THE EVALUATION OF LARCH ARABINOGALACTAN AS A NEW CARRIER IN
THE FORMULATION OF SOLID DISPERSIONS OF POORLY WATER-SOLUBLE
DRUGS

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Kalpana Thakare

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Advisory Committee:
David Lebo, Ph.D. (Dissertation Advisory Committee (D.A.C.) Chair
Reza Fassihi, Ph.D. (Examining Chair)
Michael Borenstein, Ph.D.
Stephanie Wunder, Ph.D. Department of Chemistry, Temple University (External Reader)
ABSTRACT

Advanced drug discovery techniques have produced more lipophilic compounds. Formation of an amorphous solid dispersion of such poorly water-soluble drugs improves their solubility and dissolution. This results in greater in vivo bioavailability. Thus, it is one of the recent trends in the development of oral dosage forms. In solid dispersions, the carrier is crucial for ensuring the functionality and stability of these systems. Larch arabinogalactan FiberAid grade (AGF) is generally recognized as safe (GRAS) designated, amorphous polymer. The objective of this dissertation project was to perform a comprehensive evaluation of AGF as a carrier for amorphous solid dispersions.

First, a detailed characterization of the AGF polymer was performed. A special focus on its use as a solid dispersion carrier was emphasized. The glass transition temperature and the degradation temperature of the AGF polymer were ~82 °C and ~185 °C, respectively. The AGF polymer had good hygroscopicity. Ibuprofen-AGF solid dispersions were evaluated for dissolution enhancement. Ibuprofen-Hydroxypropyl methylcellulose grade K3 (HPMCK3) solid dispersions were investigated simultaneously as a control polymer dispersion. The ibuprofen-AGF solid dispersions were amorphous at nearly 20% ibuprofen load. The dissolution of the ibuprofen from AGF solid dispersions was significantly greater than that of the neat ibuprofen. The formation of the amorphous state of ibuprofen and solution-state ibuprofen-AGF interactions were the mechanisms of the ibuprofen dissolution enhancement. At a 10% ibuprofen load, the dissolution of the AGF solid dispersion was found greater than that of the dissolution of the HPMCK3 solid dispersion.
Secondly, the itraconazole-AGF solid dispersions and the ketoprofen-AGF solid dispersions were characterized and compared them with the ibuprofen-AGF solid dispersions. The comparisons were established for the miscibility and dissolution enhancement. The order of increase in dissolution was ketoprofen-AGF solid dispersions > itraconazole-AGF solid dispersions > ibuprofen-AGF solid dispersions. The same order was observed for the solid-state miscibility of these drug-AGF solid dispersions.

Additionally, the solid dispersions of 9 drugs with the AGF polymer were investigated to elucidate the detailed mechanism of drug crystallization inhibition by the AGF polymer. The inherent tendency of the AGF polymer to inhibit the drug crystallization, drug-AGF solid-state hydrogen bonding and the anti-plasticizing effect of AGF were the mechanisms underlying the crystallization inhibition by the AGF polymer.

Last, a storage stability of ibuprofen-AGF amorphous solid dispersions after storage under accelerated conditions (for 3 months) and ambient conditions (for 6 months) was investigated. The amorphous ibuprofen from AGF solid dispersions was physically and chemically stable under stability conditions.

In summary, the AGF polymer was evaluated as a novel carrier for formation of an amorphous solid dispersions. The studies established that the AGF polymer was comparable to HPMCK3 polymer. The AGF polymer could be more advantageous than the HPMC polymer for the preparation of solid dispersion when faster dissolution is desired at lower drug load.
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DEDICATION

This dissertation is dedicated to:

My husband Amol,

My son Devesh, and

My Parents
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CHAPTER 1
INTRODUCTION

Oral bioavailability of a drug primarily depends on its aqueous solubility, permeability across the biological membrane, and dissolution rate. Additional factors such as first-pass (presystemic) metabolism and susceptibility of drug to efflux mechanisms influence the oral bioavailability (reviewed by Savjani et al., 2012). Poor bioavailability of an orally administered poorly water-soluble drug is often the result of their inadequate solubility and dissolution in the gastrointestinal fluids (reviewed by Savjani et al., 2012). Therefore, formulating an oral dosage form of poorly water-soluble drugs is the greatest challenge currently faced by the pharmaceutical industry. Dissolution and solubility enhancement is the first rationale step towards improving the oral bioavailability of these drugs.

1.1. Dissolution enhancement

According to the modified Noyes Whitney equation based upon a diffusion layer model depicted in Figure 1.1, the dissolution rate dM/dt is described using the following equation (Dokoumetzidis and Macheras, 2006).

\[
\frac{dM}{dt} = \frac{D \cdot S \cdot (C_s - C)}{V \cdot h} \tag{1.1}
\]

M - Mass/amount of drug material dissolved (mg or mmol)

t- Time in s

D- Diffusion coefficient of the drug (cm²/sec)

S-Surface area (cm²)
h- Thickness of the stagnant layer

V-Volume of the dissolution medium

Cs-Concentration of the drug at the surface of the drug particle (saturation solubility)

C-Concentration of the drug in the bulk medium

![Diffusion layer model of drug dissolution](image)

Figure 1.1 Diffusion layer model of drug dissolution
(Modified from Nickerson., 2011)

Evaluation of each term in the above equation indicated that three parameters that would directly improve the dissolution rate are- (a) decreasing the boundary level thickness and thus maintaining the sink condition, (b) increasing the surface area by a reducing the particle size of the compound and by improving the wetting characteristics of the compound surface, and (c) enhancing the solubility of the compound (reviewed Leuner and Dressman, 2000; Dokoumetzidis and Macheras, 2006). The first parameter of
decreasing boundary level thickness and maintaining the sink condition is difficult to modify in vivo. It depends on hydrodynamic conditions in the gastrointestinal (GI) tract such as permeability of the drug across the GI mucosa, composition and volume of luminal fluids, and agitation in the GI system. The second parameter of particle size reduction and improvement of wetting characteristic can be achievable using various physical modification approaches (section 1.1.2). The third parameter of solubility increment can be achieved using chemical and physical approaches (Section 1.1.1 and section 1.1.2). The solubility enhancement directly improves the oral bioavailability of the drugs with dissolution and solubility rate-limited absorption (Dokoumetzidis and Macheras, 2006; Takano et al., 2008).

Therefore, studies on improvement in bioavailability of a hydrophobic drug are often focused on solubility enhancement (reviewed by Verma et al., 2011).

1.1.1 Chemical modifications

Salt formation and prodrug formation are chemical approaches to improve the solubility of a hydrophobic drug without changing the active target. However, the major limitation of the chemical approach is that it produces a product which is designated as a new chemical entity (NCE). An NCE has to undergo the entire new product development cycle. Limitations of the salt formation approach include in vivo conversions of the salt to the original base or acid. Further, salt formation is feasible only in the case of acidic and basic drugs and not neutral drugs (reviewed by Vasconcelos et al., 2007; reviewed by Verma et al., 2011).

1.1.2 Physical modifications
Physical modification techniques include- (a) reduction of particle size (micronization), (b) modification of crystal habit (highly soluble amorphous, polymorph or pseudo polymorph formation), (c) solubilization using surfactant, (d) drug dispersion in a polymer matrix, and (e) combination of any of the 2 or more approaches (reviewed Leuner and Dressman, 2000; reviewed by Verma et al., 2011).

Among all these formulation approaches, formation of a dispersion is the most promising strategy to improve dissolution and consequently in vivo drug bioavailability (Piao et al., 2007; Lee et al., 2001; Yuksel et al., 2003; Park et al., 2009). Solid dispersion (SD) formulation has advantages over the other physical modification techniques. The SDs have good flow properties (Nie et al., 2011; Yadav and Yadav, 2009). Additionally, the molecular dispersion is the best alternative to salt formation for weakly ionizable compounds as well for neutral compounds (reviewed by Mohanachandran et al., 2010; reviewed by Verma et al., 2011).

1.2. Solid dispersions

According to the Chiou and Riegelman (1971), a solid dispersion is defined as “the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent, or melting-solvent method” (Chiou and Riegelman, 1971). The active ingredient in the SD can be in a finely crystalline, a solubilized or in an amorphous form (Chiou and Riegelman, 1971).

The SDs are classified into the following categories as first discussed by Chiou and Riegelman (1971) (Figure 1.2).
1.2.1 Simple eutectic mixture- An eutectic mixture (EM) is an intimate blend of two crystalline components in a specific composition. These components are completely soluble in the liquid state but crystallize upon cooling. The carrier in the EM of a poorly water-soluble drug dissolves rapidly and leaves the fine crystalline drug particles behind. This results in an instantaneous increase in the drug dissolution. The primary mechanisms of solubility and dissolution enhancement using an EM are reduction in particle size, depression in melting point, increased wetting, and prevention of agglomeration (reviewed by Verma et al., 2011; reviewed by Vasconcelos et al., 2007; Charoenchaitrakool et al., 2000; Gorniak et al., 2013). EMs were the first type of SDs prepared (Sekiguchi and Obi, 1961) (reviewed by Chiou and Riegelman, 1971). For example, a chloramphenicol-urea EM enhanced drug dissolution (Goldberg et al., 1966).
The EM of carbamazepine-poly ethylene glycol (PEG) 6000 enhanced drug dissolution and *in vivo* bioavailability (Zerrouk et al., 2001).

1.2.2. **Solid solution** - A solid solution is described as a solid solute dissolved in a solid solvent. A solid solution consists of a crystalline carrier. The concept of a solid solution is an extension of EM at the extreme drug or polymer composition where the particle size of a drug is reduced significantly. Therefore, compared to an EM, poorly water-soluble drugs achieve a faster dissolution rate (reviewed by Chiou and Riegelman, 1971; reviewed by Leuner and Dressman, 2000; Ali et al., 2010). On the basis of miscibility, solid solutions are categorized as continuous (drug polymer miscible at all ratios) or discontinuous solid solutions (drug polymer miscible at some weight fraction). Based on the relative size of the drug and carrier, they are classified as interstitial (carrier molecule larger than the drug molecule) and substitutional solid solutions (drug and carrier molecules of a similar size). They are often called SDs when the drug is in the crystalline form and is dispersed in a crystalline carrier. Sometimes, the drug is molecularly dispersed into the amorphous chain of the crystalline polymer (reviewed by Janssens and Van den Mooter, 2009; Chokshi et al., 2007; reviewed by Chiou and Riegelman, 1971; reviewed by Leuner and Dressman, 2000). The solid solution of a poorly water-soluble drug-poloxamer 188 successfully enhanced the drug dissolution (Chokshi et al., 2007).

1.2.3. **Glass solutions** - A glass solution consists of an amorphous carrier in which the drug is molecularly dispersed or present as an amorphous precipitate. It is a system of a carrier and poorly water-soluble drug, which lacks a strong crystalline lattice. The high-energy amorphous form results in enhanced drug dissolution (reviewed by Chiou and Riegelman, 1971; reviewed by Janssen and Van den Mooter, 2009). Sulfathiazole-PVP
was the first amorphous SD system formulated during the early sixties (Simonelli et al., 1961). The amorphous SDs are classified as glass solution or glass suspension on the basis of their molecular dispersion. In a glass solution, the drug is molecularly distributed in the amorphous carrier and therefore, exhibits single glass transition temperature (Tg). When amorphous clusters of a drug are distributed in an amorphous carrier, the system is known as glass suspension. A glass suspension is a non-homogenous system characterized by two Tgs, one for the amorphous clusters of a pure drug and the second Tg for the drug-polymer molecular dispersion (reviewed by Chiou and Riegelman, 1971). A number of examples of glass solution and glass suspension system can be found in literature. Few of them include itraconazole (ITRA)-hydroxylpropyl methylcellulose (HPMC) E5 solution (Six et al., 2003), ritonavir-poly vinylpyrrolidone-vinyl acetate (PVPVA) glass solution (Poddar et al., 2011), naproxen-poly vinylpyrrolidone (PVP) glass solution (Nair et al., 2001), ibuprofen-PVPVA glass solution (Moneghini et al., 2008), troglitazone-PVP K30 glass solution (Hasegawa et al., 2005), and diazepam-PVP glass suspension (van Drooge et al., 2006).

1.2.4 Amorphous precipitation in a crystalline carrier- In this type of SD, the drug precipitates out in an amorphous form in the crystalline polymer (reviewed Chiou and Riegelman, 1971). Albendazole-urea SD and albendazole-PEG 6000 SD are some of the examples of this system found in the literature (Kalaiselvan et al., 2006). Depending upon the type of carrier used, the SDs are classified as described below. (reviewed by Verma et al., 2011).

1.2.5. First-generation SDs- The SDs produced in the decade of 1960s can be categorized as first-generation SDs. They are characterized by the use of crystalline carriers such as...
sugar, urea, and mannitol. They are formed mostly as EMs (reviewed by Vasconcelos et al., 2007). Examples include chloramphenicol-urea EM (Goldberg et al., 1966; reviewed by Verma et al., 2011).

1.2.6. Second-generation SDs- These SDs are produced to overcome the disadvantages of first-generation crystalline SDs. These SDs made the use of semi synthetic amorphous polymer or natural product-based amorphous polymer to disperse the drug into the SD (reviewed by Vasconcelos et al., 2007; reviewed by Verma et al., 2011). A number of glass solutions found in the literature can be categorized as second-generation SDs. Examples are discussed in section 1.2.3.

1.2.7. Third-generation SDs- The third-generation SDs were produced with the intention of avoiding crystallization of the drug and preventing precipitation of the drug upon dissolution. This would achieve the highest degree of absorption. These SDs are produced using a carrier either with surfactant activity or with self-emulsifying properties. Combination of an amorphous carrier and surfactant are also used (reviewed by Vasconcelos et al., 2007; reviewed by Verma et al., 2011). Some examples of the third-generation SDs include but not limited are piroxicam- Gelucire 44/14 SD (Yuksel et al., 2003), felodipine-HPMC-poloxamer SD (Won et al., 2005), ibuprofen-HPMC-poloxamer 407 SD (Park et al., 2009), ITRA-D-α-tocopheryl PEG 1000-poly vinyl pyrrolidone-vinyl acetate 64 (PVPVA 64) SD (Janssens et al., 2008), and ITRA-PEG6000-HPMC E5 SD (Janssens et al., 2008).
1.3. The underlying mechanisms of enhanced drug dissolution and improved bioavailability by solid dispersions

The dissolution enhancement from the solid dispersion takes place by the following mechanisms.

1.3.1. Reduction of particle size and agglomeration- Particle size of the drug is reduced to an absolute minimum in SDs. This creates a larger surface area. This enhances dissolution and consequently bioavailability. Further, the carrier reduces the agglomeration of the drug particles (reviewed by Craig, 2002). For example, fenofibrate-poloxamer 407 SD showed a 14-fold increase in dissolution because of particle size reduction and prevention of aggregation (Patel et al., 2010).

1.3.2. Improvement in drug wetting and dispersibility- Hydrophilic carriers and the carriers with surface activity improve the wetting characteristics of the drug by encircling the single crystallite of the drug. This causes water to contact and wet the drug. Improvement in the drug wetting in a SD system concomitantly increases the dissolution (reviewed by Vasconcelos et al., 2007; reviewed by Chiou and Riegelman, 1971; reviewed by Verma et al., 2011). The naproxen-HPMC SD, nifedipine-HPMC SD, and carbamazepine-HPMC SD enhanced the drug dissolution by improving the drug wetting and dispersibility because of the surface activity of the HPMC (Mitchell et al., 2003).

1.3.3. Formation of highly porous particles- Some of the SD preparation techniques produce the high-porosity particles which result in a higher dissolution rate (reviewed by Vasconcelos et al., 2007). The porous piroxicam-PVP SD produced by flash evaporation technique showed a significant increase in dissolution compared to nonporous SD obtained by the conventional solvent evaporation technique (Dhall et al., 2011). Nagpal
et al. (2012) reported that the porous glimepiride-modified gum karaya SD resulted in dissolution enhancement (Nagpal et al., 2012).

1.3.4. Formation of amorphous/metastable drug form- The dissolution enhancement of a drug from SD is also achieved when the amorphous form of the drug is produced. The amorphous form of a drug does not require energy to break the crystal lattice and thus has the highest solubility. Upon dissolution, the supersaturated solution of the drug is produced, which enhances the bioavailability of the drug. Troglitazone-PVP K30 SD enhanced the dissolution by forming amorphous troglitazone (Hasegawa et al., 2005). Although the drug may precipitate out of this supersaturated solution, it acts like a metastable form which has higher solubility than its crystalline form (reviewed by Vasconcelos et al., 2007; reviewed by Chiou and Riegelman, 1971). The metastable form of the drug is sometime formed during processing, which enhances the dissolution. The metastable forms of the drug was formed in indomethacin-PEG 6000 SD (Ford and Rubinstein, 1978) and in carbamazepine-PEG SD (El-Zein et al., 1998) while processing.

1.3.5 Formation of water-soluble complexes- The molecular-level interactions such as hydrogen bonding, hydrophobic interactions, acid base-based interactions, and complexation result in an increase in the drug solubility and consequently enhancing dissolution (reviewed by Mohanachandran et al., 2010; Rajebahadur et al., 2006; Rawlinson et al., 2007; Dushkin et al., 2008; Medvedeva et al., 2010).

1.3.6 Salt formation in the SD- The salt formation between polyacrylic acid and basic drug in SD increased the dissolution of SDs (Watts et al., 2005).
1.4. Mechanism of drug release from water-soluble polymer based solid dispersions

Craig (2002) proposed a model to describe the mechanism of drug release from a SD (Figure 1.3). This model is applicable to the SDs with both the high drug loading and low drug loading. This model explains the discrepancy associated with the release of a drug from a SD at low drug loadings. It has been shown that at low drug load, the drug release is controlled by carrier in some instance and by the drug in other instances (reviewed by Craig, 2002).

According to this model, in the carrier- controlled dissolution, the drug particles dissolve into the carrier- rich diffusion layer rapidly. The drug gets molecularly dispersed into the concentrated layer of the carrier first. Thus, the viscosity of the diffusion layer and
dissolution of the polymer are the rate-limiting steps for carrier-controlled drug release from the SD (reviewed by Craig, 2002).

In the drug-controlled dissolution, the dissolution of the drug in the carrier diffusion layer is slower than diffusion of the drug. Therefore, the properties of the drug (physical form, size etc.) would determine the drug release (reviewed by Craig, 2002).

Thus, according to Craig’s model, the release mechanism depends on whether the drug dissolves into the polymer diffusion layer and whether the polymer dissolution takes place rapidly (reviewed by Craig, 2002).

Although these are the basic mechanisms of drug release, alterations may happen in a practical scenario. For example, rapid stirring speed may shift the release mechanism from carrier-controlled to drug-controlled. For the amorphous SD where the drug is in an amorphous form, the dissolution kinetics in the diffusion layer may shift to the carrier-controlled mechanism. Thus multiple mechanisms may take place during dissolution of the drug from the SD (reviewed by Craig, 2002).

1.5. Methods for preparation of solid dispersions

1.5.1. Melt methods

The melt method consists of melting a drug within a carrier followed by rapid cooling. Sekiguchi et al. (1964) were the first to employ this method to produce EMs (Sekiguchi et al., 1964). Amorphous solid solutions were successfully prepared using the melting method (Chokshi et al., 2007). Recent melting methods employ dissolution or suspension of the drug into the molten polymer. This reduces the processing temperature (reviewed
by Vasconcelos et al., 2007). However, the major limitations of the melting method are-
(a) possibility of degradation of the drug and polymer which inhibits the use of this
method to obtain a SD of thermally labile drugs and polymers (reviewed by Vasconcelos
et al., 2007), (b) difficulties in pulverization if a hard or sticky melt is formed (reviewed
by Serajuddin et al., 1999). Therefore, recently these conventional melting methods are
often used for screening studies (Srinarong et al., 2011).

To overcome these limitations several modifications have been made to the melting
method which led to the emergence of advanced techniques. These include melt
agglomeration, hot melt extrusion (HME), Meltrex™, Kinetisol, direct capsule filing etc.
(reviewed by Vasconcelos et al., 2007).

1.5.1.1. Melt agglomeration

Melt agglomeration technique includes addition of the molten carrier to the preheated
drug and excipient. Then this mixture is mixed in a conventional shear mixer. This
technique may employ heating the mixer of drug, excipient, and carrier above the melting
temperature of the carrier (reviewed by Vasconcelos et al., 2007). Melt agglomerated
diazepam-PEG 3000 and diazepam-Gelucire SD were prepared using lactose
monohydrate as an excipient (Seo et al., 2003).

1.5.1.2. Hot melt extrusion

HME is a thermomechanical technique. It includes extrusion of the previously mixed
drug and polymer at a high rotational speed at a melting temperature for a very short
period of time. The obtained product is cooled to room temperature and milled to obtain a
powdered SD. Further, modifications to the HME method include the use of supercritical
carbon dioxide (CO₂) as a plasticizer to lower the process temperature. ITRA-ethycellulose SDs were prepared by using supercritical CO₂ (Verreck et al., 2007). This method provides a better control of operating parameters. Thus, the HME is environmentally friendly, low cost, scale-up option. Some of the recent advancements to the HME are Meltrex™, Kinetisol, etc.

1.5.1.2A. Meltrex™

The Meltrex™ patented technology allows continuous mass flow of the material by employing a specially designed twin-screw extruder with two independent hoppers. This technology facilitates the varying temperature range (30 °C-250 °C). In addition, this integrated system includes an online device to shape the extruded strand. The attractive features of this technology include- (a) solvent-free and dust-free environment processing, (b) feasibility of the process in the case of thermolabile drugs and the drugs susceptible to oxidative and hydrolytical degradation (Meltrex™ patented technology) (Breitenbach and Lewis., 2003). Kaletra (Abbot) is a marketed product prepared using the Meltrex™ patented technology.

1.5.1.2B. Kinetisol

Kinetisol uses frictional and shear energies to mix the drug and carrier/excipient on a molecular level to produce an amorphous SD. The residence time for the drug carrier mixture is often less than 20 s. Therefore, this technique is best for processing SDs of thermolabile drugs. The examples include amorphous SD of DS901 (an oncology compound) with HPMCAS-LF, with HPMCAS-MF, with Eudragit® L100-55, and with Soluplus (Miller et al., 2012).
1.5.1.3. Direct capsule filling method

This method involves direct filing of the SD into the hard gelatin capsule as a melt, which solidifies at room temperature (reviewed by Serajuddinet al., 1999). The surface active and self-emulsifying carriers are often used for preparation of these SDs. The SD of Gelucire 44/14 with the drug produced fine oily globules upon dissolution, which resulted into higher dissolution rate and bioavailability of REV 5901, α-pentyl-3 (2-quinolinylmethoxy) benzenemethanol-Gelucire SD (Serajuddin et al., 1988). Serajuddin et al. (1990) used the same method to prepare the SDs of poorly water-soluble drugs with PEG and polysorbate 80 (Serajuddin et al., 1990). The major advantage of this method is its potential for scale-up. However, some of the limitations are- (a) limited number of orally safe amphiphilic agents, (b) inadequate solubility of the drug in a carrier, and (c) inability to increase the processing temperature above 70 °C (the maximum acceptable temperature of the gelatin capsule shell) (reviewed by Serajuddinet al., 1999).

1.5.2. Solvent methods

The most common method of SDs preparation consists of solubilization of the drug and the carrier in a common solvent followed by evaporation of the solvent. These methods are often known as solvent evaporation methods. Tachibana and Nakamura, (1965) were the first to prepare a SD of β-carotene and PVP using the solvent evaporation method (Tachibana and Nakamura, 1965). The suspension of a carrier in a common solvent (rather than dissolution) has been successfully used by Ohara et al. (2005) to prepare SDs (Ohara et al., 2005).

The most common solvents used in this methods are organic solvents such as ethanol and chloroform. A mixture of solvents is also used. Because the evaporation of the organic
solvent requires low temperature, the drugs are not exposed to high temperature. A stream of nitrogen gas or a rotary evaporator or a vacuum dryer are employed to evaporate the solvent (reviewed by Vasconcelos et al., 2007).

When water is used as a solvent, it is usually used in combination with a miscible solvent such as acetone or ethanol. Usually the drug is dissolved into the organic solvent, and the polymer is dissolved in the water. These two solutions are mixed while stirring to evaporate the solvents followed by drying in an oven to obtain the SD (Al-Hamidi et al., 2010). Carbamazepine-glucosamine hydrochloride SD was prepared by using water as the solvent (Al-Hamidi et al., 2010). Some of the modified solvent evaporation techniques are listed below. Among them, spray drying, freeze drying, supercritical fluid technology, spin coating, and electrostatic spinning have a greater scale-up potential.

1.5.2.1. Co-precipitation method

The co-precipitation method involves addition of a non-solvent to the solvent containing the dissolved drug and polymer. The filtration and air drying of this suspension yield the desired co-precipitated SD (reviewed by Vasconcelos et al., 2007). A SD of a BCS (Biopharmaceutical classification system) class 2 model compound-hypromellose acetate succinate (HPMCAS) was prepared using the co-precipitation technique (Dong et al., 2008).

1.5.2.2. Solvent deposition method

In the solvent deposition method, first the hydrophobic drug is completely dissolved into the organic solvent and then mixed with the carrier. The product is dried to evaporate the solvent and oven-dried to remove the residual solvent. Williams et al. (2005) prepared the
ibuprofen-PVP cross-linked (PVPCL SD) and ibuprofen-carboxymethyl cellulose (CMC SD) using this method (Williams et al., 2005)

1.5.2.3. Flash evaporation technique

This technique involves dissolution of the drug and polymer into a common solvent. The boiling drug carrier solution is subjected to vacuum which results in flash evaporation of the solvent. Flash evaporation usually results in highly porous SDs with increased bulk volume. Thus, it further enhances the drug dissolution. Piroxicam-PVP SD was prepared by Dhall et al. (2011) (Dhall et al., 2011).

1.5.2.4. Emulsion solvent evaporation technique for microspheres preparation method (MSD)

This modified technique involves dissolving the drug and polymer in a solvent followed by emulsification into an aqueous phase containing a certain amount of polyvinyl acetate (PVA). The solvent is removed by evaporation while stirring. This modified method yields a final SD which is a free-flowing powder of spherical particles. This method eliminates the need of further pulverization (Chang et al., 1987). Progesterone-polycaprolactone MSD (Chang et al., 1987), chlorpromazine-polycaprolactone MSD (Chang et al., 1987), and ibuprofen-poly (ε-caprolactone) MSD (Zhu et al., 2005) have successfully enhanced the drug dissolution.

1.5.2.5. Spray drying

Spray drying is the most commonly used robust technique among the solvent evaporation techniques. This method has numerous applications in the pharmaceutical industry (Sollohub and Cal, 2010). It is an attractive choice for continuous processing. The
process involves atomization of the polymer dispersion followed by drying of the atomized droplets and finally collection of the dried particles. Heated air or gas (nitrogen) is used as a drying gas. The parameters such as feed rate, atomized air flow, inlet temperature, outlet temperature, and solid concentration in the feed can be readily optimized (Cal and Sollohub, 2010). Both an organic solvent or a mixture of organic solvent and water can be used as a solvent. Ethanol-water mixture was used to obtain a spray-dried SDs of piroxicam-sodium hyaluronate, of piroxicam-PEG (Piao et al., 2007), and of cyclosporin A-sodium lauryl sulfate-dextrin (Lee et al., 2001). Spray-dried SD of ibuprofen-HPMC-poloxamer 407 SD was prepared using water as the solvent (Park et al., 2009). Recent advancements in this technique include closed cycle spray drying (CSD) which includes an additional drying of the SD to remove residual solvents. CSD technology claims to produce the stable amorphous SDs (reviewed by Alam et al., 2012).

1.5.2.6. Freeze drying

The freeze drying method consists of first dissolving or suspending the drug and carrier into the solvent. Then the solution is frozen. Lyophilization of this frozen material yields a freeze-dried SD (reviewed by Vasconcelos et al., 2007). Nivarpine-dextran SD was prepared using the freeze drying method (Lokamatha et al., 2011).

1.5.2.7. Supercritical fluid (SCF) technology

The supercritical fluid (SCF) technology consists of use of chemically inert, non-toxic and nonflammable carbon dioxide (CO$_2$) as a SCF. The solution of drug and carrier (solubilized or suspended) is introduced into a particle forming vessel along with CO$_2$. Rapid extraction of the solvent yields precipitated SD particles (reviewed by Vasconcelos et al., 2007). Some of the examples of SDs prepared using this method include
budesonide-polyethylene oxide SD (Liu et al., 2007) and ketoprofen-PVP microparticle SD (Manna et al., 2007).

The recent advancement RightSize™ uses controlled precipitation of the poorly water-soluble drug using SCF. This technology claims to have a good control over particle size of the obtained SD (reviewed by Alam et al., 2012).

