INVESTIGATION OF DISSOLUTION PERFORMANCE AND PHYSICAL CHARACTERIZATION ON DEVELOPMENT OF SOLID DISPERSION DOSAGE FORM

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INVESTIGATION OF DISSOLUTION PERFORMANCE AND PHYSICAL CHARACTERIZATION ON DEVELOPMENT OF SOLID DISPERSION DOSAGE FORM

by

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DEDICATION

I dedicate this thesis to my wonderful parents, sister and brothers, for their perpetual moral support and emphasis on the values of education. They pushed me to pursue my dreams and supported me through it.

To my wife, who has always been supportive and present for me and given motivation and strength to me. To my children, Yara and Laith, Who by being a part of me have given me the reason to accomplish my goal.

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LIST OF ABBREVIATIONS AND SYMBOLS

ANOVA	Anylasis of variance
API	Active Pharmaceutical Ingredients
ASD	Amorphous soliD dispersion
ATR-FTIR	Attenuated total reflectance- Fourier tranform infrared
AUC	Area under the curve
Avg.	Average
BCS	Biopharmaceutic Classification System
CAc	Contact angle of crystal
CAFF	Caffeine
CAqc	Contact angle of quenced-cooled
CLO	Clotrimazole
CP	Carbopol
DE	Dissolution efficiency
DSC	Differential scanning calorimetry
EE100	Eudragit E100
ETOR	Etoricoxib
f_2	Similarity factor
FBP	Flurbiprofen
FTIR	Fourier tranform infrared
GFA	Glass Forming Ability
GLZ	Gliclazide
HPMC	Hydroxy propyl methyl cellulose
IBU	Ibuprofen
J	Joule
K	Kelvin
KET	Ketoconazole
KTP	Ketoprofen
MD	Molecular dynamic
min	Minute
MSD	Mean square displacement

mTrg	Modified reduced glass temperture
nm	Nano meter
NPT	National pipe taper
ns	Nano second
P.E	Potential energy
PCM	Paracetamol
PIX	Piroxicam
PM	Physical mixture
ps	Picosecond
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrilodone
PVPVA	Polyvinyl pyrrilodone vinyl acetate
QC	Quench-cooled
R	Gas constant
Rg	Radius of gyration
RH	Relative humidity
SD	Solid dispersion
SEM	Scanning electron microscope
SPSS	Statistical package for the social sciences
T	Temperture
T.E	Total energy
Tg	Glass transition temperature
TGA	Thermogravimetric Analysis
Tm	Melting temperature
Trg	Reduced glass temperture
XRPD	X-ray powder diffraction
ΔG	Change of free energy
ΔH_F	Change in heat of fusion
ΔCp	Change heat capacity

PENYIASATAN PRESTASI PERLARUTAN DAN PENCIRIAN FIZIKAL DALAM PEMBANGVNAN BENTUK DOS SEBASAN PEPEJAL

ABSTRAK

Formulasi pepejal terampai (SD) telah menarik perhatian kerana potensinya dalam peningkatan prestasi perlarutan bahan farmaseutikal aktif (API) yang kurang larut. Walau bagaimanapun, rumusan daripada kajian yang diterbitkan menunjukkan prestasi perlarutan SD adalah tidak konsisten. Tidak ada peraturan umum dalam penalaan pemilihan pengangkut dan API untuk pelaburan yang bermanfaat untuk pembangunan perumusan pepejal terampai. Oleh itu, Objektif utama kajian ini adalah untuk mengkaji kriteria sistem pengangkut yang baik dan calon API dalam formulasi SD bagi meningkatkan prestasi perlarutan API kurang larut dan pertimbangan dalam pembangunan bentuk dos tablet SD. Bagi mencapai matlamat ini beberapa sistem SD telah disediakan secara semburan pengeringan. Kaedah digunakan untuk mencirikan sistem SD; seperti DSC, XRPD, ATR-FTIR, Imbas SEM, dan simulasi dinamik molekul (MD). Untuk mengetahui kesan pengangkut pada persembahan perlarutan pada sistem SD; flurbiprofen dipilih sebagai API model dengan tujuh pengangkut yang berbeza. Pemilihan pengangkut berdasarkan perbezaan fizikokimia mereka, iaitu; polyvinyl alcohol (PVA), hydroxyl propyl methylcellulose (HPMC), carpobol (CP), mannitol, Natrosol, Eudragit E100 (EE100) dan polyvinylpyrrolidone vinyl acetate (PVPVA). Di sini, kriteria untuk sistem pengangkut yang baik adalah berkait rapat dengan interaksi pengangkut -API dan saiz zarah yang dihasilkan ketika semburan kering. Untuk mengenal pasti kesesuaian API bagi formulasi sistem SD, sepuluh API yang berbeza dipilih dengan sifat fizikokimia yang berlainan. Bentuk amorfus setiap API telah disediakan dengan

