process. These factors are: API and excipients size [87,90,100,107,150,220]; extruder types; extrusion speed; properties of extrusion screen; spheronization speed [80]; spheronization time [98,103,140,145] and spheronization load [103,104,140].

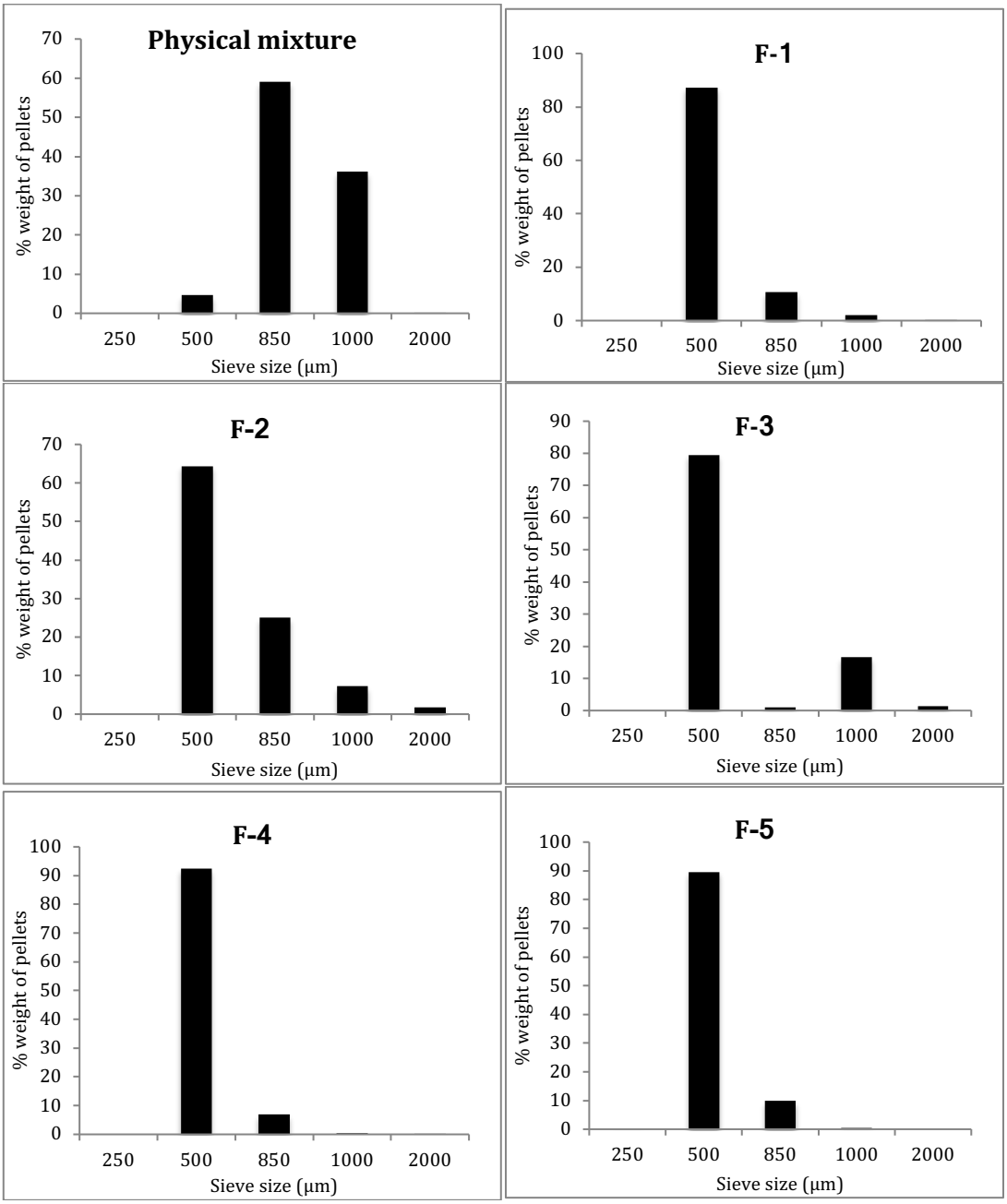


Figure 9.1. Graphs showing particle size distribution of all formulations via sieve method

9.4.5 Friability studies

The friability test results of all formulations are shown in Table 9.4. All liqui-tablet formulations show acceptable robustness as they all passed the friability test. This is crucial in the perspective of quality control test involved in commercialization. The physical mixture tablet, which does not contain liquid vehicle failed the friability test due to fracturing. Since all formulations were subjected to a compression force of 800 PSI, compression force parameter can be excluded; thus, it is reasonable to claim that the liquid vehicle is responsible for liqui-tablet robustness. It is postulated that the presence of liquid

vehicle in the tablet increases the tablet plasticity and reduces the brittleness; hence, the tablet can absorb impact better without fracturing the tablet during the tumbling in the friabilator.

