DEVELOPMENT OF HOT MELT EXTRUDED SOLID DISPERSION FORMULATION FOR STABILISING CO-AMORPHOUS COMPOUNDS

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Abstract

Polypills have been proven to improve the patient compliance to multi-drug treatment. However it is still poorly understood when the drugs of a polypill formulation are manufactured as a mixture. The formations of co-amorphous mixtures are one of the possible results of blending multiple drugs in a single process. This project investigated the co-amorphous mixtures of two model drugs, felodipine and paracetamol prepared by melt-cool method. The rationale of the model drug selections is based on the high interaction potentials (hydrogen bonding) between the two drugs as both contain hydrogen donors and acceptor groups. Three molar ratios of the co-amorphous systems of paracetamol and felodipine (P-F) were prepared and their physical stabilities were studied using SEM, DSC, ATR-FTIR and PXRD. It was noted that there is no clear intermolecular interaction between felodipine and paracetamol was identified. Higher paracetamol content led to poorer physical stability of the co-amorphous system which also led to hindered release of paracetamol. The dissolution rates of felodipine from the co-amorphous systems showed no significant improvement in comparison to crystalline felodipine indicating the rapid recrystallization of felodipine during the dissolution process. However the linear nearly zero order release of paracetamol indicated the entrapment of paracetamol in the recrystallized felodipine lattice. This confirmed the formation of co-amorphous mixture without specific hydrogen bonding between the two species. Soluplus was used as the polymeric excipient with an attempt to further improve the physical stability of the co-amorphous systems. The stability of P-F 1:1 loaded Soluplus HME extrudates showed significant improvement than the co-amorphous sample. However no significant dissolution enhancement was observed. This could be partially attributed to the use of the extrudates in the rod form instead of power form in the dissolution tests. Controlled release of paracetamol and poor dissolution of felodipine were obtained from the HME samples indicating the poor solubility enhancement capability of Soluplus in this formulation. The results of this project provided further understanding of the behaviour of co-amorphous system which non-specific interactions.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ATR-FTIR</td>
<td>Attenuated Total Reflectance Fourier Transform Infrared</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential Scanning Calorimetry</td>
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<tr>
<td>HME</td>
<td>Hot Melt Extrusion</td>
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<td>PXRD</td>
<td>Powder X-Ray Diffraction</td>
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<td>RH</td>
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<td>$T_g$</td>
<td>Glass Transition Temperature</td>
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Chapter 1 Introduction

Background

Polypills, such as Triveram (perindopril, amlodipine, and atorvastatin) from Servier, as approved products are used in more than 30 countries worldwide. Polypills are the medications that contain more than 1 pharmaceutical active ingredient. Clinical data has shown the improved patient adherence with using polypills for particular chronic diseases such as cardiovascular disease (CVD). The CVD polypills can be defined as combination medication containing at least one blood pressure-lowering and one lipid-lowering drug (Huffman et al., 2017). Several studies have found improvement in medication adherence with the polypill. For example, 2,004 patients with established CVD or calculated 5-year CVD risk >15% were randomized to a polypill or usual medical therapy in UMPIRE (Use of a Multidrug Pill In Reducing cardiovascular Events) the adherence was improved to 33% in the polypills cohort, accompanied by a significant reduction in systolic blood pressure and low-density lipoprotein (Liu et al., 2010).

Many of the drugs in the polypills are poor water-soluble. In the recent years, the high throughput screening methods have led to more than 80% of the new chemical entities have poor aqueous solubility (Guo and Huang, 2014). By modifying chemical structure of the compound, the solubility of the compound can be improved. Formulation strategies such as reduction of particle size, formation of complexes, surface properties and solid dispersion technology have been widely used to improve the dissolution rate of the poorly soluble drugs (Guo and Huang, 2014).

For polypills, depending on the physicochemical properties of the drugs, traditional processing methods such as granulation, tableting and hot melt extrusion (HME) techniques can be used for polypills formulation production. In the manufacturing process, often all APIs of the polypills are processed together. In processes such as HME which has been used widely for producing formulations of poorly soluble drugs, when all drugs are mixed and melted in the extruder, co-amorphous systems are likely to form. However the behaviour of co-amorphous systems are still not fully understood. Therefore this project is particularly dedicated to providing a fuller understanding of co-amorphous systems containing poorly soluble drugs and their physical stabilities.

1.1 Co-amorphous materials
1.1.1 Amorphous materials

An amorphous material can be defined with the reference to its crystalline counterpart. The lattice structure of crystallization drugs can be broken (such as melting and dissolution) by inputting certain
amount of energy to overcome the intermolecular bonds. During such events, the molecular arrangement of the drug can be changed from ordered state to random state which is either a disordered state or the fully amorphous state. The more thermodynamically stable the lattice structure is, the more energy is required to disrupt or break the structure. Amorphous materials are thermodynamically instable with higher molecular mobility than their crystalline state. As it has been mentioned above that the physical stability of the co-amorphous system can be attributed to intermolecular interactions (e.g. H-bonding and/or π–π interactions). The changes in H-bonding or π–π interactions of functional groups are usually detectable via two main approaches such as: a Flory–Huggins interaction and quantum mechanical calculations. The Flory–Huggins interaction is good approach for predicting the physical stability of co-amorphous system. It relies on the thermodynamic and reaction kinetic factors for the modelling successful a stable co-amorphous system, the two factors govern transformational stages in experimental phases. The approach is usually used in the fast screening of the potential drug–drug combinations to produce a stable amorphous formulation. The second approach is based on the quantum mechanical calculations (Density functional theory (DFT)), where the calculations are based on fitted Coulomb integrals to reduce the computational time and generating accurate energy values. The DFT has been utilised in the pharmaceutical field and has revealed to be a valuable tool in predicting interactions in detail. Consequently, changing the state of drugs from crystallization state to amorphous state can significantly increase the dissolution rate as well as the physical instability (Bates et al., 2006). By changing the state of drugs from crystallization to amorphous state, the oral bioavailability of poorly water-soluble drugs can be improved greatly (Bates et al., 2006). There are two commonly reported methods to transform a crystalline material into its amorphous state, milling and super-cooling from melt/solvent evaporation (Hancock and Zografi, 1997).

1.1.2 Definition of co-amorphous material
The co-amorphous drug delivery systems have been widely investigated in pharmaceutical community as an alternative formulation strategy for delivery poorly soluble drugs. As illustrated in Figure 1.1, a co-amorphous system can be described as a multi-component single phase amorphous solid system which lacks periodicity in lattice and is associated by weak and discrete intermolecular interactions between the components (Suresh et al., 2014). There are two types of co-amorphous systems that have been reported recently, drug–drug combinations and drug–excipient mixtures (Löbmann, 2014). For drug-drug co-amorphous systems, two pharmacologically relevant drugs intended for multidrug therapies are combined, where one of drugs stabilize other one in the amorphous form. Both drugs act as an active component and stabilizing excipient at the same time (Swapnil et al., 2016). This is the type of co-amorphous drug system investigated in this project. In the second type, some small molecular weight excipients such as amino acids and carboxylic acids are used to prepare co-amorphous drug-excipient system with higher solubility (Rahul and Chavana, 2016).
1.1.3 Preparation methods of co-amorphous systems

Three types of preparation methods have been reported in the literature for preparing co-amorphous systems: thermal method (melt-quenching), solvent evaporation method and milling method. Melt-quenching is a method which can be used for production of small quantities of co-amorphous materials. In order to produce the amorphous materials, the melt needs to be subsequently vitrified by rapid cooling (Lenz et al., 2015). Milling method is one of the most widely used techniques for preparation of co-amorphous materials. The advantage of ball milling is that low chemical degradation and high recovery compared to other preparation methods (Jensen et al., 2014). However the ball milling may not always be easy to break crystal lattice and the purity of co-amorphous materials is often questionable. The solvent evaporation method is another method that can be used for large-scale preparation of co-amorphous materials. For example, this method was successfully used for the preparation of indomethacin and arginine co-amorphous system (Lenz et al., 2015). However, suitable solvent selection could be challenging for both components. Moreover, solvent residues within the co-amorphous samples could also lead to stability problem during the storage process (e.g. recrystallisation) and safety concerns.

Similar to the amorphous materials, the physicochemical properties of co-amorphous materials are often affected by the preparation methods. Lim, et al compared the co-amorphous systems of indomethacin-cimetidine and naproxen-cimetidine prepared by ball milling, co-evaporation and quench cooling methods (Lim et al., 2016). The molecular mobility for three methods is different. The molecular mobility of the naproxen-cimetidine samples followed the order co-evaporation ($\ln \tau(\beta) = 0.8$), quench cooling ($\ln \tau(\beta) = 1.6$) and ball milling ($\ln \tau(\beta) = 1.8$) indicating faster relaxation of ball milled co-amorphous than quench-cooled and the co-amorphous prepared by solvent evaporation has the slowest relaxation process. Experimentally, all samples can be stored as co-amorphous systems up to 7 months (Lim et al., 2016).
1.1.4 Physical stabilities of co-amorphous systems

Many co-amorphous examples have been reported in the literature in terms of improved physical stability than the individual amorphous drugs (Dengale et al., 2016). There are several factors can contribute to this observed stability improvement. Intermolecular interactions between the components in the co-amorphous mixture, such as hydrogen bonding and π–π interaction, have been one of the main factors discussed in the literature (Alleso et al., 2009; Lobmann et al., 2011; Suresh et al., 2014). Similar intermolecular interactions are also observed in drug-excipient co-amorphous systems (Dengale et al., 2016). For instance, citric acid has recently been shown strong potential to stabilize drugs in the co-amorphous form. Wang., et al prepared co-amorphous formulations of loratadine and citric acid (Wang et al., 2017). The results showed the co-amorphous of loratadine-citric acid system (molar ratio 1:1) was stable after 90 days at 25°C under both 0% and 60% RH, which is more stable than amorphous loratadine (Wang et al., 2017). For the loratadine-citric acid co-amorphous systems, hydrogen bonding was found to be responsible for the increased physical stability. Similar physical stability enhancement was observed intranilast and diphenhydramine hydrochloride co-amorphous systems. The individual amorphous recrystallized within 1 day, whereas the co-amorphous systems were stable for up to 30 days (Ueda et al, 2016).