1.5.2.8. Spin coating

The spin coating technique involves evaporation of the solvent while spinning using a spin coater. The solution of drug and carrier is dropped onto a clean substrate to form the SD. This technique is especially employed for moisture-sensitive drugs (reviewed by Vasconcelos et al., 2007). Examples of the SDs prepared using this method include flurbiprofen-HPMC SD, chlorpropamide-HPMC SD, benzamide-HPMC SD, phenacetin-HPMC SD, flurbiprofen-HPMC SD, flufenamic acid-HPMC SD, chlorpropamide-HPMC SD, chlorzoxazone HPMC SD, bifonazole-HPMC SD, and lidocaine-HPMC SD (Van Eerdenbrugh and Taylor, 2010).

1.5.2.9. Electrostatic spinning

This technique uses voltage to overcome the surface tension of the drug polymer at the air interface. This results in a jet; the subsequent removal of the solvent results in a non-woven fiber with diameter in the nano to micrometer range. This method was used to obtain ITRA-HPMC amorphous SD at a high voltage of 15-24kV (Brewster et al., 2004). Additional examples reported previously are ibuprofen-PVP electrospun fiber SD (Yu et al., 2009).

1.5.3. Melting-solvent method (fusion solvent method)
This modified method combines aspects of both the solvent method and the melt method. In this method, the drug is first dissolved in a minimum amount of a suitable solvent. Then this solution is incorporated into the molten carrier. Examples of the SDs prepared using this method are ketoconazole-PEG6000 SD, ketoconazole-cyclodextrin SD, ketoconazole-mannitol SD, and ketoconazole-PVPK30 SD (Najmuddin et al., 2010). One of the major limitations of this method is that this method can only be used for drugs with a low therapeutic dose, less than 50 mg (reviewed by Chiou and Riegelman, 1971).

In essence, the recent advancements in spray drying and HME methods have the greatest potential for scale-up and continuous processing.

1.6. Advantages of solid dispersions

The advantages of the SDs include

1.6.1. Enhanced solubility, dissolution, and in vivo bioavailability

Several studies have reported an increase in solubility, dissolution, and in vivo bioavailability with SD formulation. Few of the examples of these formulations are listed below:

(a) Itraconazole-hydroxypropyl-β-cyclodextrin (HP-β-CD)- HPMC SD increased the solubility (Rambali et al., 2003)

(b) Itraconazole-Eudragit SD increased the solubility of itraconazole by ~141-fold (Jung et al., 1999)

(c) Felodipine-HPMC-poloxamer SD achieved faster dissolution (Won et al., 2005)
(d) Piroxicam-Gelucire 44/14 SD enhanced in vitro dissolution and in vivo bioavailability (Yuksel et al., 2003)

(e) Ibuprofen-HPMC-poloxamer 407 SD enhanced dissolution and in vivo bioavailability (Park et al., 2009)

(f) Repaglinide-PVPK30 SD improved dissolution and bioavailability (Yin et al., 2012).

1.6.2. Decrease in dose- In the case of some drugs, the improved bioavailability led to a reduction in the dose. These studies include but are not limited to the reserpine-PVP SD (Stupak and Bates, 1972), piroxicam-PEG6000 SD (Pan et al., 2000), and SD of poorly water-soluble drug-poloxamer 188 (Chokshi et al., 2007).

Because of the above advantages, a numbers of SD products have made their way to the market (Table 1.1).

1.6.3. Flexibility of addition of different inactive ingredients to improve the performance - Different pH modifiers (CaCO₃, Na₂CO₃ and K₂HPO₄) can be added while preparing the SD system to enhance the solubility of the weakly acidic or weakly basic poorly water-soluble drugs (reviewed by Tran et al., 2010).
Table 1.1 Examples of commercially available solid dispersion products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Carrier</th>
<th>Brand name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirin</td>
<td>HPMC</td>
<td>Intelence</td>
<td>Tibotec</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>EVA</td>
<td>Implanon</td>
<td>Organon</td>
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<tr>
<td>Everolimus</td>
<td>HPMC</td>
<td>Certican</td>
<td>Novartis</td>
</tr>
<tr>
<td>Fenoglide</td>
<td>PEG</td>
<td>Fenofibrate</td>
<td>Santarus, Inc</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>PEG6000</td>
<td>Gris-PEG</td>
<td>Pedinol Pharmacal Inc.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>HPMC</td>
<td>Sporanox</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td>Lopinavir, Ritonavir</td>
<td>PVPVA</td>
<td>Kaletra</td>
<td>Abbott</td>
</tr>
<tr>
<td>Nabilone</td>
<td>PVP</td>
<td>Cesamet</td>
<td>Valeant Pharmaceuticals</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Poloxamer/PVP</td>
<td>Afeditab</td>
<td>Elan</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>PEG</td>
<td>Nimotop</td>
<td>Bayer</td>
</tr>
<tr>
<td>Nivaldipine</td>
<td>HPMC</td>
<td>Nivadil</td>
<td>Fujisawa Pharmaceutical Co., Ltd</td>
</tr>
</tbody>
</table>
Table 1.1 Examples of commercially available solid dispersion products (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Carrier</th>
<th>Brand name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>PEGglyceride</td>
<td>Norvir®</td>
<td>Abbott</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>HPMC</td>
<td>Prograf</td>
<td>Fujisawa Pharmaceutical Co., Ltd</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>HPMC</td>
<td>LCP-Tacro</td>
<td>Lifecycle Pharma.</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>PVP</td>
<td>Rezulin</td>
<td>Developed by Sankyo, manufactured by Parke-Davis division of Warner-Lambert</td>
</tr>
<tr>
<td>Verapamil</td>
<td>HPC/HPMC</td>
<td>Isoptin SR-E</td>
<td>Abbott</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>PEG</td>
<td>Rapamune</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>HPMC 2910</td>
<td>Tricor</td>
<td>Abbot</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>HPC</td>
<td>Emend</td>
<td>Merck</td>
</tr>
</tbody>
</table>

Note -1. Information obtained from reviewed by Janssens and Van den Mooter, 2009; Duarte et al., 2011; McGuffy, 2011; Alam et al., 2012.

2. Rezulin has withdrawn from the market in 2000 due to adverse drug reaction; Phase III clinical trials of Torcetrapib-HPMCAS (Pfizer) were halted due to adverse drug event; Ritonavir capsules (Norvir, Abbott) have been withdrawn temporarily from the market because of crystallization.

1.7. Limitations of solid dispersions

1.7.1. Preparation method and scale-up

Identifying a common solvent for a hydrophilic polymer and a hydrophobic drug can be difficult. Further, although different techniques such as rotary evaporation, freeze drying, and spray drying have been commonly used for evaporation of the solvent, very few
studies have addressed the issue of residual organic solvent (Majerik et al., 2007; Weuts et al., 2005). Large-scale production of SDs using the solvent evaporation technique with an organic solvent poses a great challenge because of the environmental concerns (reviewed by Verma et al., 2011).

The melt method usually employs melting at~ 85 °C to 100 °C and sometimes up to~ 250 °C. Although, residual solvent is not a concern in melt methods, the melt method can not be used in the case of thermally labile drugs (reviewed by Serajuddin et al., 1999). Thus, both melt and solvent methods have their limitations. Further, the cost associated with the production of SDs using these methods is often high (reviewed by Verma et al., 2011).

1.7.2. Reproducibility of physicochemical properties

It is often very difficult to achieve the reproducibility of the physical characteristics of a SD. For example, in the melting method little variation in melt temperature, heating rate, holding time at the melt, cooling rate, cooling method or pulverization process affects the physiochemical properties of the obtained SD (reviewed by Serajuddin et al., 1999). Oxazepam-PEG 4000 SD prepared at 100 °C resulted in the crystalline form of oxazepam and spherulite form of PEG 4000. SD prepared at 150 °C generated oxazepam in an amorphous form and PEG 4000 in the hedritic form (Gines et al., 1996). Tolbutamide-urea SD prepared by rapid cooling formed molecular dispersion of the drug in crystalline urea. On the other hand, slow cooling resulted in complete loss of crystallinity of both the drug and urea (McGinity et al., 1984). Further, pulverization of griseofulvin-PEG 6000 SD converted the amorphous griseofulvin to its crystalline form (Chiou, 1977).

For the solvent methods, the solvent evaporation rate and the variation in process parameters affect the physiochemical properties of the SD. A high evaporation rate
inhibited drug nucleation and drug crystallization in the piroxicam-PVP SD (Wu et al., 2011). Variation in the nitrogen flow rate resulted in a spray-dried particle with different solubility and physical stability in nilvadipine-HPMC SD as well as in nifedipine-HPMC SD (Kojima et al., 2012).

1.7.3. Dosage form development

Very few studies have described the systematic development of the SD dosage form (Dinunzio et al., 2012; Sharma and Jain., 2010; Leonardi et al., 2013). The difficulties in the development of SD dosage form are discussed previously (reviewed by Serajuddin et al., 1999). They are-

(a) Difficulty in pulverization and tablet compression- The difficulty in pulverization and compression is often encountered because of hardness of SD (by melting method), because of formation of sticky and tacky SD. This often poses difficulties in high speed processing (Akbuga et al., 1988; Jani et al., 2009; reviewed by Serajuddin et al., 1999; Ford and Rubinstein, 1980).

(b) Lack of flow properties and compressibility of the prepared amorphous SD- Difficulty in compressibility was encountered during the dipyridamole-PVP SD dosage form development (Chen et al., 2007). This often results in requirement of a large amount of excipient and thus hampers development of the dosage form, especially in the case of high-dose drugs. An adsorbent was added to the ezetimibe-Gelucire 44/14 and ezetimibe-PEG SDs to improve the flow (Parmar et al., 2011). A high amount of disintegrant was required during the dosage form development of the furosemide-PVP SD (Akbuga et al., 1988).
Lack of disintegration and dissolution of the prepared compact- Indomethacin-Kollidon® VA64 HME was compressed with microcrystalline cellulose. The dissolution of this dosage form decreased significantly at and above 50% loading of the SD (Dinunzio et al., 2012). Further, the dissolution of the SD compacts was lower than that of the powdered amorphous SD (Langham et al., 2012). The investigators have reported that the dissolution of benznidazole-PEG6000 solid solution was higher than that of the respective physical mixture. However, the dissolution of solid solution tablet was lower than the respective physical mixture tablet (Leonardi et al., 2013). Thus, development of the SD dosage form is still in the burgeoning phase.

1.7.4. Stability

The conversion of the amorphous form of the drug to its crystalline form upon aging is the primary problem associated with the physical stability. This physical instability negate the dissolution increase obtained by the amorphous SD. This conversion is irreversible. Thus, the performance of the SD is compromised and even leads to product recall (Norvir, Abbot) (reviewed by Verma et al., 2011). The excursion in humidity to a high level has a greater deleterious effects on the stability of the amorphous form than the excursion in temperature (Suzuki and Sunada, 1998; Doherty and York, 1989; Yang et al., 2010). Although, the SD is physically stable, chemical stability cannot be assured as discussed in section 6.1 (Chapter 6). Sometimes, the SD processing results in physical instability. The compression of the amorphous SD induces phase separation which affects the stability (Ayenew et al., 2012).
1.8. Recent trends in solid dispersions research area

1.8.1 Evaluation of advanced SD preparation techniques- The examples of the advanced preparation techniques include Kinetisol Technology (Hughey et al., 2012; Hughey et al., 2011; Hughey et al., 2010; DiNunzio et al., 2010), Solumer™ technology which is an advanced spray drying technology to produce a stable amorphous SD (Temsin-Krayz et al., 2007), and Suba™ technology, which uses various polymers with an acidic functional group to improve bioavailability of the obtained SD (reviewed by Alam et al., 2012). Right Size™ and CSD produce SDs with improved characteristics as discussed earlier (reviewed by Alam et al., 2012).

1.8.2 Evaluation of high-throughput screening techniques for polymer selection and for determining the stability of the amorphous SD- The examples include Crystallics, a 96-well plate method for screening and selection of stable amorphous SD developed by Crystallics (www.assainternational.com/index_htm_files/CrystallicsNews12.pdf). High -throughput screening technique for drug load and polymer selection for SD preparation was investigated (Chiang et al., 2012). A 96-well plate miniaturized screening of polymers for amorphous drug stabilization (SPADS) was developed. This method includes SPADS dissolution, SPADS interaction and SPADS imaging assay (Wyttenbach et al., 2013).

1.8.3 Elucidation of the mechanism of phase separation of the amorphous solid dispersion using advanced techniques- Recently, stability of SDs under high humidity was studied using advanced technique such as atomic force microscopy (AFM) and nano-thermal analysis to understand the mechanism of stabilization of felodipine-PVP K29/32 SD (Qi et al., 2013). Recently, AFM was used to screen drug polymer miscibility and stability
(Lauer et al., 2011). Baird and Taylor (2012) have discussed various advanced techniques to evaluate amorphous SDs in their review article (reviewed by Baird and Taylor, 2012).

1.8.4. Evaluation and development of SDs with a special emphasis on drug-polymer interactions (hydrogen bonding)- The drug-polymer interactions are the mechanism of-
(a) control of the physical state of the drug i.e. amorphous or crystalline (Karavas et al., 2007); (b) drug-polymer phase behavior in SD (Paudel et al., 2012); (c) enhanced solubility by SD formulation (reviewed by Mohanachandran et al., 2010; Rajebahadur et al., 2006); (d) enhanced dissolution of SD at high drug loading (Srinarong et al., 2010; Gupta et al., 2002); (e) enhanced stability of SD against moisture-induced recrystallization (Wegiel et al., 2013); (f) enhanced stability of SD against accelerated stability condition (Wegiel et al., 2013; Ng et al., 2013; Miyazaki et al., 2004; Van Eerdenbrugh and Taylor, 2010); (g) enhanced chemical stability (Papageorgiou et al., 2009); and (h) enhanced solid dispersion stability upon compression (Ayenew et al., 2012). Therefore, development and evaluation of SDs on the basis of drug-polymer interactions has recently attracted the attention of many investigators.

1.8.5. Exploration of new polymeric carriers for preparation of SDs with emphasis on improving dissolution, efficacy, and stability of SDs

The nano-sized flaked carboxymethyl cassava starch-acetylsalicylic acid SD substantially improved the drug dispersion and in vitro drug dissolution (Lin et al., 2012). The examples of polymer with surfactant properties to improve the dissolution or/and efficacy of the SD include polyoxyethylene 32 distearate (Sivert et al., 2010) and Soluplus (Liu et al., 2012). The SDs were prepared using a novel carrier hydroxypropyl and methoxyl substituted cellulose ether to stabilize the supersaturated ITRA SD
(Hughey et al., 2012). The new class of polymers POLYOX WSR-N10 (DOW), Soluplus (BASF), Solumer (Solubest), and Neusilin (Fuji Chemicals) have become popular in the preparation of thermodynamically stable SDs (reviewed by Alam et al., 2012).

1.9. Carriers used for solid dispersions

The carriers used for dissolution enhancement are classified into the categories as described below (reviewed by Saharan et al., 2009).

**Polymers**- PVP, PVA, HPMC, methacrylic copolymers (Eudragit S100 and Eudragit RL, Eudragit RS), and polyethylene glycols

**Surfactants**- Poloxamers, polyglycolized glyceride, polyoxyethylene sorbitan monoesters (Tweens), sorbitan esters (spans), polyoxyethylene stearates, poly (β-benzyl-L-aspartate)-β-poly (ethylene oxide), and poly (caprolactone)-β-poly (ethylene oxide)

**Polyglycolized glycerides**- Gelucire 44/14, Gelucire 50/13, and Gelucire 62/05

**Superdisintegrants**- PVP-CL, sodium starch glycolate, croscarmellose sodium, cross-linked alginic acid, gellan gum, xanthan gum, and calcium silicate

**Carbohydrates**- Lactose, Soluble starch, British gum, galactomannan, sorbitol, mannitol, chitosan, maltose, galactose, xylitol, and amylopectin

**Cyclodextrins**- Cyclodextrins and hydroxypropyl-cyclodextrins

**Acids**- Citric acid, succinic acid, and phosphoric acid

**Dendrimers**- Starburst® polyamidoamine (PAMAM)
Hydrotropes- Urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate, sodium-\(o\)-hydroxy benzoate, sodium-\(p\)-hydroxy benzoate, and sodium citrate

Others- Microcrystalline cellulose, dicalcium phosphate, and silica gel

The carriers used for SDs are also classified as follows (reviewed by Tiwari et al., 2009).

a) **First-generation crystalline carriers**- Urea and sugar

b) **Second-generation carriers**- Povidone, PEGs, polymethacrylate, and cellulose derivatives

c) **Third-generation carriers**- Gelucires and poloxamer

The carriers used for preparation of SDs can be classified as crystalline carriers and amorphous carriers (Table1.2 and Table 1.3).

Table 1.2 Crystalline carriers used for solid solution preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide</td>
<td>Gelucire 44/14</td>
<td>Tashtoush et al., 2004</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>PEG4000, PEG6000</td>
<td>Reddy and Gudsoorkar, 2005</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>PEG6000</td>
<td>Guyot et al., 1995</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Poloxamer407</td>
<td>Patel et al., 2010</td>
</tr>
</tbody>
</table>

1.9.1. **Solubility and dissolution enhancement by the solid dispersion carrier**

In general, the carrier exerts the desired solubility and dissolution enhancement effect by various mechanisms. These include wetting effect, surface tension lowering effect,
aggregation prevention/reduction effect, and the solubilizing effect of the polymer (reviewed by Saharan et al., 2009).

1.9.2. Function of a carrier in the amorphous solid dispersions

In glass solutions, the drug is in a high-energy amorphous state and tends to recrystallize upon storage (Hancock and Zografi, 1997). The carrier protects the drug against nucleation and crystal growth while processing and upon aging (Yang et al., 2010; Konno and Taylor, 2006; Konno and Taylor, 2008; Ilevbare et al., 2012; Trasi and Taylor, 2012). The mechanisms of the protective effect of the carrier in amorphous SD include-

1.9.2.1 Decrease in molecular mobility- The carrier decreases the molecular mobility which slows down the kinetics of crystallization (reviewed by Janssens and Van Den Mooter, 2009). A low concentration of the PVP polymer (1%, 2%, 5%) reduced the molecular mobility and inhibited the crystal growth and consequently prevented the crystallization of amorphous indomethacin (Crowley and Zografi, 2003). Korhonen et al. (2008) observed a similar decrease in molecular mobility and reduction in crystal growth rate in a 8% phenobarbital-PVP SD (Korhonen et al., 2008). The mere presence of the carrier provides a barrier to nucleation and stabilizes the SD system (Yang et al., 2010).

1.9.2.2 Anti-plasticizing effect- The polymer often exerts an anti-plasticizing effect by increasing the viscosity in the local environment. This inhibits the drug diffusion required to form the crystal lattice which results in an increase in the kinetic and thermodynamic barrier to crystallization (Van den Mooter et al., 2001; reviewed by Bhugra and Pikal, 2008). The amorphous ketoconazole in the ketoconazole-PVP K25 SD was stabilized primarily by an anti-plasticizing effect (Van Den Mooter et al., 2001). Nilutamid e
inhibited the crystal growth of amorphous futamide by increasing the glass transition of the system (Trasi and Taylor, 2012).

1.9.2.3 Drug-polymer specific interactions- The crystal growth rate is inversely related to drug-polymer hydrogen bonding interaction as observed in felodipine-PVP SD, felodipine-HPMCAS SD, felodipine-PVPVA SD, and felodipine-PVA SD system (Kestur and Taylor, 2010). Nucleation and crystal growth of the amorphous futamide was inhibited by the presence of a polymer additive because of drug-polymer hydrogen bonding (Trasi and Taylor, 2012). The drug polymer interactions inhibited the dimer formation of indomethacin. This is a prerequisite for indomethacin crystallization (Tong and Zografi, 2001). Hydrogen bonding increases solid solubility of the drug into the polymer (Vasanthavada et al., 2005) and raises the energy of activation for amorphous phase separation and crystallization. This results in the stabilization of SD system (reviewed by Janssens and Van Den Mooter, 2009).

1.9.2.4 Adsorption of the carrier onto the crystal surface- A carrier with adequate hydrophobicity can adsorb onto the surface of the crystalline drug. This inhibits the crystal growth (Ilevbare et al., 2012). Ilevbare et al. (2012) reported that a cellulosic polymer with intermediate hydrophobicity prevented the crystal growth of amorphous ritonavir (Ilevbare et al., 2012).
### Table 1.3 Amorphous carriers used for solid dispersion preparations

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMCE5</td>
<td>Itraconazole</td>
<td>Janssens et al., 2008</td>
</tr>
<tr>
<td>HPMCE5</td>
<td>Itraconazole</td>
<td>Six et al., 2003</td>
</tr>
<tr>
<td>HPMC 2910</td>
<td>Poorly water-soluble Novartis compound</td>
<td>Ghosh et al., 2011</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Itraconazole, Magestron Acetate</td>
<td>Smithey et al., <a href="http://www.pharma-ingredients.basf.com">www.pharma-ingredients.basf.com</a></td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Poorly water-soluble Novartis compound</td>
<td>Ghosh et al., 2011</td>
</tr>
<tr>
<td>HPC</td>
<td>Phenytoin, Carbamazepine</td>
<td>Sarode et al., 2013</td>
</tr>
<tr>
<td>HPMC phthalate</td>
<td>Poorly water-soluble Novartis compound</td>
<td>Ghosh et al., 2011</td>
</tr>
<tr>
<td>PVP K90</td>
<td>Acetaminophen, Naproxen, Salicylamide,</td>
<td>Nair et al., 2001</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, or Propranolol hydrochloride</td>
<td></td>
</tr>
<tr>
<td>PVP K30</td>
<td>Ketoprofen</td>
<td>Di Martino et al., 2004</td>
</tr>
<tr>
<td>PVP K25</td>
<td>Ketoconazole</td>
<td>Van Den Mooter et al., 2001</td>
</tr>
<tr>
<td>PVPK30</td>
<td>Ketoconazole</td>
<td>Kumar P et al., 2011</td>
</tr>
<tr>
<td>PVPK17</td>
<td>Oxeglitazar</td>
<td>Majerik et al., 2007</td>
</tr>
<tr>
<td>PVPK25/PVPK30/PVP-CL/PVPK64</td>
<td>Ibuprofen</td>
<td>Xu et al., 2007</td>
</tr>
<tr>
<td>PVP-VA</td>
<td>Ritonavir</td>
<td>Poddar et al., 2011</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>Itraconazole</td>
<td>Six et al., 2002</td>
</tr>
<tr>
<td>Eudragit E100, PSSA PAA, PVP-VA, HPMCAS</td>
<td>Benzamide ,Phenacetin, Flurbiprofen, Chlorpropamide, Chlorzoxazone, Flufenamic, Bifonazole, Lidocaine</td>
<td>Van Eerdenbrugh and Taylor, 2010</td>
</tr>
</tbody>
</table>
1.10. Natural polymers as a carrier for solid dispersions

Apart from the established synthetic and semi-synthetic polymers, various natural polymers or their derivatives have been investigated as carriers for SDs. These SDs include but are not limited to diazepam-inulin SD, nifedipine-inulin SD (Srinarong et al., 2010), ITRA-inutec SP1 (Van Den Mooter et al., 2006), licofelone-gaur gum SD (Shah et al., 2010), nimodipine-gum karaya SD (Murali Mohan Babu et al., 2000), simvastatin-chitosan SD (Pattewar et al., 2012), indomethacin-pullulan SD (Sakamaki and Miyamoto, 1978 Jap. Pat. 7812,417), nifedipine-gelatin SD (Acartiirk et al., 1992), gliclazide-carrageenan SD (Sarkar et al., 2012), and nevirapine-dextranSD (Lokmatha et al., 2001).

1.11. Super Carrier

![Diagram of Super Carrier Attributes]

Figure 1.4 Desired attributes of a super carrier for solid dispersion preparations
The desired attributes of a SD super carrier used for dissolution and bioavailability enhancement are shown in Figure 1.4 (The information obtained from Newman et al., 2012; Papageorgiou et al., 2008; reviewed by Saharan et al., 2009; reviewed by Janssens and Van den Mooter, 2009; Konno et al., 2008; reviewed by Verma et al., 2011; http://www.fujihealthscience.com/Fuji_Email_Blast_Neusilin_JAN21.pdf and http://www.neusilin.com/faq/).

These characteristics include that the carrier should be amorphous and hydrophilic in nature. It should be water-soluble and safe to use. It should have less hygroscopic tendency, high Tg and, multiple hydrogen donor/acceptor group to stabilize the SD. The super carrier should be chemically compatible with the drug. It should be soluble in common organic solvent if the solvent method is intended to be used. It should have adequate flow and compressibility for development of the tablet formulation. It should have surfactant-like properties to enhance wetting effect and prevent aggregation. Further, the carrier should be able to prevent drug precipitation from the supersaturated solution. Most importantly it should form the SD with desired physical characteristics, which can be easily formulated in a solid dosage form (Papageorgiou et al., 2008.; reviewed by Saharan et al., 2009; reviewed by Janssens and Van den Mooter, 2009; Konno et al., 2008; reviewed by Verma et al., 2011; http://www.fujihealthscience.com/Fuji_Email_Blast_Neusilin_JAN21.pdf and http://www.neusilin.com/faq/).

The commonly used polymers HPMC, PVP, Soluplus possesses most of these attributes, but each them has some limitation as listed in Table 1.4. These polymers have been
successfully used to formulate SDs regardless of these limitations. Therefore, exploration of novel carrier for SD preparation has been always desirable.

Table 1.4 Limitations of the commonly used carrier for solid dispersion preparations

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Limitations</th>
<th>Drug-carrier system</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP</td>
<td>Hygroscopic, sticky SD</td>
<td>Allopurinol-PVPK30 SD becomes sticky</td>
<td>Jagdale et al., 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ibuprofen-PVPVA SD becomes sticky after treatment at 600W for 10 min</td>
<td>Moneghini et al., 2008</td>
</tr>
<tr>
<td></td>
<td>Maintaining supersaturation</td>
<td>Felodipine-PVP SD</td>
<td>Konno et al., 2008</td>
</tr>
<tr>
<td></td>
<td>Stability</td>
<td>Nifedipine -PVP SD not physically stable in humidity conditions</td>
<td>Sugimoto et al., 1982</td>
</tr>
<tr>
<td>HPMC</td>
<td>Slow dissolution due to high viscosity</td>
<td>Fluconazole-HPMC SD slower release at higher polymer load</td>
<td>Papageorgiou et al., 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quercetin-cellulosic derivatives slows down the Quercetin release</td>
<td>Li et al., 2013</td>
</tr>
<tr>
<td>Soluplus</td>
<td>Sticky SD at low drug loading (33%), non-pulverizable</td>
<td>Artemether-Soluplus SD</td>
<td>Fule et al., 2013</td>
</tr>
</tbody>
</table>
1.12. Larch arabinogalactan

Larch arabinogalactan (AG) is a long and densely branched polysaccharide. Commercially available AG is extracted from *Larix Occidentalis* (genus *Larix*, also called as larch tree). It has a reproducible molecular weight (MW) and physiochemical properties (Groman et al., 1994). AG is available in a 99.9% pure form. It is biodegradable (Salyers et al., 1981; Grieshop et al., 2002; Tanaka et al., 2004; Neverova et al., 2011) and biocompatible (Ehrenfreund-Kleinman et al., 2002). AG was reported to function as an immune enhancer. In addition, AG is also beneficial for the gut microflora (Grieshop et al., 2002; Hauer and Anderer, 1993; reviewed by Kelly, 1999).

The chemical formula of AG is [(C5H8O4) (C6H10O5) 6]x and chemical name is L-arabino-D-galactan. The AG comprises 98% of arabinogalactan and consists of two monosaccharides, galactose and arabinose in a 6:1 ratio.
The chemical structure of the AG is shown in Figure 1.5. It comprises of a main chain consisting of β-(1→3)-linked galactose residues. The side chain consists of β-(1→6)-linked galactopyranose dimmers, galactopyranose monomers, and arabinose in aggregates. Arabinose exists as α-(1→6)-linked disaccharide of β-L-arabinofuranose (1→3)-α-L-arabinofuranose and terminal residues of β-L-arabinopyranose, β-D-arabinofuranose, and β-L-arabinofuranose. The content of the glucuronic acid varies from non-detectable to a few percent (Trofimova et al., 2012; Cui et al., 2005).

In the United States, AG is categorized as GRAS (generally recognized as safe) and is approved by the US FDA for use as a dietary fiber and food additives (www.accessdata.fda.gov/scripts/fcn/gras_notices/grn0084.pdf; Lonza et al., 2009; reviewed by Kelly, 1999).