Table 9.4. Friability test results of all formulations

Formulation	% weight loss	Fractured (Yes/No)	Passed/Failed
Physical mixture		Yes	Failed
F-1	0.01	No	Passed
F-2	0.01	No	Passed
F-3	0.02	No	Passed
F-4	0.02	No	Passed
F-5	0.01	No	Passed

9.4.6 Tablet hardness test

The results from tablet hardness test are shown in Table 9.5. Note that the physical mixture tablet was too brittle and fractured too easily that the tablet hardness test could not be performed. All other liqui-tablet formulations could undergo tablet hardness test, which suggests that liquid vehicle can improve tablet hardness.

It is clear that different liquid vehicles can influence the tablet hardness. Formulation containing PG is the hardest (F-3 hardness of 172.6 N) followed by kolliphor EL (F-4 hardness of 40 N), tween 85 (F-5 hardness of 34.8 N), span 80 (F-1 hardness of 25.2 N) then PEG 200 (F-2 hardness of 19.2 N). Since measuring tablet hardness is part of quality control test, it is crucial that liqui-tablets have acceptable hardness; thus, the choice of liquid vehicle may become an important factor regarding the dosage form hardness.

Table 9.5. Tablet harness test results of all formulations

Formulation[a]	Mean thickness (mm) ± SD[b]	Mean diameter (mm) ± SD[b]	Mean hardness (N) ± SD[b]
Physical mixture			
F-1	6.85 ± 0.04	10.09 ± 0.02	25.20 ± 1.92
F-2	6.74 ± 0.03	10.08 ± 0.04	19.20 ± 0.45
F-3	6.31 ± 0.01	10.2 ± 0.00	172.60 ± 10.53
F-4	6.72 ± 0.02	10.06 ± 0.01	40.00 ± 1.58
F-5	6.80 ± 0.01	10.09 ± 0.01	34.80 ± 2.59

[a] For the composition of each formulation refer to Table 9.1
[b] SD, standard deviation from the mean.

9.4.7 In-vitro dissolution test

The dissolution profile of all formulations at pH 1.2 is shown in Figure 9.2. Formulation F-2 shows the fastest drug release rate, where ~92% drug is released within 2 h. This is considered fast considering ketoprofen is virtually insoluble in acidic aqueous condition and that the formulation has not yet been optimized, i.e incorporation of an effervescent agent or optimizing composition ratio.

The next fastest enhanced release formulation is F-5, followed by either F-1 or F-4, then F-3. Formulation F-1 and F-4 dissolution profiles are similar, which is indicated in f_1= 9.12 and f_2= 67.54. As seen in saturation solubility test in Table 9.2, not all dissolution profiles correspond with the solubility test results, reminding that API solubility in liquid vehicle is not the only factor influencing the drug release rate.

Under alkaline pH of 7.4, the dissolution profile of all formulations generally improves (Figure 9.3); however, the hierarchy trend of drug release rate of various formulations is different from at acidic condition of pH 1.2. This indicates that the influence of liquid vehicle on liqui-tablets drug release rate is influenced by the environmental pH. Formulation F-2 remains to be the fastest enhanced drug release formulation followed by F-1, either F-3 or F-5, then F-4.

The drug release rate of F-2 at pH 7.4 is very rapid, where 100% drug is released within 5 min. This is extremely fast in comparison to ketoprofen liquisolid compact. In studies by KamalaKumari, TrinadhaRao *et al*, 100mg ketoprofen liquisolid compact achieved 100% drug release after 30 min under phosphate buffer solution of pH 7.4 [43]. It is clear that liqui-tablet drug release rate is by far more superior than liquisolid compact.

Ketoprofen liqui-tablet can achieve rapid drug release rate at pH 7.4 and reasonable dissolution rate at pH1.2 considering the formulation is yet to be optimized. The drug release performance along with acceptable dosage form weight and excellent pre-compressed flow property are ideal for commercial manufacturing.