1.1.5 Dissolution advantage of co-amorphous systems

Improvement in the dissolution rate is another advantage of the co-amorphous material. Shayanfar et al. demonstrated that the dissolution rate of atorvastatin calcium could be improved by the formation of the co-amorphous formulation of atorvastatin calcium and nicotinamide (Ueda et al., 2016). Furthermore, the oral bioavailability of the drugs also can be improved by the use of their co-amorphous systems. For example, the oral bioavailability of the co-amorphous talinolol-naringin 1:1 was significantly higher than crystalline talinolol (Teja et al., 2015). Figure 1.2 summarises the proposed underpinning mechanism of the physical stability and dissolution enhancement associated by the formation of co-amorphous systems.
1.2 Solid dispersion

1.2.1 Definition of solid dispersion

Over 5 decades ago Sekiguchi and Obi made a eutectic mixture of chloramphenicol and urea by the melt method (Sekiguchi and Obi, 1961). The formulation showed that the dissolution rate and bioavailability increased when the drug and carrier were cooled from melting (Sekiguchi and Obi, 1961). This is the first demonstration of solid dispersion as a formulation method for poor soluble drugs. Solid dispersion in the literature was first defined as “the dispersion of one or more active ingredients in an inert carrier or matrix at solid state by the melting (fusion), solvent or melting-solvent method” (Chiou and Riegelman, 1971). Since the introduction of solid dispersion, the technology can not only enhance the solubility of the drug and bioavailability, but also is used to control drug release and target drug delivery (Crowley, 2007). For instance, the drug has characterization of controlled drug release and enteric feature when the drug made by insoluble polymer or enteric polymer (Huang et al., 2008).

1.2.2 Types of solid dispersion

Solid dispersion by definition is a wide range of materials with different molecular level arrange of the API and excipients. There are often loss uses of terminology of sub-species of solid dispersions. Figure 1.3 summarised the sub-types of solid dispersions. Here the 3 most commonly studied solid dispersions are discussed in further detail as below.
Eutectic mixtures
The eutectic mixture usually prepared by drug and carrier. It can be melted with suitable ratio and low temperature, followed by cooling to solidification immediately. In the eutectic mixture, the dispersion of drugs is of the form of extremely small crystals in the carrier. Thermodynamically, such system is regarded as an intimately blended physical mixture of its two crystalline components (Savchenko, 1959). Some of poorly water-soluble drugs showed to form eutectic mixtures with excipients so that enhance their dissolution properties. For example, Yong et.al reported that ibuprofen dissolution rate was improved by eutectic mixture formation with menthol resulting in a significant improvement in the initial plasma concentration of the drug (Gala et al., 2015).

Solid solution
Compared to the eutectic mixtures, solid solution is made of a solid solute (drug) dissolved in a solid solvent (often polymeric excipients). It is shown that two components are crystalized and mixed together in the homogeneous one-phase system. That is the reason why it is also called mixed crystal (Savchenko, 1959). The dissolution rate of poorly soluble drugs can be enhanced when the poorly soluble drug is in rapidly soluble carrier and the dissolution rate of solid solution is faster than that of
the eutectic mixture because the particle size in solid solution has already decreased to minimum (Mollan, 2003).

**Glass solution**

The glass solution can be defined as the drug is either molecularly dispersed as single phase (glass solution) or phase separated mixtures in which the drug present as amorphous domains and/or crystalline fraction distributed in an amorphous polymer or polymeric blend (Yee, 2013). The reason why the researchers focus on glass solution is that the mixtures can significantly improve the dissolution rate of drugs owning to the amorphous nature of the system. Because the amorphous systems lack repetitious order, the molecules in such systems are distributed randomly which makes the incorporation of the drug in the interstitial spaces between the polymer chains easier compared to crystalline polymers. Therefore, amorphous systems exhibit a characteristic behaviour of existing in the solid-like (glass) and liquid-like (supercooled liquid or rubbery) states.

**1.2.3 Preparation of solid dispersion**

**Thermal fusion method**

The process of melting means that the drug and a carrier are mixed and heated to melt, then rapidly cooled under violent stirring to generate solid dispersions (Sekiguchi and Obi, 1961). The melting method is simple and low-cost, but only suitable for the thermally stable drugs. Normally, these solid dispersions use either amorphous carriers or crystalline carriers with low melting points (Savchenko, 1959).

**Solvent evaporation methods**

The solvent evaporation method can be translated into a range of scalable manufacturing processes including freeze drying (Xu W-J et al., 2016), rotary evaporation (Bennett et al., 2015), spray drying (Bennett et al., 2016), electrospinning (Tipduangta et al., 2016), electrospaying (Jahangiri et al., 2016) and supercritical fluid process (SCF) (Potter et al., 2015). For the solvent evaporation method, the physical mixture of drug and polymer is dissolved in a common solvent, followed by the solvent evaporation and drying. The solvent method is suitable for the thermally liable drugs. However, higher cost of preparation and environmental concerns of solvent wastes are the main disadvantages of this method. In addition, incomplete solvent removal from the result solid dispersions could lead to safety issues of the product.

**Hot-melt extrusion method (HME)**
Chapter 1

Introduction

HME is a widely used technology in the plastic industry. It has been used to manufacturing a range of pharmaceutical products that are mainly solid dispersion based formulations. HME is a heating-based method for preparation of solid dispersions without solvent. The pharmaceutical HME process can be described as conveying raw materials with rotating screw under elevated temperatures, and products with a special shape (determined by the die) can be collected at the end of the extruder. In the late 1930s, twin-screw extruders were invented in Italy (Tachibana and Nakamura, 1965) and it is main type of HME used in pharmaceutical industry. As the name implied, twin-screw extruders have two screws arranged side by side. The screws can either rotate in the same or opposite direction (co-rotation and counter-rotation, respectively). A pharmaceutical extruder consists of a control panel, an inlet feeding hopper, a steel barrel with different heating zones, screws for extrusion, a die attached to the end to specially shape the products, and a cooling system, as illustrated in Figure 1.4. However, the lab-scale twin-screw extruder used in this project does not have various heating zones. During the process of hot-melt extrusion, there is only one temperature that can be operated by the machine. At the end of screws, a valve can be closed to make sure the drugs and polymers are mixed completely during the process of extrusion. By blocking the outlet, the material can be circulated through the mixing zone at a constant temperature.

Basically, the HME formulation can be separated three components including drugs, polymer and plasticizers. During the HME process, the polymer should be soften or molten. For the plasticizers, it necessary to ease the HME process when the HME system are viscous.

The main application for hot melt extrusion in pharmaceutical industry include fast release formulation and sustained release formulation. By using hot melt extrusion, fast release formulation are based on the preparation of amorphous solid dispersion (Kalivoda, Fischbach and Kleinebudde, 2012). The poorly water soluble drug dissolution rate can be improve significantly because of use HME to process drug and polymer mixtures into amorphous solid dispersion. For example, a study shows itraconazole and hydroxypropylmethyl-cellulose (HPMC) 2910 solid dispersion were prepare by HME and its amorphous solid dispersion were confirmed by MTDSC and PXRD(Rambali et al., 2003). In this study, Itraconazole is a typical BSC II drug with low solubility (1.8ug/ml in PH 1.2 solution) (Jung et al., 1999). The results shows the drug release of formulation was reached to 90% after 120min under sink condition (Rambali et al., 2003). By using hot melt extrusion prepare solid dispersion with water insoluble polymeric carriers, the drug release can be sustained from formulations (Yang et al., 2008). A report shows that using twin-screw hot melt extruder to prepare controlled release diclofenoc sodium formulation with different matrices (Sato et al., 1997). The results shows that the dissolution rate can be controlled by adjusting the drug loadings (Sato et al., 1997).
1.2.4 Physical stabilities of solid dispersions

Despite some of advantages of solid dispersion for improving dissolution rates of drugs, poor long-term physical stability is the common drawback of solid dispersion. The main consequence is drug recrystallization which reduces the dissolution rate of the drug in the solid dispersion formulation. For instance, due to the stability problem of solid dispersion formulation, Norvir, which is solid dispersion product of an antiviral drug Ritonavir from Abbot, was withdrawn from the market (Mooter et al., 2001). There is a wide range of factors contributing to the often observed poor stability of solid dispersion. Moisture is one of the major factors affecting the solid dispersion stability. A research showed that the reason why moisture can effect physical stabiliy of solid dispersion (Andronis et al., 1997). The moisture in the solid dispersion could increase the molecular mobility so that it increased the rate of recrystallization of the API in the solid dispersion. Therefore, the selection of appropriate storage condition is extremely important for the stability of solid dispersions. For instance, A paper showed that the solid dispersion of nifedipine, nicotinamide and HPMC were stored in the environment at 30 °C with 60% and 75% RH for a month (Suzuki and Sunada, 1998). The recrystallization of nifedipine led to the great reduction of the drug dissolution rate. However, the solid dispersion of nifedipine, nicotinamide and HPMC did not change the state when stored at drying environment even with higher temperature. Guillaume, et al reported that if the solid dispersion of oxodipine and PVP was stored at a relative humidity less than 55% at different temperatures, there was no crystallization occurs within the solid dispersion (Suzuki and Sunada, 1998). However the drug recrystallization occurred when the storage environment was at 80% RH.

The thermodynamic instability of the solid dispersions is originated from the molecular mobility of the systems. The glass transition temperature ($T_g$) is one of the indictors of the potential physical instability of the solid dispersions. $T_g$ is defined as a kinetic parameter where the transformation of material form from glassy state to a super cooled liquid state upon heating. The amorphous material has an increased viscosity when the amorphous material below glass transition temperature and the
mobility of molecular are decreased. This phenomenon helps amorphous material ‘relaxes’ into their thermodynamically stable form and this process is called molecular relaxation (Hancock et al., 1997). For a glass solution or often called an amorphous solid dispersion, a single \( T_g \) should be detected, if the binary system is miscible. If more than one \( T_g \) are detected, it indicates the system having phase separation (Craig et al., 2000). For a miscible system, the \( T_g \) of the dispersion should be between the \( T_g \) of the individual compound. As an example, using higher \( T_g \) amorphous polymers could potentially enhance the physical stability of amorphous solid dispersions compared with amorphous drugs alone due to the anti-plasticisation effect of the polymer (Serajuddin, 1999).