1.13. Properties of larch arabinogalactan

1.13.1. Molecular weight (MW)

The molecular weight (MW) of AG has been reported to be in the 10–120 kD range (Di Colo et al., 2009; reviewed by Fitzpatrick et al., 2004). Researchers have used size exclusion chromatography (SEC) and gel permeation chromatography (GPC) to determine the MW. Ehrenfreund-Kleinman et al. (2004) performed GPC and reported the MW of AG to be 20 kD. The investigators used AG from Larix International (now Lonza) (St. Paul, MN) however, the specific grade of AG is not mentioned in their research article (Ehrenfreund-Kleinman et al., 2004). The MW of the purified stractan 2 grade was reported to be 40 kD using a light scattering method (Groman et al., 1994).
The intensity light scattering and sedimentation equilibrium technique reported the average MW of AG as 37 kD and 38 kD respectively (Prescott et al., 1995). The MW of FiberAid grade larch arabinogalactan (AGF) determined using SEC was 38 kD (Utermoehlen et al., 2010). Fitzpatrick et al., (2004) reported the MW of Larix’s FiberAid grade polymer as 22 kD (Fitzpatrick et al., 2004). Thus, the MW of the AG polymer varies with the grade of the polymer and also with the method used for the MW analysis.

1.13.2. Water solubility

AG dissolves rapidly and completely regardless of the temperature. AG is a highly water-soluble polymer with water solubility up to 60%. The solubility of AG increases with an increase in temperature. AG is insoluble in most of the organic solvents and oils. The pH of a typical AG solution is 4 to 4.5 (Nazareth et al., 1961 Part I).

1.13.3. Viscosity

AG forms low viscosity solutions. The viscosity of a 5% AG solution in water is nearly 1.38 mPa s while that of a 10% solution is 1.58 mPa s (Burgalassi et al., 2007). Other studies have reported a similar range of AG viscosity (Nazareth et al., 1961, part I). Addition of electrolytes, pH, and aging does not have an impact on the viscosity (Nazareth et al., 1969, Part I). Thus, viscosity of the AG solution is very low compared to the viscosity of the other hydrocolloid gums solutions. The viscosity of the 1% dispersion of the guar gum was reported to be ~700–800 mPa s and that of gum arabic is 20–30mPa s (http://ametisjapan.com/arabinogalactan.pdf).

Moreover, the viscosity of the 2% dispersion of the HPMCE5, a commonly used polymer for SD preparation at 20 °C is 4–6mPa s.
The viscosity of the 40% PVPK29-32 grade dispersion at 25 °C in water is 350–600 mPa s (http://www.sigmaaldrich.com PVP product specifications).

1.13.4. Surface activity

![Figure 1.6 Surface tension as a function of polymer solution concentration](image)

Figure 1.6 Surface tension as a function of polymer solution concentration

Note-AG data obtained from Nazareth et al., 1961 part I; Methylated AG data obtained from Nazareth et al., 1961 part II.

AG possesses surfactant like properties (Nazareth et al, 1961 part I; D’adamo et al 1996). The phenolic compound constituting 1% of AG imparts this surfactant-like property to this protein-free polymer (Neverova et al., 2011; Alistair et al., 2010). Addition of AG lowered the surface tension of water (Figure 1.6) (Nazareth et al, 1961 part I). The surface activity of AG is much lower than that of the modified AG and HPMCE5 (Nazareth et al., 1961 part II; Machiste et al., 1996).
1.14. Larch arabinogalactan in drug delivery

AG has been widely investigated in the field of drug delivery. This includes- (a) AG for hepatic targeting (Kaneo et al., 2000; US Patent 5336506; EP 1497442), (b) AG as an immunomodulant and immunostimulant (Kim et al., 2002; Udani et al., 2010), (c) AG as a scaffold system in tissue engineering and cell transplant (Ehrenfreund-Kleinman et al., 2002), (d) AG conjugation to various drug molecules (Table 1.5), and (e) mechanochemical activated complexes of AG with drugs (Table 1.6).

Essentially the chemical conjugation and mechanochemical activation approaches have been successfully used to develop drug delivery systems using the AG polymer. The conjugation protocols however, often include multiple steps or involve the modification of the polysaccharide itself. Further, the drug-polymer conjugate demands extensive purification and toxicological studies (US Patent 5336506; Kaneo et al., 2000).
Table 1.5 Drug-AG conjugates and drug-AG derivative conjugates

<table>
<thead>
<tr>
<th>Arabinogalactan</th>
<th>Conjugates with</th>
<th>Improved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>Iron oxide coated with arabinogalactan</td>
<td>Efficacy</td>
<td>US Patent 5336506</td>
</tr>
<tr>
<td>AG</td>
<td>Folic acid</td>
<td>-</td>
<td>US Patent 5336506</td>
</tr>
<tr>
<td>Arabinogalactan</td>
<td>Nanobiocomposite ferroarabinogalactan with 3.5% iron</td>
<td>Stabilized iron, efficacy</td>
<td>Aleksandrova et al., 2011</td>
</tr>
<tr>
<td>AG poly and oligosaccharides</td>
<td>5 Aminosalicylic acid</td>
<td>Anti-ulcer and anti-inflammatory</td>
<td>Badykova et al., 2005</td>
</tr>
<tr>
<td>Oxidized AG</td>
<td>Kanamycin</td>
<td>Antitubercular activity</td>
<td>Mudarisova et al., 2010</td>
</tr>
<tr>
<td>Oxidized AG</td>
<td>5 Aminosalicylic acid</td>
<td>-</td>
<td>Mudarisova et al., 2008</td>
</tr>
<tr>
<td>Oxidized AG</td>
<td>AmphotericinB</td>
<td>Enhanced solubility, reduced toxicity, Improved PK of the drug</td>
<td>Elgart et al., 2010</td>
</tr>
<tr>
<td>Oxidized AG</td>
<td>Amphotericin-B</td>
<td>Efficacy and safety leishmaniasis infections.</td>
<td>Golenser et al., 1999</td>
</tr>
<tr>
<td>Oxidized AG</td>
<td>Isonicotinic acid hydrazide</td>
<td>-</td>
<td>Badykova et al., 2008</td>
</tr>
<tr>
<td>Arabinogalactan DTPA</td>
<td>Methylprednisolone</td>
<td>-</td>
<td>US Patent 5336506</td>
</tr>
<tr>
<td>AG amine</td>
<td>Adenine arabinoside 5'-monophosphate</td>
<td>Decreased serum level of woodchuck hepatitis virus DNA</td>
<td>Enriquez et al., 1995</td>
</tr>
<tr>
<td>AG-tosylate and mesylate derivatives</td>
<td>Amphotericin-B</td>
<td>Improved efficacy against yeast Candida albicans, and against Leishmania major parasites; reduced toxicity and hemolytic activity</td>
<td>Ehrenfreund-Kleinman et al., 2004</td>
</tr>
<tr>
<td>Dialdehyde AG</td>
<td>Amphotericin-B</td>
<td>Efficacy</td>
<td>Falk et al., 1999</td>
</tr>
</tbody>
</table>
Table 1.5 Drug-AG conjugates and drug-AG derivative conjugates (continued)

<table>
<thead>
<tr>
<th>Arabinogalactan</th>
<th>Conjugates with</th>
<th>Improved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxymethyl AG</td>
<td>Chromium treated perfluoroheptane/air filled microspheres</td>
<td>Efficacy</td>
<td>US Patent 6193953</td>
</tr>
<tr>
<td>Phosphoryl AG, glutaryl AG, succinyl AG, carboxyethyl AG, carboxymethyl AG, hydrazino AG, brominated AG etc.</td>
<td>Intended to use for targeted drug delivery of therapeutic agents via receptor mediated endocytosis</td>
<td>-</td>
<td>US Patent 5478576</td>
</tr>
</tbody>
</table>

Table 1.6 Mechnochemical activated drug-AG complex/clathrate

<table>
<thead>
<tr>
<th>Arabinogalactan</th>
<th>Drug</th>
<th>Improved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larch Arabinogalactan</td>
<td>Nifedipin</td>
<td>High hypotensive and anti-arrhythmic effect</td>
<td>Tolstikova et al., 2010</td>
</tr>
<tr>
<td>Arabinogalactan</td>
<td>Warfarin</td>
<td>PK parameters improvement to reduce the risk of bleeding during anticoagulant therapy.</td>
<td>Khvostov et al., 2012</td>
</tr>
<tr>
<td>Larch Arabinogalactan</td>
<td>Diazepam, Mezapam, Indomethacin, Azaleptin</td>
<td>Reduced the adverse effect of the drug; Enhancement in solubility</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Larch arabinogalactan</td>
<td>Dihydroquercetin (biologically active compound)</td>
<td>Enhancement in solubility</td>
<td>Medvedeva et al., 2010</td>
</tr>
</tbody>
</table>

The mechanochemical treatment results in chemical degradation of AG (planetary mill) (Dushkin et al., 2008) and chemical modification of AG with increased reactivity (Medvedeva et al., 2010).
Table 1.7 Fold increase in drug solubility by drug-AG physical mix and drug-AG mechanochemical activated complex

<table>
<thead>
<tr>
<th>Drug-AG complex</th>
<th>Physical mix</th>
<th>Planetary mill</th>
<th>Rotary ball mill</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam-AG (1:10)</td>
<td>1.2</td>
<td>2.4</td>
<td>48.2</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Indomethacin-AG</td>
<td>1.1</td>
<td>9.9</td>
<td>39.7</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Mezapam-AG</td>
<td>4.9</td>
<td>19.1</td>
<td>140.6</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Clozapine-AG</td>
<td>4.4</td>
<td>20.5</td>
<td>107.9</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Nifedipine-AG</td>
<td>-</td>
<td>6.9</td>
<td></td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Dihydroquercitin (DQ)-AG (1:10)</td>
<td>-</td>
<td>5.9</td>
<td></td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>DQ-AG (1:20)</td>
<td>3</td>
<td>-</td>
<td>38</td>
<td>Medvedeva et al., 2010</td>
</tr>
<tr>
<td>DQ-AG (1:10)</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>Medvedeva et al., 2010</td>
</tr>
<tr>
<td>Quercitin-AG</td>
<td>-</td>
<td>11.6</td>
<td></td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Ibuprofen-AG</td>
<td>1.2</td>
<td>28.4</td>
<td></td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Beta-Carotene-AG (1:40)</td>
<td>-</td>
<td>2000</td>
<td>-</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Warfarin-AG (1:40)</td>
<td>-</td>
<td>5.3</td>
<td>-</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Albendazol-AG (1:10)</td>
<td>-</td>
<td>8.0</td>
<td>58.0</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Carbenazim-AG (1:10)</td>
<td>-</td>
<td>-</td>
<td>16.2</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Simvastatin-AG (1:10)</td>
<td>-</td>
<td>36.7</td>
<td>-</td>
<td>Dushkin et al., 2012</td>
</tr>
<tr>
<td>Azaleptin-AG (1:10)</td>
<td>12.4</td>
<td>20.5</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Azaleptin-AG (1:20)</td>
<td>14.3</td>
<td>38.8</td>
<td></td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Mezapam-AG (1:10)</td>
<td>6.9</td>
<td>19.1</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Mezapam-AG (1:20)</td>
<td>10.8</td>
<td>46.8</td>
<td></td>
<td>Dushkin et al., 2008</td>
</tr>
</tbody>
</table>
Table 1.7 Fold increase in drug solubility by drug-AG physical mix and drug-AG mechanochemical activated complex (continued)

<table>
<thead>
<tr>
<th>Drug-AG complex</th>
<th>Physical mix</th>
<th>Planetary mill</th>
<th>Rotary ball mill</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibazon-AG (1:10)</td>
<td>1.7</td>
<td>2.4</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Sibazon-AG (1:20)</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Indomethacin-AG (1:10)</td>
<td>1.2</td>
<td>9.9</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
<tr>
<td>Indomethacin-AG (1:20)</td>
<td>1.7</td>
<td>16.6</td>
<td>-</td>
<td>Dushkin et al., 2008</td>
</tr>
</tbody>
</table>

Some studies have reported solubility enhancement because of the formation of drug-AG complex (Table 1.7). However, none of these studies included dissolution enhancement due to AG polymer as a study parameter.

In formulation, AG has been shown to be a good tablet binder. Previously, 20% (w/v) AG was used as a binder for tablets containing riboflavin, folic acid, ascorbic acid and aspirin. AG improved the tablet stability because of its moderate pH (Nazareth et al, 1961 part II). AG has reported to be an emulsifier, especially in the preparation of low viscosity, stable emulsions (Nazareth et al, 1961 part I). In addition, AG has been used as a coating material (US Patent 20040234608). Most recently, Burgalassi et al. (2007) have developed a 5% AG dispersion for dry eye, which significantly reduced the healing time in corneal lesions (Burgalassi et al., 2007). Thus, AG has been successfully used in pharmaceutical formulation as an inactive ingredient.
The rationale of selecting AGF as a carrier for solid dispersions for dissolution enhancement

Previous studies have shown an increase in the solubility of the poorly water-soluble drugs because of AG (Table 1.7). Formation of water-soluble drug-polymer complexes were thought to be the reason underlying the increased solubility (Dushkin et al., 2008).

However, to our knowledge, there is no published study where the dissolution enhancement potential of the AG carrier has been explored. The solubility enhancement capability of AG sets the ground for its likely dissolution enhancement potential.

The property of AG such as its amorphous nature is likely to result in the formation of amorphous state of the drug in SD. The hydrophilic nature and high-water solubility would result in dissolution enhancement. Further, the AG would aid in wetting of the hydrophobic drug.

Another attractive functional property of AG which can be exploited with perspective for the dissolution enhancement is its low viscosity. The Noyes Whitney equation (equation 1.1) and drug release mechanism of a water-soluble polymer (section 1.4) indicate that the low viscosity would result in increase the dissolution of poorly water-soluble drug from the SD.

Formulations containing carriers that form a viscous gel layer retard the diffusion of the drug through the stagnant layer. This results in a decrease in the dissolution rate of the drugs (Dabbagh et al., 2007; Papageorgiou et al., 2008; Nagpal et al., 2012). Dabbagh et al. (2007) observed that the HPMC reduced the dissolution of the ibuprofen from the ibuprofen-HPMC SD system prepared using the solvent method (Dabbagh et al., 2007).
Papageorgiou et al. (2008) reported a finding with the HPMC system similar to that reported previously (Papageorgiou et al., 2008). The gum karaya retarded the diffusion of the drug and thus dissolution from glimepiride-gum karaya solid dispersion (Nagpal et al., 2012).

The use of low viscosity polymers increased the rate of drug dissolution. A low viscosity grade HPC polymer successfully enhanced the dissolution of phenytoin and carbamazepine via SD preparation (Sarode et al., 2013). Gum karaya was modified as a low viscosity modified gum karaya. This enhanced the dissolution of nimodipine (Murali Mohan Babu et al., 2002) and glimepiride (Nagpal et al., 2012). Guar gum and locust bean gum were modified to enhance the dissolution of poorly water-soluble drug licofelone and lovastatin respectively (Shah et al., 2010; Patel et al., 2008). The investigators attributed the dissolution enhancement to the low viscosity of the modified gum compared to that of the original guar gum (Shah et al., 2010; Patel et al., 2008).

Portero et al. (1998) also reported an increase in dissolution because of the low viscosity of the carrier (Portero et al., 1998). Pullulan, a low viscosity natural polysaccharide has successfully enhanced the dissolution rate of diazepam from diazepam-pullulan cogrinded mixtures (Chaudhari and Sanghvi, 1993). Indomethacin-pullulan spray-dried SD has been successfully formulated for the dissolution enhancement purpose (Sakamaki and Miyamoto, 1978 Jap. Pat. 78 12,417).

Moreover, AGF has many OH functional groups available for the hydrogen bonding with the drug. Drug-polymer hydrogen bonding is very important as discussed in section 1.8.4. This led to our research hypotheses.
Research Hypotheses

Larch arabinogalactan (FiberAid grade) polymer and poorly water-soluble drug form amorphous solid dispersions, which would successfully enhance the dissolution rate.

Research Objectives

Solid dispersions of poorly water-soluble drugs, and an amorphous carrier have shown to enhance drug dissolution and \textit{in vivo} bioavailability. Larch arabinogalactan (FiberAid grade), a GRAS designated polymer, is amorphous and hydrophilic in nature. Therefore, AGF has a great potential as a carrier for amorphous solid dispersion preparation. In this study, we systematically investigated larch arabinogalactan (FiberAid grade) AGF-based solid dispersions. This dissertation is divided into 5 chapters.

Chapter 2- This chapter describes the characterization of the larch arabinogalactan FiberAid grade (AGF) polymer for its relevant properties as a solid dispersion carrier. HPMCK3 was used as a control polymer for the evaluation of flow and compaction properties.

Chapter 3- We have investigated the ibuprofen-AGF solid dispersion in detail. This chapter includes the feasibility of preparation of the ibuprofen-AGF solid dispersions, detailed solid-state and solution-state characterization and \textit{in vitro} dissolution studies. Ibuprofen-AGF solid dispersions were compared with ibuprofen-HPMCK3 solid dispersions for solid-state characterization and dissolution enhancement potentials.
Chapter 4- This chapter describes the evaluation of dissolution enhancement of ketoprofen-AGF solid dispersions and itraconazole-AGF solid dispersions in detail. Detailed comparison were made among ibuprofen-AGF solid dispersion, ketoprofen-AGF solid dispersion and itraconazole-AGF solid dispersions with respect to equilibrium solubility, dissolution enhancement, and miscibility.

Chapter 5- The AGF solid dispersions with additional 9 drugs were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and Fourier-transform infrared (FTIR) spectroscopy. The underlying mechanism of AGF polymer to inhibit the drug crystallization was investigated.

Chapter 6- This chapter includes the evaluation of the physical and chemical stability of the ibuprofen-AGF solid dispersions at 25 ºC/60% RH (for 6 months) and at 40 ºC/C75% RH (for 3 months).
CHAPTER 2
THE CHARACTERIZATION OF LARCH ARABINO GALACTAN: A CARRIER FOR SOLID DISPERSIONS

2.1. Introduction

Although solid dispersions (SDs) have attracted considerable attention, to date, very few polymers have been investigated as carriers for SDs. Hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl cellulose (HPC), polyethylene glycol (PEG), and poloxamers are the most commonly used SD carriers that have been investigated extensively (Chapter 1. Table 1.2; Table 1.3). Among these polymers, HPMC, a semi-synthetic amorphous polymer, and PVP, a synthetic amorphous polymer has been successfully used in commercial amorphous SD products (Chapter 1 Table 1.1). However, the hygroscopicity of PVP can result in a sticky mass upon processing and storage (Jagdale et al., 2011; Caron et al., 2013; Dabbagh et al., 2007; Chen et al., 2007). The high viscosity of HPMC imposes hurdle to the drug dissolution enhancement especially at high drug loading (Papageorgiou et al., 2008; Dabbagh et al., 2007).

Additionally, none of the polymers are optimal- (a) to form an amorphous SD (Van Eerdenbrugh and Taylor, 2010), (b) to produce a desired increase in vitro dissolution (Nagpal et al., 2012), (c) to produce desired in vivo bioavailability (Chokshi et al., 2007), and (d) to impart physical and chemical stability to the SD (Chokshi et al., 2007; Kanaujia et al., 2011; Pan et al., 2000). In fact, Van Eerdenbrugh and Taylor (2010)
investigated spin-coated SD prepared using various combinations of 8 different drugs and 7 different chemically diverse polymers at different drug to polymer ratio. The results of their study established that the inherent properties of both the polymer and the drug govern the formation and stability of amorphous SDs (Van Eerdenbrugh and Taylor, 2010). Therefore, exploration of a novel SD carrier is always desired.

Among the different attributes of a carrier of SDs (Chapter 1 section 1.11), Tg of the polymer is the major indicator of the stability. If the SD is stored at 50 °K below the glass transition (Tg) of the system, molecular mobility is approximately non-existent which imparts physical stability to the SD (Hancock et al., 1995). Therefore, Tg of the AGF polymer is an important property which should be evaluated. The degradation profile of the polymer will provide the insight in the processing temperature. The absorbed water acts as a plasticizer which lowers the Tg of the SD (Hancock and Zografi, 1993; Hancock and Zografi, 1994; Oksanen and Zografi, 1990; Taylor et al., 2001). Therefore, the next step will be evaluation of the hygroscopicity of the AGF polymer. Low viscosity of the carrier polymer is equally important as discussed previously (Chapter 1). Other properties that are pivotal in developing a tablet dosage form from the formulated AGF SD include particle morphology, flow, and compaction profiling.

AGF is the natural polysaccharide and thus variation in chemical composition is expected. Therefore, we analyzed the AGF polymer samples received as a gift using FTIR spectroscopy and established FTIR an identification and quality control test similar to reported previously (Neal-Kababick et al., 2010).

Although drug-AG conjugates and drug-AG mechanochemical activated complexes have been studied (Chapter 1, Table 1.5 and Table 1.6), the investigation of the AGF as a
carrier matrix for SDs has not been investigated thus far. In addition, the properties relevant to its use as a carrier for SDs have not been examined either.

Thus, the objectives of the current investigations were as follows.

1) To investigate FTIR spectroscopy as an identification and quality control tool for the AGF polymer samples received as a gift
2) To evaluate glass transition temperature, thermal degradation temperature, and hygroscopicity of the AGF polymer
3) To determine the viscosity of the aqueous solution of the AGF polymer
4) To compare the flow, compaction, and morphological properties of the AGF polymer with those of the low viscosity grade HPMCK3 polymer

2.2. Materials and Experimental Methods

2.2.1 Materials
Larch Arabinogalactan FiberAid grade was a generous gift from Lonza Inc (Allendale, NJ) and Del-Val Food Ingredients (Mooresstown, NJ). HPMCK3 was gifted by The Dow Chemical Co. (Midland, MI).

2.2.2 FTIR spectroscopy of neat AGF
The infrared spectra of the neat AGF polymer was analyzed using PerkinElmer Spectrum 100 FTIR spectrometer (PerkinElmer Inc. Waltham, MA) equipped with a PerkinElmer Universal diamond Attenuated Total Reflectance (ATR) polarization accessory (PerkinElmer Inc.). Approximately, 2 mg of powdered samples were placed on the crystal. The swing arm was placed above the sample, and the pressure knob was turned
clockwise until the force gauge displayed 60-64. Scans were obtained at a resolution of 2 cm\(^{-1}\), from 4000 to 650 cm\(^{-1}\) at 64 scans/s. The FTIR spectra were analyzed using spectrum (version 10) (PerkinElmer Inc.).

2.2.3 Conventional and modulated differential scanning calorimetry for evaluation of Tg

Differential scanning calorimetry (DSC) was performed using a DSC Q 200 system (TA Instruments, New Castle, DE) with dry nitrogen purge. Approximately 4–5 mg of AGF polymer sample was placed in a standard aluminum pan and sealed with a lid. Heating rate of 20 \(^{\circ}\)C/min was applied from 20 \(^{\circ}\)C to 200 \(^{\circ}\)C.

For modulated differential scanning calorimetry (mDSC), approximately 4–5 mg of the AGF polymer was placed in a standard aluminum pan and sealed with a pinhole lid. Initially, the sample was heated from 20 \(^{\circ}\)C to 103 \(^{\circ}\)C at a heating rate of 10 \(^{\circ}\)C/min, equilibrated at 103 \(^{\circ}\)C and cooled to -30 \(^{\circ}\)C after keeping in isothermal conditions for 5 min. Finally, a heating ramp of 0.75 \(^{\circ}\)C/min was applied from -30 \(^{\circ}\)C to 160 \(^{\circ}\)C with modulation amplitude of +/- 1\(^{\circ}\)C every 60 s. Indium was used as a standard to calibrate temperature and heat flow. The data were processed and analyzed using Universal Analysis 2000 software (TA Instruments).

2.2.4 Dynamic mechanical analysis for evaluation of Tg

The dynamic mechanical analysis (DMA) spectra of neat AGF polymer was recorded on a Q800 DMA instrument. The protocol included a heating rate of 3 \(^{\circ}\)C/min from 20 \(^{\circ}\)C to 107.76 \(^{\circ}\)C at a frequency of 1Hz, and an amplitude of 20 \(\mu\)m. The air was used as a gas. The data were acquired and analyzed using Universal Analysis 2000 software (TA Instruments).
2.2.5 Thermomechanical analysis for evaluation of Tg

Thermomechanical analysis (TMA) was performed on a Q400 TMA equipped with a penetration probe (TA Instruments). Approximately 5 mg of the AGF polymer sample was compacted into a disc using a sample press (TA Instruments). The thickness of the compact was 1.4-2 mm. The compact was placed on a glass stage for analysis. The protocol included a heating rate of 10 °C/min up to 160 °C/min and a force of 0.020N. The purge gas was nitrogen (200mL/min). Universal Analysis 2000 software (TA Instruments) was used to acquire and analyze the data.

2.2.6 Thermogravimetric analysis for evaluation of degradation profile of AGF polymer

The thermogravimetric analysis (TGA) data were collected using TGA Q5000 V3.13 (Build 261, TA Instruments). A neat AGF polymer sample was heated under dry nitrogen gas at a rate of 40 °C/min from room temperature to 800 °C. Data were acquired and analyzed using Universal Analysis 2000 software (TA Instruments).

2.2.7 Evaluation of hygroscopicity and sorption characteristic

The dynamic dewpoint isotherm (DDIs) was obtained using Aqualabs Aquasorp Isotherm Generator (Aqua Lab, Decagon Devices Inc., Pullman, WA). The experiment was conducted at room temperature. Neat AGF polymer sample of 653 mg was placed in a stainless steel cup. The sample was dried (desorption) to a water activity (aw) of 0.03 then hydrated (adsorption) to a aw of 0.90 and finally redried to a aw of 0.03. The flow rate of the hydrated and desiccated air was 80 mL/min. Weight change at each aw was converted to moisture content (% wet basis). The data were processed and analyzed using SorpTrac software (version 1.14) (Decagon Devices Inc). The calibration method consists
of testing of 4 standards of the known aw (Pullman, WA) using the initial measured moisture content value.

### 2.2.8 Rheological assessment of aqueous solutions of AGF polymer

The viscosity of the aqueous solutions of AGF was measured using *m-VROC* version 2.5 (Viscometer/Rheometer-on-a-Chip from RheoSense Inc.). The viscosity measurements were recorded at 25 °C and 70 °C. The AGF polymer samples of 3 different concentrations were prepared using nanopure water and equilibrated them for 5 min before each experiment. Measurement time was between 1.1 s to 2 s, and the wait time was 3 s. The multipoint shear rate measurements were performed. The *m-VROC* software version 2.5 was used for data processing, acquisition and analysis.

### 2.2.9 Scanning electron microscopy evaluation

Scanning electron microscopy (SEM) of the neat AGF polymer was performed and microphotographs were obtained using a FEI Quanta 600 FEG Mark II Environmental Scanning Electron Microscope (ESEM) located at the University of Pennsylvania (Philadelphia, PA). The samples were coated with thin gold-palladium layers using a sputter coater (Cressington Sputter Coater 108).

### 2.2.10 Evaluation of the angle of repose

The angle of repose was determined using a modified fixed-base cone method using culture plates of 14 cm diameter as a base. A glass funnel was fastened to an iron support at a fixed height (15 cm). An excess amount of polymer (45 g of neat AGF and 50 g of neat HPMCK3) was poured through the funnel to form a conical pile on the bottom plate covering the entire base. The sample was poured until the maximum height was obtained.
The experiment was performed in triplicate. The height of the cone of the polymer powder was measured and the angle of repose was calculated using the following formula

\[ \text{Angle of Repose} = \tan^{-1}\left(\frac{h}{r}\right) \]  

2.1

\[ h = \text{Cone height} \]

\[ r = \text{Radius of the powder cone} \]

2.2.1. Compaction evaluation

The compaction evaluation of the neat AGF and neat HPMCK3 polymer were performed. Approximately 500 mg of the polymer was weighed and transferred to a compact die and compressed on a manual carver hydraulic press (Model 3912; Carver Inc., Wabash, IN). The compacts were prepared using 1.2-cm diameter, round, standard-cup punches. The polymer was compressed applying a compression force from 1000 to 4000 LB in increments of 500 LB. The dwell time to form the compact was 30 s. The compacts were evaluated for weight, diameter, hardness and thickness using Dr. Schleuniger Pharmatron Multi Test Tablet Tester (Pharmatron Inc., Manchester, NH).

2.3. Statistical Analysis

Minitab 16.0 (Minitab Inc.) software was used for statistical analysis. The statistical analysis of angle of repose data and compact hardness data was performed using one-way analysis of variance (ANOVA) with a pairwise multiple comparison procedure.
Differences were considered significant when $p < 0.05$. Tukey’s test for multiple comparisons was used to calculate the significance differences.