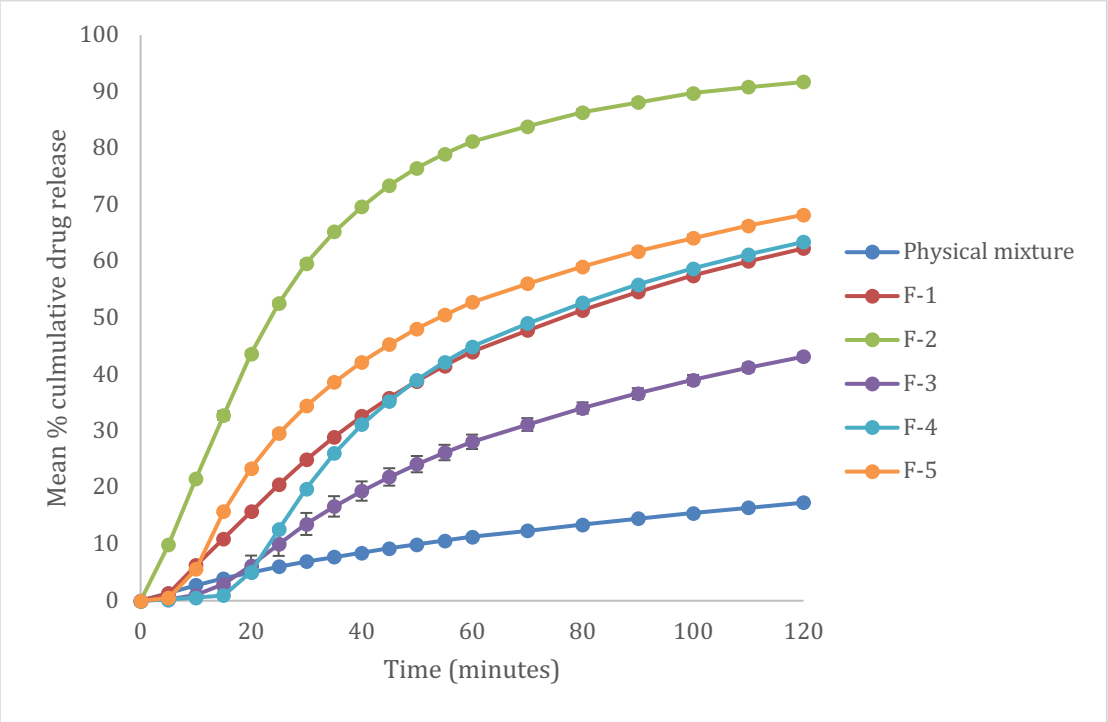


Figure 9.2. Dissolution profile of all formulations at pH 1.2 (n = 3)