The \( T_g \) of the miscible amorphous dispersions can be predicted using Gordon-Taylor (G-T) equation, which is expressed using Eq. 1.1

\[
T_{gmix} = \frac{[w_1T_{g1} + (Kw_2T_{g2})]}{[w_1 + (Kw_2)]} \quad \text{Eq. 1.1}
\]

where \( T_{gmix} \) is the glass transition temperature of mixture, \( T_{g1} \) and \( T_{g2} \) represent the glass transition temperature of individual component respectively. \( w_1 \) and \( w_2 \) are the weight fraction of each component. \( K \) is a constant which can be describe as:

\[
K \approx \frac{(\rho_1T_{g1})}{(\rho_2T_{g2})} \quad \text{Eq. 1.2}
\]

Where \( \rho_1 \) and \( \rho_2 \) represent the true density of individual component. The G-T equation can be used to make comparison between theoretical glass transition temperature and experimental glass transition temperature. Because the G-T equation is based on the assumption of ideal mixing in which the molecules from the two components are blended completely. In the literature it was recognised that if theoretical glass transition temperature and experimental glass transition temperature are deviated, it may indicates interactions between the components depending on whether the deviation being negative or positive (Shamblin et al., 1998).

1.3 The objectives of this study
The main aim of this study is to enrich the existing knowledge of co-amorphous materials by gaining more in depth knowledge of the physical stability of co-amorphous systems. There are 2 main objectives of this MSc project:

- Investigate the physical stability of co-amorphous material and provide insights into the impacts of molecular interactions on the physical stability of co-amorphous systems
- Investigate the stabilisation capability of amorphous polymeric dispersions for co-amorphous drugs
Chapter 2 Materials and methods

2.1 Introduction
In this chapter the key physicochemical properties of the two model drugs and main polymeric excipients will be analysed and discussed. This information is ready used in the following chapters for interpreting the behaviour of the co-amorphous and solid dispersion stabilised co-amorphous systems. Serveral of characterisation technologies were used for physicochemical properties of amorphous solid dispersion. For example, Differential Scanning Calorimetry (DSC) results presenting a single glass transition which may indicates a single-phase amorphous solid solution (Verdonck et al., 1999). A amorphous halo detected by Powder X-ray Diffraction (PXRD) may indicates the majority of samples in the solid dispersion was mainly amorphous (Margarit et al., 1994). Moreover, Fourier Transform Infrared Spectroscopy (FTIR) can be used judge the interaction between drugs and polymer by analysing peak position (Larkin, 2011). So, a brief introduction of the methodologies used for characterisation in this project is also discussed in this chapter.

2.2 Materials
2.2.1 Felodipine
Felodipine (1,4-dihydropyridine) (Figure 2.1a) a long-acting calcium channel blocker with poor aqueous solubility (Patil et al., 2009) was purchased from Afine chemicals Ltd. (Hangzhou, China). For crystalline felodipine, four polymorphic forms have been reported in literature. The melting point for forms I-IV are 143.8 ± 0.2°C, 134.8 ± 0.2°C, 143.7 ± 0.2°C and 145.7 ± 0.2°C respectively (Surov AO et al, 2012). The NH group and C=O group can be detected by ATR-FTIR with different forms. For crystalline felodipine, the NH peaks were reported at 3372,3334, 3370, 3329 cm\(^{-1}\) for crystalline felodipine form I, II, form III and form IV, respectively. The NH group of amorphous state felodipine was detected at 3339 cm\(^{-1}\). IR was also able to detect inter-molecular hydrogen-bonded C=O stretching and non-hydrogen bonded C=O peaks for form I, II and IV (Lou B, 2009). For NH group and hydrogen-bonded C=O stretching peaks were reported at 1690, 1683 and 1654 cm\(^{-1}\). On the other hand, non-hydrogen bonded C=O group of form I, II, IV were detected at 1699, 1698, 1703 cm\(^{-1}\), respectively. For IR spectra of hydrogen-bonded C=O stretching peaks and non-hydrogen bonded C=O group peaks of amorphous felodipine was 1682 and 1701 cm\(^{-1}\)(Wang et al., 2015).
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![Chemical structures of paracetamol and felodipine](image)

**Figure 2.1 Chemical structures of paracetamol and felodipine**

### 2.2.2 Paracetamol

Paracetamol is a non-steroid anti-inflammation drug used to control mild-moderate pain or to reduce opioid exposure as part of multimodal analgesia. It is typically used for mild to moderate pain. Paracetamol used in this project was purchased from Sigma-Aldrich Company Ltd. (Dorset, UK). Three polymorphs of crystalline paracetamol have been reported in literature. The melting point of form I is 170°C, 159°C for form II, 143°C for form III, respectively (Simon et al., 2010). In the IR spectra, crystalline paracetamol form I has O-H peaks at 3321cm⁻¹, N-H bond at 3157cm⁻¹, and C=O bond at 1650cm⁻¹ as its key characteristic peaks.

### 2.2.3 Soluplus

Soluplus (Figure 2.2), is a graft amorphous polymer which has a low glass transition temperature (approximately 70 °C) and purchased from BASF (Ludwigshafen, Germany). Sodium chloride and hydrochloric acid were purchased from Sigma-Aldrich Company Ltd (Dorset, UK). All the organic solvents and water were of high-performance liquid chromatography (HPLC) grade. Felodipine has 5 hydrogen bond acceptors and 1 hydrogen bond donor, whilst Paracetamol has 2 hydrogen bond acceptors and 2 hydrogen bond donors. Together, they are a suitable combination of model drugs because there is the potential of hydrogen bonding formation, which benefits stability and the formation of a co-amorphous system and solid dispersion system.
2.3 Methods

2.3.1 Differential scanning calorimetry (DSC)

DSC is an essential technique for thermal analysis of materials. DSC was first commercially introduced in 1963 and it also usually be used in development of pharmaceutical materials. (Theeuwes et al., 1974). The theory of DSC method is that the detection of thermal transitions events of materials like melting, crystallization, glass transitions, and decomposition reactions (Verdonck et al., 1999). Generally, there are two parts of DSC instruments which is power compensation and heat flux. For the power compensation DSC, two separated furnaces can be used for the reference and for the sample and both of them are heated and maintained at the same temperature. Compare to power compensation DSC, the heat flux DSC uses two pans (crucibles) for the sample and for the reference within one furnace as seen in Figure 2.2 and the heat flux DSC will be used for this project. They are both heated from the same temperature program and the temperature difference between the sample and the reference is measured (Duncan and Craig, 2008).

Heat flow from the furnace to each crucible can be explained in Eq. 2.1

$$\frac{dQ}{dt} = \frac{\Delta T}{R}$$  \hspace{1cm} Eq. 2.1

where $Q/\text{dt}$ is the heat flow. $\Delta T$ is the temperature difference between the sample and the reference and $R$ is the thermal resistance of the heat paths between the furnace and the crucible. The total heat content of a material is in linear relationship to its heat capacity (Cp J/g °C) which is the quantity of heat required to change the temperature of the material by 1K:
\[ Cp = \frac{dQ}{dT} \]  \hspace{1cm} Eq 2.2

Rearranging this equation with time:

\[ \frac{dQ}{dt} = Cp \left( \frac{dT}{dt} \right) \]  \hspace{1cm} Eq 2.3

where \( \frac{dQ}{dt} \) is the heat flow and \( \frac{dT}{dt} \) is the heating rate. With this equation, the differential heat flow can be a measure of the sample heat capacity. DSC data is normally expressed with the heat flow as a function of the temperature.

In this study, a Q-2000 DSC equipped with a RC90 cooling unit (TA Instruments, Newcastle, USA) was used to perform all thermal analysis shown in Figure 2.3. A full range of temperature and heat capacity calibrations were performed prior to sample measurements. Approximately 2 – 5 mg of samples were weighed and sealed into the aluminium pans and lids (TA Instruments, Newcastle, USA). 10 °C/min heating rate was used for all samples. All samples were tested in at least triplicate.

![Illustration of working mechanism of heat flux DSC (Kodre et al., 2014)](image)

**Figure 2.3 Illustration of working mechanism of heat flux DSC (Kodre et al., 2014)**

### 2.3.2 Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR)

FTIR is one of technique that can be used to identify chemical structure of different materials. By using the mid-infrared electromagnetic radiation within the wavenumber range of \((4000-400 \text{ cm}^{-1})\), The Chemical bonds in molecules can be stretched so that the radiations can be absorbed and stimulate molecular vibrations and rotations at specific frequencies (Watson, 2012).
The principle of ATR-FTIR is shown in Figure 2.4. ATR-FTIR method is based on a high refractive index crystal such as diamond is used (Schuttlefield and Grassian, 2008). The sample for investigation could be liquid or solid. And the sample can be placed in contact with the diamond, and infrared light from an FTIR source is allowed entering the diamond at a specific angle and reflecting at the surface (Schuttlefield and Grassian, 2008). There are several benefits of ATR-FTIR for material investigation. The main advantage is that this method is time-saving compared to other techniques and no need for further sample preparation. The depth of penetration $\text{dir}$, defined as the distance normal to the interface which the intensity falls to $1/e$ of the intensity at the surface, is expressed in Eq. 2.4

$$\text{dir} = \frac{\lambda}{2\pi n_1 (\sin^2 \theta - n_1^2 n_2^2)^{1/2}}$$  \hspace{1cm} \text{Eq. 2.4}$$

where $\lambda$ is wavelength of IR beam, $n_1$ is the refractive index of the ATR crystal, $\theta$ is the angle of incidence of IR radiation, and $n_{sp} = n_2/n_1$ is the ratio of the refractive indices between the sample and the internal reflective element (crystal) (Larkin, 2011).

In this study, all of experiments were conducted using an IFS 66/S FTIR spectrometer (Bruker Optics Ltd., Coventry, U.K.). It is also fitted with a Golden Gate ATR accessory (Specac, Orpington, U.K.) equipped with diamond internal reflection element. All ATR-FTIR spectra were obtained using a scanning resolution of 2 cm$^{-1}$ with 32 repeated scans in the absorbance mode. OPUS software (Bruker Optics Ltd., Coventry, U.K.) was used for spectra analysis. The variable temperature ATR-FTIR experiments were carried out using the same instrument set-up. The ATR sample stage was heated up from room temperature to 20°C at 190°C/min.
2.3.3 Powder X-ray Diffraction (PXRD)

PXRD is a method to analysis the crystal lattice parameter, crystal defect, content of drug or formulations (Serajuddin, 1999). The diffraction will occur if a crystalline material is interacted with a focused X-ray beam according to Bragg’s law,

\[ n\lambda = 2dsin\theta \]

where \( d \) represent the interplanar spacing of the diffracting planes. \( \theta \) represent the incidence angle of X-rays and \( n \) is an integral number of wavelengths, and \( \lambda \) is the wavelength of the incident X-ray beam.