2.4. Results and Discussions

HPMCK3 premium LV polymer (HPMCK3/Hypromellose USP2208) (Figure 2.1) was selected as a control polymer in the present and subsequent investigations. HPMCK3 is an amorphous polymer similar to AGF. HPMCK3 has been used for dissolution enhancement of naproxen by formulating it into compressed slug or roller compacts (Mitchell et al., 2003). It is one of the lowest viscosity grades methocel available. The viscosity of 2% dispersion of HPMCK3 in water at 20 °C is 2.4 to 3.6 mPa s (Methocel cellulose ethers in aqueous systems for tablet coating http://www.dow.com). The viscosity of AG solution in water is lower than that of HPMCK3 solutions (Nazareth et al., 1961 part I). HPMC stabilized the amorphous SD by forming hydrogen bonds with its stronger hydrogen donor group OH (Nakayama et al., 2009). AGF has numerous OH groups as well.
2.4.1 FTIR spectroscopy

The AGF polymer used throughout the dissertation project was gifted by Lonza Inc., and Del-Val Food Ingredients. Because AGF is a naturally sourced material, consistent polymer samples were required. The literature searches have revealed a reference where FTIR spectroscopy was explored as a quality control tool for AG polymer (Neal-Kababick et al., 2010).

Additionally, a number of studies have shown that the FTIR was used for the characterization of AG, AG derivatives and drug-AG system. This included the FTIR analysis of purified AG (Groman et al., 1994), oxidized AG (Borisov et al., 2004; Mudarisova et al., 2005), AG-drug conjugates (Ehrenfreund-Kleinma et al., 2002; Ehrenfreund-Kleinma et al., 2004), and the AG products cross-linked with chitosan or
protein (Ehrenfreud-Kleinma et al., 2003). Therefore, AGF polymer as received was first subjected to FTIR spectroscopy analysis.

Figure 2.2 shows the FTIR spectra of neat AGF polymer. The detailed IR band assignment is listed in Table 2.1. The FTIR spectra of the neat AGF polymer is consistent with that reported in previous studies (Neal-Kababick et al., 2010; Pogodaeva et al., 2012; Borisov et al., 2004). The AGF polysaccharide-specific bands in fingerprint regions (1200-800 cm\(^{-1}\)) were found at 1067.85 cm\(^{-1}\) and 1035.17 cm\(^{-1}\). These bands were associated with galactopyranose in the backbone and arabinofuranose units in the side branches, respectively (Robert et al., 2005; Kakurakova et al., 2000).

The FTIR of the spectra of the samples received from Lonza Inc. and Del-Val Food Ingredients is shown in Figure 2.3. The IR bands in the fingerprint region were observed in these samples at 1067.85 cm\(^{-1}\) and 1035.17 cm\(^{-1}\) indicating that AGF polymer samples received throughout the study period were consistent and authenticate.

![Figure 2.2 FTIR spectrum of NEAT AGF polymer](image-url)
Table 2.1 IR peak assignment of NEAT AGF polymer

<table>
<thead>
<tr>
<th>IR band (cm$^{-1}$)</th>
<th>IR band shape and intensity</th>
<th>Assignment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3308.63</td>
<td>Broad, strong</td>
<td>OH stretching (H-bonded)</td>
<td>Borisov et al., 2004</td>
</tr>
<tr>
<td>2891.31</td>
<td>Broad, weak</td>
<td>C-H stretching in CH3 and CH2</td>
<td>Borisov et al., 2004</td>
</tr>
<tr>
<td>1590.84</td>
<td>Sharp, strong</td>
<td>Carboxylate of the uronic acids</td>
<td>EP 1940427; Borisov et al., 2004; Jiang et al., 2004; Li-Chan et al., 2011; Neal-Kababick et al., 2010</td>
</tr>
<tr>
<td>1370.75 and 1308.9</td>
<td>Sharp, strong and; broad, weak</td>
<td>C–O–H bending vibrations O-C-H and C-C-H stretch</td>
<td>Guolin et al., 2012; Li-Chan et al., 2011.</td>
</tr>
<tr>
<td>1135.48</td>
<td>Broad, weak</td>
<td>Glycosidic linkage (C-O-C)</td>
<td>Kacurakova et al., 2000; Zhou et al., 2009</td>
</tr>
<tr>
<td>1067.85</td>
<td>Sharp, weak, duplet</td>
<td>Galactopyranose in the backbone</td>
<td>Robert et al., 2005; Kacurakova et al., 2000</td>
</tr>
<tr>
<td>1035.17</td>
<td>Sharp, weak, duplet</td>
<td>Arabinofuranose side branches</td>
<td>Robert et al., 2005; Kacurakova et al., 2000</td>
</tr>
<tr>
<td>876.75 and 773.64</td>
<td>Sharp, weak; Sharp, medium</td>
<td>Pyranose ring deformation (glycoside bonds in the pyranose ring)</td>
<td>Groman et al., 1994; Mudarisova et al., 2005</td>
</tr>
</tbody>
</table>
Figure 2.3 FTIR spectra of AGF polymer samples (as an identification tool)

Note- A-From Lonza Inc; B-From Del-Valley Food Ingredients.
2.4.2 Glass transition temperature evaluation

The Tg of the AGF polymer was determined using DSC, mDSC, DMA, and TMA.

2.4.2.1 DSC and mDSC

The conventional DSC thermogram of the neat AGF polymer is shown in Figure 2.4. The neat AGF polymer showed a transition at around 66 °C which represented the glass transition temperature (Tg) of the AGF polymer. Repeated DSC scans showed the Tg at the same temperature. In addition, the DSC thermogram showed a broad endotherm at around 110 °C in the range from 90 °C to 130 °C which represented water vaporization. Water vaporization endotherm was observed in the same temperature range for methocel, corn starch, and avicel (Mura et al., 1995). The Tg of the AGF polymer could not be detected using conventional DSC after complete drying of AGF (removing the water vapor). Therefore, mDSC of the AGF polymer was performed.

The mDSC thermogram of the neat AGF polymer (Figure 2.5.) shows a Tg value of 82.29 °C. The Tg obtained by conventional DSC was lower than that obtained using mDSC. This is a typical findings when water acts as a plasticizer and lowers the Tg of the AGF polymer (Dhawade and Jagtap, 2012). In mDSC, the first heating cycle removes the water. The Tg is accurately determined in the second heating cycle.
Figure 2.4 Conventional DSC thermogram of NEAT AGF polymer

Figure 2.5 Modulated DSC thermogram of NEAT AGF polymer
2.4.2.2 DMA

The dynamic storage modulus spectra of the neat AGF polymer is shown in Figure 2.6. The drop in the storage modulus indicates the relaxation phenomenon associated with the Tg of the amorphous phase (Ohkoshi et al., 2000). The Tg of the neat AGF polymer detected using DMA was around ~82 °C.

![DMA spectrum of NEAT AGF polymer](image)

Figure 2.6 DMA spectrum of NEAT AGF polymer

2.4.2.3 TMA

TMA measures the dimensional changes as a function of temperature. TMA is based on the principle that at the Tg, the polymer chains are moving and the strength of their inter-and intra-segmental bonds is strongly reduced. Thus, the free volume, the flexibility, and penetrability of the polymer increases. Therefore, at the Tg, the minimum
resistance to penetration is observed (Frohoff-HuElsmanna et al., 1999). The TMA analysis of neat AGF shows the Tg at approximately 86.49 °C (Figure 2.7).

![TMA spectrum of NEAT AGF polymer](image)

Figure 2.7 TMA spectrum of NEAT AGF polymer

The Tg of the AGF polymer obtained using mDSC (82.29 °C), DMA (82.39 °C) and TMA (86.49 °C) were consistent. These experimental values were close to the values of the softening temperature (74 °C) listed in the MSDS (Material Safety Data Sheet) of the AGF polymer (Lonza Inc.).

The Tg of AGF is lower than that of HPMC and PVP polymers. The Tg of HPMC is in the range of 160-185 °C, depending on the grade and MW (Ali et al 2010; McPhillips et al., 1999; Kararli et al., 1990). The Tg of PVP is in the range of~ 86.85-136.85 °C (del Pilar Buera et al., 1992).
The Tg of the AGF polymer is comparable to that of other polymers such as PVA, Soluplus, and PVPK12. These polymers have been successfully used for the preparations of the SDs (Lim et al poster; Liu et al., 2012; Dani et al., 2013; Taylor et al., 2001).

The Tg of the SD system can be described using simple Fox equation (Fox and Bull, 1956).

\[
\frac{1}{T_g} \text{blend} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}}
\]

where

\( W_1 \) - Weight fraction of drug

\( T_{g1} \) - Glass transition temperature of drug

\( W_2 \) - Weight fraction of the polymer

\( T_{g2} \) - Glass transition temperature of the polymer

The Tg of the blend is composition dependent. Thus, the Tg of the SD system depends on the Tg of the polymer and the Tg of the drug. However, the polymer with high Tg does not guarantee that the SD will have a high Tg. Sakurai et al. (2012) showed that the Tg of the amorphous SD prepared using HPMC, a polymer with a high Tg (~145 °C), was 12 °C. On the other hand, Tg of the SD prepared (same drug) using PVP (Tg ~140 °C) and PVP-VA (Tg ~100 °C) was 45 °C and 40 °C, respectively (Sakurai et al., 2012).

Interestingly, in the current solid solution era, a greater number of polymers with low Tg have been explored (Ali et al., 2010). Soluplus with a Tg of 70 °C has been successfully used for the preparation of the SDs. Further, Smithey et al. (www.pharma-
ingredients.basf.com)) reported that the stability of the 1:1 indomethacin-Soluplus SD was superior to that of 1:1 indomethacin-HPMCAS SD (Smithey et al., www.pharma-ingredients.basf.com) despite lower Tg value of the Soluplus (HPMCAS Tg ~120 °C versus soluplus Tg 70 °C). Therefore, exploring AGF polymer with a Tg value of 82 °C as a carrier for the preparation of SDs would be rationale.

2.4.3 TGA

The objective of the TGA investigation was to measure the % weight loss as the AGF polymer is heated. The amount of water which evaporates in the first part of the TGA curve was 7% starting at 50 °C and finishing at 150 °C (Figure 2.8). This weight loss was most likely because of the bound water vapor (Shi et al., 2009). The degradation of the polymer starts just above 185 °C. The degradation is accelerated above 230 °C (corresponding to a nearly 10% weight loss). A TGA profile similar to that reported above was obtained when air instead nitrogen was used as a purge gas (Appendix Figure A. 1). This indicates that the degradation is same in an oxygen environment, and the polymer does not auto oxidize (Douroumis et al., 2012). Thus, the AGF polymer, which begins to degrade starting at 185 °C, is comparable with other polymers used for preparation of SDs (Perfetti et al., 2007; Shi et al., 2009). The results of this study suggested that the optimum temperature to prepare the SDs should not exceed 185 °C.
2.4.4 Evaluation of hygroscopicity and sorption characteristic

The DDI method was used to evaluate the hygroscopicity of the AGF polymer. According to AquaSorp Isotherm Generator Manual, the DDI method involves direct measurement of aw using chilled mirror dew point sensor while the change in sample weight is measured using gravimetric analysis. This method does not control the water activity or water content. The samples are progressively exposed to either water-saturated air (adsorption) or dry-air (desorption) after passing it through the desiccant at a predetermined air flow. After an approximate change in specific aw was attained, the aw and the weight of the sample were measured by stopping the airflow. A large number of aw data points were collected over a period of a few days (AquaSorp Isotherm Generator Manual Version 3.0 and Version 2.0, Decagon Devices Inc.).
It took 4 days to obtain an DDI isotherm for the neat AGF sample. The moisture sorption isotherm, the plot of moisture content versus water activity (or relative humidity (RH); RH=100aw) at a constant room temperature is shown in Figure 2.9.

The initial moisture content of AGF was 9.12%. The DDI moisture sorption isotherm of AGF showed an initial low moisture content region (up to 0.57aw), which corresponds to the adsorption of the surface water because of limited binding sites in the material. At critical aw_{critical} (~0.57), a sudden increase in the moisture content (designated by the sharp inflection point) was observed, which is because of the adsorption of bulk water. The aw_{critical} is the transition between surface adsorption and bulk adsorption. The increase in the water adsorption was due to dissolution of the material (after 0.67 aw)
(Burnett et al., 2004). The two inflections corresponding to these transitions were observed in the Savitsky-Golay derivative. A DDI isotherm very similar to that of AGF was observed for amorphous polydextrose (Yuan et al., 2011) and for spray-dried lactose (Burnett et al., 2004).

The moisture sorption profile of neat AGF exhibited type II behavior characteristics of monolayer and multilayer absorption (IUPAC classification -Sing et al., 1985; Spackman and Schmidt, 2010). Further, type II isotherms are also characteristic of an intermediate hygroscopic material (Fundamentals of Moisture Sorption Isotherms. Application Note http://www.aqualab.com/assets/Uploads/13947-04-AN-Fundamentals-of-Moisture-Sorption-Isotherms.pdf). Gum Arabic, which mostly consist of arabinogalactan shows type II behavior (Laine et al., 2008). The pharmaceutical excipient HPMCE5 (http://www.ashland.com/Ashland/Static/Documents/ASI/PC_10370_Benecel_HPMC_M C.pdf); microcrystalline cellulose, Kollidon CL, Kollidon VA64; magnesium stearate, colloidal silica, and lactose monohydrate (Roskar and Kmetec, 2005), all exhibit type II behavior.

The moisture sorption isotherm data of HPMC and PVP reported previously (Cavinato et al., 2010) was compared to that of the moisture sorption data of AGF obtained in this study (on dry basis). AGF had intermediate hygroscopicity compared to that of HPMC and PVP, i.e., AGF appears to be more hygroscopic than the HPMC but less hygroscopic than PVP. Thus, the results of the DDI study implied that AGF to be more advantageous than PVP as a carrier for SDs. At high humidity, hygroscopicity rather than drug-polymer hydrogen bonding governs the inherent inhibition of crystallization and stabilization of the amorphous form of the drug in SD (Ng et al., 2013). Further, formation of SD may
result in reducing the hygroscopicity compare to neat AGF polymer. van Drooge et al. (2006) observed that the hygroscopicity of the the diazepam-PVP SD was lesser than that of the original PVP polymer (van Drooge et al., 2006).

2.4.5 Rheological assessment of aqueous solutions of neat AGF polymer

![Graph showing viscosity of aqueous solution of NEAT AGF at 25°C and 70 °C](image)

Figure 2.10 Viscosity of aqueous solution of NEAT AGF at 25°C and 70 °C

The m-VROC version 2.5 (Viscometer/Rheometer-on-a-Chip from RheoSense Inc.) was used to measure the viscosity of an aqueous solution of the AGF polymer. This viscometer measures the viscosity using the pressure drop of the solution as it flows through the glass slit fixed with a pressure sensor at an increasing distance from the inlet. The graph of pressure drop versus the sensor position usually produces a straight line; the slope of this line is proportional to the viscosity of Newtonian fluids (http://www.rheosense.com/m-VROC%20Catalog_v2.1.pdf).
The multipoint shear rate measurements were performed to determine the Newtonian/non-Newtonian behavior of the AGF solutions. The AGF solutions with concentration up to 30% behaved like Newtonian fluids (Appendix Figure A.3).

Figure 2.10 presents the viscosity versus concentration profile at 2 different temperatures. The mean viscosity of 2%, 10% and 30% aqueous solution of AGF polymer at 25 °C was 0.99 mPa s, 1.458 mPa s and 4.04 mPa s respectively. These values were consistent with those reported previously for 10% aqueous solution of AG FiberAid grade, 1.58 mPa·s. (Burgalassi et al., 2007 and http://ametisjapan.com/arabinogalactan.pdf). The viscosity of the AGF solution increased with the increase in the AGF polymer concentration. Peng et al., (2011) attributed the positive correlation between viscosity and concentration to the stronger entanglement of the polymer chain of hemicellulose and carboxymethyl hemicellulose (Peng et al., 2011).

The viscosity values obtained in the current investigation were higher than those reported by Nazareth et al., (1961 part I). The investigators performed the viscosity measurement at 20 °C (Nazareth et al., 1961 part I).

At a given concentration, the viscosity values were higher at 25 °C compared to those at 70 °C. Nazareth et al.(1961 part I) showed viscosity-temperature relationships similar to those reported in our study (Nazareth et al., 1961 Part I).

The viscosity values of the HPMCK3, HPMCE3, and PVP (different grade) reported in a literature were significantly higher than the viscosity values of the aqueous solution of the AGF polymer observed in the current investigation (Methocel cellulose ethers in aqueous systems for tablet coating http://www.dow.com.; http://www.sigmaaldrich.com
PVP product specifications). The highly branched structure and comparatively low average MW of the AGF polymer (MW 50 kD with a polydispersity index of 1.65-Appendix Figure A.2) and weak interactions among the polymer chain may impart the observed rheological properties to AGF polymer.

2.4.6 Angle of repose evaluation

Table 2.2 Angle of repose of the AGF and HPMCK3 polymer

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Angle of repose±Std Dev</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGF</td>
<td>29.96±1.08</td>
<td>Fair</td>
</tr>
<tr>
<td>HPMCK3</td>
<td>32.06±0.62</td>
<td>Passable</td>
</tr>
</tbody>
</table>

The angle of repose of the neat AGF polymer was statistically equivalent to the angle of repose of the HPMCK3 polymer (Table 2.2). Thus, AGF and HPMCK3 polymers have quite similar flow properties (Table 2.2). The angle of repose for PVP K90 was 29.28° as reported by Teixeira et al. (2009) (Tieixeira et al., 2009). To determine why the AGF polymer has better flow properties than HPMCK3 polymer, we performed SEM analyses of neat AGF and HPMCK3 polymers.

The SEM microphotographs show that the neat AGF consisted of relatively uniform particles (Figure 2.11). The HPMCK3 particles were larger in size and were irregularly shaped (Figure 2.11). Most of the particles of AGF polymer were within the size range of 40-100µm. Particles lesser than 10 µm often has issues with flow (Padden et al., 2011). Thus, particle size and particle morphology imparted good flow properties to the AGF polymer.
2.4.7 Compaction evaluation

Figure 2.11 SEM microphotographs of AGF and HPMC polymer
Note- A-AGF polymer; B-HPMCK3 polymer

Figure 2.12 The compression force versus compact hardness of AGF and HPMCK3
Hardness (local plasticity) and the tensile strength (global strength) are a measure of compaction properties. These parameters are indicators for producing non-friable tablets (reviewed by Leuenberger and Rohera, 1986; Gereg et al., 2002).

The tensile strength was calculated using the following formula (data—Appendix Table A.1 and Table A.2).

\[
\text{Tensile Strength (}\sigma\text{)} = \frac{2F}{\pi DT}
\]

F-Force required to cleave the compact

D-Diameter of the compact

T- Thickness of the compact
The compression force versus compact hardness profiles and compression force versus tensile strength profiles are shown in Figure 2.12 and 2.13 respectively. HPMCK3 had significantly greater compact hardness (13-40 kp) compared to the AGF (1.6-10 kp). This suggests that compared to HPMCK3 polymer, the AGF polymer has compromised compaction profile.

Both HPMC E5 and PVP have superior compact hardness properties than AGF polymer when compression force (kN) versus hardness data from Teixeira et al. (2007) are compared to the compression force (kN) versus hardness data obtained in the current investigation. However, the investigators used different (21 x 12 mm) punch (Teixeira et al., 2007) from that used in the current investigation. We compared the data of compression force versus hardness (up to 4000 LB) obtained from the study by Gereg et al. (2002) with the data obtained in our study; we found that the AGF polymer was slightly superior to the regular grade lactose (Gereg et al., 2002).

Compared to PVP, AGF has moderate compaction property. The compaction property of the SD prepared with AGF is expected to be better than that prepared using PVP because of the less hygroscopic nature of the AGF polymer (Chen et al., 2007).

The compactions properties of neat AGF may improve upon formation of the SD. A previous study has reported that the compaction of the SD prepared using Crospovidone was superior to that of neat Crospovidone polymer (Shibata et al., 2005). Compared to a physical mixture of albendazole and pluronic, the albendazole-pluronic SD has improved compaction properties (Castro et al., 2010). The compaction of the AGF SD can be further improved using highly compressible additives like microcrystalline cellulose (Dinunzio et al., 2012; Sharma and Kolab, 2010).
2.5. Summary and Conclusions

The current investigation evaluated relevant properties of the neat AGF polymer such as glass transition temperature, thermal degradation, hygroscopicity, solution viscosity, particle morphology, powder flow, and compaction. The Tg of the AGF polymer was 82 °C and degradation temperature was ~185 °C. Thus, the AGF polymer was thermally stable. The AGF polymer has good hygroscopicity characteristics as shown by DDI isotherm data. The aqueous solutions of AGF in the 2–30% concentration range had substantially low viscosity (less than 4 mPa·s) at 25 °C. Morphological evaluation using SEM showed that the AGF polymer consisted of uniform particles and had a smooth surface. The AGF polymer had adequate flow and moderate compaction properties. Thus overall, the current investigation indicated the suitability of AGF polymer as a potential carrier for preparation of solid dispersion for dissolution enhancement.
CHAPTER 3
THE EVALUATION OF DISSOLUTION ENHANCEMENT
OF IBUPROFEN-LARCH ARABINOGALACTAN SOLID
DISPERSIONS

3.1. Introduction
Because of the advanced combinatorial and parallel synthesis techniques of drug
discovery, new chemical entities (NCE) are being synthesized routinely. These NCEs
have been subjected to high-throughput screening for solubility and permeability
evaluation. However, because of these advancements, lipophilic NCEs are being added to
the pool of poorly water-soluble compounds (Verma et al., 2004; Lipinski et al., 2000).
Because of poor solubility and bioavailability, these lipophilic molecules are difficult to
deliver orally. Among the various approaches to enhance the solubility and
bioavailability of these poorly water-soluble drugs (Chapter 1, Table 1.2 and Table 1.3),
formation of solid dispersions (SDs) has been extensively studied. Some of these SDs are
commercially available (Chapter. Table 1.1).

There are 3 major types of SDs. These are eutectic mixtures (EMs), solid solutions and
glass solutions. Each of these types has its advantages and limitations. Although, the
crystalline form of the drug in the EMs is stable, it is associated with lower solubility and
dissolution rate compared to its non-crystalline forms (reviewed by Hancock and Zografi,
1997; Law et al., 2003).

A solid solution, in which the drug is in a crystalline/non-crystalline form and the
polymer is in a crystalline form has a greater potential to increase the drug dissolution
and bioavailability (reviewed by Chiou and Riegelman, 1971; reviewed by Leuner and Dressman, 2000; reviewed by Janssens and Van den Mooter, 2009; Ali et al., 2010). However, the solid solution can be physically stable only if the drug is in the crystalline form (Chokshi et al., 2007).

Glass solutions, where the drug and polymer are in an amorphous form, have shown the highest increase in dissolution and in vivo bioavailability (Yuksel et al., 2003; Park et al., 2009; Piao et al., 2007; Lee et al., 2001). However, physical and chemical instability is the major limitation of this system (Chokshi et al., 2007; Liu et al., 2012).

As discussed earlier, the carrier is an essential part of the SD. The carrier dictates the performance, stability, and dosage form development of the system. Few polymers have been extensively investigated and successfully stabilized the amorphous SD. Very few of them are present in commercially available SD products. These carriers include but not limited are HPMC, HPMCAS, PEG, and PVP (Chapter 1, Table 1.1, Table 1.2 and Table 1.3). Thus, there is always a need to explore the new carrier for the preparation of SD.

In the previous investigation (Chapter 2), larch arabinogalactan FiberAid grade (AGF) polymer was characterized focusing its potential use as SD carrier. The findings showed that AGF has a Tg value of ~82 °C and thermal degradation temperature of 185 °C. AGF has good hygroscopicity and low viscosity. The AGF polymer showed good flow properties and moderate compaction properties. Additionally, some of the other attributes of AGF polymer include its hydrophilic nature, GRAS designation and multiple OH groups that are capable of forming hydrogen bond with the drug. Therefore, the current study aimed to formulate and evaluate the SD of the poorly water-soluble drug ibuprofen (IBU) and the AGF polymer for dissolution rate enhancement.
The current investigation had the following objectives.

1) To prepare and perform solid-state characterization of IBU-AGF solid dispersions
2) To perform solution-state characterization of IBU-AGF solid dispersions
3) To evaluate dissolution enhancement of IBU-AGF solid dispersions
4) To compare IBU-AGF solid dispersions with IBU HPMCK3 solid dispersions with respect to solubility, solid-state characterization and in vitro dissolution

3.2. Materials and Experimental Methods

3.2.1 Materials

Larch arabinogalactan FiberAid grade (AGF) was gifted by Lonza Inc. (Allendale, NJ) and Del-Val Food Ingredients (Moorestown, NJ). HPMCK3 was gifted by The Dow Chemical Co. (Midland, MI). IBU was purchased from Spectrum Chemicals (Gardena, CA). All other chemicals and reagents were either of high-performance liquid chromatography (HPLC) or ACS grade and purchased from either Fisher Scientific (Fair Lawn, NJ) or Sigma–Aldrich (St. Louis, MO).

3.2.2. Equilibrium solubility study of IBU in AGF polymer solution in 0.1 N HCl

The equilibrium solubility of IBU was determined in the presence of various concentrations of AGF (in 0.1N HCl) according to the Higuchi and Connors (1965) method (Higuchi and Connors, 1965). An excess of IBU (200 mg) was added to 10 mL of polymer solution in 0.1N HCl. The polymer concentrations ranged from 0% to 3% (0 mg/mL to 30 mg/mL). These samples were placed in a stoppered glass vial and bath-sonicated for 30 min. The vials were kept in a shaking water bath at 37 °C and at 50 rpm.
for 72 h. After 72 h, the samples were allowed to settle at 37 °C for 3 h. The supernatant was filtered using a 0.45 μm filter. After suitable dilution, the IBU content was assayed by measuring the UV absorption at 222 nm (Agilent/HP 8453 UV-Vis spectrophotometer). Each experiment was performed in triplicate. A similar set of experiments was performed using the control polymer HPMCK3.

3.2.3 Preparation of the IBU-AGF microspheres solid dispersions using modified water-in-oil solvent evaporation technique

The IBU-AGF microspheres SD (MSD) of 10%, 20% and 30% drug load (DL) were prepared using modified water-in-oil emulsion solvent evaporation technique. Briefly, IBU was dispersed in a 28-36% aqueous solution of AGF. This drug-polymer solution was heated to the melting point (T_m) of the drug (~76 °C). This led to a viscous inner phase comprising of the molten drug. Then, this thick inner viscous phase was emulsified with 200 mL of safflower oil at room temperature while stirring using an overhead electronic stirrer with an impeller (Heidolph Brinkmann Model-RZR 2051). The stirring continued for 3 h. After evaporation of the remaining water from the inner phase, the solidified microspheres were obtained. The microspheres were washed with HPLC-grade acetone, air dried at room temperature and then in an oven at 45 °C (overnight). The microspheres were stored in an airtight container until further analysis.

The MSD batches with a drug load ranging from 10% to 75% were prepared using this protocol. In addition, the MSDs were prepared using the control polymer HPMCK3 at 10%, 20% and 30% of IBU load.
3.2.3.1. IBU content assay

The IBU content was analyzed by dissolving crushed microspheres equivalent to 25 mg of IBU in 250 mL of phosphate buffer (pH 7.2). This solution was stirred for 2 h. Then, the amount of drug was determined using a UV spectrophotometer at 222 nm (Agilent/HP 8453 UV-Vis spectrophotometer). The percent encapsulation efficiency and % yield were calculated using the equations below:

\[
\text{% Encapsulation efficiency} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100 \quad \text{..................3.1}
\]

\[
\text{% Yield} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100 \quad \text{.................................................3.2}
\]

3.2.4. Preparation of IBU-AGF solid dispersions by modified solvent evaporation method

The IBU-AGF SDM were prepared using the modified solvent evaporation method described by Rane et al., (2007) and Karavas et al. (2001). A few modifications to these methods were made. Accurately weighed drug was dissolved in ethanol while stirring until a clear solution was obtained (below its saturation solubility). Accurately weighed polymer was placed in a round-bottom flask. Nanopure water was added to the polymer (AGF/HPMCK3) to obtain a polymer wet mass. The entire volume of the drug-ethanol solution was added to the polymer wet mass. The entire solvent was evaporated using Rotovap (R-114, Buchi Corp) at 70 °C under vacuum. To ensure complete drying, the flask was kept in an oven at 45 °C overnight. The prepared SDMs were stored in an
airtight container. In addition, some batches of IBU-AGF SDM were prepared using the revised SDM method (Chapter 4 section 4.3.2).