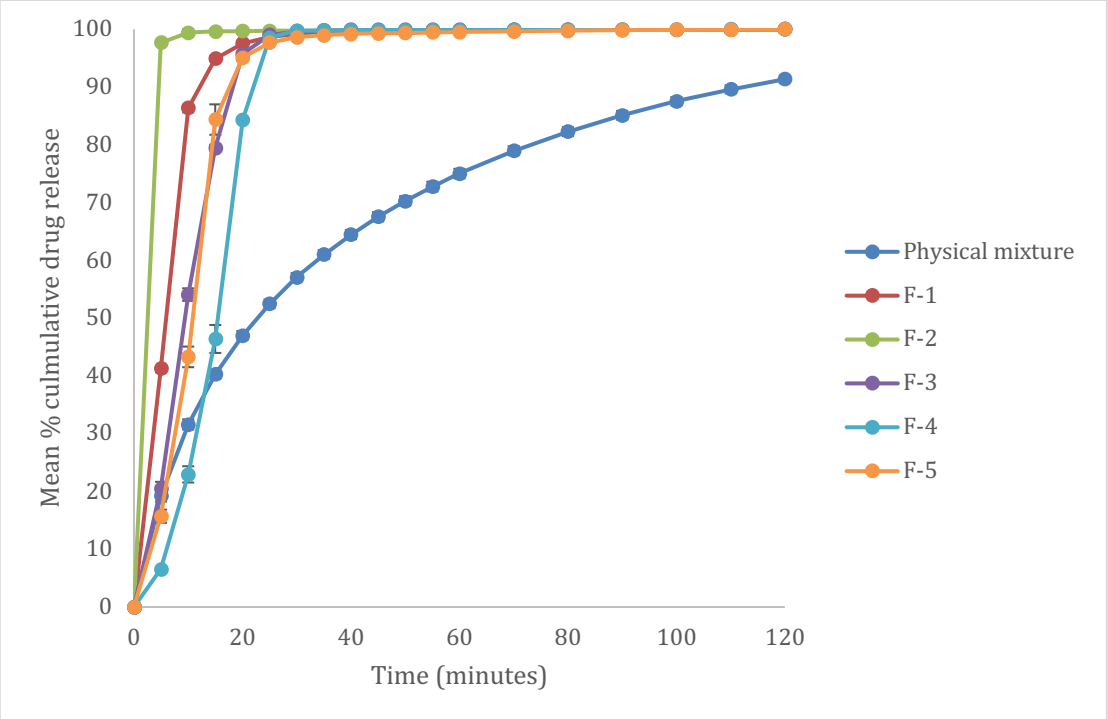


Figure 9.3. Dissolution profile of all formulations at pH 7.4 (n = 3)

9.4.8 Accelerated stability studies

The drug release rate of formulation F-2 (Figure 9.4) was investigated under stress condition specified under the accelerated stability test over 3 months. In comparing F-5 drug dissolution profile at month 0 and a month after it (month 1), there is no significant difference in the dissolution profile (f_1 = 9.2 and f_2 = 61.03). This is also observed after the first month where F-5 drug dissolution profile in month 1 and month 2 show f_1 = 2.98 and f_2 = 82.37. A similar observation is made between month 2 and month 3 where f_1 = 4.82 and f_2 = 75.67.

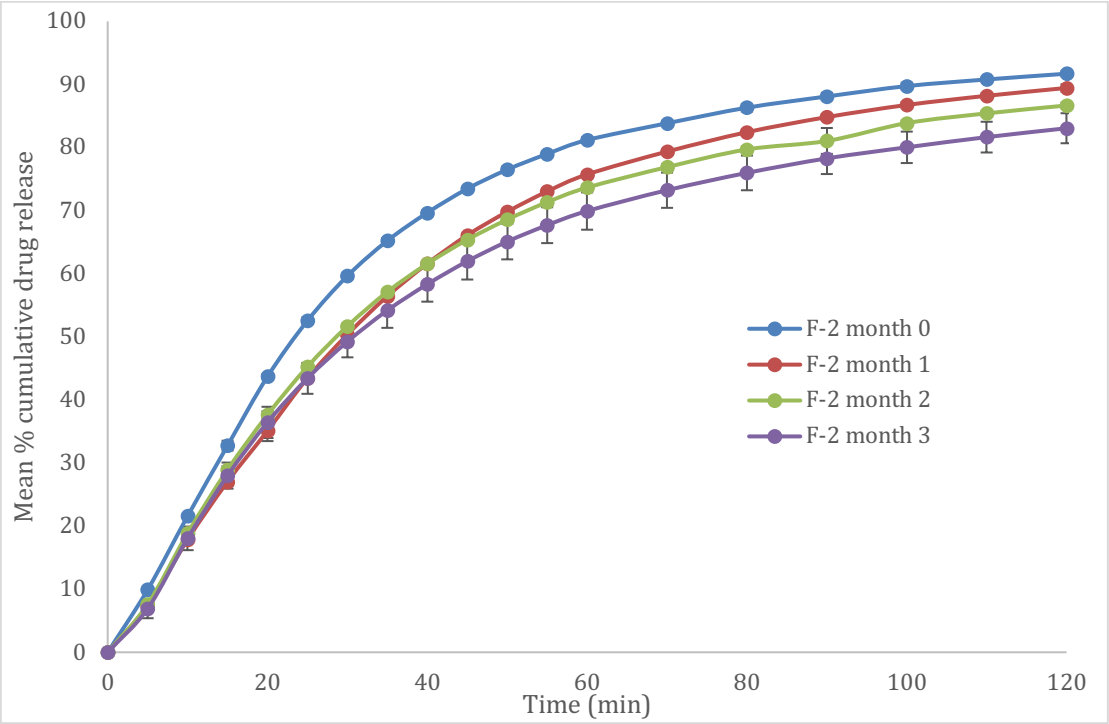


Figure 9.4. Stability test of formulation F-2 represented through dissolution profile taken each month over the period of 3 months under pH 1.2 (n = 3)

9.4.9 Kinetic model analysis of drug release

Correlation coefficients value (R^2) for each formulation in relation to zero order, first order and Higuchi's drug release kinetic model is shown in Table 9.6. All ketoprofen liqui-tablet formulation is best described by first order kinetic model under pH 1.2 except for F-4. Kinetics studies for F-2 under accelerated stability test condition show that the drug release kinetic remains to best first zero order kinetic, hence showing drug release kinetic of ketoprofen liqui-tablet does not change over the investigated time (Table 9.7).