PXRD is considered a fundamental tool for the pharmaceutical solid dispersions research and product development. The main advantage is that the physical state of a solid dispersion can be rapidly tested being amorphous or crystalline as well as identification of polymorphic forms of crystalline materials (Margarit et al., 1994). If no diffraction peaks can be detected by PXRD, the system can be considered as ‘PXRD amorphous’. However, caution should be taken during data analysis as nano-crystal diffraction patterns may also appear as amorphous halo without processing using pair distribution function (PDF) (Margarit et al., 1994).

In this study, a Thermo ARLXtra X-ray diffractometer (Thermo Scientific, Switzerland) equipped with a copper X-ray tube (\( \lambda = 1.540562 \text{ Å} \)) were used for all sample analysis shown in Figure 2.5. The samples were measured using an X-ray beam with voltage of 45 kV and a current of 40 mA. The angular scan range was (5 ° < \( \theta < 60 \) °) using a step scan mode with step width of 0.01 ° and scan speed of 1s/step.
2.3.4 Scanning electron microscopy (SEM)
SEM is a type of electron microscope that used for investigating morphology of the samples at a micron to submicron scale. It has high magnification compared to the normal light microscopes. The interactions between the beam and the atoms in the sample can be detected by scanning the sample with a high-energy electron beam. In this work, AJSM5900LV field emission scanning electron microscope (Jeol Ltd., Japan) equipped with a tungsten hairpin electron gun was used to visualize the surfaces and the cross sections of solid dispersion. To avoid damaging the surfaces of the solid dispersion, the samples can be used directly for the investigation of surface of the sample. Before imaging, the samples have to be attached onto SEM specimen stubs by double-sided tape and coated with gold using a Polaran SC7640 sputter gold coater (Quorum Technologies, East Sussex, UK).

2.3.5 Thermogravimetric Analysis (TGA)
TGA refers to analysis on the relationship between temperature and weight of the solid dispersion with the program that can control temperature. It is usually used to study the thermal stability of materials and components. TGA in research is a relatively common means of detection for the drug development. In this study, at a heating rate of 10 °C/min to 250 °C were used to study the thermal degradation behavior of the samples. A TGA Q500 (TA Instruments, New Castle, DE) was used for all sample measurements. All samples were tested in at least triplicate.

2.3.6 In vitro drug release studies
The dissolution testing apparatus (Caleva ST, Germany) with BP paddle method was used to test the in vitro drug release profile of the co-amorphous and dispersion formulations. For all measurements, using paddle rotation speed of 100 rpm and 900 ml of hydrochloric acid (HCl) with pH 1.2 (simulated
gastric fluid) at 37 °C ± 0.5 °C. Then, the samples should be filtered by filtration membrane of 0.22μm pore size (Minisart NML single use syringe, Sartorius, UK). After sampling, 5ml fresh media were added back to each dissolution vessel. Finally, a UV − vis spectrophotometer (PerkinElmer lambda 35, USA) at 363 nm (for felodipine) and 247 nm (for paracetamol) was used to quantify the drug content in each dissolution sample. All drug releases were studied in triplicate. The calibration curves of paracetamol and felodipine are shown in Figure 2.6.

![Graph a](image1)

![Graph b](image2)

Figure 2.6 UV calibration curves of paracetamol (a) and felodipine (b)

2.4 Solid-state characterisation of the raw materials

The crystalline paracetamol and felodipine as well as the polymer, Soluplus, used in Chapter 5 for preparing the solid dispersions were characterised using DSC, PRXD, SEM and ATR-FTIR. The ATR-FTIR spectra of crystalline paracetamol and felodipine will describe in Chapters 3 and 5 when they were compared to the spectra of co-amorphous and solid dispersion systems. The melting of the crystalline model drugs and their glass transition temperatures were studies using DSC heat-cool-reheat method. The scanning rate was 10°C/min. The melting point of crystalline paracetamol and felodipine is determined as 147 °C and 169 °C, respectively, indicating being form I for both. As shown in Figure 2.7, the glass transition temperatures were detected for both of model drugs at 26 °C and 47 °C for amorphous paracetamol and felodipine, respectively. Amorphous paracetamol recrystallized upon reheating and melted at 158 °C, which indicates the recrystallization
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of paracetamol form II. The DSC result of Soluplus shows the $T_g$ of 73.6 °C, which agrees well with the literature, reported values (Mohammad and Steven, 2016). It is also noted that Soluplus contained some level of moisture, thus a clear water loss endothermic peak is observed in the first heating cycle.
Figure 2.7 DSC results of crystalline paracetamol (a) felodipine (b) and Soluplus (c)
Figure 2.8 shows the PXRD of crystalline paracetamol, felodipine and Soluplus. It can be seen that the paracetamol and felodipine are in full crystalline form. After comparing with the literature data, the PXRD results confirmed again that both paracetamol and felodipine were in their polymorphic form I. The PXRD result of Soluplus shows being a fully amorphous halo.

Figure 2.8 PXRD results of crystalline paracetamol, crystalline felodipine and Soluplus
The SEM images of crystalline paracetamol, felodipine and amorphous Soluplus are shown in Figure 2.9. As seen in the SEM images, paracetamol shows needle-like crystals, whereas felodipine crystals are mainly in cubic shape. Soluplus particles show rough but round edges which may be attributed to its amorphous nature.

Figure 2.9 SEM images of crystalline paracetamol (a), crystalline felodipine (b) and (c) Soluplus

2.5 Thermal analysis of physical mixtures of crystalline paracetamol and felodipine

The physical mixtures of the two crystalline drugs were prepared by pestle and mortar mixing with a range of w/w rations from 1:9 to 9:1. It should be highlighted here that the w/w 3:7 and 7:3 of felodipine-paracetamol is close to the molar ratio of 2:1 and 2:1 used later in the co-amorphous study. The purpose of this part of the study is to investigate the miscibility of the two drugs. As reported in the literature, if the two compounds having good miscibility, the melting point depression accompanied by reduced melting enthalpy can often be observed for the crystalline material. As seen in Figure 2.10, instead of melting point depression, a new melting point (peak temperature) at 133 °C was detected for all physical mixtures. This new melting was initially associated with the possibility of forming eutectic of the two drugs. However, this was not possible as with all mixing ratios, the new melting was observed. So this indicates that the new melting is not associated with eutectic mixture of the two drugs as eutectic system normally only forms at eutectic point with a specific mixing ratio of
the two compounds. The enthalpy of this new melting point changes with the weight ratio of paracetamol to felodipine in the mixes. As seen in Figure 2.11, there seems to be a linear correlation between the melting enthalpy (indicating the quantity of the new species) and the w/w ration of the two model drugs. It is not clear why there are two linear regions, 10-40% paracetamol and 50-90% paracetamol in the mixtures. Nevertheless, it is noted that the melting enthalpy increases with increasing the amount of crystalline felodipine in the mixtures indicating that the new melting is highly associated with felodipine rather than paracetamol. Further investigation was carried out with the intention to identify the new species with 133 °C melting. Therefore, variable temperature ATR-FTIR experiments were performed.

Figure 2.10 DSC results of all physical mixtures of crystalline paracetamol and felodipine
Figure 2.11 The plot of melting enthalpy of 133 °C peak against the w/w ratio of paracetamol in paracetamol-felodipine physical mixtures

The variable temperature ATR-FTIR data are shown in Figure 2.12-14. The 3500-3200 cm\(^{-1}\) regions were the key focus for detailed analysis as these regions showed more significant changes in comparison to other regions. Within this region, the N-H peak of felodipine and O-H peak of paracetamol can be clearly seen. Although there is some overlap, the two peaks can still be distinguished as two separate peaks. As seen in Figure 2.12, the N-H peak of crystalline felodipine shows more significant changes during heating for the paracetamol-felodipine physical mixture with the ratio of 3:7 (w/w). Little changes in the peak shape and intensity were observed for the O-H peak of crystalline paracetamol. The N-H felodipine peak at 3371 cm\(^{-1}\) almost disappeared when the temperature reached 140°C. Instead, a weak peak 3426 cm\(^{-1}\) was gradually developed between 130-140°C. With decreasing the amount of felodipine in the mixtures (Figure 2.13 and 14), the final intensity of this new peak is decreased. This again indicates that the formation of the new low melting species is associated with felodipine which agrees well with the DSC data. However due to time constrain, the identification this new species was not continued further.
Figure 2.12 Variable temperature ATR-FTIR spectra of paracetamol:felodipine 3:7 (w/w)
Figure 2.13 Variable temperature ATR-FTIR spectra of paracetamol:felodipine 1:1 (w/w)
2.6 Conclusion

This chapter introduced the basic physicochemical properties of the model drugs and polymer used in this project. All the characterisation methods were also introduced in terms of their basic working mechanisms and the generic methods used in the project. The characterisation of the amorphous drugs agreed well with the literature data. Interesting data were generated when the physical mixtures of the crystalline model drugs were studied. A new species related to felodipine was generated during the heating of the crystalline physical mixture of the two model drugs. Whether this new low melting species is a polymorphic form of felodipine is unclear and was not further investigated within the timeframe of this project. However, it is unlikely to be the depressed melting of felodipine form I as the variable temperature ATR-FTIR results showed the development of a new N-H peak with a shift to a higher wavenumber than the felodipine form I.
Chapter 3 Preparation and characterisation of freshly prepared co-amorphous systems

3.1 Introduction
As discussed in Chapter 1, co-amorphous systems are considered an effective method used to improve poor dissolution problem. With the understanding established in Chapter 2 on the physical mixtures of the two model drugs, the co-amorphous systems of the two drugs are the focus of this chapter. The objectives of this chapter are preparing the co-amorphous system samples with different molar ratios of paracetamol and felodipine (1:1, 1:2 and 2:1) and performing solid-state characterisations of the co-amorphous sample.

3.2 Methods
3.2.1 Preparation of co-amorphous systems
In this study, physical mixture of crystalline paracetamol and felodipine (PF) was prepared with different molar ratios of 1:1 (PF 1:1), 1:2 (PF 1:2) and 2:1 (PF 2:1) in aluminium dishes. The heater plate was preheated to 170°C. The dishes containing the physical mixes were then placed on the heater plate to allow both drugs melted completely. Isotherm heating was held for 7 minutes to ensure that no drug particle was visible in aluminium dishes. Finally, air cooling the samples by removing the dishes off the heater plate to the bench surface immediately (room temperature about 20°C). The samples were stored indifferent chambers with relative humidity (RH) of 75% RH/40°C and 0% RH/room temperature(RT) for further stability studies (Chapter 4).