3.2.5. Preparation of IBU AGF physical mixture

The physical mixtures (PMs), a crystalline control samples were prepared by triturating the drug and the polymer in a mortar and pestle using geometric dilution. The IBU-HPMCK3 PMs were also prepared using the same technique.

3.2.6. Conventional DSC

DSC study was performed using a DSC Q 200 system (TA Instruments, New Castle, DE). Approximately 4-5mg of the sample was placed in a standard aluminum pan and sealed with a lid. A heating rate of 20 °C /min was applied from 20 °C to 160 °C /200 °C. Indium was used as a standard to the calibrate temperature and heat flow. The data were processed and analyzed using Universal Analysis 2000 software (TA Instruments).

3.2.7. XRPD

The powdered samples (150-250 µg) were placed in a sample holder, and the diffractograms were collected using a Bruker D8 diffractometer (Madison, WI) with Cu Kα radiation. A voltage of 40 kV was used, and the current was 40 mA. The samples were scanned from 2° to 40° at a rate of 2 θ/min. The data analysis was performed using Bruker-AXs EVA software (version 15.0).

The diffractograms of the SDM samples were collected using a Rigaku D-Max B X-ray diffractometer (Tokyo, Japan). A sample size of 0.5 g was used and the samples were run at 35 kV, 15 mA and 0.9 W. Datascan program (MDI) was used to process and acquire the XRPD data. Software JADE version 9 (MDI) was used to analyze the data (MDI).
3.2.8. FTIR

The method has been discussed in Chapter 2, section 2.2.2

3.2.9. SEM

The SEM of MSD and PM samples were obtained using the method discussed in Chapter 2, section 2.2.9

The SEM of SDM samples were obtained using Hitachi S-3500N SEM located at Pennsylvania State University (Environmental Scanning Electron Microscope) (University Park, PA). The samples were mounted on an aluminum sample holder with carbon tape and sputtered with a thin film of Au. Few samples were gold coated, and images were obtained using FEI Quanta 200 ESEM.

3.2.10. TMA

TMA of IBU-AGF SDM samples were performed using the method discussed in Chapter 2, section 2.2.5

3.2.11. Solution-state characterization of IBU-AGF SDs using proton nuclear magnetic resonance

The solution-state proton nuclear magnetic resonance (\(^1\)H-NMR) spectra of neat IBU, neat AGF polymer, IBU-AGF SDs, and IBU-AGF PMs were recorded using Bruker Ultrashield TM Plus 400 Mz NMR spectrometer (Bruker Corp). Approximately 4–5 mg of sample was dissolved in 3 mM of NaOD solution (in D\(_2\)O) just before the analysis. The solution was placed in 5-mm NMR tubes, and the spectra were recorded. The \(^1\)H-NMR spectra were analyzed using TOPSPIN 21 software (Bruker Corp).

3.2.12. In vitro dissolution of IBU-AGF SDs
In vitro drug dissolution studies were performed using modified USP basket method (270 mesh basket, 53 µm pore size). Van Kel VK7010 dissolution system was used. The dissolution medium was 900 mL of 0.1 N HCl at 37 °C. The dissolution experiment was performed at 100 rpm. Each sample contained MSD or SDM or PM equivalent to 25mg of IBU to maintain the non-sink conditions. At appropriate time intervals, samples were collected and replaced with fresh media. Each sample was filtered, and the drug was analyzed using an Agilent/HP 8453 UV-Vis spectrophotometer (λmax = 222 nm).

3.3. Statistical Analysis
Minitab 16.0 (Minitab Inc.) software was used for statistical analysis. The statistical analysis of solubility and dissolution data were performed using ANOVA with a pairwise multiple comparison procedure. Differences were considered significant when p < 0.05. Tukey’s test for multiple comparisons was used to calculate the significance differences among different dissolution profiles.

3.4. Results and Discussions
IBU (Figure 3.1) was selected as the candidate drug for the preparation of SDs because of the following reasons:

(a) IBU is BCS class II drug with dissolution as a rate limiting step in its in vivo absorption and bioavailability,

(b) A previous study has reported solubility enhancement of IBU in the presence of AG (Dushkin et al., 2012/chapter 22),
(c) IBU is monomorphic in nature,

(d) IBU has C=O and COOH functional group and is capable of forming hydrogen bonds with the carrier, and

(e) It has a low melting point, IBU melts at a much lower temperature than its decomposition temperature (Ribeiro et al., 1996; Tita et al., 2011).

Further, adequate literature is available about IBU loaded SDs (Table 3.1).

Figure 3.1 Chemical structure of Ibuprofen
(Adapted from Ghorab and Adeyeye, 2001).
Table 3.1 Examples of IBU solid dispersions

<table>
<thead>
<tr>
<th>IBU-carryer SD</th>
<th>Preparation method</th>
<th>Improved</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU-PVPVA64</td>
<td>Microwave</td>
<td>Dissolution</td>
<td>Moneghini et al., 2008</td>
</tr>
<tr>
<td>IBU-Poloxamer 127</td>
<td>Spray drying</td>
<td>Dissolution</td>
<td>Elkordy and Essa, 2010</td>
</tr>
<tr>
<td>IBU-HPMC; IBU-PVP; IBU-PEG6000, IBU-Eudragit</td>
<td>Fusion solvent</td>
<td>Dissolution</td>
<td>Dabbagh et al., 2007</td>
</tr>
<tr>
<td>IBU-HPMC-Poloxamer</td>
<td>Spray drying</td>
<td>Bioavailability</td>
<td>Park et al., 2009</td>
</tr>
<tr>
<td>IBU-Poloxamer 188</td>
<td>Melt</td>
<td>Dissolution and bioavailability</td>
<td>Newa et al., 2007</td>
</tr>
<tr>
<td>IBU-Mesoporous SPA-15</td>
<td>Spray drying</td>
<td>Dissolution</td>
<td>Shen et al., 2010</td>
</tr>
<tr>
<td>IBU-Kollidon</td>
<td>Pulse combustion dryer system, HYPULCON</td>
<td>Dissolution</td>
<td>Xu et al., 2007</td>
</tr>
<tr>
<td>IBU-Microcrystalline Chitosan</td>
<td>Freeze drying</td>
<td>Dissolution</td>
<td>Bodek, 2002</td>
</tr>
<tr>
<td>IBU-PVPCL; IBU-Microcrystalline cellulose</td>
<td>Solvent deposition</td>
<td>Dissolution</td>
<td>Williams et al., 2005</td>
</tr>
<tr>
<td>IBU-Kaolin</td>
<td>Ball milling</td>
<td>Dissolution</td>
<td>Mallick et al., 2008</td>
</tr>
<tr>
<td>IBU-PVPVK30</td>
<td>Electrospining</td>
<td>Dissolution</td>
<td>Yu et al., 2009</td>
</tr>
</tbody>
</table>

3.4.1. Equilibrium solubility

The results of the equilibrium solubility study of IBU in the presence of AGF and HPMCK3 polymer are presented in Figure 3.2.
The equilibrium solubility of the neat IBU in 0.1 N HCl was 0.037 mg/mL. AGF polymer enhanced the solubility of IBU at all concentrations of the polymer ranging from 0% to 3% (w/v). HPMCK3 did not enhance the solubility of IBU with an increase in HPMCK3 concentration.

Compared to HPMCK3, AGF showed a statistically significant increase in the equilibrium solubility of IBU. The gel forming ability of the HPMCK3 could have reduced the diffusion of IBU as discussed by Dabbagh et al. (2007) (Dabbagh et al. 2007). Drug solubility at a high carrier concentration (>0.4%) was lower than expected because of increased viscosity (Amit K et al., 2011). Very low viscosity of the AGF solution at comparatively high concentrations enabled determination of the increase in solubility at concentrations of AGF as high as 3%.

Figure 3.2 Solubility of IBU in presence of AGF/HPMCK3 solutions
IBU solubility showed a linear increase with an increase in the concentration of AGF. The $R^2$ value of 0.9854 suggests the solubility curve of Higuchi’s type $A_L$ (Higuchi and Connors, 1965). Choudhari and Sanghvi. (1993) observed a similar Higuchi Type A curve for diazepam-pullulan system (Choudhari and Sanghvi, 1993). The value of the slope is less than 1. This implies the possibility of formation of an IBU-AGF soluble complex (Higuchi and Connors, 1965). A similar phase solubility behavior of IBU was observed in the presence of poloxamer 188 (Nawa et al., 2007) and in the presence of $\beta$-cyclodextrin (Ghorab and Adeyeye, 2001). A linear increase in solubility was observed for valdecoxib-PVP 30 systems and for furosemide-HPMCE50 LV systems (Modi and Tayade, 2006; Raval et al., 2010).

The formation of in solution IBU-AGF water-soluble complex and increased IBU wetting because of the hydrophilic nature of AGF could be the reasons for the observed solubilizing effect of AGF. In addition, enhanced wetting reduces aggregation of drug particles, which results in high solubility (Rajebahadur et al., 2006). Formation of intermolecular complexes of AGF with diazepam, medazepam, indomethacin, azlaeptin, and the biologically active compound dihydroquercetin (DQ) resulted in a significant increase in solubility (Dushkin et al., 2008; Medvedeva et al., 2010).

Mere presence of AGF at a concentration of 3% increased the solubility of IBU by 7.3-fold. Further, a similar experiment using a coground mixture of IBU and AGF showed ~18 fold increase in IBU solubility at an IBU:AGF ratio of 2:8 (Appendix Figure C.1). The 1:9 (IBU:AGF) coground mixture would show a more than 18-fold increase in IBU solubility. The IBU:AGF mixture (1:10) prepared using a rotary ball mill increased the
IBU solubility by 28 fold (Dushkin et al., 2012 and Chapter 1, Table 1.7). The IBU-AGF SDs are expected to enhance the solubility substantially.

3.4.2. Solid dispersions preparation methods

Various methods were attempted (Appendix B). Solvent methods were modified to use water as a solvent because of unavailability of common solvent for the AGF polymer and IBU. Finally, the IBU-AGF microsphere solid dispersion (MSD) and IBU-AGF SDM prepared using modified solvent evaporation method (SDM) were found the optimum formulations to form amorphous IBU and enhance the IBU dissolution (Appendix Figure B.11).

The MSD and SDM preparation techniques used for preparing the IBU-AGF SDs, involved processing temperature near the melting temperature of the neat IBU. Molten IBU globules were observed during the preparation. Thus, the SD processing techniques used were the combination of melt and solvent evaporation to obtain the amorphous IBU. Li and Yao.(2009) reported similar melt and solvent method to prepare the SD.

The fastest dissolution correlated with the formation of amorphous IBU in the SD and the tightly held porous matrix structure of the SD. The spray-dried SD (SPRDY) did not increase the dissolution of IBU even in the presence of amorphous IBU. The nonporous structure of the inner phase solid dispersions (IPSD) and freeze-dried formulation (FRZD) did not enhance IBU dissolution (Appendix Figure B.10).

Therefore, this entire chapter is focused on the IBU-AGF SD prepared using emulsion solvent evaporation technique (MSD) and modified solvent evaporation techniques (SDM).
The free flowing, spherical microspheres were obtained for IBU-loaded AGF MSD at all DLs as shown in SEM microphotographs (Figure 3.11). Additional IBU-AGF MSD batches with a DLs of 40%, 50% and 75% were prepared. The low encapsulation efficiency made exclusion of them from further investigation (Appendix Table C.1). The hydrophobic drug has an affinity to the outer oily phase. The viscous inner phase prevented partitioning of the hydrophobic IBU into the outer oily phase after emulsification. However, partitioning of IBU in the outer phase increased as the theoretical DL increased. The encapsulation efficiencies of IBU-AGF MSDs with a DL of 10%, 20%, and 30% were above 80%, and the yield was above 58% (Appendix Table C.1).

HPMCK3 was used at a concentration of 14-18% to prepare IBU-HPMCK3 MSD because of its colloidal and the gel forming nature. HPMCK3 formed free flowing, spherical IBU-loaded microspheres with very low encapsulation efficiency (less than 4%). The repetitive batches of HPMCK3 MSD prepared with a 10% DL did not result in encapsulation efficiency higher than 7%. HPMCK3 did not result in the incorporation of IBU into the microspheres.

HPMC did not dissolve in water at a given concentration, but it dispersed out as colloidal solution. Further, it did not form a consistent thick viscous inner phase similar to that formed by AGF polymer. Therefore, the drug partitioned into the outer oily phase, which resulted in very low encapsulation efficiency. Therefore, we did not perform further evaluations of the IBU-HPMCK3 MSD formulations.

The SDMs were obtained as free flowing porous IBU-AGF matrices (off-white in color) (Figure 3.12 and 3.13). HPMCK3 SDM were formed as nonporous and hard to
pulverizable matrices (Figure 3.15). The revised method yielded IBU-AGF SDMs having properties similar to those of the SDMs prepared using the above method (Appendix Figure C.3 and Figure C.4). A drying time of 45 min to 2 h was required to obtain the dried mass using SDM method. The PMs were white colored powders (Figure 3.14).

3.4.3. DSC and XRPD

The DSC thermogram of neat IBU showed an apparent endothermic peak at 76.56 °C which represents the melting point of crystalline IBU. This sharp IBU peak was not observed in 10 IBU AGF MSD and 20 IBU AGF MSD, which suggested the loss of crystallinity of IBU in these MSDs.

![Figure 3.3 DSC thermograms of IBU-AGF MSDs](image)

Figure 3.3 DSC thermograms of IBU-AGF MSDs
However, a small amount of IBU was present in the crystalline form in 30 IBU AGF MSD formulation (Figure 3.3).

IBU was completely amorphous in 10 IBU AGF SDM and 20 IBU AGF SDM formulations. The 30 IBU AGF SDM formulations, on the other hand, retained some of the IBU in the crystalline form (Figure 3.4). The 10 IBU HPMCK3 SDM formed the amorphous SD, whereas partially crystalline IBU was present in 30 IBU HPMCK3 SDM formulation (Figure 3.4). All the PMs retained the crystalline form of IBU (Figure 3.5).

The depression in melting point was evident in the presence of the AGF polymer. The depression in melting point suggests stronger drug-polymer interactions (Paudel et al., 2012).

Figure 3.4 DSC thermograms of IBU-AGF SDMs and IBU-HPMCK3 SDMs
Figure 3.5 DSC thermograms of IBU AGF PMs and IBU HPMCK3 PMs

The X-ray diffractograms of IBU-AGF MSDs, IBU-AGF SDMs and IBU-AGF PMs are shown in Figure 3.6, 3.7 and 3.8 respectively. The XRPD diffraction pattern of neat IBU showed high-intensity peaks at 6.1°, 12.2°, 16.7°, 17.8°, 19° and 22.3° (2θ). These diffraction peaks, which are attributed to the crystallinity of IBU, were present in all IBU AGF PMs. XPRD diffraction patterns of 10 IBU AGF MSD and 10 IBU AGF SDM showed that IBU was in the amorphous form. IBU in 20 IBU AGF MSD and 20 IBU AGF SDM was almost amorphous. The diffractograms of 30 IBU AGF MSD and 30 IBU AGF SDM showed a partial loss of crystallinity of IBU. The XRPD diffractograms of 10 IBU HPMCK3 SDM showed that IBU was in the amorphous form (Figure 3.9).
Figure 3.6 XRPD diffractograms of IBU-AGF MSDs

Note: NEAT IBU; 10 IBU AGF MSD; 20 IBU AGF MSD; 30 IBU AGF MSD.

Figure 3.7 XRPD diffractograms of IBU-AGF SDMs

Note: NEAT IBU; 30 IBU AGF SDM; 20 IBU AGF SDM; 10 IBU AGF SDM; NEAT AGF.
The XRPD findings confirmed the findings obtained using DSC of conversion of crystalline IBU to its amorphous form in IBU-AGF SD. These findings are consistent with those reported by Moneghini et al. (2008); Xu et al. (2007); and Williams et al. (2005) about the formation of amorphous IBU SD. IBU-PVP VA64 SD at a 1:1 drug to polymer ratio treated at 600 W for 6 min was almost amorphous (Moneghini et al., 2008). DSC and XRD showed that IBU-Kollidon 30 and IBU-Kollidon VA 64 SDs were amorphous at a 1:5 ratio (Xu et al., 2007). IBU-PVPCL, IBU-MCC solvent deposited SD, and hot mixes were amorphous at 1:4 drug to polymer ratio (Williams et al., 2005).
Figure 3.9 XRPD diffractograms of IBU HPMCK3 formulations

Note - NEAT IBU; 10 HPMCK3 PM; 10 IBU HPMCK3 SDM; NEAT HPMCK3.

3.4.4. SEM

The SEM microphotographs of neat IBU, neat AGF, MSDs, SDMs and PMs are shown in Figure 3.10, 3.11, 3.12, 3.13, 3.14. In 30 IBU AGF MSD, crystalline IBU was present on the surface as well as inside the MSD as observed in the cross-section of these microspheres. The absence of IBU crystals in 20 IBU AGF MSD and in 10 IBU AGF MSD suggests completely amorphous IBU (Figure 3.11).

In addition, crystalline IBU was observed in 30 IBU AGF SDM. However, no crystalline drug was present in 10 IBU AGF SDM and 20 IBU AGF SDM, which suggests complete conversion of IBU to its amorphous form in these formulations. (Figure 3.12).
The SEM of a cross-section of the MSD and SDM showed the porous nature of the SD. The porosity may be because of the rapid evaporation of the solvent (Najmuddin et al., 2010). This finding is consistent with that reported previously by Elkordy and Essa (2010).

The PMs irrespective of the DL show the presence of crystalline IBU however in a micronized form. SEM of 10 IBU HPMCK3 SDM showed absence of crystalline IBU. Additionally, the HPMCK3 SDM was nonporous in nature (Figure 3.15).

These results are consistent with those reported by Xu et al. (2007) about the presence of IBU crystals in the PM and absence of IBU crystals in the SD in their respective SEM microphotographs (Xu et al., 2007). Thus, the SEM results further confirmed the DSC and XRPD findings of amorphous IBU at 10% DL and 20% DL and partially crystalline IBU at 30% DL.

![SEM microphotographs NEAT IBU and NEAT AGF](image)

**Figure 3.10** SEM microphotographs NEAT IBU and NEAT AGF

Note-A- Larch arabinogalactan FiberAid grade (AGF); B-Neat Ibuprofen.
Figure 3.11 SEM microphotographs of IBU-AGF MSDs

Note- A- 10 IBU AGF MSD; B-20 IBU AGF MSD and C-30 IBU AGF MSD (I-MSD; II-cross-section).
Figure 3.12 SEM microphotographs of IBU-AGF SDMs

Note-A-NEAT IBU; B-10 IBU AGF SDM; C-20 IBU AGF SDM; D-30 IBU AGF SDM.

Figure 3.13 SEM microphotographs of 10 IBU AGF SDM

Note-A -10 IBU AGF SDM; B-Cross- section of 10 IBU AGF SDM.
Figure 3.14 SEM microphotographs of IBU AGF PMs
Note-X-10 IBU AGF PM; Y-20 IBU AGF PM; Z-30 IBU AGF PM.

Figure 3.15 SEM microphotographs 10 IBU HPMCK3 SDM
Note-A-SDM; B-cross section.
3.4.5. FTIR spectroscopy

Figure 3.16 FTIR spectra of IBU-AGF MSDs
Figure 3.17 FTIR spectra of IBU-AGF SDMs
Figure 3.18 FTIR spectra of IBU AGF PMs
Figure 3.19 FTIR spectra of NEAT IBU and NEAT AGF
Figure 3.20 FTIR spectra of IBU HPMCK3 PM and IBU-HPMCK3 SDM
The FTIR analysis of the SDs and PMs were performed to elucidate whether the solid-state drug-polymer interactions were present as suggested by the depression in the melting point shown in DSC findings.

The neat IBU showed a sharp IR band associated with C=O stretching of dimeric IBU at 1708.7 cm\(^{-1}\) and another band at 2954 cm\(^{-1}\) associated with OH stretching (Figure 3.19). The major IR bands at 3300-3500 cm\(^{-1}\) associated with OH stretching, those at 2891.31 cm\(^{-1}\) associated with C-H stretching in CH\(_2\) and CH\(_3\), and those at 1590 cm\(^{-1}\) associated with carboxylate stretching were present in FTIR spectrum of neat AGF (Figure 3.19).
In this study, the IR spectrum of the PM was found to be the algebraic sum of the IR spectrum of the neat drug and of the neat polymer with nearly no shifts in the major IBU IR bands. The IR band at around ~1710 cm\(^{-1}\) was present in all the PMs, which suggested the presence of dimeric IBU (Figure 3.18).

The C=O stretching band of IBU was shifted to a higher wave number in SDM, MSD by a value of 4 cm\(^{-1}\) to 10 cm\(^{-1}\). The IR band of OH group (AGF polymer) showed corresponding shifts in MSD and SDM formulations (Figure 3.16 and Figure 3.17). Thus, blue shift in C=O of IBU and a shift in OH of AGF was associated with the solid-state hydrogen bonding between IBU and AGF polymer. Thus, complete disruption of IBU dimer hydrogen bonding and formation of solid-state hydrogen bonds between IBU and AGF led to the IR band at a higher wave number. Hydrogen bonding between C=O groups of IBU and OH group of HPMC has been reported by Nakayama et al. (2009).

The IR band at 1716-1717 cm\(^{-1}\) was observed in the SDM formulations irrespective of the drug polymer ratio. The IR band was observed at ~1719 cm\(^{-1}\) in MSD formulations irrespective of the drug polymer ratio. This observation further suggested that the entire IBU formed a hydrogen bond with the OH group of the polymer. The IR band associated with the crystalline IBU dimer was absent in IBU-AGF SD unlike the findings by Ali et al. (2010). The investigator discussed in detail how the excess crystalline IBU resulted in the IBU dimer band in addition to the hydrogen bonded IBU IR stretching band (Ali et al., 2010). This observation contradicts our finding of the presence of crystalline IBU in 30 IBU AGF SDM and 30 IBU AGF MSD. Thus, unlike that in other studies (Ali et al., 2010; Crupi et al., 2011), amorphization of IBU observed in our study was not based only on solid-state hydrogen bonding between the IBU and AGF polymer. Ali et al. (2010)
observed a blue shift in the IR band at 1734 cm\(^{-1}\) in IBU-poloxamer SD similar to that observed for the IBU-AGF SD in the current investigation.

The carboxylate stretching band of AGF (1590 cm\(^{-1}\)) shifted in SDM, MSD, and PM, which indicated a modified environment because of hydrogen bonding. The shift in the IR band at 2954 cm\(^{-1}\) because of OH stretching of the IBU was of less magnitude (1 cm\(^{-1}\) to 2 cm\(^{-1}\)) (Appendix Table B.2). Therefore, the possibility of solid-state intermolecular hydrogen bonding between the COO\(^-\) of the AGF (1590 cm\(^{-1}\)) and OH group of the IBU (2954 cm\(^{-1}\)) is minimal. The natural AGF polymer usually has few carboxylic acid groups (Ehrenfreund-Kleinma et al., 2002; Mudarisova et al., 2008). The intramolecular hydrogen bonding between the OH group and the COO\(^-\) group of the AGF polymer, however, could be possible. Further, the steric hindrances may preclude the formation of a hydrogen bond between OH groups of the drug and C=O groups of the polymer. Thus, extensive hydrogen bonds were formed between the C=O group of IBU and OH group of AGF in IBU-AGF SD.

Shifts in the IR bands of the C=O group of IBU and OH group of HPMCK3 showed the presence of solid-state hydrogen bonding in 10 IBU HPMCK3 SDM and 30 IBU HPMCK3 SDM formulations (Figure 3.20 and Figure 3.21). These findings are similar to those reported in the literature (Nakayama et al., 2009).

The presence of solid-state hydrogen bonding suggests the presence of IBU in the AGF matrix as a dispersion rather crystalline or molecular clusters at least up to a 20% DL (Shah et al., 2012). Similarly, the presence of hydrogen bonding in IBU SD was associated with the amorphization of IBU in these formulations up to a 20% DL. The presence of hydrogen bonding with the loss in crystallinity of IBU (by DSC and XRPD)
was reported in the IBU-PVP CL system (Rawlinson et al., 2007), IBU-Kollidon system (Xu et al., 2007), IBU-Kaolin system (Mallick et al., 2008), and IBU-poloxamer systems (Ali et al., 2010).

3.4.6. TMA

TMA was used to measure the Tg of the IBU-AGF SDM formulations. TMA measures the dimensional changes as a function of temperature (Gabbott, 2007). The TMA spectrum of the SDM formulations are shown in Figure 3.22. The 10 IBU AGF SDM formulation showed a single Tg (78.14 °C) which indicated that the IBU and the AGF were miscible and homogeneously mixed at the molecular level. The TMA scans of 20 IBU AGF SDM showed 2 thermal events (58.03 °C and 83.88°C). The first one was the melting of crystalline IBU, and the second one was the Tg of the binary dispersion where the drug was molecularly dispersed into the amorphous AGF matrix. Three transitions at 63.67 °C, 79.54 °C and 124.49 °C were observed for 30 IBU AGF SDM. The first transition was the melting of the crystalline IBU which was also observed in the 20 IBU AGF SDM formulations. The second and third transitions corresponded to the Tg’s of the IBU-AGF dispersion. Thus multiple phases were present in 20 IBU AGF SDM and 30 IBU AGF SDM formulations which suggested that these systems were immiscible. However phase separation was less pronounced in 20 IBU AGF SDM compared to that in the 30 IBU AGF SDM.
Thus, the DSC and XRPD data were consistent with the TMA data of the presence of crystalline IBU at 20% and 30% DL. A previous study has shown concomitant presence of Tg of molecularly dispersed drug-polymer domain and Tm of crystalline drug-rich domain. The investigators performed localized TMA scan using microthermal analysis of the 20% DL of paracetamol-Eudragit HME SD (Qi et al., 2008). Such heterogeneity in the solid-state of carbamazepine-HPMC SD at 50% DL was reported by Zhang et al. (2009) (Zhang et al., 2009).
Table 3.2 Experimental and theoretical Tg of IBU-AGF SDMs

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Experimental Tg/ Thermal Transition (°C)</th>
<th>Predicted Tg (°C) (Fox equation)</th>
<th>Predicted Tg (°C) (Couchman-Karasz equation)</th>
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<tr>
<td>NEAT IBU</td>
<td>-45 (Tg) (Dudognon et al., 2008) and 78.09 (Tm)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 IBU AGF SDM</td>
<td>78.14 (Tg)</td>
<td>58.38</td>
<td>72.67</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>58.03 (Tm); 83.88 (Tg)</td>
<td>46.26</td>
<td>63.92</td>
</tr>
<tr>
<td>30 IBU AGF SDM</td>
<td>63.67 (Tm); 79.54 (TgI); 124.49 (TgII)</td>
<td>31.02</td>
<td>52.52</td>
</tr>
<tr>
<td>AGF</td>
<td>82 (Tg)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note- ∆Cp for Couchman-Karasz equation was obtained from mDSC data of neat drug and neat polymer. For IBU ∆Cp₁=0. 43J/g °C; For AGF ∆Cp₂=0. 61 J/g °C.

The Couchman-Karasz (CK) and Fox’s equation were used to predict the Tg of the IBU-AGF SDM. Two models were selected because the first one is the commonly used model for the prediction of the Tg for the two-component system. The second CK model has been used previously for an accurate prediction of the experimental Tg of the SDs (Forster et al., 2003). The predicted Tg values and experimental Tg values are listed in Table 3.2.

The CK model accurately predicted the experimental Tg for 10 IBU AGF SDM. Forster et al. (2003) reported similar comparable values of Tg obtained using experimental methods and that obtained using the CK model for indomethacin-PVP, nifedipine-PVP, and tolbutamide-PVP system (Forster et al., 2003).
At 20% DL and 30% DL, Tg values deviated from those obtained using the CK model and Fox’s predicted value. The difference of more than 20 °C could not be explained only by experimental uncertainty. A positive deviation in Tg is common when strong interacting components are present (Pinal et al., 2008; Scheider, 1989). Huang et al. (2003) observed such a deviation in the single Tg from that in the Fox’s equation in PMMA and PMAA blend (Huang et al., 2003). Thus, the positive deviation in the Tg values can be attributed to the stronger solid-state hydrogen bonding between IBU and AGF (FTIR spectroscopy findings).

Usually, the Tg of the SD is between the Tgs values of the individual components (van Drooge et al., 2006). However, the Tg of the SDM formulations was close to the Tg of the neat AGF. In 20 IBU AGF SDM and 30 IBU AGF SDM, Tg at around 80 °C was because of the IBU AGF molecular dispersion domain. It is unlikely that the Tg at 80 °C in 20 IBU AGF SDM was because of the polymer rich domain. Thus, in 10 IBU AGF SDM, one would expect another Tg value for the molecular dispersion of the amorphous drug into the AGF polymer. Our DSC, XRPD, and FTIR spectroscopy results confirmed the presence of amorphous SD at this DL. Whereas the second Tg at 124.49 °C in 30 IBU AGF SDM could be because of the polymer rich domain. Thus, the Tgs values of the heterogeneous system were well above the Tg values of the individual components (-45 °C for IBU and 82 °C for AGF) for 20 IBU AGF SDM and 30 IBU AGF SDM.