Table 9.6. Release parameters of ketoprofen liqui-tablet formulations at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
Physical mixture	0.967	0.976	0.985
F-1	0.940	0.986	0.971
F-2	0.989	0.996	0.939
F-3	0.983	0.983	0.864
F-4	0.960	0.957	0.815
F-5	0.873	0.958	0.958

Table 9.7. Release parameters of ketoprofen liqui-tablet formulations that was used in the accelerated stability test at pH 1.2

Formulation	Zero order R^2	First order R^2	Higuchi R^2
F-2 (after 0 month)	0.989	0.996	0.939
F-2 (after 1 month)	0.987	0.998	0.947
F-2 (after 2 month)	0.976	0.998	0.955
F-2 (after 3 month)	0.986	0.997	0.937

9.5 Conclusion

The studies show that it is possible to produce high dose liqui-tablet (100mg ketoprofen), whilst maintaining acceptable weight (483.8mg) and excellent pre-compression flow properties. This is a major advancement as it takes liquisolid concept into a commercially feasible direction for high dose drug, which is impossible or near impossible in the liquisolid technology. Through overcoming dosage form bulky weight issue of high dose drug in liquisolid formulation, liqui-tablet will have a wider range of high dose API it can be applied to. Not only acceptable weight and excellent pre-compression flow properties are observed, but the studies also show ketoprofen liqui-tablet to have acceptable robustness and acceptable stability, which is considered ideal in terms of manufacturing and quality control test.

Among the liquid vehicle used in the study, PEG 200 is the most suitable for enhanced drug release of ketoprofen liqui-tablet. It is also observed that at different pH the influence of liquid vehicle on drug release rate changes to a point that some formulations may perform better than others depending on the pH environment.

Liqui-tablet PEG 200 shows an extremely rapid drug release at pH 7.4 (100% after 5 min), which is much more superior than liquisolid compact. At pH 1.2 the drug release is reasonable considering the formulation is yet to be optimized. There is still potential for formulation parameters to be optimized and functional excipients (i.e effervescent agent) to be incorporated. Furthermore, since liqui-tablet is essentially compressed liqui-pellet, the new findings also apply to high dose liqui-pellet formulation.

Chapter 10: Summary, conclusion and future work

10.1 Summary and general conclusion

The fundamental aim of the investigation is to enhance drug release rate to improve the bioavailability of poorly water-soluble drug, which is a major challenge in the pharmaceutical industry. In order to do this, an endeavour to bring forward the concept from liquisolid technology into a commercially feasible oral dosage form is the primary purpose of this investigation. This was done by attempting to overcome key drawbacks in liquisolid formulation, which included poor flow property and the inability to produce dosage form with high dose drug that had acceptable weight and size for swallowing. This led to the invention of liqui-pellet, a combination of concept from liquisolid technology and pelletization technology. Liqui-pellet mechanism of enhanced drug release was similar to that of liquisolid formulation. The mechanism for enhancing drug release included: increased in surface area available for dissolution, increased solubility of the drug and improved wettability of drug particle.

Naproxen liqui-pellet was successfully made and showed promising results in terms of flow property. The liqui-pellets were able to achieve high liquid load factor (or just high amount of liquid vehicle) whilst maintaining excellent flow property, which has not yet been seen in liquisolid technology. Although excellent flowability was achieved in the initial studies, the drug release rate was too slow, which was not surprising as the carrier used was MCC. MCC-base pellet is known to not disintegrate well and is not suitable for fast release formulation. Hence, an attempt was made to optimize the formulation to improve the drug dissolution rate. It was observed that formulations with less water (granulating liquid) added during the mixing process formed liqui-pellet with better drug dissolution rate. The reduced water content in liqui-pellet formulations clearly improved the propensity of disintegration, which seemed to be the rate-limiting factor for liqui-pellet drug release.

One of the optimized naproxen liqui-pellet formulations achieved excellent-good flow property despite containing high liquid load factor of 1.52, where 38% of the total mass is co-solvent. This is a crucial indication of the potential in liqui-pellet as such a result would not have been possible with liquisolid formulation.