3.2.2 Characterisation of the co-amorphous systems
SEM, PXRD, DSC and ATR-FTIR were used to characterise the freshly prepared co-amorphous systems. The detailed methods were described in Chapter 2.

3.3 Results and discussion
3.3.1 Visual observation of the PF co-amorphous system samples
The freshly prepared PF co-amorphous samples are shown in Figure 3.4. All samples immediately after preparation show yellow glassy appearance with smooth surface and no crystals can be observed.
3.3.2 DSC
The DSC results of PF co-amorphous systems were different from two model drugs. As described in Chapter 2, the melting points of crystalline paracetamol and felodipine are 169°C and 145°C, respectively. In the co-amorphous samples, no original crystalline drug melting can be detected for PF co-amorphous 1:1 and 1:2 systems. However, it can be seen in Figure 3.2 that the PF co-amorphous system 2:1 shows an endothermic transition at 152°C which is likely to be the depressed melting of paracetamol form II. A clear exothermic recrystallisation peak with an onset of 95-100 °C can also be seen before the melting indicating the likelihood of the significant amount of the melted crystalline material was generated by heating induced crystallisation. In contrast, PF 1:1 and PF 1:2 only show T_g without any detectable melting indicating the full amorphous states of the samples. Paracetamol is known in the literature having high tendency of recrystallization and a low T_g= 21 °C (Qi et al., 2008). As PF 2:1 contains more paracetamol, the recrystallization of amorphous paracetamol may contribute to the melting observed in PF 2:1. In the literature, the recrystallization paracetamol form II was reported following melt-cool preparation (Shadi and Iba’a, 2011). This could also explain why the co-amorphous formulation with high ratio of paracetamol was not stable in the later stability study section. The PF co-amorphous systems all have a single T_g which is 35.7, 36.1 and 41.5°C, for PF1:2, 1:1, 2:1, respectively. These T_g values are between the T_g values of amorphous paracetamol and felodipine and increasing with the increased felodipine content in the co-amorphous systems. The clear single T_g detected for all systems indicates that PF co-amorphous systems were successfully prepared by melt-cool method (Swapnil et al., 2016). These T_g were compared to the T_g of the mixtures calculated by Fox equation which is a simpler version of Gordon-Taylor (G-T) equation (Witold et al., 2008).

\[
\frac{1}{T_{g_{mix}}} = \frac{w_1}{T_{g1}} + \frac{(1-w_1)}{T_{g2}} \quad \text{Eq. 3.1}
\]

where T_{g_{mix}} is the glass transition temperature of the drug-polymer system, T_{g1} is the glass transition temperature of component 1 (amorphous paracetamol, 25 °C), T_{g2} is the glass transition temperature of component 2 (amorphous felodipine, 45 °C) and w1 is the weight fraction of component 1.
Chapter 3 Preparation and characterisation of freshly prepared co-amorphous systems

Table 3.1 Comparison of $T_g$ values of P-F 1:1, 1:2 and 2:1 measured experimentally by DSC (cooling cycle) and the predicted values by Fox equation

<table>
<thead>
<tr>
<th></th>
<th>P-F 1:1</th>
<th>P-F 1:2</th>
<th>P-F 2:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental $T_g$ ($^\circ$C)</td>
<td>36.1</td>
<td>41.5</td>
<td>35.7</td>
</tr>
<tr>
<td>Predicted $T_g$ ($^\circ$C)</td>
<td>34</td>
<td>39</td>
<td>31</td>
</tr>
</tbody>
</table>

According to the Fox equation calculation, the calculated $T_g$ values of the co-amorphous systems are shown in Table 3.1. For PF all of co-amorphous system, the measured $T_g$ values negatively deviated from the Fox equation predicted values. This indicates that the P-F co-amorphous system is miscible and some level of molecular interactions may be responsible for the negative deviation from the predicted values (Shamblin et al., 1998).

Figure 3.2 DSC results of freshly prepared P-F co-amorphous system 1:1, 1:2 and 2:1

3.3.3 PXRD

The fresh PF co-amorphous system samples were tested by PXRD as seen in Figure 3.3. The results show that no paracetamol and felodipine diffraction peak can be detected by PXRD. This indicates that the freshly prepared PF co-amorphous systems are fully ‘PXRD’ amorphous. The PXRD results of PF 2:1 system were not in good agreement with DSC result because by DSC some paracetamol crystallisation was detected. This may be due to differences in the sensitivity and detection limits of the instruments. It is also possible that the melting observed in PF 2:1 DSC result was originated from the drug recrystallized during the heating process of the DSC run instead of having crystalline drug present in the sample.
3.3.4 ATR-FTIR spectroscopy

The ATR-FTIR results of the PF co-amorphous system 1:1, 1:2 and 2:1 also showed agreement with DSC results. As seen Figure 3.4 (a), pure amorphous felodipine shows single NH group peak at 3331 cm$^{-1}$ and one peaks shows at 1701 cm$^{-1}$ in carbonyl groups region which is belong to crystalline felodipine. For amorphous paracetamol, the peak at 1557 cm$^{-1}$ can be ascribed to a carbonyl group. A single NH peak at 3315 cm$^{-1}$, C=N at 1559 cm$^{-1}$ and C-O group at 1171 cm$^{-1}$ can also be observed (Figure 3.4). The result of PF co-amorphous system 1:1 shows similar NH peak wavenumber as prediction result which is 3312 cm$^{-1}$ for paracetamol. Compare to wavenumber of pure amorphous felodipine NH group, the PF co-amorphous system 1:1 shows same results indicating no significant hydrogen bonding occurred in the co-amorphous systems. Similar results were obtained for 1:2 and 2:1 samples.
Figure 3.4 ATR-FTIR spectra of freshly prepared P-F co-amorphous systems (a) 1:1; (b) 1:2 and (c) 2:1
3.3.5 SEM

The SEM results of the freshly prepared PF co-amorphous systems are shown in Figure 3.5. For the surfaces of PF 1:1 and 1:2 co-amorphous systems, no paracetamol and felodipine crystal could be detected by SEM. However, there are some particles on the surface of the PF 1:1 and 1:2. These particles are likely to be the fragmented pieces attached to the surface during the samples preparation as they seemed loosely adsorbed on the surfaces of the samples. In comparison to PF 1:1 and 1:2 co-amorphous systems, the SEM results of PF 2:1 co-amorphous system show some difference and it is very clear that the surface of PF 2:1 is not smooth and some drug particles with defined edges (likely to be crystalline particles) can be seen on the surface. This is indicated that the PF 2:1 was not in amorphous state when the sample were fresh.

For the cross section of these three samples, same results can be seen compare to the surface of samples. The cross section of PF 1:1 and 1:2 co-amorphous system shows that no crystal occurred when the sample were fresh. As mentioned before, the particles seen on the cross section are fragmented solids instead of crystalline drug particles. However, the cross section of PF 2:1 shows clearer appearance of drugs particle embedded in the sample than PF 2:1 surface. This indicates that PF 2:1 was not fully amorphous. Therefore, the SEM data are in good agreement with the DSC results.
Chapter 3 Preparation and characterisation of freshly prepared co-amorphous systems

3.3.6 Dissolution

Figure 3.6 shows the *in vitro* dissolution behaviour of co-amorphous drug release system 1:1, 1:2 and 2:1 under pH 1.2 at 37°C. For all co-amorphous samples, felodipine showed some dissolution improvement than the crystalline drug up to 30 minutes. After 30 minutes, such improvement was reduced to similar level as the crystalline drug. This may be attributed to the fact that the amorphous felodipine was recrystallized after 30min and the poor solubility of crystalline felodipine. As discussed in the Chapter 4 and 5, the amorphous felodipine can be recrystallised easily at certain conditions, for
example RH75% and 40°C/RT. During the dissolution experiment, the media environment is 35°C and PH 1.2, when the extrudates dissolve in the media, the amorphous felodipine may recrystallised at the same time. To prove this point, extra experiments may be needed in the future. For instance, taking 50ml media after dissolution, drying the sample completely, a few particles may show after drying and performed the DSC test. However, paracetamol in P-F co-amorphous systems shows significantly higher dissolution rates than felodipine. This is partially because paracetamol has a higher solubility than felodipine. However, the dissolution rate of paracetamol in the co-amorphous systems were slower than the crystalline paracetamol alone. This dissolution rate shows significant increase in the P-F 2:1 system. This is likely due to the high paracetamol content of the systems. For P-F 1:2 and 1:1, the slower dissolution than the crystalline paracetamol could be attributed to the entrapment of amorphous paracetamol within the crystallised felodipine which hindered the dissolution of paracetamol.
Figure 3.6 Dissolution of freshly prepared co-amorphous P-F 1:2(a), 1:1(b) and 2:1(c)
3.4 Conclusion
In this chapter the freshly prepared co-amorphous P-F 1:1, 1:2 2:1 samples were investigated. According to the DSC results, all three co-amorphous systems formed homogeneously mixed amorphous materials with a single $T_g$. Little evidence shown in the ATR-FTIR results suggested extensive interaction between paracetamol and felodipine. This indicates the co-amorphous systems were formed simply as mixtures of paracetamol and felodipine molecules blended together in their amorphous state. This may explain the poor dissolution enhancement of felodipine in the co-amorphous systems. Due to the recrystallization of felodipine in the co-amorphous system during dissolution, the dissolution rate of paracetamol was reduced due to the entrapment of paracetamol molecules in the crystallised felodipine. The physical stability of the co-amorphous system will be investigated in the next Chapter.
Chapter 4 Physical stability studies of co-amorphous systems

4.1 Introduction
Despite the dissolution enhancement was not observed in the model systems studied in this project, the co-amorphous systems enhancing the dissolution rate for poorly water-soluble drugs has been reported in literature (Dengale et al., 2016). However the preservation of the long-term physical and chemical stability of the co-amorphous systems still remains the main challenge for the formulation scientists. As discussed in Chapters 2 and 3, paracetamol has low a T_g and showed high recrystallization tendency in the co-amorphous systems with high paracetamol content. This may be related to the supersaturation of paracetamol in the co-amorphous mix. In order to rationalise the formulation strategy for improving the physical stability of co-amorphous systems, it is important to first understand their physical instabilities in a great depth. In this chapter, three of co-amorphous samples were prepared and then aged under two different storage conditions, 0% RH/room temperature (RT) and 75% RH/40°C, for up to two weeks. The rationale of the selections of these 2 conditions was to provide understanding on the physical stability of co-amorphous system at two highly contrast storage conditions.