menggunakan kaedah yang penyejukkan kedap. Kelebihan keterlarutan amorfus dikira untuk setiap API sebagai tambahan kepada TGA, ATR-FTIR, pengukuran sudut sentuh, dan kajian. Respons API apabila tersentuh air dikaji dengan simulasi molekul (MD) dalam air sulingan. Perisian ini memberikan maklumat berguna sekecil saat nano yang dianggap sebagai parameter penting untuk API amorf. Ini kerana amorf adalah keadaan pepejal API yang sangat tidak stabil, meneliti maklumat berkaitan mobiliti melalui MD akan memberi manfaat dalam meramalkan hasil proses perlarutan. Adalah didapati bahawa, Tg dan Tm sahaja tidak boleh digunakan sebagai penunjuk tunggal untuk meramal hasil perlarutan sistem pepejal API-APIan yang larut. Sebaliknya, Trg, interaksi pengangkut API, kelebihan kelarutan amorf didapati didapati berkait rapat dengan hasil perlarutan. Walau bagaimanapun, semua faktor ini mempengaruhi secara bebas yang sukar digunakan sebagai ukuran ramalan. Dalam tesis ini, tenaga kinetik dari API dalam 50 nano detik telah didapati berkorelasi dengan baik untuk hasil perlarutan sistem SD API yang tidak larut. Akhirnya analisis regresi dengan parameter MD sebagai faktor dan kecekapan perlarutan sebagai hasil telah dilakukan. Data yang diperolehi dari MD adalah ukuran kolektif Trg serta kelebihan kelarutan amorf. parameter ini telah digunakan dengan sempurna untuk menghasilkan persamaan ramalan bagi calon API kurang larut dalam formulasi sistem SD yang berkesan. Bahagian terakhir tesis melibatkan pembangunan bentuk dos sistem SD dengan menggunakan dua calon API yang sebelum ini terbukti berkesan dalam formulasi SD, iaitu tablet flurbiprofen (FBP) dan ketoconazole (KET) dengan PVPVA dan Carbopol. Perlarutan setiap SD selepas pemadatan dilakukan dan dibandingkan dengan sistem SD-binari serbuk yang sepadan. Berdasarkan hasil perlarutan, kedua-dua sistem menunjukkan nilai F_2 lebih daripada 50 yang menunjukkan tiada kesan pemadatan terhadap prestasi

perlarutan sistem SD ini. Selain itu, kajian kestabilan dilakukan selepas keadaan penyimpanan (75% RH, 30 $_{o}$C) dalam jangka masa yang ditetapkan (6 dan 24 bulan). FBP dan KET dengan sistem PVPVA menunjukkan kestabilan yang lebih rendah berbanding pengangkut CP. Ini adalah disebabkan oleh kecenderungan penghabluran sistem amorfus sepenuhnya (sistem PVPVA) berbanding dengan sistem separa kristal (sistem CP). Kesimpulannya, kehadiran segelintir hablur dalam sistem SD tidak menjejaskan perlarutan SD secara dramatik. Prestasi perlarutan sistem SD adalah berkait-rapat dengan kelebihan kelarutan amorf, pengukuran sudut sentuhan dan nilai Trg yang telah iubah suai. Selain itu, kajian simulasi MD dianggap sebagai kaedah yang baik untuk ramalan awal kesesuaian API yang akan menghasilkan SD yang berkesan bagi kepentingan penjimatan masa dan kos. Pertimbangan pemadatan didapati tidak mempengaruhi perlarutan tablet system SD dari segi pembangunan bentuk dos. Untuk kestabilan, kedua-dua sistem KET & FBP menunjukkan penghabluran semula selepas kajian kestabilan. Walau bagaimanapun, hasil perlarutan didapati konsisten sehingga 24 bulan kajian kestabilan dipercepat kecuali sistem SD KET-PVPVA.

INVESTIGATION OF DISSOLUTION PERFORMANCE AND PHYSICAL CHARACTERIZATION ON DEVELOPMENT OF SOLID DISPERSION DOSAGE FORM

ABSTRACT

Solid dispersion (SD) formulation has attracted much attention due to its potential in enhancing dissolution performance of poorly soluble active pharmaceutical ingredients (API). However, an overview of the dissolution performance of SDs implies inconsistent degree of dissolution improvement of poorly soluble APIs in SD. Therefore, the main objective of this study is to determine the criteria of a good carrier system and drug candidate for enhanced dissolution performance of a solid dispersion system for a poorly soluble drug and dosage form consideration particularly the impact of compaction. To achieve these objectives, several SD systems were prepared in this study by spray drying and quenched –cooled methods. To identify the suitability of drug to be formulated in SD systems, ten different drugs were chosen with different physicochemical properties. Amorphous form of each drug was prepared using quenched-cooled method. Theoretical and experimental amorphous advantages were calculated for each drug. In addition, TGA, ATR-FTIR, contact angle measurement, MD and dissolution studies were performed. From the results, it was found that these predicating factors could not be used as a single indicator for predicting dissolution outcome of a solid dispersion system of poorly soluble drugs. The last part of the thesis involved dosage form developments of SD systems using two drug candidates that were effective in SD formulation. Dissolution performances of each SD after compaction was performed and compared with the corresponding SD- binary systems. Based on the

dissolution results, both systems showed f2 values more than 50, which indicated negligible effects of compaction on the dissolution performance of these SD systems. Additionally, stability studies were performed after storage conditions (75 % RH, 30 °C) in predetermined intervals (6 and 24 months) and compared with a fresh sample. The presence of trace amount of crystallinity in SD systems did not affect dramatically its dissolution performance. Dissolution performance of SD systems was significantly related to the contact angle measurement and Tg values, MD simulation study was considered a good tool for early estimation of the suitability of drugs to be formulated by SD technique, which could save time and money. Compaction did not to significantly influence the dosage form development of the solid dispersion system. In terms of stability, both KET & FBP system revealed recrystallized trend. However, the dissolution results were found to be consistent up to 24 months in accelerated stability study except KET-PVPVA SD system.

CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water (Hassan et al., 2019). Solubility is a major challenge for formulation scientis. The Biopharmaceutics Classification System (Maheshwari et al., 2018) classifies drugs into different groups based on solubility and permeability (Table 1.1).

Table 1.1 Biopharmaceutical classification system

	High solubility	Low solubility
High permeability	I	II
Low permeability	III	IV

It has been estimated that over 80% of all recently developed drugs are Class II chemical entities (Marano et al., 2016). Therefore, there is a high demand for techniques that improve the solubility and enhance the dissolution rate of drug formulations.

According to Noyes-Whitney equation 1.1, the parameters that influence the dissolution rate can be tweaked to tackle the poor solubility issues of Class II drugs (Hirai et al., 2017):

$$\frac{dC}{dt} = \frac{DA}{d}(Cs - Cb) \qquad \text{(Equation 1.1)}$$

; where

$\frac{dc}{dt}$ = solute dissolution rate (Kg. S-1)

c = mass of dissolved material

t = time

A = surface area or interface between dissolving material and solvent

D = diffusion coefficient

d = thickness of boundary layer of solvent at dissolving materials' surfaces

C_s = mass concentration of material on the surface

C_b = mass concentration of material in solvent bulk

Based on the presented equation above, several parameters can be modified to improve the dissolution efficiency of a poorly soluble drug such as drug solubility and surface area. These are the most common modifications made to achieve a desirable dissolution performance. Several techniques have been developed over the years to overcome solubility challenges (Kimura et al., 2014), some of which are listed in Table 1.2, such as salt formation, particle size reduction, soluble prodrug formation, complexation with a surfactant, and amorphous solid dispersion. Of all the aforementioned techniques, solid dispersion (SD) stands out as the most favourable approach due to a high success rate with regard to the improvement of the dissolution performance of a Class II drug (Harmon et al., 2016).

Table 1.2 Strategies to enhance the solubility of drugs with poor water-solubility

Chemical Modification	Physical Modification
Salt formation	Reduction of particle size
Formation of prodrug	Solid dispersion
Complexation	Solubilization
	Modification of solid form

1.2 Solid dispersion systems

Solid dispersion (SD) refers to the dispersion of a drug within a solid matrix, which is usually a polymer or a carrier that can impart hydrophilicity to the system (Baghel et al., 2016). SD improves solubility and dissolution profiles primarily because when a lipophilic drug is dispersed in a hydrophilic carrier, the mean particle size is reduced and wettability is improved (Ghanavati et al., 2017). Furthermore, SD can improve the solubility and dissolution performance of a poorly soluble drug by replacing the crystalline form of the drug with an amorphous one, i.e., by the formation of an amorphous solid dispersion.

1.3 Classification of solid dispersions

Solid dispersion (SD) can be classified according to the physical states of the carrier and drug as summarized in Table 1.3. Different SD terms have been coined at different time points of researching on SD. The earliest description of SD was termed as Eutectics by Chiou and Riegelman in 1976. Later, extensive research about SD have been carried out which further classified the SD systems into amorphous precipitations of a drug in a crystalline carrier, solid solutions, glass suspensions and

glass solutions. These different types of SD will be briefly introduced in the subsequent subsections.

Table 1.3 Different categories of solid dispersion according to the physical states of the carrier matrix and API.

Types of solid dispersion	Matrix	Drug	Phases
I Eutectics	C	C	2
II Amorphous precipitates in crystal matrix	C	A	2
III Solid solutions	C	M	-
Continuous VS. discontinuous	C	M	1 or 2
Substitutional VS. interstitial	C	M	1 or 2
IV Glass suspension	A	C/A	2
V Glass solution	A	M	1

C= Crystal, A= Amorphous, M= Molecularly dispersed

1.3.1 Simple eutectic mixture

A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components (Sekharan et al., 2019). Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry. Eutectic mixture formation is usually, governed by following factors (Shaikh Siraj et al., 2019): (a) the components must be miscible in liquid state and mostly immiscible in solid state, (b) Intimate contact between eutectic forming materials is necessary for contact induced melting point depression, (c) the components should have chemical groups that can interact to form physical bonds such has intermolecular hydrogen bonding etc., (d) the molecules which are in accordance to modified VantHoff's equation can form eutectic mixtures.

1.3.2 Solid solution

The term "solid solution" refers to a solid solute that is dissolved in a solid solvent, rendering the two components fused together in a homogenous one-phase system. It is noteworthy that solid solutions of poorly soluble drugs and rapidly soluble carriers usually dissolve faster than their corresponding eutectic mixtures. This disparity is due to the particle size of the drug being reduced to its minimal value in a solid solution (Chiou and Riegelman 1971). Solid solutions can be classified either as continuous or discontinuous, based on drug solubility (Singh et

al., 2017). Solid solutions may alternatively be classified based on solute distribution within the crystalline carrier as substitutional or interstitial.

1.3.2 (a) Continuous vs. discontinuous solid solutions

A continuous solid solution is characterized as containing components that are miscible a all proportions. Discontinuous solid solutions, on the other hand, are made up of components that have limited solubility in one another (Leuner and Dressman 2000), though that might not be the case for the entire compositional range. A continuous solid solution is only possible to achieve if it is more favourable for the components' molecules to bond with different chemical entities than to bond together. Needless to mention, such solid solutions are rare in the pharmaceutical industry because most organic molecules do not behave this way (Shaikh Siraj et al., 2019).