This upward shift in the Tg with an increase in the DL (20 DL < 30 DL) was expected considering crystalline drug in these formulations. Puadel et al. (2012) observed similar upfield shifts in the Tg at 40% DL compared to that at 10% DL, 20% DL, and 30% DL. They attributed this shift to the presence of the crystalline drug in this formulation.
(Paudel et al., 2012). At high DL, non-homogenous distribution of the drug results in an increase in excess volume of mixing and a high degree of crystallization. On the other hand, ordered crystalline drug domain imposes steric hindrances to the polymer chain in the vicinity of the crystalline domain. This results in an increase in the Tg by counterbalancing the excess volume effect (Kalogeras et al., 2011).

In addition, the upfield shifts in the Tg of the formulation are indicative of the strong anti-plasticizing effect of the polymer (Huang et al., 2008). Thus, the presence of hydrogen bonding, presence of crystalline IBU, and strong anti-plasticizing effect of the AGF polymer result in an upward shift in the Tg in the current investigation.

In summary, the results of the TMA study showed that IBU and AGF were miscible at 10% DL SD whereas were immiscible at and above 20% DL. The miscibility limit is between 10-20 % DL. The miscibility limit of the IBU AGF SD is most likely ~17.5% (Appendix Figure C.5) which should be confirmed by performing TMA or mDSC analysis of 12.5 % DL, 15 % DL and 17.5 % DL IBU-AGF SD.

A combination of techniques was used for solid-state characterization of IBU-AGF SD. The results of DSC, XRPD, SEM, FTIR spectroscopy and TMA complemented each other. The results of these studies showed a decrease in the crystallinity of IBU because of the AGF polymer. The loss in IBU crystallinity can be attributed to the ability of AGF to change the state of the crystalline IBU because of its amorphous nature. Additionally, the process of manufacturing a SD played a role in the loss of crystallinity. A similar effect of the process was observed by Elkordy and Essa, (2010). They reported that the spray-dried formulation reduced the crystallinity of IBU and spray-chilled formulation retained the crystallinity of IBU in the IBU-poloxamer SD (Elkordy and Essa, 2010). The
mechanochemical treatment resulted in the amorphization of DQ in the DQ-AGF complex as confirmed by XRPD was reported previously (Medvedeva et al., 2010).

3.4.7. Proton nuclear magnetic resonance

The solubility study suggested formation of water-soluble IBU-AGF complexes in solution. To further understand the IBU-AGF interactions in the solution state, the proton nuclear magnetic resonance (\(^1\)H-NMR) investigations were performed. The nature of the drug-carrier interactions of the SD (Yu et al., 2011; Guedes et al., 2011; Abu-Diak et al., 2011; Yu et al., 2011) and of the binary mixture (Krupa et al., 2010) were successfully elucidated by solution-state \(^1\)H-NMR. These studies focused mainly on the chemical shift in proton resonances, which were involved in hydrogen bonding.

The NaOD solution (in D\(_2\)O) was used as a NMR solvent because D\(_2\)O alone did not produce a \(^1\)H-NMR spectra of neat IBU with good resolution. The \(^1\)H-NMR spectra of neat IBU, neat AGF polymer, and the IBU AGF formulations obtained in D\(_2\)O/NaOD are shown in Figures 3.23, 3.24, and 3.25. Their corresponding peak resonances are listed in appendix (Appendix Table C.2).

The \(^1\)H-NMR spectra was acquired with sharp peaks and good resolution. All the spectra showed a solvent peak at around 4.8 ppm because of D\(_2\)O (Kaassis et al. 2012 Abstract and http://www.isotope.com/uploads/File/NMR_Solvent_Data_Chart.pdf).
Figure 3.23 $^1$H-NMR spectra overlay of IBU-AGF MSDs

Figure 3.24 $^1$H-NMR spectra overlay of IBU-AGF SDMs
The $^1$H-NMR spectra of neat IBU obtained in our study was similar to that reported in previous studies (Al-Omari et al., 2009; Ghorab and Adeyeye, 2001; Mizrahi et al., 2009) with similar integration assignment (Qandil et al., 2009); except that the COOH proton resonance at 11.6 ppm was absent in the $^1$H-NMR spectra of neat IBU. This finding suggests that the proton in the COOH group is in chemical exchange with other COOH group forming the dimer form of IBU or in chemical exchange with a residual OH group of the water molecule (Fatnassi et al., 2012).

The $^1$H-NMR spectra of the AGF polymer obtained in our study is consistent with that reported previously (Ponder and Richards., 1997). The resonance of interest in the AGF polymer was the broad peak at around 6.1 ppm. This broad peak is attributed to the proton from the OH group of the AGF polymer (Ponder and Richards, 1997).
The $^1$H-NMR spectra of IBU AGF PMs (Figure 3.25) showed the characteristic signals of IBU proton resonances nearly at the same chemical shift as those of neat IBU. The signal of AGF OH resonance was present in all PMs with equal intensity. This indicates that the PM did not initiate any interactions in the solution-state.

The $^1$H-NMR spectra of MSD at 10 DL showed an upfield shift in the IBU proton H1, H2, H3, H4/H6, H5/H7, and H9. In addition, the hydroxyl resonance of AGF at 6.1 ppm was absent. On the other hand, compared to neat IBU, MSD formulations with 20% and 30% DL did not show a significant chemical shift in the proton signal. This finding indicates comparatively weaker interactions in these formulations.

Compared to neat IBU, the SDM showed chemical shifts. The upfield shifts were observed for all IBU protons (H1, H3, H2, H9, H4/H6, H5/H7 [except H8 proton]). The 6.1 ppm resonance representing the hydroxyl proton of AGF was completely absent in SDM formulations which suggested that the solution-state interactions were present in IBU AGF SDMs.

Overall, the shift in the hydroxyl resonances of AGF in the SD formulations implies solution-state hydrogen bonding between the C=O group of IBU and the OH group of AGF in IBU-AGF formulations. Further, $^{13}$C-NMR will provide an insights into the solution-state hydrogen bonding between IBU and AGF.

The upfield shifts of H1, H3, H2, H9, H4/H6, and H5/H7 protons in SDMs and 10 MSD formulations suggest an interaction between the aromatic, methyl, and isopropyl group of IBU and the hydroxyl group of AGF in the solution-state. Hydrophobic interactions similar to those mentioned above were observed between the benzene ring of IBU and PVP CL carrier in their PMs (Rawlinson et al., 2007).
Additionally, the $^1$H-NMR spectra of IBU-AGF formulations did not show broadening, which indicated that the process used for manufacturing SDs did not alter the AGF polymer. Broadening was observed in 5-aminosalicyclic acid-oxidized AG complex, which had a higher concentration of carboxyl group in the AG (Mudarisova et al., 2012). Interestingly, a new triplet from 0.8324 ppm to 0.9195 ppm was observed in SDM formulations irrespective of the DL. The triplet was most likely given by the residual ethanol in the SDM formulations. Cao et al. (2011) observed the triplet at 0.90 ppm and quartet at 3.5 ppm because of ethanol in the freeze-dried samples (Cao et al., 2011). Anick et al. (2004) observed NMR resonances corresponding to the ethanol contaminant at 1.17 ppm and quartet at 3.65 ppm in homeopathic remedies (Anick et al., 2004). This residual ethanol quartet was overlapped by the IBU quartet at 3.58 ppm in the current investigation.

Thus, the $^1$H-NMR study results showed the presence of solution-state IBU-AGF interactions in IBU-AGF SDs.

3.4.8. *In vitro* dissolution of IBU-AGF SD and IBU-AGF PM

An appropriate dissolution method should be able to differentiate between the effect of formulation and processing variables on the dissolution of IBU from IBU-AGF SDs. However, evaluation of an appropriate dissolution method for the intended purpose was the most challenging part of this study.

The intrinsic dissolution method was attempted. Although, the compacts of IBU AGF formulations were obtained without any difficulty, the pellets became uneven in the dissolution media. Thus, the standard intrinsic dissolution method (Woods apparatus) and
stationary disk inverted die intrinsic dissolution method did not provide satisfactory results (Appendix D).

Therefore, performing the dissolution study with the basket method was investigated next. The basket would provide a place where the dissolution media would come in contact with the formulation without significant agitation compared to the paddle method. The first experiment in this direction was conducted using the standard 40 mesh basket. However, because of the large pore size, the particles leached out of the basket pores immediately and satisfactory dissolution profiles were not obtained, especially in the case of SDs with 10 DL. Therefore, 270 mesh basket was used next. Although pore size was small, no clogging was observed during the experiments. Park et al. (2009) used the basket method to investigate the dissolution profile of IBU-HPMC-Poloxamer SD (Park et al., 2009). Adeyeye and Price (1994) constructed and successfully used 100 mesh screen basket to perform dissolution studies of microspheres. They mentioned that the microspheres were floating in the dissolution media (Adeyeye and Price, 1994).

We used 0.1 N HCl as a dissolution medium to mimic the gastric pH and to allow greater discrimination in the dissolution profiles of IBU-AGF SDs and to evaluate the effect of the formulation and processing on IBU dissolution. Phosphate buffer, pH 7.2, did not yield discriminatory dissolution profiles among the formulations (Appendix Figure C.2).

Thus, the optimized dissolution method included a rotating basket method (USP I), 270 mesh size basket, 0.1N HCl dissolution medium, 900 mL dissolution medium volume, and 100 rpm rotating speed.

The dissolution study was performed under non-sink conditions. The non-sink condition is a discriminating tool to evaluate the impact of formulation and processing parameters

The mean (n = 3) dissolution profiles of the IBU-AGF MSDs, IBU-AGF SDMs and IBU-AGF PMs are shown in Figure 3.26. The similarity factor ($f_2$) between the dissolution profiles was not calculated because more than 85% IBU released within 15 min at 10% DL SDs (USP Chapter 1092; Shah et al http://www.dissolutiontech.com/DTresour/899Art/DissProfile.html; Shah et al., 1998).

Statistical analysis showed that the dissolution of 10 MSD, 20 MSD, 30 MSD, 10 SDM, 20 SDM formulations, and 10 PM was significantly faster than that of neat IBU. The dissolution of IBU was significantly higher from 10 MSD formulations than in all PMs and 30 SDM formulation. The dissolution profiles of each of the 20 MSD and 30 MSD formulations were statistically equivalent to those of 10 PM. The dissolution profiles of each of the 20 MSD and 30 MSD formulations were significantly greater than the individual dissolution profiles of 20 PM and 30 PM, respectively. The dissolution of 10 SDM and 20 SDM formulations was significantly greater than that of 30 SDM formulation. The dissolution profiles of PM were statistically equivalent.

Thus, the order of IBU release with respect to the DL was 10% DL > 20% DL > 30% DL for MSD, SDM, and PM.
The enhanced dissolution of IBU from MSD and SDM formulations can be attributed to drug amorphization and solution-state interactions. Although IBU was present in the amorphous form in MSD and SDM formulations, as it goes into solution, it may convert to the crystalline form with time. Therefore, solution-state interactions were necessary to maintain the supersaturation and to enhance the IBU dissolution. The oven-dried granules of IBU and β-cyclodextrin showed complexation upon dissolution in the solution-state NMR study (Ghorab and Adeyey, 2001).

The wetting effect of the AGF polymer could be the other auxiliary mechanism that led to the dissolution enhancement. The decreased dissolution in 30 IBU AGF SDM and 30
IBU AGF MSD formulations was expected because these formulations contained crystalline IBU. Janssens et al. (2008) reported decreased dissolution at a higher DL in 40% itraconazole-HPMCE5 SD (Janssens et al., 2008).

Formation of amorphous IBU, which results in dissolution enhancement has been reported in IBU-Kollidon SD (Xu et al., 2007), IBU-PVPCL SD, IBU-MCC SD (Williams et al., 2005), IBU-kaolin SD (Mallick et al., 2008), IBU-PVP SD (Moneghini et al., 2008), IBU-microcrystalline chitosan SD (Bodek, 2002), IBU-Mesoporous SBA-15 SD (Shen et al., 2009), and IBU-PVP electrospun SD (Yu et al., 2009) systems. Elkordy and Essa, (2010) attributed the remarkable dissolution enhancement in IBU-poloxamer 127 spray-dried microparticles to the decrease in the crystallinity of IBU (Elkordy and Essa, 2010).

At a SD with 20% DL, dissolution enhancement was observed even when the system was not homogeneously miscible. Six et al., (2003) reported a similar observation of increase in ITRA dissolution from ITRA-HPMC HME in the absence of a homogenous system (Six et al., 2003).

The combined action of the particle size reduction, solubilization, and wetting effect of AGF may be responsible for the dissolution enhancement in IBU AGF PM. The investigators attributed the dissolution enhancement of diazepam-pullulan PM to the wetting effect of the polymer and the ability of the polymer to reduce the agglomeration of diazepam particles (Choudhari and Sanghavi, 1993). Furthermore, a better dispersibility of IBU in the AGF polymer may have contributed to the dissolution enhancement in the PMs. Enhanced dissolution of a co-grounded mixture of valdecoxb
and PVP K30 (Modi and Tayade, 2006) and diazepam-pullulan (Choudhari and Sanghavi, 1993) was attributed to the better drug dispersibility.

The relative standard deviation (RSD) values of MSD dissolution profiles were 11–14% at the earliest time point and ranged from 3% to 8% at the later time points. The %RSD of SDM was 8–18% and less than 7% at initial time points and at later time points, respectively. On the other hand, initial time point % RSD values were 11% (20PM) and 19% (30PM) for the PM.

To date, very few studies have discussed the %RSD of dissolution profiles of SDs. The homogeneity of release among triplicates of SDs with %RSD values below 5% have been reported in a study in which the paddle method was used (Karavas et al., 2001). On the other hand, %RSD value as high as 10.29% at the earlier time point (5 min) was observed for rimonabant SD using the paddle method at 50 rpm (Hurtado et al., 2012).

The high %RSD in our study was expected because of the use of the basket apparatus with a 270-mesh size. Compared to the paddle method, the basket method yields higher %RSD values (Qureshi and McGilveray, 1999). Further, dissolution testing of a marketed product had a %RSD value as high as 37% (Qureshi and McGilveray, 1999). We observed the highest %RSD value of 19% for the IBU-AGF PM. There is a possibility that aggregation might have occurred in the PMs. In addition, the high %RSD value could suggest that the IBU content is not uniform across the SD.

The dissolution profiles of the IBU SD reported by Mallick et al. (2008) (IBU-Kaolin milled system), Yu et al. (2009) (IBU-PVP electrospun fibers SD), Park et al. (2009) (IBU-HPMC poloxamer), Newa et al. (2007) (IBU-poloxamer), and Moneghini et al.
(2008) (IBU-PVP) showed standard deviation in the similar range as that observed in our study.

Greater than 85% IBU was released in less than 15 min from 10 IBU AGF SD, classifying this formulation under immediate release type. The %RSD values of 20% (the initial time point) and 10% (latter time point) are forgiving for immediate release formulations (USP Chapter 1092).

3.4.9. In vitro dissolution of IBU-AGF formulation versus IBU-HPMCK3 formulations

The mean in vitro dissolution profiles of PM (Figure 3.27) and SDM (Figure 3.28) prepared with AGF and HPMCK3 polymer were compared to evaluate the dissolution enhancement potential of these 2 carriers for IBU. We selected 10% and 30% DLs as the lowest and highest DLs among the 3 DLs selected for the investigations.

Figure 3.27 Mean in vitro dissolution profiles of IBU AGF PMs and IBU HPMCK3 PMs
The dissolution profiles of all PMs were statistically equivalent. The dissolution of 10 AGF PM was found significantly higher than that of neat IBU. However, the dissolution profiles of neat IBU, 10 HPMCK3 PM, 30 AGF PM, and 30 HPMCK3 PM were statistically equivalent.

Statistical analysis of the dissolution data up to 30 min indicated that 10 IBU AGF PM showed a significantly faster initial dissolution rate than 10 IBU HPMCK3 PM. After 40 min, the IBU dissolution increased in the 10 IBU HPMCK3 PM; however, the dissolution was constantly slower than that of 10 IBU AGF PM. This was expected considering the substantially high viscosity of HPMCK3 carrier compared to that of AGF. At this high polymer load, HPMC would form a hydrocolloid gel mass on its external surface and thus retarding the diffusion and release of the IBU in the dissolution medium. Papageorgiou et al. (2008) observed that the release of fluconazole was slower from HPMC SD than from PVP SD at 10% DL (Papageorgiou et al. 2008). Additionally, the high viscosity of the solution here may have led to coalescence of the micronized IBU particles in the IBU-HPMCK3 PM.

With an increase in the DL to 30%, the dissolution profiles of the IBU AGF PM and IBU HPMCK3 PM were comparable. In fact, after 30 min, the 30 IBU HPMCK3 PM showed a higher dissolution rate. It was obvious that at a 30% DL, HPMC required 30 min to get into the solution and exert its solubilization effect to enhance drug dissolution.
The dissolution profiles of 10 IBU AGF SDM and 10 IBU HPMCK3 SDM were statistically equivalent. However, the order of dissolution was 10 IBU AGF SDM > 10 IBU HPMCK3 SDM. The dissolution of 30 IBU HPMCK3 SDM was greater than that of 30 IBU AGF SDM.

The enhanced dissolution from 30 IBU HPMCK3 formulation could be because of 2 mechanisms. Compared to the AGF polymer, HPMCK3 might enhance IBU wetting and dispersibility because of its surfactant property (Mitchell et al., 2003; Machiste et al., 1996; Nazareth et al., 1969 Part I; Nazareth et al., 1961 part II). The microenvironment in which HPMCK3, HPMCE3, and HPMCE5 remained in close proximity to the poorly soluble drug and enhanced their dissolution by exerting its surfactant effect has been discussed earlier (Mitchell et al., 2003).
Another mechanism of this observed difference could be the difference in the precipitation inhibition potential of these 2 carriers. The ability of the polymer to maintain the drug in a supersaturated state has a profound effect on drug dissolution (Tajarobi et al., 2011). Compared to AGF, HPMCK3 may exert a better inhibitory effect on the precipitation of IBU from the supersaturated solution once the amorphous IBU dissolves in the dissolution media creating super saturation.

Suzuki and Sunada. (1998) reported that the inhibition of nifedipine precipitation from a supersaturated solution was greater in the presence of HPMC than that of pullulan. AGF may fall into the category of xanthan gum and locust gum, which are inferior to HPMC in inhibiting drug precipitation from a supersaturated solution (Warren et al., 2010). A detailed study should be performed to evaluate the potential of the AGF polymer to inhibit precipitation of IBU from a supersaturated solution similar to that performed by Konno et al. (2008) (Konno et al., 2008).

Another possible explanation of the greater dissolution effect of HPMCK3 than of AGF at 30% DL is that the AGF polymer is hydrophilic in nature whereas HPMC possesses intermediate hydrophobicity. HPMC showed marked inhibition of crystal growth because of its intermediate hydrophobicity on the hydrophilic-hydrophobic scale (Ilevbare et al., 2012). Similarly, HPMC, which is more hydrophobic than PVP (Chen et al., 2012) inhibited felodipine precipitation a greater extent in SD systems (Alonzo et al., 2011).

It is important to note that HPMCK3 enhances IBU dissolution only when the solution viscosity barriers are crossed at and above 30% DL. Thus, below 30% DL, AGF polymer was better to enhance the dissolution of IBU.
The HPMC grade commonly used for SD preparation is HPMCE5 2910 (Janssens et al., 2008; Six et al., 2005; Six et al., 2003; Six et al., 2003; Park et al., 2009; Brewster et al., 2004). HPMC grade 2910 has a higher solution viscosity than HPMCK3 grade used in this study. Methocel cellulose ethers in aqueous systems for tablet coating (http://www.dow.com). Therefore, it is expected that 10 IBU AGF SDM and IBU HPMCE5 SDM would have a marked difference in the dissolution rate of a poorly water soluble drug. Thus, AGF would be a better polymer to enhance the dissolution of poorly water-soluble drugs at a low DL from the SD system.

3.5. Summary and Conclusions
The larch arabinogalactan (FiberAid grade) AGF polymer was evaluated as a carrier for preparation of SD and dissolution enhancement of the poorly water-soluble drug IBU. The current study showed a 7.3-fold increase in IBU solubility at 3% (w/v) AGF concentration. The water-in-oil emulsion solvent evaporation and modified solvent evaporation technique were the most effective techniques to obtain amorphous SD and enhance the IBU dissolution. The AGF SDs were highly porous and free flowing powders. The HPMCK3 SDs were obtained as nonporous and hard to pulverize matrices. Solid-state characterization of the SD showed formation of an amorphous SD up to nearly 20% DL. The IBU-AGF SD showed solid-state hydrogen bonding between IBU and AGF. The IBU-AGF SDM was found miscible up to 10% DL and had one Tg. Solid-state characterization of the SD prepared with HPMCK3 showed formation of an amorphous dispersion at 10% DL. The 30 IBU-HPMCK3 SD showed the presence of partially crystalline IBU.
The solution-state interactions were present between IBU and AGF. These solution-state interactions resulted in increased IBU solubility. The dissolution of IBU was found significantly faster from the IBU-AGF SD at 10% DL and 20% DL than that from neat IBU, which released 50% of IBU in less than 5 and 8 min, respectively. The dissolution was faster from the SD than from the respective PMs.

The dissolution profiles of 10 IBU-AGF SDM and 10 IBU-HPMCK3 SDM were comparable; however, the percentage of drug dissolved was higher from the former formulation than that from the later. The dissolution rate of 10 IBU-AGF PM was significantly higher than that of 10 IBU-HPMCK3 PM up to 30 min.

Overall, the AGF SDM was superior to HPMCK3 SDM at 10% DL in terms of porosity, pulverability, and the rate of increase in dissolution. At 30% DL, although both the SDMs contained crystalline drugs, the dissolution was higher from the HPMCK3 SDM. Further studies should be performed to determine the precipitation inhibition potential of the AGF polymer for IBU and the stability of the amorphous IBU-AGF SD.
CHAPTER 4
THE EVALUATION OF DISSOLUTION ENHANCEMENT OF ITRAFONAZOLE AND KETOPROFEN FROM LARCH ARABINOGALACTAN SOLID DISPERSIONS

4.1. Introduction

Formation of solid dispersions (SDs) increases the solubility and dissolution, and improves the in vivo bioavailability of poorly water-soluble drugs. Therefore, a SD is the most attractive formulation option available to formulation scientists.

New carriers for preparation of SDs are evaluated using the following types of studies-

(a) A SD is prepared using the new carrier and the poorly water-soluble drug and is evaluated (Van Den Mooter et al., 2006; Sivert et al., 2010; Lin et al., 2012) and/or;

(b) The SDs of different poorly water-soluble drugs prepared using the new carrier are evaluated and compared (Hirasawa et al., 1999) and/or;

(c) The SD prepared using the new carrier is compared with that prepared using an established polymer using single poorly water-soluble model drug (Tanno et al., 2004).

In Chapter 3, we have discussed the findings of larch arabinogalactan FIBERAID grade (AGF) polymer for preparation of the amorphous SD using ibuprofen (IBU).

Our findings showed that compared to neat IBU, IBU-AGF SD showed a significant increase in the dissolution of IBU up to 20%DL. However, the IBU-AGF SD system showed limited solid-state miscibility (between 10–20%). The probable reason is the intermediate glass forming ability of IBU (Zhu et al., 2011; Baird et al., 2012).
Ketoprofen (KETO) and itraconazole (ITRA) have good glass forming ability and slow crystallization tendency (Baird et al., 2012; Baird, 2011, Ph.D. dissertation; Van Eerdenbrugh et al., 2010). Therefore, we selected these 2 drugs to prepare SDs using AGF to further evaluate AGF as carrier for SD.

The methods for preparing IBU-AGF SDs (SDM and MSD) included processing at a temperature close to the melting temperature of IBU. Therefore, preparation of the SD of the drugs with melting temperature higher than the processing temperature of the SDM method (70 °C) (Chapter 3) should be evaluated. KETO has slightly higher Tm (95 °C) than IBU. KTEO is a weak acid similar to IBU. ITRA has a high Tm (169 °C) and is basic in nature. ITRA has a very low aqueous solubility. KETO belongs to BCS class II and ITRA belongs to BCS class IV.

The objectives of this study were as follows:

1) To perform extensive solid-state characterization and evaluation of dissolution enhancement of KETO-AGF solid dispersions and ITRA-AGF solid dispersions.

2) To compare solid-state solubility, equilibrium solubility, and the dissolution enhancement of the IBU-AGF solid dispersions, KETO-AGF solid dispersions, and ITRA-AGF solid dispersions.

The findings of this investigation would clearly differentiate whether the drugs with good glass forming ability and slow crystallization kinetics would have greater solid-state solubility and dissolution enhancement. The results would show whether the dissolution enhancement from the AGF SD is specific for the acidic versus the basic drugs. Further, the results would answer the question, whether the processing temperature of the SDM method needs to be close to the melting temperature to obtain an amorphous SD.
4.2. Materials and Experimental Methods

4.2.1 Materials

AGF was a generous gift from Lonza Inc. (Allendale, NJ) and Del-Val Food Ingredients (Mooresetown, NJ). ITRA was a gift from the Albermarle Corporation (Baton Rouge, LA). KETO was purchased from MP Biomedical (Irvine, CA). All other chemicals were of ACS grade or HPLC-grade and purchased from Sigma–Aldrich (St. Louis, MO) or Fisher Scientific (Fair Lawn, NJ).

4.2.2 Equilibrium solubility study of ITRA and KETO

The experiments were performed according to the method discussed in Chapter 3, section 3.2.2. The changes in ITRA equilibrium solubility protocol included (a) 50 mg ITRA was added to 20 mL of AGF polymer solution in 0.1 N HCl, and (b) the ITRA content was assayed using UV absorption at 257 nm (Agilent/HP 8453 UV-Vis spectrophotometer).

For the equilibrium solubility study of KETO, the changes in the protocol included (a) 400 mg of KETO was added to 10 mL of AGF polymer solution in 0.1 N HCl, and (b) the KETO content was assayed using UV absorption at 260 nm (Agilent/HP 8453 UV-Vis spectrophotometer).

4.2.3 Preparation of ITRA-AGF and KETO-AGF solid dispersions using modified solvent evaporation method

The method described previously (Chapter 3, section 3.2.4) was used to prepare the SDM. Additionally, the SDM method was revised. An accurately weighed physical mixture of AGF with ITRA or KETO was placed in a round-bottom flask. Nanopure
water was added to the PM to obtain the wet mass. Then, 5–7 mL of ethanol was added at once to this polymer wet mass. The entire solvent was removed using rotovap evaporation at 70 °C. To ensure complete drying, the SDM samples were kept in the oven at 45 °C overnight. The prepared SDM samples were stored in an airtight container until further analysis.

4.2.4 Conventional DSC

The method has been discussed in Chapter 3, section 3.2.6

4.2.5 XRPD

The method has been discussed in Chapter 3, section 3.2.7

4.2.6 FTIR spectroscopy

The method has been discussed in Chapter 3, section 3.2.8

4.2.7 SEM

The method has been discussed in Chapter 3, section 3.2.9

4.2.8 TMA

The method has been discussed in Chapter 3, section 3.2.10

4.2.9 *In vitro* dissolution studies of ITRA-AGF SDM and KETO-AGF SDM formulations using the basket method

The method has been discussed in Chapter 3, section 3.2.12

Few changes to the ITRA dissolution studies included (a) Each sample of ITRA-AGF SDM contained an amount equivalent to 25 mg of ITRA to maintain the non-sink
conditions, and (b) the level of ITRA was analyzed using Agilent/HP 8453 UV-Vis spectrophotometer (λ\text{max} = 257 \text{ nm}).

For \textit{in vitro} dissolution studies of KETO, the changes to the method included (a) 450 mL dissolution medium volume, (b) each sample containing an amount equivalent to 50 mg of KETO to maintain the non-sink conditions, and (c) UV analysis at (λ\text{max} = 260 \text{ nm}).

4.3. Statistical Analysis

Minitab 16.0 (Minitab Inc.) software was used for statistical analysis. The statistical analysis of solubility and dissolution data were performed using ANOVA with a pairwise multiple comparison procedure. Differences were considered significant when p < 0.05. Tukey’s test for multiple comparisons was used to calculate the significant differences among different dissolution profiles.

4.4. Results and Discussions

The chemical structures of ITRA and KETO are shown in Figure 4.1.