4.2 Methods

4.2.1 Storage condition
Co-amorphous system samples were stored in two different aging conditions, 75% RH/40 °C and 0% RH/RT. The samples stored in a desiccator containing saturated sodium chloride in ultrapure water to achieve 75% RH. The desiccator was incubated at 40°C. The samples were also stored in a desiccator with 0% RH (provide by P_2O_5) at room temperature. Characterisation tests were performed after 1, 3, 7 and 14 days to detect any change in physical state of the co-amorphous samples.

4.2.2 Physicochemical characterisation
DSC, PXRD and ATR-FTIR were used for monitoring physical stability of co-amorphous system. The detailed methodologies were described in Chapter 2.

4.3 Results and discussion

4.3.1 Physical stability of PF co-amorphous system under 0% RH/RT

4.3.1.1 DSC
Physical stability of PF co-amorphous systems under 0% RH/RT were studies using DSC in the first instance. After 7 days aging, all three co-amorphous systems still show clear T_g indicating the significant amount of amorphous contents in the samples. The clear melting of crystalline compound
can be only detected in PF 2:1 samples. As seen in Figure 4.1a, a broad exothermic crystallisation peak with an onset of approximately 100 °C and peak temperature 123°C can be clearly seen followed by a sharp melting point at 152 °C. According to the literature data, this melting belongs to paracetamol form II (Shadiand and Iba’a, 2011). This indicates the high instability of PF 2:1 even under mild storage condition. The existence of the exothermic transition, which is likely to be the recrystallization of the material, indicates that the heating of the DSC run accelerated the crystallization. Although no clear melting can be seen in the DSC results of the aged PF 1:1 samples, a weak endothermic transition (likely to be a melting) with an onset of 110°C can be identified. The aged PF 1:2 samples showed no melting in the DSC results suggesting being the most stable amorphous sample. However a weak Tg like transition at around 50 °C is observed for PF 1:2 after 7 days aging. If this is a true Tg, it indicates the phase separation of some proportions of phase separated amorphous felodipine. The above results indicate that the physical stability of the three systems after 7 days aging is in the order of P:F 1:2> 1:1>2:1. Figure 4.1b shows the physical stability studies of PF co-amorphous system under 0% RH/room temperature after 14 days aging. Similar to the 7 days aging data, clear Tgs were detected for all samples. The PF 2:1 shows similar results as the physical stability of 7 days aging, a broad recrystallization followed by a melting peak at 152 °C can be observed. For the aged PF 1:1a clear but broad melting point at 116 °C can be seen which indicates the clear instability of PF 1:1 after 14 days aging. The DSC results of the aged PF 1:2 show a sharp melting point at 113°C indicating the instability after 14 days aging. The low melting compounds observed in the DSC results of 14 days aged P:F 1:1 and 1:2 could be the same origin. However this low melting does not match any melting point of the polymorphic forms of either paracetamol or felodipine, indicating the possibility of the formation of co-crystals. This new species was also observed in the co-amorphous system stored under 75% RH/40 °C. Its origin was later further investigated by PXRD and ATR-FTIR in section 4.3.2. It is also interesting to note that the weak Tg around 50 °C again is observed for both PF 1:2 and 2:1 after 14 days aging. As discussed above, if this is a true Tg, this could be the evidence of the phase separation of amorphous felodipine from the co-amorphous mixture.

Overall, under 0% RH/RT, the P:F 1:1 and 1:2 demonstrated similar behaviour and the recrystallization of a small quantity of a new species was observed. However, P:F 2:1 exhibited different physical stability in comparison to 1:1 and 1:2. The high tendency of paracetamol form II recrystallization was clearly demonstrated indicating the supersaturation of paracetamol in the co-amorphous system.
Figure 4.1 DSC results of P-F co-amorphous 1:1, 1:2 and 2:1 aged under 0% RH/RT for 7 days (a) and 14 days (b)

4.3.1.2 ATR-FTIR
As the Figure 4.2, no crystalline NH peaks of paracetamol and felodipine can be seen in the IR spectra of the aged PF 1:1 and 1:2 systems after 1, 3, 7 and 14 days. For carbonyl groups, a peak at 1661 cm\(^{-1}\), this peak is same as carbonyl group of fresh sample, indicating the PF 1:1 co-amorphous system is stable within 14 days under 0%RH/RT. The detected small amount of the crystalline material with a melting of 113 °C is not evident in the ATR-FTIR results. This is likely to be due to the poorer limit of detection of IR of crystalline materials than DSC. A good physical stability was observed in PF 2:1
system under the same condition for only up to 3 days. After 3 days aging, the O-H regions of the samples show significant alternation indicating the crystallisation of paracetamol.

According to ATR-FTIR results, both PF 1:1 and 1:2 systems show good physical stability under 0% RH/RT. As there is no clear hydrogen bonding between paracetamol and felodipine was identified via IR as discussed in Chapter 3, the mechanism of stabilisation is likely to be associated with the 0% RH which eliminate the plasticisation effect of moisture sorption for the samples as well as the increased overall T_g than the T_g of amorphous paracetamol. The poor physical stability of the PF 2:1 system is mainly associated with the recrystallisation of paracetamol form II. This indicates that the system is likely to have gone through amorphous phase separation of the amorphous paracetamol and amorphous felodipine. Because of the higher content and poorer stability of amorphous paracetamol, recrystallisation of paracetamol was detected as a result of this phase separation. This phase separation was evidenced by the T_g-like transition observed in the DSC results.

![Figure 4.2 ATR-FTIR results of P-F co-amorphous 1:1, 1:2 and 2:1 aged under 0%RH/RT after 1, 3, 7 and 14 days](image)

**Figure 4.2 ATR-FTIR results of P-F co-amorphous 1:1, 1:2 and 2:1 aged under 0%RH/RT after 1, 3, 7 and 14 days**

4.3.2 Physical stability of PF co-amorphous systems under 75% RH/40 °C

4.3.2.1 **DSC**

For PF 1:1 co-amorphous system, it can be clearly observed that the samples shows melting points after 1, 3, 7 and 14 days at a range of temperatures 126, 134, 145 and 158 °C indicating they are different species of crystalline material. The identifications of the crystalline materials based on the
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Physical stability studies of co-amorphous systems

DSC results are difficult as both paracetamol and felodipine have polymorphic forms with melting points similar to these temperatures. Therefore in the following sections, PXRD and ATR-FTIR were used to further characterise them. The fact that no clear presence of exothermic recrystallization peak indicating these crystalline materials were not generated through the DSC heating which is different from the fresh PF 2:1 samples. For PF 1:2 co-amorphous system after 1 days, it shows a small melting peaks at approximately 120 and 125 °C. After 3 and 7 days aging a melting point at 109 °C can be seen. There is a melting point at 120 °C after 14 days aging of the PF 1:2 co-amorphous system. For the PF 2:1 system, after 1, 3, 7 and 14 days aging similar results were obtained. A melting point between 148-151 °C was observed. As this system contained more paracetamol, this is likely to be the melting of paracetamol form II.

If judging by the amount of recrystallized materials, the PF 1:2 co-amorphous system is the most stable system under related humidity 75%RH/40 °C with the least amount of crystalline melting enthalpy. Although the PF 1:2 system was in the progressing of recrystallization, the speed of recrystallization was slower than the other systems. This may be attributed to the higher overall $T_g$ of PF 1:2 system is higher than the other systems ($T_g$ of PF 1:2 is 41.5 °C). However overall none of the systems are stable under this stressed condition.

It is worth mentioning that there are low melting transitions between 110-120 °C were observed in aged PF 1:2 system. This low melting does not match any melting of polymorphic forms of paracetamol and felodipine. Therefore there is a possibility of the crystallisation of paracetamol-felodipine co-crystals. However due to the time constrain, the formation of co-crystal was not investigated further.
Figure 4.3 DSC results of P-F co-amorphous 1:1 (a), 1:2 (b) and 2:1 (c) under 75% RH/40 °C after 1, 3, 7 and 14 days
4.3.2.2 PXRD

PXRD results of the physical stability of PF co-amorphous systems aged under 75% RH/40 °C are summarised in Table 4.1. Despite DSC detected the presence of small amount of crystalline materials, PXRD still ‘recognised’ the PF 1:2 system being fully amorphous. Again this may be associated with the difference in the limit of detection of different characterisation techniques. The PF 1:1 co-amorphous system showed amorphous features up to 3 days. Significant crystalline peak were seen after 7 days, indicating the samples started recrystallizing after 7 days. The PF 2:1 showed recrystallization after 1 days again. The order of the physical stability of the co-amorphous system agrees well with the DSC results.

PXRD was further used to identify the recrystallized materials. By comparing the crystalline paracetamol and felodipine PXRD peak with the crystalline peaks of in the diffraction patterns of PF 1:1 and 2:1 (Figure 4.4 and 4.5), it can be clearly observed that most of the diffraction peaks in the diffraction pattern of aged PF 2:1 belong to crystalline paracetamol. Moreover, in both cases as the recrystallization progresses, more paracetamol diffraction peaks were detected with increased intensities.