1.3.2 (b) Substitutional vs. interstitial solid solutions

A continuous/discontinuous solid solution can be turned into a substitutional solid solution by replacing the crystalline carrier with a solute. However, as illustrated in Figure 1.1, this process can only occur if the replacement molecules are similar in size to the substituted molecules (Bag et al., 2015). Conversely, interstitial solid solutions, which are formed strictly from discontinuous solutions, may only be obtained if the solute molecules are smaller than the solvent's molecules. This condition is needed for the solute molecules to be able to occupy interstitial spaces in the crystalline lattice (Weizman et al., 2013).

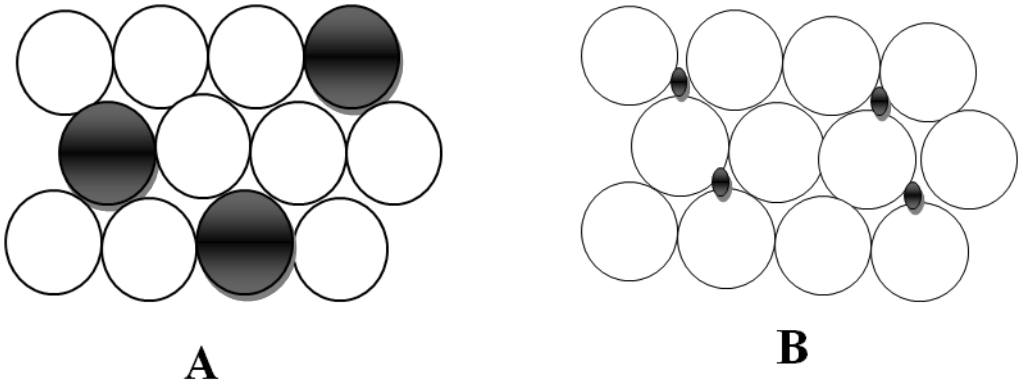

Figure 1.1 Solid solutions classified based on solute (●) distribution: (A) Substitutional crystalline solid solution; (B) Interstitial crystalline solid solution.

1.3.3 Glass suspension

A glass suspension can either be crystalline or amorphous (Chan et al., 2015). A crystalline glass suspension is a two-phase system comprised of drug particles that are dispersed as crystals in an amorphous polymer phase (Semjonov et al., 2017). A glass suspension can be very stable due to the drug being in the crystalline form. On the other hand, an amorphous glass suspension consists of a drug in the amorphous state dispersed in an amorphous polymer phase. Such a system may not be molecularly dispersed and can undergo rapid recrystallization (Chan et al., 2015).

1.3.4 Glass solution

A glass solution refers to a system wherein drug molecules are dispersed into an amorphous carrier at the molecular level, producing a homogenous single-phase system. The term “glassy” denotes abrupt quenching of the melt. The dissolution efficiency of a glass solution is typically much higher than that of lower-energy solid solutions because interactions between similar molecules in a glass solution are less

abundant compared with interactions between different chemical species. According to Chan (2013), a glass solution, such as citric acid-PVP, is preferable due to its great dissolution power compared with other SD systems, and its stability. However, a principal disadvantage of glass solutions is that they are more prone to recrystallization under normal storage conditions, making carrier selection more difficult.

1.4 Amorphous form of active pharmaceutical ingredients

As mentioned in the previous section, one of the criteria of categorising the SD is based on physical state of the drug. Theoretically, an amorphous solid dispersion state of drug is more soluble than its crystal counterpart. A summary from the literature search shows that amorphous is a main factor in determining dissolution improvement of most SD research. Therefore, it is crucial to understand the nature of amorphous state and relate its importance to the outcome of dissolution and ultimately bioavailability.

An amorphous state can be obtained through thermodynamic and kinetic pathways. In the thermodynamic pathway, the API is converted to a thermodynamically stable disordered state by heating or dissolving, followed by a rapid change into the amorphous state by quench cooling or solvent evaporation. Meanwhile, the kinetic pathway requires an increase in the number of crystal defects introduced into the crystalline solid until an amorphous product is formed (Blaabjerg et al., 2017). Generally, a material needs to bypass its thermodynamic tendencies to nucleate and crystallize to become amorphous (Weber et al. 2017). In the kinetic

pathway, mechanical activation such as milling is important to induce crystal defects until the amorphous form is obtained (Blaabjerg et al., 2017).