![Chemical structures of Itraconazole and Ketoprofen](image)

Figure 4.1 Chemical structures of Itraconazole and Ketoprofen
The ITRA-AGF SDM and KETO-AGF SDM were successfully prepared using a modified solvent evaporation method (SDM) and revised method. The modified method described by Rane et al. (2007) used the drug solution at the saturation solubility to prevent the crystallization of the drug in drug-polymer systems (Rane et al., 2007; Thompson, 2003. Ph.D. Thesis). The ITRA solubility in ethanol is ~300μg/mL (http://www.freepatentsonline.com/6346533.html). Therefore, ITRA-AGF SDM could not be processed using the laboratory-scale optimized SDM method to obtain an adequate amount of SDM. Therefore, the method was revised. Thus, the revised method was useful to obtain the SD of such drugs.

4.4.1. The evaluation of ITRA-AGF SDMs

4.4.1.1 Equilibrium solubility study of ITRA in the presence of the AGF polymer
The equilibrium solubility of ITRA in 0.1N HCl was 5.72 µg/mL (Figure 4.2). A linear increase in the solubility was observed with an increase in AGF concentration up to 3% (w/v). At a 3% concentration of AGF, a 16-fold increase in ITRA solubility was observed. Previously, a maximum of 10-fold increase in ITRA solubility was observed in the presence of 10 mM of β-cyclodextrin in PB, pH 7.4 (Al-Marzouqi et al., 2006). Jung et al. (1999) reported an increase in ITRA solubility in the presence of SD of poloxamer (7.4-fold), PEG 20,000 (92.5-fold), PVP (41.77-fold), HPMC (90.44-fold), and Eudragit (141-fold) (Jung et al., 1999). Additionally, a study showed a 25.34-fold increase in ITRA solubility from the ITRA-poloxamer 188 EM (Liu et al., 2006).

4.4.1.2 DSC and XRPD

Almost a complete loss of crystallinity was observed in the ITRA-AGF SDM formulations up to 30% DL (Figure 4.3). The loss in crystallinity was associated with a
depression in melting point. The DSC thermograms of ITRA formulations did not show an endotherm at 70 and 90 °C. This indicates the absence of nematic mesophase of ITRA. EL Maghraby and Alomrani (2009) and Janssens et al. (2008) found the absence of ITRA nematic mesophase in SDs (EL Maghraby and Alomrani, 2009; Janssens et al., 2008).

Crystalline ITRA has a distinct XRPD peak at 14.59°, 17.64°, 20.49°, 23.60°, 25.50°, and 27.25° at 2θ (Figure 4.4 and Figure 4.5). The 10 ITRA AGF SDM and 20 ITRA AGF SDM display a reduction of some XRPD peaks or complete disappearance of the

Figure 4.3 DSC thermograms of ITRA AGF formulations
remaining XRPD peaks. The 30 ITRA SDM XRPD diffraction peaks have shown a shift (Figure 4.4). The PMs retained the ITRA in a crystalline form (Figure 4.5).

Figure 4.4 XRPD diffractograms of ITRA-AGF SDMs

Note-**NEAT ITRA; 10 ITRA AGF SDM; 20 ITRA AGF SDM; 30 ITRA AGF SDM; NEAT AGF.**
No observable crystalline drug was present in 10 ITRA AGF SDM and 20 ITRA AGF SDM formulations, whereas little crystalline ITRA was observed in the 30 ITRA AGF SDM (Figure 4.6). Thus, DSC, XRPD and SEM results showed that amorphous ITRA was present in the ITRA-AGF SDM formulation. The maximum drug load without presence of a crystalline drugs was close to 30%. This was an interesting finding because the SDM method employs heating of the drug and polymer to only 70 °C. Conducting the HME at 413K (139.86°C) which was below the melting point of ITRA resulted in the formation of an
amorphous ITRA-Eudragit 100 SD. The maximum DL was only 13% (mass/mass) (Six et al., 2002).

In addition, a complete loss of crystallinity of ITRA was reported in ITRA-HPMCE5 SD (Janssens et al., 2008; Six et al., 2003). The binary and ternary solid dispersions of ITRA prepared using different polymers pluronic F68, pluronic F127, Eudragit EPO, and PVP K25 showed a complete loss in ITRA crystallinity (Badawi et al., 2011).

Figure 4.6 SEM microphotographs of ITRA AGF formulations
Note-A-NEAT ITRA; B-10 ITRA AGF PM; C-10 ITRA AGF SDM; D-20 ITRA AGF SDM; E-30 ITRA AGF SDM.
4.4.1.4 FTIR spectroscopy

Figure 4.7 FTIR spectra of ITRA-AGF SDMs
Figure 4.8 FTIR spectra of ITRA AGF PMs
The FTIR spectra of neat ITRA showed characteristic IR bands at 3382.8 cm\(^{-1}\), 3128 cm\(^{-1}\), 3069 cm\(^{-1}\), 2962 cm\(^{-1}\), 1698.03 cm\(^{-1}\), 1509.8 cm\(^{-1}\), 1609 cm\(^{-1}\), 1451.46 cm\(^{-1}\), and 1425 cm\(^{-1}\) (Figure 4.9) The neat ITRA IR band assignment was similar to that reported in previous studies (Nesseem et al., 2001; Badawi et al., 2011).

Contrary to our expectation, the IR band at 1698.03 cm\(^{-1}\) because of C=O stretch did not show any change in the wave number in the SDMs and PMs. The IR spectra of the SDM formulations at all DLs were observed to be the addition of pure components (Figure 4.7).
This was contrary to the previous finding of the presence of solid-state hydrogen bonding between the C=O group of ITRA and the OH group of the HPMCAS in ITRA-HPMCAS SD (Hong, 2009 M.Sc Thesis). Hydrogen bonding between the C=O of ITRA and OH group of HPMC has been reported in a previous study (Six et al., 2003). There is a possibility that the steric hindrances of the surrounding aromatic ring precluded this hydrogen bonding formation between ITRA and AGF.

4.4.1.5 TMA

The Tg of values of the ITRA-AGF SDM formulation obtained from the TMA analysis are listed in Table 4.1. The 10 ITRA SDM and 20 ITRA SDM have a single Tg, which indicate that ITRA and AGF were molecularly dispersed (Appendix Figure E.1). The 30 ITRA SDM formulation showed 2 thermal transitions. The first one was the Tg of the system, and the second one is because of the melting of the ITRA. The 30 ITRA SDM contains a small amount of crystalline ITRA. This was previously confirmed by DSC, XRPD, and SEM findings. Thus, 30 ITRA AGF SDM formulations consisted of a drug polymer dispersion-rich domain and a crystalline drug domain.

A negative deviation was observed in the TMA determined Tg values compared to that predicted value (Fox equation). A negative deviation to the simple rule of mixing was observed in ITRA-HPMCE5 SD system (Six et al., 2003) and in ITRA-Eudragit SD (Six et al., 2002). A negative deviation of the Tg of ITRA-Eudragit SD compared to the Gordon–Taylor Tg was reported in the absence of drug-polymer hydrogen bonding. The researchers attributed it to phase separation and a presence of polymer-rich phase in the SD (Six et al., 2002).
However, in our study, phase separation is unlikely as evident from the single Tg in 10 ITRA AGF SDM and 20 ITRA AGF SDM formulations. A negative deviation to the simple rule of mixing indicates weaker drug-polymer interaction than drug-drug or polymer-polymer interactions (Janssens et al., 2010). Thus, the absence of solid-state ITRA-AGF hydrogen bondings (FTIR findings) can explain the observed negative deviation in the ITRA-AGF SDMs up to 20% DL and phase separation can explain the negative deviation in 30 ITRA-AGF SDM.

The ITRA AGF miscibility up to 20% ITRA load was an interesting finding. The miscibility limits of ITRA-Eudragit E100 amorphous SD prepared using HME and spray-drying were found up to 13% and up to 27.5%, respectively (Six et al., 2002; Janssens et al., 2010).

Table 4.1 Experimental and theoretical Tg of ITRA-AGF SDMs

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Experimental Tg (°C) / Thermal transition</th>
<th>Predicted Tg (°C) (Fox equation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT ITRA</td>
<td>58.23 (Tg)</td>
<td>-</td>
</tr>
<tr>
<td>10 ITRA AGF SDM</td>
<td>67.30 (Tg)</td>
<td>79.29</td>
</tr>
<tr>
<td>20 ITRA AGF SDM</td>
<td>64.18 (Tg)</td>
<td>76.77</td>
</tr>
<tr>
<td>30 ITRA AGF SDM</td>
<td>72.56 (Tg); 133 (Tm)</td>
<td>74.26</td>
</tr>
<tr>
<td>AGF</td>
<td>~82</td>
<td>-</td>
</tr>
</tbody>
</table>
The results of DSC, XRPD, and TMA studies together with SEM and FTIR data showed that ITRA was amorphous in the AGF SDM up to nearly 30% DL. ITRA-HPMC SD and ITRA-HPMC-pluronic F68 ternary SD prepared using solvent evaporation method successfully formed the amorphous ITRA (EL Maghraby and Alomrani, 2009). Other studies have reported the formation of amorphous ITRA-Eudragit 100 SD up to 13% DL (Six et al., 2002), ITRA-HPMCE5 HME SD up to 60% DL (Six et al., 2003), ITRA-HPMC SD up to 40% DL (Janssens et al., 2008), and ITRA-Eudragit SD up to 60% DL (Janssens et al., 2010).

4.4.1.6 In vitro dissolution of ITRA AGF SDM formulations

Figure 4.10 shows the mean in vitro dissolution profiles of ITRA-AGF SDMs. The dissolution of SDM formulations was faster than that of neat ITRA. Statistical analysis of
the dissolution data showed that compared to neat ITRA, SDM formulations showed a significant increase in dissolution. The dissolution of 10 ITRA AGF SDM was significantly greater than that of 30 ITRA AGF SDM dissolution. No significant differences were observed in the dissolution profiles of the 10 ITRA AGF SDM and 20 ITRA AGF SDM. Similarly, the dissolution profiles of 20 ITRA AGF SDM and 30 ITRA AGF SDM were found statistically equivalent. The dissolution enhancement for SDM formulation was in the order of 10% DL > 20% DL > 30% DL. The %RSD values were within 10%, except for 30 ITRA-AGF SDM, which showed a %RSD of 16. Phase separation may have contributed to the %RSD value in this formulation.

Thus, the significant dissolution enhancement in SDM formulations can be attributed to the presence amorphous ITRA in these ITRA-AGF SDM formulations. ITRA should be in the amorphous form to produce a significant increase in dissolution (Janssens et al., 2008). The solubilization effect of AGF polymer, solution-state acid base interactions, and wetting effect of the AGF polymer were the other factors that contributed to dissolution enhancement of ITRA in ITRA-AGF SDM.

The dissolution enhancement of 10 ITRA AGF SDM formulation was comparable to that observed by Hong, (2009) in their study with a 10 ITRA-PVP film (Hong., 2009 M.Sc. Thesis). The dissolution rate of 20 ITRA AGF SDM in the current investigation was greater than the 20 ITRA- PVP-EC (70:30) film formulations (Hong., 2009 M.Sc. Thesis). However, Six et al. (2003) observed a 80% ITRA release within 30 min in simulated gastric fluid. 25% ITRA-HPMCE5 HME were used in this study (Six et al., 2003). Additionally, the dissolution profile of 30 ITRA AGF SDM was compared to that of 33 ITRA-HPMC SD (EL Maghraby and Alomrani, 2009), the HPMC SDs had a faster
ITRA dissolution rate than that observed in the present study (EL Maghraby and Alomrani, 2009; Six et al., 2003). The increase in the dissolution rate of ITRA with HPMCE5 polymer was attributed to the inhibition of precipitation of ITRA using HPMCE5 (Janssens et al., 2008). A small amount of ITRA crystals were present in 30 ITRA-AGF SDM formulations (Figure 4.6). These crystals may have seeded the crystallization of ITRA in the dissolution media. Therefore, the observed dissolution enhancement was not that high at this DL.

4.4.2. The evaluation of KETO-AGF SDMs

4.4.2.1 Equilibrium solubility study of KETO in the presence of the AGF polymer

![Figure 4.11 Solubility of KETO in AGF solutions (in 0.1N HCl)](image)
The equilibrium solubility of neat KETO in 0.1N HCl was 0.074 mg/mL (Figure 4.11). The solubility of KETO increased in a linear manner as a function of AGF concentration. At an AGF concentration of 3%, a 2-fold increase in solubility was observed. Thus, AGF exerted a weak solubilizing effect on KETO. Chitosan at a concentration of 0.4% showed a 2.94-fold increase in KETO solubility (Amit K et al., 2011). A weak solubilizing effect of β-cyclodextrin on KETO was reported by Fukuda et al. (2008) (Fukuda et al. (2008).

4.4.2.2 DSC and XRPD

Figure 4.12 DSC thermograms of KETO AGF formulations

KETO was completely amorphous up to 30% DL in KETO-AGF SDM formulations (Figure 4.12). In addition, a complete loss of KETO crystallinity was observed in 10
KETO-AGF PM. The KETO crystalline completely lost in KETO-PVPK30 co-mixer (Mura et al., 1995).

Figure 4.13 XRPD diffractograms of KETO-AGF SDMs
Note-NEAT KETO; 10 KETO AGF SDM; 20 KETO AGF SDM; 30 KETO AGF SDM; NEAT AGF.
The high-intensity diffraction peaks at 6.3°, 13.14°, 17.3°, 18.3°, 20.04°, 22.6°, and 23.85° (2θ) are attributed to the KETO crystallinity (Figure 4.13 and Figure 4.14). The crystalline peak of KETO shifted from 22.6° to 22.9° in the KETO-AGF SDM formulations. This could be because of crystalline transformation of the KETO because of processing in the presence of AGF. Fukuda et al. (2008) reported a transformation similar to that observed in our study (Fukuda et al., 2008). The remaining peaks corresponding to crystalline KETO were completely absent in 10 KETO AGF SDM, 20 KETO AGF SDM, and 10 KETO AGF PM. The intensity of the XRPD peak at 22.6° (2θ) was very weak in 30 KETO AGF SDM. A small amount of crystalline KETO was present in 30 KETO AGF SDM formulations (Figure 4.13).
4.4.2.3 SEM

The SEM microphotographs showed a small amount of crystalline KETO in 30 KETO AGF SDM. The crystalline KETO was absent in 10 KETO AGF SDM and 20 KETO AGF SDM (Figure 4.15).

Together, the DSC, XRPD, and SEM results suggested the formation of an amorphous KETO-AGF SDM up to a DL of 30%. These findings are consistent with those reported previously for KETO-Gelucire amorphous SD up to a DL of 33% (Nagar et al., 2011), KETO-PVP amorphous co-precipitate SD up to a DL of 50% (Di Martino et al., 2004), and KETO-PVP SD up to a DL of ~58% (Manna et al., 2007).

Figure 4.15 SEM microphotographs of KETO AGF formulations
Note-A-NEAT KETO; B-10 KETO AGF SDM; C-20 KETO AGF SDM; D-30 KETO AGF SDM.
4.4.2.4 FTIR spectroscopy

KETO exists in the dimer form (Vueba et al., 2006; Manna et al., 2007). The IR spectra of neat KETO showed 2 major IR bands (Figure 4.18). The first one at ~1694 cm\(^{-1}\) because of C=O stretching of the dimeric carboxylic acid group. The second at 1654 cm\(^{-1}\) because of C=O stretching in the ketone group. Both these IR bands shifted to a higher wave number in the 10 KETO AGF SDM, 20 KETO AGF SDM (Figure 4.16) and in 10 KETO AGF PM (Figure 4.17). This indicates hydrogen bonding in monomeric KETO. The C=O of carboxylic acid rather the ketone carbonyl was found to be predominantly involved in solid-state KETO-AGF hydrogen bonding. A blue shift in the C=O stretching band has been reported previously in the SD of KETO due to hydrogen bonding (Ali et al., 2010; Manna et al., 2007).

However, in 30 KETO-AGF SDM formulations, the shifts in these IR bands were substantially low, which indicated weak interactions. The solid-state hydrogen bonding was absent in 20 KETO AGF PM and 30 KETO AGF PM. The presence of hydrogen bonding in 10 KETO-AGF PM was an important finding (Figure 4.17).

The carboxylic C=O group of KETO and OH group of the AGF polymer were involved in solid-state hydrogen bonding in KETO-AGF SDM. The carboxylic C=O or the carboxylic OH group of KETO were actively involved in hydrogen bonding within the SD (Ali et al., 2010; Manna et al., 2007). Hydrogen bonding between the carboxylic C=O group and OH group of the poloxamer was reported in KETO-poloxamer SD (Ali et al., 2010). The carboxylic OH group of KETO and C=O group of PVP formed hydrogen bonding in KETO-PVP SD (Di Martino et al., 2004; Manna et al., 2007). The carboxylic
OH group of KETO and C=O group of PLGA along with polymer backbone forms hydrogen bonding in KETO-PLGA system (Blasi et al., 2007).

Figure 4.16 FTIR spectra of KETO-AGF SDMs
Figure 4.17 FTIR spectra of KETO AGF PMs
Comparison of experimental Tg values for KETO-AGF SDM formulations with theoretical Tg values is summarized in Table 4.2. KETO and AGF were completely miscible up to a 20% DL. 10 KETO AGF SDM and 20 KETO AGF SDM formulations showed a single Tg (Appendix Figure E.3). However, the presence of crystalline KETO in the 30 KETO-AGF SDM formulation (Figure 4.15) resulted in also a melting transition at 71.91 °C. We observed a positive deviation in the experimental Tg value compared to
the predicted value (Fox equation). This suggests a strong KETO-AGF interaction (Feldstein et al., 2003; DiNunzio et al., 2008).

Table 4.2 Experimental and theoretical Tg of KETO-AGF SDMs

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Experimental Tg / Thermal transition (°C)</th>
<th>Predicted Tg (°C) (Fox equation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT KETO</td>
<td>-3.15 (Di Martino et al., 2004)</td>
<td>-</td>
</tr>
<tr>
<td>10 KETO AGF SDM</td>
<td>77.11 (Tg)</td>
<td>71.01</td>
</tr>
<tr>
<td>20 KETO AGF SDM</td>
<td>75.33 (Tg)</td>
<td>61.98</td>
</tr>
<tr>
<td>30 KETO AGF SDM</td>
<td>71.91 (Tg); 91.44 (Tm )</td>
<td>55.21</td>
</tr>
<tr>
<td>AGF</td>
<td>~82 (Tg)</td>
<td>-</td>
</tr>
</tbody>
</table>

4.4.2.6 In vitro dissolution of KETO-AGF SDM formulations
Figure 4.19illustrates the mean dissolution profiles of KETO formulations. A statistical analysis of the dissolution data showed a significantly greater dissolution rate for the SDM formulations, and 10 PM compared to NEAT KETO. The dissolution rate of the 10 KETO AGF SDM and 20 KETO AGF SDM and 10 KETO AGF PM were significantly greater than the dissolution rate of 30 KETO AGF SDM.

The dissolution of 10 KETO AGF PM was greater than that of the KETO-PEG physical mixture (Mura et al., 2005) and KETO-PVP physical mixture (Yadav et al., 2013). The dissolution enhancement observed in our study was comparable to that observed in other studies for nearly same DL (Manna et al., 2007; Fukuda et al., 2008; Coppens et al. 2009; Amit K et al., 2011; Yadav et al., 2013).
The mechanism of the observed dissolution enhancement included loss of KETO crystallinity, solid-state hydrogen bonding between KETO and AGF, and wetting and solubilizing effect of the AGF polymer.

The % RSD values of the dissolution data were within 6%, except that at the initial point, which was 18% for the 10 KETO AGF SDM. % RSD values were higher for 30 KETO AGF SDM than for the other DL KETO-AGF SDMs. The presence of a little amount of crystalline KETO in 30 KETO-AGF SDM could be the possible reason for the observed high %RSD.

4.4.3. Comparison of drug-AGF miscibility in drug-AGF solid dispersions

The IBU-AGF SDM were miscible at 10% DL as evident from the Tg values determined using TMA. ITRA-AGF SDMs and KETO-AGF SDMs were miscible at 20% DL (Appendix Table E.1). The anti-plasticizing effect (increase in the Tg of the amorphous drug) of the AGF polymer was greater for IBU-AGF SDMs and KETO-AGF SDMs than that for the ITRA-AGF SDMs. An absence of solid-state hydrogen bonding between ITRA and AGF could be the possible reason.
4.4.4. Comparison of solubility enhancement potential of AGF for IBU, ITRA, and KETO

The solubilizing power of the AGF polymer for different drugs IBU, ITRA, and KETO is shown in Figure 4.20. The solubility enhancement because of the AGF polymer was in the order of ITRA > IBU > KETO. Statistical analysis of the data of solubilizing power for IBU, ITRA and KETO did not show significant differences for the AGF polymer concentration range used in this study. In the presence of the AGF polymer ~1.2-to 14.3-fold increase in solubility was observed for various crystalline drugs. The drug polymer weight fraction was 1:10 to 1:20 (without any treatment) (Chapter 1, Table 1.7).
We investigated the solution-state interactions between IBU and the AGF polymer (Chapter 3). The investigation of solution-state interactions between ITRA-AGF and KETO-AGF was beyond the scope of this study. The solid-state studies showed an absence of hydrogen bonding in ITRA-AGF SDM.

The observed enhanced ITRA solubility in the presence of ITRA could be explained by one more mechanism. AGF has weak acidic properties (Nazareth et al., 1961 part I) and thus the solution-state acid-base interactions between ITRA-AGF may have led to the observed solubility enhancement. Dushkin et al. (2008) have discussed in detail the interactions between the basic compounds azaleptin/mezapam and acidic AG, which result in solubility enhancement (Dushkin et al., 2008).

4.4.5. Comparison of dissolution enhancement potential of AGF for IBU, ITRA, and KETO

\[
\text{RDR}_{\text{time} (t)} = \frac{\% \text{ Drug Release Formulation}_{\text{time} (t)}}{\% \text{ Drug Release Respective Neat Drug}_{\text{time} (t)}}
\]

The RDR is the relative drug release with respect to respective neat drug at a specific time. RDR was calculated using equation 4.1. The RDR at a specific time was used to compare the dissolution enhancement among IBU-AGF SDM, ITRA-AGF SDM, and KETO-AGF SDM.
Figure 4.21 $\text{RDR}_{15 \text{ min}}$ of SDMs and PM with respect to respective neat drug

Figure 4.22 $\text{RDR}_{30 \text{ min}}$ of SDMs and PM with respect to respective neat drug
The extent of dissolution enhancement for IBU, ITRA, and KETO in terms of RDR\textsubscript{15 min}, RDR\textsubscript{30 min}, and RDR\textsubscript{120 min} are shown in Figures 4.21, 4.22, and 4.23 (Appendix Table E.2, Table E.3 and Table E.4). The observed RDR was in the order of KETO > ITRA > IBU at 15, 30, and 120 min. On the other hand, the solubilizing capacity was in the order of ITRA > IBU > KETO.

At 10% DL, with amorphous drug and miscible system, the dissolution enhancement in terms of RDR was still in the order of KETO > ITRA > IBU. The RDR of 10 ITRA-AGF SDM was greater than that of 10 IBU-AGF SDM at 15 min, 30 min, and 120 min. The acid-base interactions in the solution-state as discussed earlier (section 4.4.4) could be the possible mechanism of the observed dissolution enhancement.

The RDR of the ITRA AGF SDM formulations was comparitively equivalent for all DLs at 15, 30, and 120 min (Figures 4.21, 4.22, and 4.23). The 10 KETO AGF SDM and 20
KETO AGF SDM had a higher RDR than 30 KETO AGF SDM at 15, 30, and 120 min. On the hand, the RDR was the highest for 10 IBU AGF SDM compared to that for 20 IBU AGF SDM and 30 IBU AGF SDM formulations.

Comparison of the RDR_{15 \text{ min}}, RDR_{30 \text{ min}} and RDR_{120 \text{ min}} data indicated that at 30% DL, where crystalline drug was present in the SD, the ITRA AGF system maintained the state of super saturation better than the KETO AGF and IBU AGF systems. There is a possibility that the precipitation inhibition potential of AGF polymer is different for different drugs, which results in different degrees of dissolution enhancement.

The acidic/basic nature of the selected drug was not correlated to the observed dissolution enhancement (RDR) from the poorly water-soluble drug-AGF SDM prepared using the solvent evaporation method.

According to Baird (2011, Ph.D. dissertation), the glass forming ability of 3 drugs on the basis of melt viscosity as a function of temperature data was in the order of KETO > ITRA > IBU (Baird, 2011, Ph.D. Dissertation). Thus, the dissolution enhancements from the AGF SDM correlated well with the glass forming ability of the individual drug for IBU, ITRA and, KETO. However, no such correlation was found between the dissolution enhancement potential of the AGF polymer for a drug and drug-AGF solid-state hydrogen bonding.

4.5. Summary and Conclusions

This study showed that the revised modified solvent evaporation method could be successfully used to form amorphous KETO-AGF SDM and ITRA-AGF SDM. In
addition, these results showed that the processing temperature for SDs can be much lower than the Tm of the drug. AGF has a strong solubilizing effect on ITRA but a weak solubilizing effect on KETO.

The extensive solid-state characterization showed that KETO and ITRA were physically amorphous in their respective AGF SDs. The maximum DL for obtaining amorphous SDs was 30%. A complete loss of crystallinity was observed in 10 KETO AGF PM. Both drugs were miscible up to a 20% DL in their respective AGF SDs. Solid-state hydrogen bonding was present in KETO-AGF SDM. However, solid-state hydrogen bonding was absent in the ITRA-AGF SDM. KETO-AGF SDM and ITRA-AGF SDM significantly enhanced drug dissolution compared to that of the respective neat drugs. Surprisingly, 20 KETO AGF SDM showed a higher initial drug dissolution than 10 KETO AGF SDM

Comparison of the solubilizing power of the AGF polymer for poorly water-soluble IBU, ITRA, and KETO indicated that AGF exerted a solubilizing effect in the order of ITRA > KETO > IBU. The dissolution enhancement (RDR\textsubscript{time}) at specific time point (15min, 30min, and 120 min) was in the order of KETO-AGF SDM > ITRA-AGF SDM > IBU-AGF SDM. The presence of the amorphous state of the drug was the predominant mechanism of the dissolution enhancement. The dissolution enhancement was correlated to the glass forming ability of the individual drug. However, no correlation was observed between the dissolution enhancement and the solid-state drug-polymer hydrogen bonding or acidic/basic nature of the drug.
CHAPTER 5
THE EVALUATION OF DRUG CRYSTALLIZATION INHIBITION POTENTIAL OF LARCH ARABINOGALACTAN POLYMER IN DRUG-LARCH ARABINOGALACTAN SOLID DISPERSIONS.

5.1. Introduction

Dispersion of drug in a polymer matrix, either in the crystalline or in an amorphous form, enhances drug dissolution and in vivo bioavailability (Janssens et al., 2008; Chokshi et al., 2007, Park et al., 2009, Shen et al., 2010; Xu et al., 2007). The formation of an amorphous drug-polymer solid dispersion (SD) is governed by a number of factors. These factors include-

(a) The inherent ability of the polymer to inhibit drug crystallization (Van Eerdenbrugh and Taylor, 2010; Van Eerdenbrugh et al., 2010).

(b) The inherent crystallization tendency of the corresponding amorphous drug (Van Eerdenbrugh et al., 2010; Baird et al., 2010; Ng et al., 2013).

(c) The anti-plasticizing effect of the carrier (Van Den Mooter et al., 2001; Vasanthavada et al., 2005).

(d) The chemistry of the carrier (Kestur and Taylor, 2010) and the drug (Baird et al., 2010; Wegiel et al., 2003).

(e) Drug polymer interactions (Kestur and Taylor, 2010, Shibata et al., 2007; Nair et al., 2001; Wegiel et al., 2013; Vasanthavada et al., 2005).
(f) Solid solubility of the drug in a polymer matrix (Vasanthavada et al., 2005).

(g) The drug polymer ratio (Lu and Zografi, 1998).

(h) The intermediate hydrophobicity of the carrier polymer (Ilevbare et al., 2012).

(i) The processing technique (Elkordy and Essa, 2010; Van Den Mooter et al., 2006; reviewed by Bhugra and Pikal, 2008).

Among these factors, the inherent ability of the carrier to inhibit crystallization of the amorphous drug, the inherent glass forming ability of the drug, and the drug-polymer hydrogen bonding were reported to be the predominant factors (Van Eerdenbrugh and Taylor, 2010; Baird, 2011, Ph.D. dissertation; Ng et al., 2013; Chapter 4).

The inherent ability of the carrier to inhibit drug crystallization can be predicted using the following factors:

(a) The anti-plasticizing effect of the carrier; the ability of the carrier to increase the Tg of the SD compare to that of the amorphous drug (Trasi and Taylor, 2012).