Table 4.1 PXRD data of P-F co-amorphous system 1:1, 1:2 and 2:1 fresh, aged under 75% RH/40 °C for 1, 3, 7 and 14 days

<table>
<thead>
<tr>
<th>Fresh</th>
<th>1days</th>
<th>3days</th>
<th>7days</th>
<th>14days</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-F 1:1</td>
<td>Amorphous</td>
<td>Amorphous</td>
<td>crystallization</td>
<td>crystallization</td>
</tr>
<tr>
<td>P-F 1:2</td>
<td>Amorphous</td>
<td>Amorphous</td>
<td>Amorphous</td>
<td>Amorphous</td>
</tr>
<tr>
<td>P-F 2:1</td>
<td>Amorphous</td>
<td>crystallization</td>
<td>crystallization</td>
<td>crystallization</td>
</tr>
</tbody>
</table>
Figure 4.4 PXRD results of P-F co-amorphous system 1:1 aged under 75% RH/40 °C for 7 and 14 days

Figure 4.5 PXRD results of P-F co-amorphous system 2:1 aged under 75% RH/40 °C for 1, 3 and 7 days
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Physical stability studies of co-amorphous systems

Figure 4.6 PXRD results of P-F co-amorphous system 1:2 aged under 75% RH/40 °C for 1, 3, 7 and 14 days

4.3.2.3 ATR-FTIR

The higher physical stability of PF 1:1 co-amorphous system and 1:2 co-amorphous systems under 75% RH/40 °C also was investigated by ATR-FTIR. The results are shown in Figure 4.6 and 4.7. For PF 1:1 co-amorphous system no characteristic crystalline paracetamol and felodipine IR peak was observed after 1 and 3 days aging. For PF 1:1 co-amorphous system after 7 days and 14 days (data not shown due to the data lose in the lab fire in July 2017) revealed a NH peak at 3322 cm⁻¹, which is typical of crystalline paracetamol, confirming the presence of crystalline paracetamol in this PF 1:1 system. In addition, the shape of NH peak for PF 1:1 system is very clear and sharp, indicating no crystalline felodipine coexistent in this system. For carbonyl peaks of the PF 1:1 system, it is evident that the C=O peak of PF 1:1 system at 1608 cm⁻¹ which agrees well with the C=O peak of crystalline paracetamol. Other evidences of the presence of crystalline paracetamol in the aged PF 1:1 include the peak at 833 cm⁻¹ which aligns with the peak at 833 cm⁻¹ of crystalline paracetamol. For aged PF 2:1 system, crystalline paracetamol was detected by the crystalline NH peak at 3321 cm⁻¹. No crystalline paracetamol and felodipine N-H and C=O peaks were detected by ATR-FTIR for PF 1:2 co-amorphous system. Overall, the ATR-FTIR results of PF 1:1, 1:2 and 2:1 systems are in good agreement with PXRD results, but show lower detection sensitive of crystalline content in the aged samples than DSC. The high level stress humidity and temperature significantly accelerated the recrystallization process of the co-amorphous systems. The PF 2:1 showed poorest stability followed by PF1:1 and PF 1:2 co-amorphous systems is most stable in comparison to PF 1:1 and 2:1 systems.
Figure 4.7 ATR-FTIR spectra of P-F 1:1 co-amorphous system fresh, aged for 1, 3 and 7 days
Figure 4.8 ATR-FTIR spectra of P-F co-amorphous system 1:2 and 2:1 fresh, aged for 1, 3 and 7 days

(*Note: 14 days data lose in the IR machine which was in a lab fire in July 2017)

4.4 Conclusion

In this chapter, physical stability studies under different aging conditions of co-amorphous materials were investigated. It is very clear that the high related humidity and temperature (75%RH/40°C) had significant effect on the stability of co-amorphous materials. By comparing the results of physical studies between different ratio of co-amorphous material, the co-amorphous PF 1:2 showed better
physical stability under 75%RH/40C and 0%RH/room temperature than PF 1:1. The co-amorphous PF 2:1 showed least physical stability. However, as all three systems showed some recrystallization after 14 days, stabilisation of the co-amorphous is needed. Therefore, Chapter 5 investigated the stabilisation effect of polymeric additives for the co-amorphous systems.
Chapter 5 Stabilisation of co-amorphous systems by polymeric solid dispersion

5.1 Introduction
As discussed in the previous Chapter, the co-amorphous systems exhibited high physical instability under 75%RH/40 °C storage condition. Amorphous polymer based solid dispersions have been widely reported to be able to stabilize amorphous drugs (Qiang et al., 2016). Solid dispersions can be prepared using a wide range of processing methods. In this study, HME was used to prepare the solid dispersion samples containing the co-amorphous systems. HME was selected for its effectiveness in fabricating uniformly dispersed polymeric glass solutions (Laitinen et al., 2013). HME has also been already widely adopted by pharmaceutical industry, thus it is processing method that is easy to scale-up.

In Chapter 4, the significant amount of the low melting new species was detected by DSC in the aged PF 1:1 samples which was speculated as possible co-crystals of paracetamol and felodipine).

The aim of this Chapter is evaluate the stabilization capability of solid dispersion of the co-amorphous systems. PF 1:1 co-amorphous system was selected as the model system for the investigation due to its strong evidence of forming interactive complexes between felodipine and paracetamol in the 1:1 system.

5.2 Methods
5.2.1 Preparation of solid dispersion by HME
Physical mixtures of paracetamol, felodipine and Soluplus with different ratios including 1:3 (paracetamol:Soluplus PS and felodipine:Soluplus FS), 1:7 (paracetamol:Soluplus PS and felodipine:Soluplus FS), 1:1:2 (paracetamol:felodipine:Soluplus PFS) and 1:1:6 (paracetamol:felodipine:Soluplus PFS) were blended prior to HME (Table 5.1). The physical mixtures were fed into a co-rotating twin-screw extruder (HAAKE MiniLab II Micro Com-pounder, Thermo Electron, Karlsruhe, Germany) that was operated at an extrusion temperature of 140 °C and a screw speed of 100 rpm. The extrudates were collected as uniform rods.

<table>
<thead>
<tr>
<th>Table 5.1 Formulation of the HME solid dispersions</th>
</tr>
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<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Paracetamol –Soluplus (P-S)</td>
</tr>
<tr>
<td>Felodipine –Soluplus (F-S)</td>
</tr>
</tbody>
</table>
5.2.2 Storage condition
The extrudates were stored at 75% RH/RT, 75% RH/40 °C and 0% RH/room temperature for up to 4 weeks for stability studies.

5.2.3 Solid-state characterisation
SEM, DSC, PXRD, and ATR-FTIR were used to monitor the physical stability of the solid dispersions containing either single amorphous drug or the co-amorphous systems.

5.2.4 In-vitro drug release studies
Dissolution testing was carried out in dissolution testing apparatus (Caleva8ST, Germany) using BP apparatus II paddle method. All tests were performed using a paddle rotation speed of 100 rpm in 900 mL 0.1M HCl (pH 1.2) at 37 °C. The extrudates loaded with equivalent to 10mg of felodipine and paracetamol was used for individual dissolution test. The dissolution samples withdrawn at each time point were filtered through 0.22µm filtration membrane before UV testing. The samples were measured using a UV–VIS spectrophotometer (Perkin-Elmer Lambda 35, USA) at 363 nm and 257nm for felodipine and paracetamol, respectively.

5.3 Results and discussion
5.3.1 Morphologies of the extrudates
As seen in Figure 5.1, all freshly prepared HME extrudates are visually transparent indicating no significant amount of crystalline drug present in the solid dispersions. Figure 5.2 shows the SEM images of the surfaces of the freshly prepared solid dispersions. Again no crystalline drug particle was detected by SEM indicating the amorphous nature of all of solid dispersions.
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*Stabilisation of co-amorphous systems by polymeric solid dispersion*

The SEM results of the solid dispersions aged under most stressed condition (75% RH/40 °C) for 4 weeks are shown in Figure 5.3. Few small crystalline particles can be seen in the binary solid dispersions. However the solid dispersions containing co-amorphous systems show no sign of drug crystals at both surfaces and cross-sections. The SEM images of the samples aged under the other two conditions (75% RH/ RT and 0% RH/RT) showed no crystallisation in any samples (data not shown).
However after aging, the most significant physical form changes were observed in P-F-S 1:1:2 aged under the condition of relative humidity of 75%/40°C. As seen in Figure 5.4, the extrudates were completely deformed and liquidified due to the high aging temperature and relative humidity. Therefore significant moisture uptake was suspected which could be responsible for the deformation.
This is confirmed by the TGA results showed in Figure 5.4, in which approximately 1.2% weight loss (which is likely to moisture) was detected with heating up to 100°C. The continuous weight loss above 100°C is an indication of chemical degradation and thermal decomposition of the samples.

Figure 5.4 The liquification of P-F-S 1:1:2extrudates after 4 weeks aging at 75%RH/40 °C and the TGA result of the sample

5.3.2 Thermal behavior of the extrudates

Figure 5.5 shows the DSC results of the freshly prepared binary and co-amorphous solid dispersions. As seen in Figure 5.5 there is no clear melting of crystalline drug can be detected indicating the full amorphous nature of all the solid dispersions. Single $T_g$ was detected for all freshly prepared dispersions suggesting no clear amorphous phase separation in these systems. With increasing the Soluplus content, the $T_g$ of the dispersions increases. The DSC measured $T_g$ values of the fresh samples are compared with predicted $T_g$ calculated using Fox equation. As seen in Table 5.2, for all of solid dispersion systems, the $T_g$s of formulations are lower than the calculated $T_g$s. According to the literature, this indicates that the drug-polymer interactions are weaker than the molecular interactions between two drug molecules (Shamblin et al., 1998).
Chapter 5  Stabilisation of co-amorphous systems by polymeric solid dispersion

Figure 5.5 DSC results of the freshly prepared solid dispersions

Table 5.2 Comparison of $T_g$ values of P-S 1:3, P-S 1:7, F-S 1:3, F-S 1:7, P-F-S 1:1:2 and P-F-S 1:1:6 measured experimentally by DSC and predicted by Fox equation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>P-S 1:3</th>
<th>P-S 1:7</th>
<th>F-S 1:3</th>
<th>F-S 1:7</th>
<th>P-F-S 1:1:2</th>
<th>P-F-S 1:1:6</th>
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</thead>
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<td>Experimental $T_g$ (°C)</td>
<td>46.6</td>
<td>51.1</td>
<td>52.2</td>
<td>55.1</td>
<td>46.1</td>
<td>49.4</td>
</tr>
<tr>
<td>Predicted $T_g$ (°C)</td>
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<td>62.5</td>
<td>48.8</td>
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</tr>
</tbody>
</table>

for 4 weeks under 0%RH/RT (Figure 5.6), the DSC results of the solid dispersions show reductions of the $T_g$ of all samples between 5-10 °C. However, no melting was detected. Normally decreases of the $T_g$ values should be an indication of either increased amount of amorphous content or plasticisation effect. The increase in amorphous content is not possible. In this case, as the aging condition was 0% RH, it is unlikely that the observed decreases in $T_g$ is due to the moisture absorption. However, moisture uptake during the DSC samples preparation is possible. For the samples aged for 4 weeks under 75% RH/40 °C (Figure 5.7), significant moisture losses as broad endothermic peaks are detected for all samples. No clear melting peaks were detected in any of the aged samples. Amorphous phase separation is evidenced by the presences of double $T_g$ in F-S 1:3 and P-F-S 1:1:2. Clear Soluplus $T_g$ was detected in both samples indicating the phase separation of amorphous dispersions and the polymer. Overall the DSC results indicated good physical stability of most of the samples except the F-S 1:3 and P-F-S 1:1:2 systems, which show some signs of amorphous phase separation. No drug recrystallization was detected in any aged samples.
Figure 5.6 DSC results of the 4-weeks aged solid dispersions at 0%RH/RT
Figure 5.7 DSC results of the 4-weeks aged solid dispersions at 75% RH/40 °C