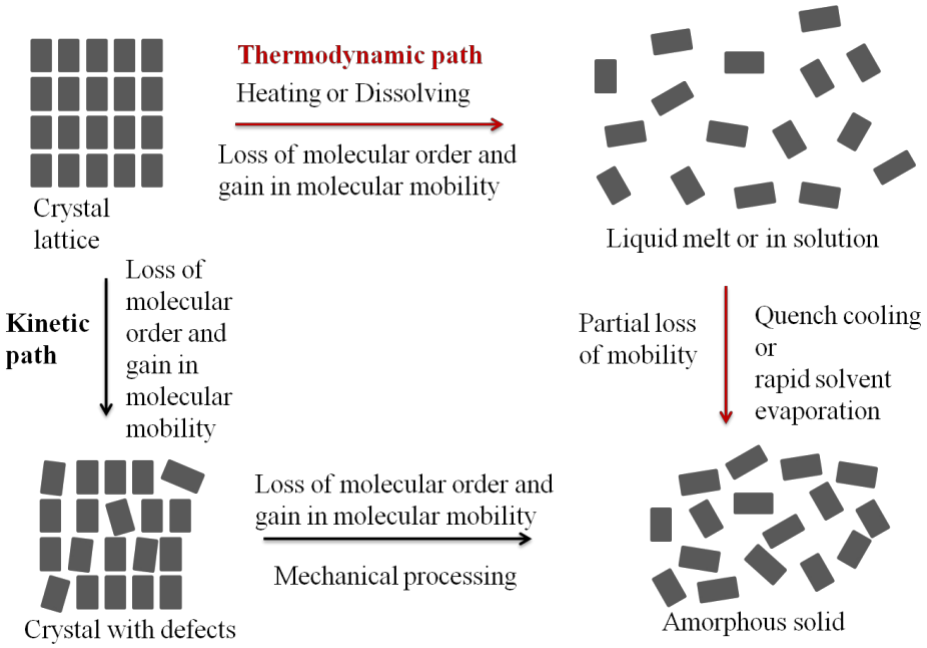

Figure 1.2 Schematic overview of the kinetic and thermodynamic pathways to prepare an amorphous form from a crystalline compound. Retrieved and modified from Blaabjerg et al., 2017

The melt quenching method is suitable for APIs that are thermally stable when exposed to a temperature slightly above their melting temperature (Genina et al., 2018). In this method, the solid material is melted using heat (above melting temperature) and rapidly cooled to obtain the amorphous form. Supercooling or supersaturation is an important processing step to form the glassy state (Sarabu et al., 2019). Thus, a sufficiently fast cooling rate is required to limit nucleation and crystal growth and ensure the formation of a satisfactory amorphous product (Blaabjerg, et al., 2017). The faster the melted material is cooled, the more disorder the molecular structure will retain. The low temperature used to solidify the molten material may affect the crystallization rate, size and hardness of the crystal (Kumar et al., 2013).

Thus, temperature selection at both steps is important to prevent these problems. Degradation can be prevented by heating the mixture at a temperature slightly higher than the highest melting point of the components.

1.5 Glass forming ability

Glass-forming ability (GFA) is defined as the ease of a material to undergo amorphization. It is determined by the critical cooling rate during melt-quenching when aiming to obtain a complete amorphous form (Blaabjerg et al., 2017). Active pharmaceutical ingredients (APIs) can be classified into three GFA categories based on their behaviours observed during differential scanning calorimetry (undercooled melts). API compounds that directly crystallize in the first cooling cycle are categorized as Class I, while compounds that only crystallize in the second heating cycle fall into Class II. Stable glass formers are classified as Class III, as they remain in an amorphous state upon cooling and display a glass transition temperature in the next heating cycle (Wyttenbach and Kuentz, 2017).

Amorphous materials are recognized by their glass-transition temperature (Tg). In the 1940s, the term reduced glass transition temperature (Trg) was defined as the Tg/Tm ratio, which can be used as an indicator for predicting the GFA of APIs (Blaabjerg et al., 2016). The formula to calculate Trg is as follows (Ueda et al., 2016):

$$\boldsymbol{Trg = Tg/Tm} \qquad \text{Equation 1.2}$$

Where Tg is the glass transition temperature and Tm is the melting temperature of the drug. Additionally, the Tm to Tg ratio can be a predictive measure

of crystallization. The higher the Tm: Tg ratio, the higher the possibility of crystallization. Thus, APIs with a high Tm and low Tg will have a higher tendency to crystallize. APIs with a high Tm tend to crystallize easily due to their high energy lattice. Meanwhile, APIs with a low Tg will have higher mobility at room temperature, meaning that the chance of crystallization is higher (Kanaujia et al., 2015). However, using Tg as predictor of GFA may not be applicable to some compounds that do not exhibit a measurable glass transition, such as fast crystallizing compounds (Class I). Thus, an attractive alternative approach to predict the GFA for these compounds is by using *in silico* predictors. This method is also helpful to determine the GFA when the thermodynamic categorization is not available due to thermal instability (Wyttenbach and Kuentz, 2017)

The instability of amorphous materials with high energy states causes them to recrystallize during long-term storage, during the manufacturing process or in the gastrointestinal tract after oral ingestion, which will reduce their solubility under these conditions (Ueda et al., 2016). To prevent recrystallization, the molecular mobility of an amorphous form should be minimized. This is because the amorphous form of an API is thermodynamically unstable and tends to convert into a more stable crystalline form. The mobility of amorphous molecules increases above the Tg; thus, to maintain its amorphous form, it should be stored 50°C below the Tg. It is difficult to maintain finished API products at the API amorphous form Tg, which usually varies from -20°C to 80°C. Therefore, incorporation of a carrier is relevant and convenient for maintaining amorphous form stability (Kanaujia et al., 2015). Solid dispersion is the most common technique used to improve solubility and overcome the instability problem (Ueda et al., 2016).

1.6 Carriers used in solid dispersions

One of the most important steps in an SD preparation is the selection of the carrier. The properties of the carrier determine the parameters to be used during subsequent processes. These properties also play a role in shaping the drug's release profile, potential drug-carrier interactions, as well as the stability of the system. Different carrier choices can lead to different melting points, glass transition temperatures and molecular weights (Khan et al., 2015).

In general, an ideal carrier for use in an SD system is pharmacologically inert (non-toxic) with a high molecular weight (MW) and a high glass transition temperature (Tg). The carrier needs to improve the solubility of the drug; therefore, the carrier should have no nucleation capacity and low hygroscopicity, and it must not form strong complexes with drug molecules (Guan et al., 2018, Pas et al., 2018) . Table 1.4 shows examples of polymers that are used as carriers in SD systems.