Due to MCC being one of the main carrier used liqui-pellet, water content was an important parameter as it contributed to the bonding within the pellet structure; thus, a

further investigation was made on the effect of the amount of water as well as the amount of liquid vehicle on the dosage form. It was observed that the combined effect of reduced water content and increase in liquid vehicle (i.e. tween 80) showed a significant increase in drug release rate. The reduction of water content effectively reduced cohesive strength of the liqui-pellet, improving the propensity for disintegration; thus, enhancing drug release rate. The increase in tween 80 concentration increased the proportion of drug being in solubilized or molecularly dispersed state, which increased surface available for dissolution. Also, tween 80 reduced surface tension or cohesive force, improving disintegration; hence, enhancing drug release rate.

In order to explore the potential of naproxen liqui-pellet enhanced release formulation, functional excipient was added to the formulation. Sodium bicarbonate was primarily an effervescent agent but has additional pH modulating function. It was observed that this effervescent agent significantly improved the drug dissolution rate via promoting disintegration, disrupting diffusion boundary layer and modulating pH at micro-environment (the alkaline $NaHCO_3$ improved the weakly acidic naproxen solubility). A remarkable note to point out was that in one of the formulations, where 42% of the total liqui-pellet mass was made up of $NaHCO_3$, the total weight of dosage form excluding capsule weight was only 231mg. This demonstrated that liqui-pellet can overcome issue of bulky dosage form, bringing possibility for more versatile formulation design and modification through the inclusion of additional functional excipient and yet achieve acceptable final weight for swallowing. This would have been very difficult or near impossible to achieve with the current liquisolid technology, particularly in high dose drug, where high liquid load factor would result to heavy and bulky formulation due to increase carrier and coating material being required, let alone the addition of functional excipient. Results from the investigation show a remarkable increase in drug release rate with $NaHCO_3$. When $NaHCO_3$ concentration increase, so does the drug release rate. However, there is a limit of how much $NaHCO_3$ could be increased before its influence on the drug release lessen. Thus, it was prudent to know such limit in order to balance the weight of dosage form and drug release performance into an ideal dosage form.

Further investigation was done to further improve naproxen liqui-pellet drug release. This was carried out by using knowledge of the key parameters influencing liqui-pellet drug dissolution rate such as water content, liquid vehicle content and functional excipients (i.e. effervescent agent and superdisintegrant). Addition to this, high specific surface area carrier called neusilin US2 was used with MCC as part of a binary mixture of

carriers to study its effect on physicochemical properties. The mentioned optimized parameters along with the incorporation of neusilin US2 led to a formulation with remarkably explosive and rapid drug release. Data from dissolution test shows naproxen liqui-pellet can achieve 100% drug release within 20 min at an acidic pH of 1.2, which naproxen was known to be practically insoluble in. Such results were more superior than naproxen liquisolid formulation or even other promising competitor such as naproxen solid dispersion. The main contributing factors to this rapid drug release were the use of $NaHCO_3$ and neusilin US2.

In order to investigate liqui-pellet as a platform for next generation oral dosage form, it was prudent to use API other than naproxen to verify the feasibility and rapid drug release of liqui-pellet with a different API than naproxen. Hydrochlorothiazide liqui-pellet was successfully made. The formulations' flow property, robustness and size distribution were generally acceptable and posed no major issue in terms of manufacturing. More importantly, an optimized HCTZ liqui-pellet was able to achieve a remarkably rapid drug release rate (100% drug release after 15 min at pH 1.2). Such dissolution profile of HCTZ liqui-pellet surpassed current technologies such as liquisolid, solid dispersion and even solid self-dispersing micelle, whilst remaining simple and cost-effective. This reflects the potential of liqui-pellet as next generation oral dosage form.