5.3.3 PXRD
The freshly prepared solid dispersions are all PXRD amorphous as seen in Figure 5.8. Similar to the conclusion drawn from the DSC results, no crystalline peaks were detected in any of the aged samples (Figure 5.9 and 10) indicating the good physical stability of all solid dispersions.
Chapter 5  Stabilisation of co-amorphous systems by polymeric solid dispersion

Figure 5.8 PXRD diffraction patterns of freshly prepared solid dispersions

Figure 5.9 PXRD of the 4-week aged solid dispersions at 0% RH/RT
5.3.4 ATR-FTIR

The ATR-FTIR spectra of the freshly prepared solid dispersions again demonstrate the full amorphous nature (Figure 5.11). Some peak shifts of the CO of paracetamol and felodipine in the spectra of the binary dispersions indicate molecular interaction (hydrogen bonding) between paracetamol, felodipine and the polymer, which contributed to the stabilisation of the dispersions. It is very hard to analyse the spectra of the carbonyl region of paracetamol between 1800 and 1500 cm\(^{-1}\) because of peak overlapping with the carbonyl peaks of Soluplus. Therefore, the NH peaks at 3369 cm\(^{-1}\) and 3327 cm\(^{-1}\), which are the signature crystalline felodipine and paracetamol peaks, respectively, were used to identify any drug recrystallisation in the aged samples. No crystalline felodipine paracetamol NH peaks were observed for the extrudates aged under all conditions (Figure 5.12 and 13). This indicates the solid dispersions were still in their amorphous states after aging. The samples aged for 4 weeks (data not shown because the data was in the PC damaged by the lab fire) showed no significant difference in ATR-FTIR spectra.

Figure 5.10 PXRD diffraction patterns of 4-week aged solid dispersions at 75% RH/40 °C
Chapter 5  Stabilisation of co-amorphous systems by polymeric solid dispersion

Figure 5.11 ATR-FTIR spectra of crystalline paracetamol, felodipine and freshly prepared P-F-S extrudates with 1:1:2 and 1:1:6 ratios (a) 4000-2000 cm\(^{-1}\) region (b) 1950-1500 cm\(^{-1}\) region
Figure 5.12 ATR-FTIR spectra of P-S extrudates with (a) 1:3 and (b) 1:7 ratios aged for 2 weeks at 75%RH/RT, 0%RH/RT and 75%RH/40 °C
5.3.5 In vitro drug release

The dissolution profiles of the freshly prepared PFS 1:1:6 and 1:1:2 dispersions in the form as cylindrical shaped extrudate rods (not as traditional powder form) are shown in Figure 5.14. For both formulations, felodipine had less than 2% dissolution. This is likely to be due to the slow dissolution of Soluplus as a cylinder rod which facilitated the crystallisation of felodipine in the extrudates and significantly hindered the dissolution of felodipine. Paracetamol in the PFS 1:1:6 shows good release profile which matches the release behaviour of the paracetamol alone. But only 6% of paracetamol dissolved from the PFS 1:1:2 solid dispersion. This may be attributed to the recrystallisation of
felodipine in the polymeric matrices which increased the hydrophobicity of the samples and reduced water penetration in the samples and the subsequent dissolution of paracetamol.

![Freshly prepared solid dispersions](image)

**Figure 5.14** The *in vitro* drug release profiles of freshly prepared P-F-S 1:1:2 and 1:1:6 extrudates

After aged 4 weeks, the dissolution profiles of paracetamol in PFS 1:1:6 show significant decreases in the dissolution rate (Figure 5.15). In fact a nearly linear zero order release profile can be seen in all aged PFS 1:1:6 samples. As the extrudates maintained the cylindrical shape throughout the dissolution test, this indicates the diffusion controlled release behaviour in aged PFS 1:1:6 samples. Different storage conditions show little impact on the paracetamol release behaviour in the aged samples. However for the aged PFS 1:1:2 samples, low paracetamol releases were observed (Figure 5.16). Similar to the fresh samples, the recrystallisation of felodipine in the extrudates during the dissolution test could be the main reason of the low paracetamol release. The releases of felodipine from the aged P-F-S extrudates were all less than 1.5% over the 8-hour dissolution tests. Therefore the data is not included in the Figures.
Figure 5.15 The *in vitro* drug release profiles of paracetamol from aged (4 weeks) P-F-S 1:1:6 extrudates

Figure 5.16 The *in vitro* drug release profiles of paracetamol from aged (4 weeks) P-F-S1:1:2 extrudates
5.4 Conclusion

This Chapter investigated the physical stability of solid dispersions of the co-amorphous systems incorporated into Soluplus matrices. From all the solid-state characterisation data, it is clear that the physical stability of the co-amorphous systems were improved. However, the in vitro dissolution data showed that with high co-amorphous content hindered the release of both drugs. Aging even had significant impact on slowing the release of paracetamol from the co-amorphous solid dispersions. However, it should be highlighted that the dissolution in this study were performed using extrudates as strands instead of power form, which could be useful for controlled release formulation applications. The results of this Chapter have highlighted the importance of effect of polymer additives on the dissolution enhancement of the co-amorphous systems.
Chapter 6 Conclusion remarks and future work

6.1 Physical stabilities for co-amorphous systems

In this project, co-amorphous paracetamol-felodipine (P-F) was selected as the model system based on the prediction of potential intermolecular interaction (mainly hydrogen bonding potentials) between the two drugs. The amorphous paracetamol has poor physical stability due to high molecular mobility at room temperature and the low T_g. Crystalline felodipine has poor aqueous solubility, therefore the conversion to its amorphous state was expected to improve the dissolution rate of felodipine and subsequently bioavailability. Therefore the rationale behind forming the co-amorphous system of P-F is to improve the physical stability of amorphous paracetamol and the dissolution rate of crystalline felodipine.

All of sample were stored under 0% RH/ room temperature and 75% RH/40 °C for up to 14 days. Under such conditions, amorphous paracetamol alone would recrystallize within 2 hours (Piera et al., 2000). Amorphous felodipine has been reported to show recrystallization within 1 day under such conditions (Umesh et al., 2013). As discuss in Chapter 4, the co-amorphous P-F 1:2 shows better physical stability (without recrystallization) than P-F 1:1 under accelerated stress condition. For P-F 1:1, the sample were stable up to 7 days under 75 RH%/40C, whereas P-F 1:2 were stable for up to 14 days. Both of formulations can be stable up to 14 days under0% RH/room temperature. Co-amorphous P-F 2:1 showed the poorest physical stability with crystallization of paracetamol observed within 1 day after aging. For both 1:1 and 1:2 systems, the stability was improved compared to amorphous paracetamol and amorphous felodipine alone. Despite the overall T_g values of the co-amorphous systems are still relatively low (approximately 35-40 °C), the results indicate that the formation of co-amorphous systems has the ability of reduce the crystallization tendency of the two amorphous drugs in comparison to their own amorphous state. This may be attributed to the intermolecular interactions between the two species. The high recrystallization tendency of P-F 2:1 system is likely to be attributed to the stronger intramolecular interaction of paracetamol molecules than intermolecular interactions between paracetamol and felodipine. This led to the rapid nucleation and crystallization of the amorphous content of paracetamol in the system.

In terms of the improvement of the dissolution rate, felodipine showed no significant improvement for the dissolution from the co-amorphous systems. Supersaturation and crystallization in the dissolution media were observed rapidly after the initiation of the dissolution test. This indicates that the co-amorphous system was not able to sustain a high level of supersaturation of felodipine. This may be due to the lack of nucleation inhibitors in the systems in comparison to other polymer based solid dispersions in which often polymers act as the nucleation inhibitor after dissolution. The dissolution
rate of paracetamol from the co-amorphous system is also hindered in comparison to eh amorphous paracetamol alone. The intermolecular interaction between paracetamol and felodipine may play a role in delaying the dissolution of paracetamol, in particular if the paracetamol molecules are trapped in the recrystallized felodipine crystals.

Overall, based on the behaviour of the co-amorphous systems, we have achieved the goal of improving the physical stability of the amorphous drugs, but not accomplished the aim of improving the dissolution rate of the two drugs. Therefore, to further enhance the stability and the dissolution rate of the drugs, polymer excipients were added to act as the stabilizer and nucleation inhibitor during dissolution. P-F 1:1co-amorphous systems were selected as the model systems to be further investigated due to their intermediate stability and in vitro dissolution results (as well as the time limit of the project).

6.2 Comparison of physical stability between co-amorphous and solid dispersions

Soluplus was selected as the model polymeric excipient for the preparation of the amorphous dispersions. This choice was made based on the good stabilizing capability of Soluplus for each individual amorphous drug (Chapter 5). After the incorporation of the co-amorphous systems into the solid dispersions via hot melt extrusion, the physical stabilities of the drugs were improved in comparison to the co-amorphous systems. All of sample stored under 75% RH/RT, 0% RH/ RT and 75% RH/40C for solid dispersion with aging up to 3 months. Under the stressed condition, the amorphous drugs were stable in the dispersions for at least 1 month. The crystallization paracetamol was still observed for longer aged samples indicating that intrinsic high molecular mobility of amorphous paracetamol is still difficult to overcome. However, the amount of recrystallization is small, thus DSC and PXRD results showed little evidence of significant crystallization. This stability enhancement can be attributed to the presence of Soluplus which anti-plasticize the two low T_g amorphous drug (DSC results confirmed) and drug-polymer interactions (ATR-FTIR results confirmed).

In terms of the dissolution rate enhancement, the incorporation into the Soluplus based solid dispersions showed significantly faster release of paracetamol from the extrudates than power form co-amorphous systems. Taking into account that the physical form difference (extrudate as matrix system and power form co-amorphous which has much higher surface area-to-volume ratio), this indicates that the presence of Soluplus significantly improve the dissolution of paracetamol. This could be explained by the dispersion of paracetamol molecules within the soluble polymer matrix instead of being trapped in the recrystallized felodipine solids (as illustrated in Figure 6.1).
Conclusion remarks and future work

6.3 Recommended future work

This project has accumulated promising results towards the understanding of co-amorphous systems which would be useful for future drug delivery applications such as polypill formulation development (when multiple drugs are being delivered in a single dose unit). However, due to the time constrain of the project there are still many aspects of in depth investigations of the subject needed. These include the thermodynamic properties of the co-amorphous systems such as molecular relaxation behaviour, the molecular interactions and their role in stabilizing both amorphous drugs, and the effect of polymeric additives on the stability and dissolution behaviour of the co-amorphous materials.


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