Table 1.4 List of carriers used in solid dispersions [Adapted from (Vasconcelos et al., 2016)]

Chemical Classification	Potential Carriers
Acids	Citric acid, phosphoric acid, tartaric acid, succinic acid.
Sugars	Mannitol, lactose, sucrose, maltose, soluble starch, chitosan, sorbitol, dextrose
Polymeric material	HPMC, PEG 4000, PEG 6000, cyclodextrin, ethyl cellulose, Eudragit®, methyl cellulose, xanthan gum
Surfactants	Tweens and spans, poloxamer, polyethylene stearate.

1.7 Preparation of solid dispersions

As previously mentioned, there are several ways to prepare an SD system, the most common of which are spray drying, fusion (Hot-Melt) and the solvent method. The subsequent paragraphs outline the principles of each preparation method.

1.7.1 Spray Drying

Spray drying has evolved dramatically since it was first used in the US 140 years ago. This process is a widely used approach to produce SD systems (Patil, Chauhan et al. 2014). Spray drying operates on the principle of moisture removal through controlled heating and feeding (Patil, Chauhan et al. 2014) and is comprised of a series of steps. Briefly, a liquid (solution, suspension or emulsion) is transferred at a constant rate to be divided into small droplets in a process called atomization. The droplets are released into a hot glass chamber where they are converted to fine dried particles. Next, the particles are separated from the drying gas using a cyclone or a bag filter. Compared with other drying methods, such as melt extrusion, spray drying is considered a gentle drying process. In any spray drier, the following four distinct steps can be observed: (1) feed solution atomization into fine droplets, (2) spray contact with hot gas, (3) evaporation and (4) particle separation.

Several parameters can be adjusted prior to the spray drying process to achieve a predetermined size and shape of SD particles, as well as a desirable degree of miscibility between the drug and the carrier.

1.7.2 Fusion method (Hot-Melt method)

The Hot-Melt method involves a starting material that is crystalline in nature. This technique allows for a melting form of the drug to be incorporated within a carrier to obtain a stable amorphous drug form. An API melt is prepared by heating the drug slightly above its melting point. Next, a homogenous drug-carrier mixture is produced with continuous stirring and gradual cooling (Djuris et al., 2013). Stirring is continued until the mixture is cooled to room temperature or to the temperature of the cooling water bath. The resultant product is then sieved and stored until further use. The improvement of dissolution achieved in this method depends upon the solubility of the drug within the carrier. The Hot-Melt technique is especially useful for drugs with a high melting point. The primary advantages that this technique offers is that it is solvent-free, fast and easy to perform. Thus, the Hot-Melt technique has many applications in the pharmaceutical industry (Kyerematenge et al., 2014).

1.7.3 Solvent method

An SD system can be created using a technique called the solvent method, which involves dissolving both the drug and the carrier in an organic solvent to form a clear solution. The solution is evaporated using heat alone or a combination of heat and vacuum pressure. The dried product undergoes milling and sieving to generate the required SD system (Homayouni et al., 2015), which can be stored until further use. However, the solvent method is not preferable in the pharmaceutical industry because the solvent may fail to completely evaporate during the preparation process, thereby leaving toxic residues along with the SD system (Sharma et al., 2016).

Although certain techniques, such as DSC, TGA and DTA, can be used to ensure the complete evaporation of the solvent, the solvent method has another shortcoming; this method is only applicable to thermostable drugs and polymers with a high melting point.

1.8 Advantages of solid dispersions

There are several advantages to SD systems (Figure 1.3), which explains the high interest in the field. In addition to enhancing dissolution performance, SD systems, such as morphine-tristearin, can be quite useful for inhibiting systemic drug metabolism by deactivating certain enzymes that are responsible for drug biotransformation (Cui et al., 2013). Such inhibition decreases the dose required to achieve a therapeutic level.