Once it was known that producing a variety of liqui-pellet was feasible (naproxen liqui-pellet, HCTZ liqui-pellet, effervescent liqui-pellet and various optimized liqui-pellet), and that it was able to achieve rapid drug release rate, whilst overcoming the key drawbacks of liquisolid technology, the focus of the investigation shifted into making a new dosage form called liqui-tablet. In the simplest form, liqui-tablet is essentially compressed liqui-pellets. Provided that liqui-tablet reverts back to the multi-unit pellet system in dissolution medium, it had the same inherent advantages as liqui-pellet and more due to being in a tablet form. The aim was to explore the potential to diversify the new technology and to respond to the strong incentive for tablet dosage form. Tablet is more commercially favourable than capsule in terms of cost-effectiveness. Other advantages of tablet over capsule included lower tendency of dosage form adhering to oesophagus during ingestion; ability to administer higher dose strength than capsule; reduced the risk of dosage form being tampered with; improved patient compliance, particularly for those who prefer not to ingest gelatin capsule. The issue with gelatin capsule is not just an individual preference but extend to chemical instability, varying dissolution rate of capsule due to varying structure and composition of gelatin, and questionable source, particularly from waste

leather which may have been treated with harmful substances. Thus, there is a strong incentive for liqui-tablet.

Naproxen liqui-tablet was successfully made, verifying the feasibility of liqui-tablet. The liqui-tablets were able to revert back into MUPS in the dissolution medium, preserving the inherent advantages of liqui-pellet. More importantly, optimized naproxen liqui-tablet was able to achieve rapid drug release rate that is more superior than naproxen liquisolid and naproxen solid dispersion from other studies. Furthermore, the investigation also confirmed that compaction force during tableting had no observable effect on liqui-tablet drug release profile. The presence of neusilin US2 in liqui-tablet formulations have shown to be an important factor to achieve ideal liqui-tablet physical properties such as, robustness and hardness, as well as allowing faster drug release to be achieved.

Once it was known that liqui-tablet was feasible and that optimized liqui-tablet was capable of explosive and rapid drug release, whilst having high liquid load factor or high amount of liquid vehicle, and no issue regarding pre-compressed flow property, an attempt was made to produce high dose liqui-tablet (ketoprofen 100mg). The aim was to tackle another drawback in liquisolid technology where high dose drug would produce bulky liquisolid compact that would usually exceed 1g which is not suitable for swallowing. Ketoprofen 100mg liqui-tablet was successfully made whilst maintaining acceptable weight (483.8mg) and achieving excellent pre-compression flow properties. This is a major advancement as it takes liquisolid concept into a commercially feasible direction for high dose drug, which has never been achieved in current liquisolid technology before. In addition, the liqui-tablets pass the friability test and the pre-compressed formulations had narrow size distribution, which is ideal in terms of manufacturing and quality control test. Also, liqui-tablets were able to revert back to its MUPS, maintaining the intrinsic advantages of liqui-pellet.

Through overcoming the size and weight issue of high dose drug that exists in liquisolid formulation, liqui-tablets potentially have wider range of APIs it may be suitable for. Not only wider range of APIs, but also wider range of functional excipients can be applied to this new oral drug delivery system.

In conclusion, liqui-pellet and liqui-tablet show promising potential as a commercially feasible next generation oral dosage form with capability for remarkably rapid drug release, capability for producing high dose drug, versatile formulation

manipulation (i.e. addition of functional excipient and possibility for application of coating), simple, cost-effective, uses green technlogy and array of advantages including: intrinsic advantages of liquisolid technology (whilst overcoming liquisolid technology drawbacks) and intrinsic advantages of pelletization technology. Also, the investigation confirms that most of the liqui-pellet and liqui-tablet, including pre-compressed liqui-tablet, can achieve good robustness and excellent flow properties with narrow size distribution, which is ideal for manufacturing and quality control test.

10.2 Future investigation

This project concluded the feasibility of enhanced drug releasing liqui-pellet and liqui-tablet, however, in order to diversify and explore the potential scope of this new dosage form, it is prudent that liqui-pellet and liqui-tablet sustained release formulation should be investigated in near future. Given that the main carrier is MCC (MCC-based pellet is known to suitable for sustained release formulation) and liqui-pellet can achieve smooth surface, which has potential to apply coating technology, it is reasonable to say liqui-pellet and liqui-tablet may fundamentally be more favourable for sustain release formulation.

The potential for coating technology to be applied is not limited only to sustained release function but may have wider application such as enteric coating and taste masking. Thus, this area of investigation may help diversify the use of liqui-pellets and liqui-tablets.

More in-depth studies on liqui-pellet and liqui-tablet is also worth investigating. Such studies include the application of analytical tools such as HPLC (for assay) thermogravimetric analyzer (solid state studies) and tomography (structure and uniformity of content studies). Furthermore, the use of mixer torque rheometer could aid and give insight into the quality control during liqui-pellet or liqui-tablet production. Since the author technology is still in its infancy, there are plenty of room for investigation.

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