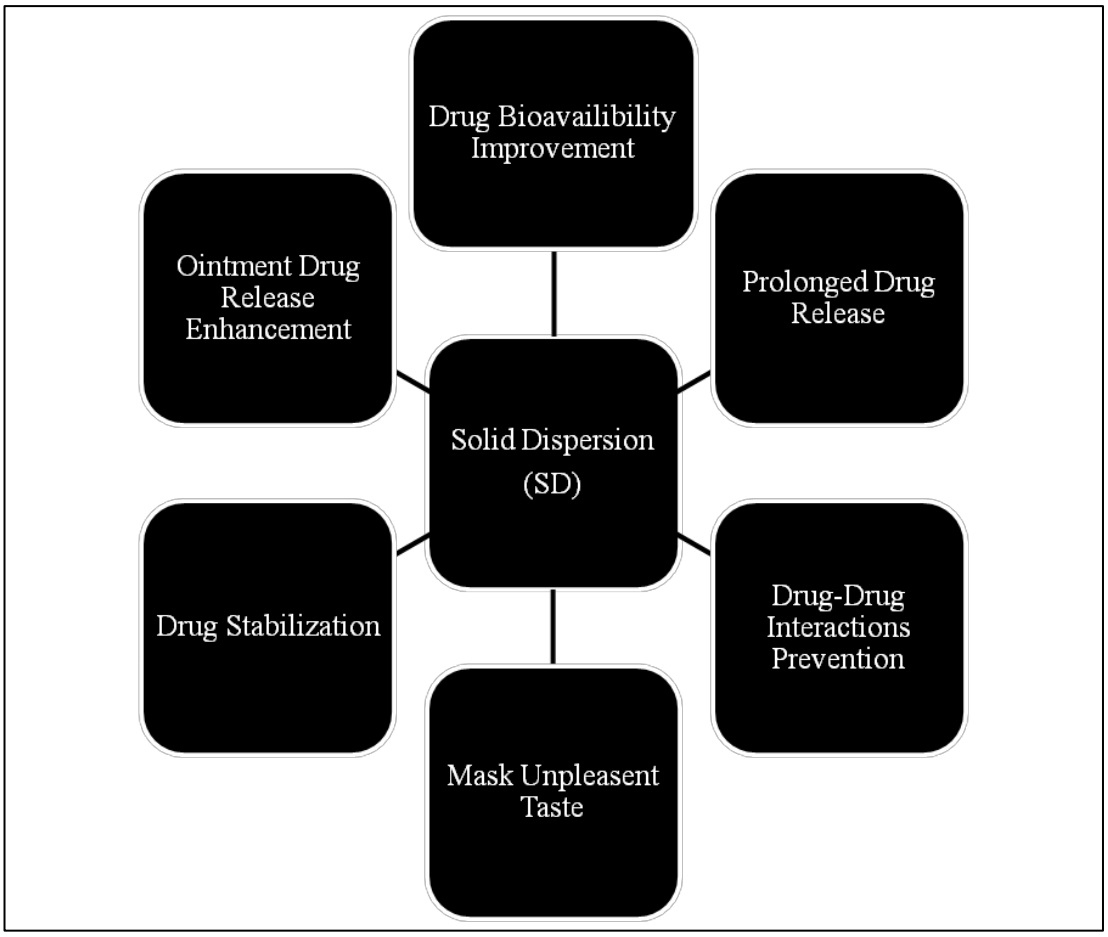

Figure 1.3 Pharmaceutical applications of solid dispersions

1.9 Factors affecting dissolution rate of SD

The dissolution profile of a poorly soluble drug can be enhanced through SD preparation. However, it is difficult to identify the primary factor behind such dissolution improvement, as several factors are usually at play. Based on literature search, the enhanced dissolution may be attributed to particle size reduction, drug porosity enhancement, wettability improvement, drug crystallinity reduction and/or processing condition.

1.9.1 Particle size reduction

During the preparation process, the size of the particles of an SD system is reduced. This phenomenon is especially clear when the drug is molecularly dispersed in the carrier, and in the case of glass and solid solutions. Particle size reduction leads to an improved dissolution rate due to the increased surface area and exposure to the dissolution media. The Kelvin equation provides a mathematical interpretation of the relationship between particle size and dissolution activity (Rouquerol et al., 2013), as follows:

$$\boldsymbol{ln}\left(\frac{\boldsymbol{a}}{\boldsymbol{a_o}}\right)= \boldsymbol{2y}\frac{\bar{\nabla}}{\boldsymbol{RTr}} \qquad \text{(Equation 1.3)}$$

; where $\frac{a}{a_o}$ = ratio of activity increase over a decrease in a large crystal

r = crystal radius

y = surface area/energy of the crystal

V = molar volume

T= temperture in Kelvin

This equation clarifies how a large surface area may be responsible for improvements in the dissolution performance of an SD system. However, a small particle size may also be equally important to prevent the recrystallization of an SD system.

1.9.2 Increased drug porosity

Particles in solid dispersion have been found to have high porosity (Kaur et al., 2016). The increased porosity of solid dispersion particles hastens

the drug release. Increase in porosity depends on carrier properties, i.e., linear polymers result in larger and more porous particles than that of reticular particles.

1.9.3 Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one to another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally, the difference in solubility between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

1.9.4 Improved wettability

The carrier choice for an SD system can result in improved drug wettability. For example, the dissolution performance of a piroxicam SD system was shown to be improved with the use of PVP as the carrier due to its hydrophilic nature, which causes a decrease in surface tension and increased wettability (Lust et al., 2015). Improved wettability can indirectly lead to improved dissolution, namely, by preventing particle agglomeration and increasing the surface area of drug particles that are exposed to the dissolution media.

According to Song (2011), felodipine's low dissolution rate was markedly improved when it was incorporated into an SD system using a hydrophilic polymer. Another study showed that the polymers PEG 6000 and HPMC increased the dissolution performance of the API, as they created a favourable microenvironment. Essentially, these polymers positioned themselves at high concentrations around the drug molecules.

Craig (2002) notes that in an SD system, a polymer forms a layer around the formulation, in which the drug dissolves upon contact with the dissolution media prior to being released (Marano et al., 2017). Jasmine et al (2015), demonstrated that the strong hydrophilic nature of PVP K90 improves water penetration to dissolve the hydrophobic molecule gliclazide more rapidly.

1.9.6 Decrease drug crystallinity

As mentioned earlier, the amorphous form of a drug generally exhibits higher solubility compared with the crystalline form, even within the same SD system. This phenomenon is because an amorphous state does not necessitate energy to breakdown strong bonds, as may be the case with a crystalline lattice. However, despite being more soluble, the amorphous drug form presents a major challenge, as it lacks the stability of the crystalline form.

1.9.7 Processing and storage conditions

The highest dissolution performance of an SD system can be obtained using an amorphous form of the components. Unfortunately, amorphous particles have a high tendency to undergo a transition into crystalline forms, which may be triggered by the temperature and humidity of their surroundings. This property renders the dissolution rate of an SD system dependent on the selection of the SD technique used and storage conditions. The cooling rate used in the Hot-Melt method, for instance, can influence the efficacy of the final SD product, because extended cooling may trigger rearrangements in amorphous particles and the creation of crystal nuclei. Similarly, the solvent method is known to cause amorphous particles to undergo conversion into the crystalline form upon contact with the solvent. Moreover, compression and pulverisation during SD preparation may prompt particles to change into a more stable crystalline form.

1.10 Problem statement

The dissolution enhancement of SD systems has been demonstrated in many previous studies. However, some studies showed SD that did not significantly improve dissolution. Chan et al., 2016 revealed that SD formulation had little or no effect on the dissolution rates of Ketoprofen and naproxen. This implies that not all drugs produce improved dissolution performance after formulated as SD system. The properties of drug/ carrier or factor that lead to the improved dissolution performance of SD system is still poorly understood. These have led to lack of commercial interest in the production of SD formulations, primarily because of multiple challenges pertaining to preparation, reproducibility, formulation, upscaling and stability of the final product.

SD techniques evolve with the discovery of new surfactants and emulsifying agents that can serve as carriers. Hence, researchers are encouraged to focus on investigating new carriers with valuable properties, as well as improving on existing carriers to enable their oral and topical usage. More carrier options may increase the chances of formulating better SD dosage forms in the future. Furthermore, efforts should be directed towards improving the stability of SD systems. The identification and assessment of new excipients and additives that may retard the conversion of amorphous forms into undesirable crystalline forms are key objectives.

Crystallization of an amorphous drug is a primary factor that can influence SD physical stability. Crystallization is a process that consists of the following two stages: nuclei formation and crystal growth (Markov et al., 2016). Both stages require mobile molecules that can form crystal nuclei and attach to one another to grow. Thus, molecular mobility is a key factor in crystallization and has a direct impact on the stability of SD systems. Several studies have shown that ASD

(amorphous solid dispersion) systems have a tendency to convert into the crystalline form and exhibit reduced dissolution performance with ageing.

Moisture and temperature are the most powerful factors that influence SD dissolution performance during storage. An early investigation of the stability of an indomethacin-PEG-6000 SD system showed a marked change in the dissolution profile and tablet colour of the system when it was stored at a temperature range of 25-41 ºC and an RH level of 71% due to the crystallization of indomethacin (Semjonov et al., 2017). The presence of active functional groups, such as carboxyl and hydroxyl moieties, in SD systems was recently shown to help reduce the risk of recrystallization upon storage (Christina et al., 2015). This phenomenon demonstrates the importance of polymer selection, as it may be a parameter that affects SD stability and the production of a completely miscible drug-carrier system.

Interestingly, stability issues may be overcome in certain cases by storing SD products at a temperature lower than their Tg values. This practice is believed to significantly lower molecular mobility and recrystallization tendencies.

1.11 Scope of the study

Many researchers have reported the advantages of SD system, especially with regard to the dissolution enhancement of BCS class II drugs. However, ASD systems appear to pose greater risk of recrystallization and agglomeration compared with physical mixtures of class II drugs and hydrophilic carriers. This risk is the primary reason why there are no more than 15 SD products available in the market (Chan et al., 2015).

It is necessary to further understand the effect of SD on various APIs and carrier molecules compared to the corresponding physical mixtures. This study was an investigation into the nature, dissolution performance and formulation processes of several SD systems obtained using the spry drying technique. Dissolution performance of SD was assessed and compared with physical mixtures. The underlying factors that influenced dissolution were determined for all studied systems.

The primary objective of the current study was to generate a step wise approach in predicting suitable drug candidate of solid dispersion system.

Furthermore, the study had the following secondary objectives:

1. To study the effects of amorphicity and drug carrier interaction on dissolution performance of solid dispersion system for poorly water soluble drugs.

2. To identify physical property of a drug that makes it a suitable candidate of a solid dispersion system for enhanced dissolution performance.

3. To investigate the mechanisms of dug release from SD system by using molecular dynamic simulation and use the parameter to predict the outcome of enhanced dissolution performance.

4. Investigate the impact of compaction development in and up scaling of solid dispersion in and system into oral tablet dosage form.

5. To perform stability study on the tablet dosage form.

CHAPTER 2 MATERIALS AND METHODS

2.1 Introduction

This chapter details the characteristics of all the materials and methods used in the current study. The active pharmaceutical ingredient models selected in this study were based on their solubility and different thermal properties. Besides, the principle of each analytical machine and its concerns and consideration will be discussed to prepare the reader for fundamental understanding and justification of the methods used in this study. Among the methods used are Differential Calorimetric Scanning (DSC), Scanning Electron Microscope (SEM), Attenuated Total Reflectance- Fourier transform Infrared (ATR-FTIR), optical and scanning electron microscope, contact angle measurement, stability study, molecular dynamic simulation and dissolution study.

2.2 Model Drugs

Ten API models; Caffeine; Clotrimazole; Etoricoxib; Flurbiprofen; Glicazide; Ibuprofen; Ketoconazole; Ketoprofen; Paracetamol and Piroxicam were chosen in this study. These APIs were chosen based on their differences in physical properties such as solubility, Tg and Tm values. Chemical structures and physicochemical properties of each of these drugs are presented in the following sub-sections.