(b) The ability of the carrier to form hydrogen bonds with the drug and extent of the hydrogen bonding (Kestur and Taylor, 2010; Khougaz and Clas, 2000; Miyazaki et al., 2004; Shibata et al., 2007; Trasi and Taylor, 2012; Wyettenbach et al., 2013; Wegiel et al. 2013).

(c) The acidic/basic nature of the carrier (Van Eerdenbrugh and Taylor, 2010).

Some of the predictors of inherent glass forming ability of the drug are as follows:

(a) Tg/Tm ratio of the compound (Turnbull et al., 1969) and fragility (Kawakami et al., 2012).
(b) MW and structural rigidity (Baird et al., 2010).

(c) The melt viscosity (Baird et al., 2012; reviewed by Angell., 2008), melt viscosity-rate of change in viscosity according to temperature (Baird et al., 2012).

The previous studies (Chapter 3, Chapter 4) have shown that the amorphous form of the poorly water-soluble drugs (IBU, ITRA and KETO) was produced and stabilized in the AGF SD. These findings indicated that the AGF polymer is capable of preventing crystallization of the drug upon SD preparation. Additionally, the inherent glass forming ability of the drug (KETO, ITRA versus IBU) governed the formation of the amorphous state.

To elucidate the mechanism of inherent crystallization inhibition of drug by AGF polymer, we prepared and evaluated SDs of various drugs with the AGF polymer. Therefore, an additional 9 poorly water-soluble drugs with a wide solubility range (1 µg/mL to 2500 µg/mL) were selected. This study had the following objectives:

1) To perform the solid-state characterization AGF solid dispersions prepared with the selected drugs.

2) To evaluate the inherent crystallization tendency of the AGF polymer and the mechanisms thereof.

5.2. Materials and Experimental Methods

5.2.1 Materials

Larch Arabinogalactan FiberAid grade (AGF) was a generous gift from Lonza Inc. (Allendale, NJ) and Del-Val Food Ingredients (Mooresstown, NJ). Chlorpropamide
(CHLORP), was purchased from MP Biomedical (Irvine, CA). Nimodipine (NIMO), flurbiprofen (FLURBI), and ritonavir (RITO) were purchased from LKT Laboratories (St. Paul, MN). Naproxen (NAPORX) and tioconazole (TIOCO) were purchased from Sigma-Aldrich (St. Louis, MO). Propranolol hydrochloride (PROPHCl), furosemide (FUROS) and ketoconazole (KETOC) were purchased from Spectrum Chemicals (Gardena, CA). All drugs were at least 98% pure. All other chemicals and reagents were either of HPLC or ACS grade and purchased from either Fisher Scientific (Fair Lawn, NJ) or Sigma–Aldrich (St. Louis, MO).

The propranolol-free base (PROPFB) was extracted from PROPHCl salt. We made a few modifications to the method described by Hunt and Ansell, (2006) for the preparation of the free base. The 10 g of PROPHCl was dissolved in 300 mL of nanopure water until a clear solution was obtained. This solution was alkalinized by adding a 10% NaOH solution. At a pH of 12–13, a white precipitate was obtained. The free base was extracted with dichloromethane (DCM). A total of 4 extractions using DCM were performed to obtain the free base. The drying agent (magnesium sulfate anhydrous) was used to absorb the remaining water, which was later filtered out. Finally, the free base was obtained using rotovap evaporation at 50–55 °C. This process was repeated by adding fresh DCM. The free base was vacuum dried for 48 h. The purity of the free base was analyzed using DSC and liquid chromatography-mass spectroscopy (LC-MS).

5.2.2 Preparation of AGF solid dispersions using the modified solvent evaporation method and revised modified solvent evaporation method
The modified solvent evaporation method (SDM) and the revised modified solvent evaporation were used to prepare the SD as discussed previously (Chapter 3, section 3.2.4 and Chapter 4, section 4.2.3).

5.2.3 Conventional DSC

The method has been discussed previously (Chapter 3, section 3.2.6)

The percent relative crystallinity (RC) of the PMS from DSC fusion enthalpy data were calculated using following equation (Rawlinson et al., 2007).

\[
\text{%Relative Crystallinity (RC)} = \frac{\text{Melting Enthalpy of Physical Mixture} \times 100}{\text{Melting Enthalpy of Neat Drug} \times \text{Wt Fraction}}
\]

5.2.4 XRPD

The method has been discussed previously (Chapter 3, section 3.2.7)

Relative degree of crystallinity (RDC) was calculated using

\[
\text{RDC} = \frac{I_{\text{sample}}}{I_{\text{drug}}}
\]

$I_{\text{sample}}$- Peak height of the formulation under investigation at the same angle ($2\theta$)

$I_{\text{drug}}$- Peak height of the neat drug with the highest intensity at angle ($2\theta$)

(Ryan, 1986; Ribeiro et al., 2003; Dalwadi et al., 2010).

Neat drug diffraction peak at ($2\theta$) was used for calculating RDC (Appendix Table F.1 and Table F.2).

5.2.5 FTIR spectroscopy

The method has been discussed previously (Chapter 2, section 2.2.2)
5.3. Results and Discussions

This study aimed to elucidate the mechanisms underlying the inherent inhibition of crystallization of poorly water-soluble drugs by the AGF polymer. An additional 9 drugs (excluding IBU, ITRA, and KETO) with a wide solubility range and various functional groups were selected. The chemical structures of these compounds are shown in Figure 5.1, and their relevant physical properties are summarized in Table 5.1. The SDM of each of these drugs was obtained as an off-white colored porous powder. The NIMO-AGF SDM has a slight yellow color. The 40 RITO AGF SDM was non-porous in nature.

SDM with a 10% DL was prepared for each drug, which was first evaluated using conventional DSC. NAPROX, a drug with a high Tm (150 °C) and RITO, a drug with good glass forming ability (Tg/Tm > 0.7) (Williams, 2012) were selected for preparing the SDs with a high DL. The SDMs were further characterized by XRPD and FTIR spectroscopy.
Figure 5.1 Chemical structures of the selected drugs
Table 5.1 Properties of the selected drugs used to prepare AGF solid dispersions

<table>
<thead>
<tr>
<th>Selected drug (MW)</th>
<th>BCS class</th>
<th>Functional group</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITO (MW 720.95)</td>
<td>BCS class II</td>
<td>Amide, Hydroxyl</td>
<td>1 µg/ml in distilled water (Sinha et al., 2010)</td>
</tr>
<tr>
<td>TIOCO (MW 387.7)</td>
<td>BCS class II</td>
<td>Aliphatic ether</td>
<td>~2 µg/ml (Wermuth et al., 2003)</td>
</tr>
<tr>
<td>FUROS (MW 330.7)</td>
<td>BCS class IV</td>
<td>Amino, Carboxyl</td>
<td>18.25 µg/ml (Shin and Kim, 2003)</td>
</tr>
<tr>
<td>KETOC (MW 531.44)</td>
<td>BCS class II</td>
<td>Carbonyl, Aliphatic ether</td>
<td>10 µg/ml (Buchanan et al., 2007)</td>
</tr>
<tr>
<td>PROPFB (MW 259)</td>
<td>-</td>
<td>Hydroxyl and Amino</td>
<td>120 µg/ml (Paker-Leggs and Neau, 2008)</td>
</tr>
<tr>
<td>NAPROX (MW 252.23)</td>
<td>BCS class II</td>
<td>Carboxyl</td>
<td>84 µg/ml (Kulkarni et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28 µg/ml (0.12 mmole) (Fauci and Mura et al, 2001)</td>
</tr>
<tr>
<td>FLURBI (MW 244.08)</td>
<td>BCS class II</td>
<td>Carboxyl</td>
<td>482 µg/ml (Varma and Pandit, 2005)</td>
</tr>
<tr>
<td>NIMO (MW 418.5)</td>
<td>BCS class II</td>
<td>Amino, Nitro, Carbonyl</td>
<td>2299 µg/ml (Yoshida et al., 1990)</td>
</tr>
<tr>
<td>CHLORP (MW 276.74)</td>
<td>BCS class II</td>
<td>Amide</td>
<td>2200 µg/ml (in water at pH 6) insoluble in pH7.3 (Chlopropamide USP)</td>
</tr>
</tbody>
</table>

5.3.1. Solid-state characterization of drug-AGF solid dispersions

The solid-state characterizations of the AGF SDs of the selected drugs were performed.

The XRPD diffraction peaks, which represent the drug crystallinity, and FTIR spectral
band assignments of each individual neat drug were consistent with those reported previously (Appendix Table F.3 and Table F.4).

5.3.1.1 RITO

RITO was completely amorphous up to a 40% DL. This was evident from the absence of RITO melting at 128.68 °C (DSC) (Figure 5.2). The sharp, highly intense diffraction peaks of RITO crystallinity either were absent or, if present, were of less intensity in RITO-AGF SDM formulations (Figure 5.3).

![Figure 5.2 DSC thermograms of NEAT RITO, RITO-AGF SDM, and RITO AGF PM](image)

The shift in the IR band at 1702 cm$^{-1}$ (C=O ester linkage) and red shift in the IR band at 3308 cm$^{-1}$ (OH) of AGF suggests the presence of solid-state hydrogen bonding in RITO-AGF SDM formulations. This was observed at all DLs as well as in10 RITO AGF PM. Another noteworthy finding was the red shift of the IR band of RITO at 2958 cm$^{-1}$ which
indicatived disruption of the solid-state hydrogen bonding within the RITO molecule (Figure 5.4 and Figure 5.5). The molecular dispersion of RITO in AGF SDM was associated with solid-state hydrogen bonding.

Figure 5.3 XRPD diffractograms of RITO-AGF SDMs
Note-NEAT RITO; 40 RITO AGF SDM; 30 RITO AGF SDM; 20 RITO AGF SDM; 10 RITO AGF SDM; NEAT AGF.
Figure 5.4 FTIR spectra of RITO-AGF SDMs
5.3.1.2 TIOCO

The melting endotherm was completely absent in the 10 TIOCO SDM formulation (Figure 5.6). Some of the XRPD peaks, which indicated TIOCO crystallinity disappeared. The remaining peaks ($22.34^\circ$ and $27.3^\circ$) showed shifts, which confirmed almost amorphous TIOCO in the 10 TIOCO AGF SDM. No change in the XRPD pattern was observed in the PM (Figure 5.7).
Figure 5.6 DSC thermograms of NEAT TIOCO, TIOCO-AGF SDM, and TIOCO AGF PM

Figure 5.7 XRPD diffractograms of TIOCO AGF formulations

Note - NEAT TIOCO; 10 TIOCO AGF PM; 10 TIOCO AGF SDM; NEAT AGF.
No shifts in the major IR bands of TIOCO and those of AGF polymer were observed. This indicates the absence of TIOCO and AGF solid-state hydrogen bonding in TIOCO AGF formulations (Figure 5.8 and Figure 5.9).

Figure 5.8 FTIR spectra of TIOCO-AGF SDM and TIOCO AGF PM
Figure 5.9. FTIR spectra of NEAT TIOCO and NEAT AGF

5.3.1.3 FUROS

The DSC thermogram (Figure 5.10) of neat FUROS showed an exothermic peak at 228.05 °C, which was associated with the melting of the drug. The endothermic peak at 275.15 °C was associated with the degradation product (Raval et al., 2010). The peak corresponding to the melting of FUROS at 228.05 °C was absent in the SDM formulation. This was confirmed by the DSC thermogram of another sample of 10 FUROS AGF SDM formulation. However, the SDM formulation showed another sharp peak at 236 °C. This transition was not likely to occur because of Tm of FUROS. It could be Tm of the degradation product at a lower temperature in the presence of the AGF polymer.
A complete loss of FUROS crystallinity was observed in 10 FUROS AGF SDM samples by XRPD (Figure 5.11). This was evident from the disappearance of the highly intense sharp XRPD peaks at 2θ of 12°, 18.1°, 19°, 23.9°, 24.8°, 28.4° indicative of FUROS crystallinity. It further confirmed that the DSC endotherm at 236 °C was because of the degradation product.

Figure 5.10 DSC thermograms of NEAT FUROS, FUROS-AGF SDM, and FUROS AGF PM.
Solid-state hydrogen bonding was present in FUROS-AGF formulations. The shift in the IR bands at 3282.76 cm\(^{-1}\) (N-H stretch), 1676.31 cm\(^{-1}\) (N-H bends), and 1561 cm\(^{-1}\) (C=O stretch) suggests involvement of these groups in the hydrogen bonding. The corresponding shifts of AGF IR bands at 3284 cm\(^{-1}\) (OH) and 1590 cm\(^{-1}\) (COO\(^{-}\)) were observed in FUROS formulations (Figure 5.12 and Figure 5.13).
Figure 5.12 FTIR spectra of FUROS-AGF SDM and FUROS AGF PM
Figure 5.13 FTIR spectra of NEAT FUROS and NEAT AGF

5.3.1.4 KETOC

Partial KETOC crystallinity was observed in the 10 KETOC AGF SDM formulation (Figure 5.14). The XRPD peaks of 10 KETOC AGF SDM were shifted and were less intense. The crystallinity of KETOC however was retained in 10 KETOC AGF PM (Figure 5.15).
Figure 5.14 DSC thermograms of NEAT KETOC, KETOC-AGF SDM, and KETOC AGF PM

Figure 5.15 XRPD diffractograms of KETOC AGF formulations
Note-NEAT KETOC; 10 KETOC AGF PM; 10 KETOC AGF SDM; NEAT AGF.
Solid-state hydrogen bonding was absent in KETOC-AGF SDM formulation. Compared to neat KETOC, SDM and PM showed no shift in the IR band at 1645 cm\(^{-1}\) (C=O stretch) (Figure 5.16 and Figure 5.17).
5.3.1.5 PROPFB

The PROPFB was obtained with 100% purity (Appendix Figure F.1 and Figure 5.18). The DSC and XRPD findings indicated amorphous PROPFB in SDM formulation at 10% DL (Figure 5.18 and Figure 5.19).
Figure 5.18 DSC thermograms of NEAT PROPFB, PROPFB-AGF SDM, and PROPFB AGF PM

Figure 5.19 XRPD diffractograms of PROPFB AGF formulations
Note-NEAT PROPFB; 10 PROPFB AGF PM; 10 PROPFB SDM; NEAT AGF.
No shifts were observed in the IR bands of PROPFB and AGF polymer (Figure 5.20 and Figure 5.21). Thus, an absence of solid-state hydrogen bonding in the PROPFB AGF SDM system was observed.
5.3.1.6 NAPROX

The DSC analysis (Figure 5.22) showed an absence of the melting endotherm of neat NAPROX in the 10 NAPORX AGF SDM formulation. The disappearance of a diffraction peak at 12.6° was found in 10 NAPROX-AGF SDM. Other peaks showed shifts and their intensity was less (Figure 5.23). The diffraction peaks were present with reduced intensity in the 20 NAPROX SDM. Thus, complete loss of NAPROX crystallinity in the 10 NAPROX AGF SDM and the presence of partial NAPROX
crystallinity in the 20 NAPROX AGF SDM formulation was observed. The PM contained NAPROX in the crystalline form.

Figure 5.22 DSC thermograms of NEAT NAPROX, NAPORX-AGF SDM, and NAPROX AGF PM

The shift in the NAPROX IR bands at 1726 cm\(^{-1}\) (C=O stretch), at 1394 cm\(^{-1}\) (COO\(^-\)) and shift in the AGF IR band at 3308 cm\(^{-1}\) (OH stretch) were present in 10 NAPROX AGF SDM. This finding indicates the presence of solid-state hydrogen bonding. No shift was observed in the NAPROX IR band at 1394 cm\(^{-1}\) (COO\(^-\)) in 20 NAPROX SDM. This indicates C=O free carboxylic group plays a little role in hydrogen bonding in 20 NAPROX AGF SDM. The PMs were devoid of any IR band shifts or quenching (Figure 5.24 and Figure 5.25).
Figure 5.23 XRPD diffractograms of NAPROX-AGF SDMs

Note-NEAT NAPROX; 10 NAPROX AGF SDM; 20 NAPROX AGF SDM; NEAT AGF.
Figure 5.24 FTIR spectra of NAPROX-AGF SDM and NAPROX AGF PM
Figure 5.25 FTIR spectra of NEAT NAPROX and NEAT AGF

5.3.1.7 FLURBI
Figure 5.26 DSC thermograms of NEAT FLURBI, FLURBI-AGF SDM, and FLURBI AGF PM

A full amorphicity in 10 FLURBI AGF SDM formulation was obvious (Figure 5.26 and Figure 5.27). The shift in the FLURBI IR band at 1694 cm\(^{-1}\) (C=O stretch) and AGF IR band at 3308 cm\(^{-1}\) (OH stretch) indicated the presence of solid-state hydrogen bonding in FLURBI AGF SDM (Figure 5.28 and Figure 5.29).
Figure 5.27 XRPD diffractograms of FLURBI-AGF SDM
Note-NEAT FLURBI; 10 FLURBI AGF SDM; NEAT AGF.
Figure 5.28 FTIR spectra of FLURBI-AGF SDM and FLURBI AGF PM
A significant reduction in NIMO crystallinity was observed in the 10 NIMO AGF SDM formulations (Figure 5.30). The diffraction peak shifted from 17.3° to 17.2° in 10 NIMO AGF SDM whereas other peaks were absent. The overall XRPD pattern of 10 NIMO AGF SDM suggested a complete loss of NIMO crystallinity (Figure 5.31). Thus, DSC and XRPD results together suggest almost a complete loss of crystallinity in the NIMO – AGF SDM sample.
A significant reduction in NIMO crystallinity was observed in the 10 NIMO AGF SDM formulations (Figure 5.30). The diffraction peak was shifted from 17.3° to 17.2° in 10 NIMO AGF SDM whereas other peaks were absent. The overall XRPD pattern of 10 NIMO AGF SDM was suggestive of complete loss of NIMO crystallinity (Figure 5.31). Thus, DSC and XRPD results together suggest almost complete loss of crystallinity in the NIMO SDM sample. Complete crystallinity of NIMO was retained in the 10 NIMO AGF PM.

Figure 5.30 DSC thermograms of NEAT NIMO, NIMO-AGF SDM, and NIMO AGF PM
Figure 5.31 XRPD diffractograms of NIMO-AGF SDM

Note: NEAT NIMO; 10 NIMO AGF SDM; NEAT AGF.
Figure 5.32 FTIR spectra of NIMO-AGF SDM and NIMO AGF PM
Solid-state hydrogen bonding was present in the 10 NIMO AGF SDM formulation as well as in the PM. We observed shifts in the IR band of NIMO at 1693 cm\(^{-1}\) (C=O stretch) and in that of the AGF polymer at 3308 cm\(^{-1}\) (OH stretch) (Figure 5.32 and Figure 5.33).

### 5.3.1.9 CHLORP

The double-melting endotherm at 127.30 °C and 130.84 °C was observed in the DSC thermogram of neat CHLORP (Figure 5.34). The double melting is characteristic of the α
form of CHLORP (Drebushchak et al., 2008). The XRPD diffractograms showed an appreciable loss in the crystallinity of the CHLORP in the CHLORP AGF SDM (Figure 5.35).

Figure 5.34 DSC thermograms of NEAT CHLORP, CHLORP-AGF SDM, and CHLORP AGF PM
Solid-state hydrogen bonding between CHLORP and AGF was present in the SDM and PM. An IR band of CHLROPR at 1709 cm$^{-1}$ (C=O stretch) was present with less intensity, and the IR band at 1666 cm$^{-1}$ (COO$^-$ stretch) shifted to a higher wave number. Similarly, a shift was observed in the IR band of AGF at 3308 cm$^{-1}$ (OH stretch) (Figure 5.36 and Figure 5.37).
Figure 5.36 FTIR spectra of CHLORP-AGF SDM and CHLORP AGF PM
Figure 5.37 FTIR spectra of NEAT CHLORP and NEAT AGF
5.3.2. Mechanism of drug crystallization inhibition by AGF polymer

Table 5.2 Enthalpy of fusion and Tg/Tm of the selected drugs

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Tm (Expt)</th>
<th>Enthalpy of fusion J/gram (Expt)</th>
<th>Tg</th>
<th>Tg/Tm</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU</td>
<td>76.56</td>
<td>135</td>
<td>-45 °C (228K) (Dudognon et al., 2008)</td>
<td>0.658</td>
</tr>
<tr>
<td>ITRA</td>
<td>169.92</td>
<td>92.41</td>
<td>58 °C (331.15K) (Expt)</td>
<td>0.747</td>
</tr>
<tr>
<td>KETO</td>
<td>96.53</td>
<td>80.1</td>
<td>3.15 °C 270K (Di Martino et al., 2004)</td>
<td>0.731</td>
</tr>
<tr>
<td>RITO</td>
<td>128.68</td>
<td>101.7</td>
<td>45 to 49 °C (318.15 to 322.15K) (EP1418174)</td>
<td>0.791-0.801</td>
</tr>
<tr>
<td>TIOCO</td>
<td>84.24</td>
<td>104.9</td>
<td>-12.67 °C (260.48K) (Expt))</td>
<td>0.728</td>
</tr>
<tr>
<td>FUROS</td>
<td>~228</td>
<td>65.32</td>
<td>44.2 °C (317.35 K) form A</td>
<td>0.633-0.652</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54 °C (327.15 Form B) (Matsuda et al., 1992)</td>
<td></td>
</tr>
<tr>
<td>KETOC</td>
<td>150.51</td>
<td>116.2</td>
<td>44.35 °C (317.5 K) (Van den Mooter et al., 2001)</td>
<td>0.749</td>
</tr>
<tr>
<td>PROPFB</td>
<td>95.86</td>
<td>160.61</td>
<td>-7.25 °C (265.9K) (Expt)</td>
<td>0.720</td>
</tr>
<tr>
<td>NAPROX</td>
<td>155.93</td>
<td>123.6</td>
<td>6.2 °C (279.35K) (Alleso et al., 2009)</td>
<td>0.651</td>
</tr>
<tr>
<td>FLURBI</td>
<td>116.96</td>
<td>145.3</td>
<td>4.65 °C (277.8 K) (Paradkar et al., 2003)</td>
<td>0.712</td>
</tr>
<tr>
<td>NIMO</td>
<td>126.77</td>
<td>96.76</td>
<td>20 °C (293.15 K) (Docsolis et al., 2007)</td>
<td>0.733</td>
</tr>
<tr>
<td>CHLORP</td>
<td>118.27</td>
<td>42.57</td>
<td>16 °C (289.15K) (Cao et al., 2002)</td>
<td>0.738</td>
</tr>
</tbody>
</table>

Note-Expt-Experimentally derived.

The RDC values for SDM formulations with 10%, 20%, and 30% DL is shown in Figures 5.38, 5.39, and 5.40, respectively (Appendix Table F.1 and Table F.2). In addition, the graphs show whether solid-state hydrogen bonding was present between the drug and AGF polymer, (Y) or (N).
At 10% DL, KETOC retained an appreciable amount of the crystalline drug whereas TIOCO, NAPROX, and CHLORP were almost amorphous. At 20% DL, NAPROX was partially crystalline whereas IBU, ITRA, and KETO were almost completely amorphous. At 30% DL, only RITO was completely amorphous. The formulation with RDC values less than 0.17 were designated as amorphous formulations previously (Ribeiro et al., 2003).

Figure 5.38 Relative degree of crystallinity (RDC) of 10%DL DRUG-AGF SDM
Note-Neat drug as a reference, RDC of neat drug is 1.
Figure 5.39 Relative degree of crystallinity (RDC) of 20% DL DRUG-AGF SDM

Note-Neat drug as a reference, RDC of neat drug is 1.

Figure 5.40 Relative degree of crystallinity (RDC) of 30% DL DRUG-AGF SDM

Note-Neat drug as a reference, RDC of neat drug is 1.
The % relative crystallinity (%RC) calculated from the fusion enthalpy data (DSC) of the PM and neat drugs is shown Figure 5.41. All the drugs were almost completely crystalline in the PM (at 1:9 drug-polymer ratio), except for KETO.

![Figure 5.41 % Relative crystallinity (RC) of 10% DL DRUG AGF PM](image)

Note-%RC of neat drug is 100%; *% crystallinity cannot be calculated for the FUROS AGF PM.

The focus of this study was to evaluate the mechanism of crystallization inhibition by AGF polymer in drug-AGF SDM. The drug AGF solid-state hydrogen bonding was related to inhibition of drug crystallization for the drugs IBU, KETO, RITO, FUROS, NAPROX, FLURBI, and NIMO. However, this was not observed in the case of ITRA, TIOCO, KETOC, and PROPFB. Surprisingly, crystalline CHLOPR was present in the SDM even in the presence of solid-state hydrogen bonding.
Examination of the functional groups of the different drugs shows that C=O group of carboxylic acid was strongly related to inhibition of crystallization of drug upon the amorphous SD up to a certain DLs. The examples included IBU, KETO, FLURBI, FUROS, and NAPROX. The C=O group of the ester was related to the existence of the amorphous state as well (example- RITO). The C=O of ITRA and KETOC did not form solid-state hydrogen bonding. The amide C=O (CHLORP) group involved in interaction with the AGF polymer was associated with inhibition of crystallization. This was not as extensive as the C=O of the carboxylic acid. The AGF polymer was not able to form hydrogen bonds with compounds containing aliphatic ether group or hydroxyl group. These groups are present in drugs PROPFB, ITRA, KETOC, and TIOCO.

Polymers with hydrogen bond donor groups (like HPMC, HPMCAS) were more effective in inhibiting crystallization of the compounds with a hydrogen bond acceptor group (C=O). Polymers with a hydrogen bond acceptor group, such as PVP, PVP-VA, and Crospovidone inhibit the crystallization of the compound with a hydrogen bond donor group (carboxyl, hydroxyl) (Baird, 2011, Ph.D. Dissertation; Shibata et al., 2007; Trasi and Taylor, 2012; Wegiel et al., 2013). The AGF polymer (the hydrogen donor group) successfully inhibited the crystallization of the compounds containing a C=O group. Thus, the AGF polymer functioned similar to HPMC to inhibit the drug crystallization.

The findings showed formation of amorphous AGF SDM with ITRA, TIOCO, PROPFB, and KETOC even in the absence of drug-polymer solid-state hydrogen bonding. In fact, the anti-plasticizing effect of the AGF polymer was observed non-substantial in ITRA-AGF SDM (Chapter 4). This suggests that an inherent tendency of the AGF polymer to inhibit the drug crystallization is the predominant mechanism in these formulations.
The AGF polymer significantly increased the Tg of the IBU-AGF SDM and KETO-AGF SDM compared to that of the neat drug (Chapter 3 and Chapter 4). Further studies should be performed to determine the Tg of TIOCO-AGF SDM, PROPFB-AGF SDM, KETOC-AGF SDM, and CHLORP-AGF SDM formulations to evaluate the anti-plasticizing effect of the AGF polymer. A similar strong anti-plasticizing effect of the polymer rather than drug-polymer solid-state hydrogen bonding was observed in KETOC-PVP amorphous SD (Van den Mooter et al., 2001). Nilutamide increased the Tg of futamide and thus exerted the crystallization inhibition (Trasi and Taylor, 2012).

Acidic polymers are good crystallization inhibitors for basic drugs, and basic polymers are good crystallization inhibitors for acidic drugs (Van Eerdenbrugh and Taylor, 2010; Shibata et al., 2007, Baird, 2011, Ph.D. dissertation; Wegiel et al., 2003). In this study, however, we observed no such trend. AGF polymer successfully inhibited crystallization of acidic (IBU, KETO, NAPROX, FLURBI, and CHLORP); basic (RITO, FUROS, ITRA, TIOCO, and PROPFB); and neutral drugs (NIMO) in SDs prepared using the SDM method.

In the absence of solid-state hydrogen bonding, the AGF polymer inhibited crystallization of basic drugs. Examples include ITRA, TIOCO, KETOC, and PROBFB. On the other hand, AGF was not able to inhibit the crystallization of NAPROX, an acidic drug at 20% DL, even in the presence of solid-state hydrogen bonding. Glucuronic acid makes the AGF polymer slightly acidic; however, it is comparable to HPMCAS and HPMC. Previously, the polymers were grouped on the acid-base scale as follows: PSSA and PAA, acidic; PVP, PVPVA, and E100, basic; and HPMC and HPMCAS, intermediate (Van Eerdenbrugh and Taylor, 2010).
Formation of the amorphous state was not related to the Tg/Tm ratio of the selected drugs (Table 5.2). Similarly, the Tg/Tm was reported to be not related to the formation and stabilization of the glass form (Fukuoka et al., 1989; Baird et al., 2012).

Van Eerdenbrugh et al., (2010) and Baird et al., (2010) performed extensive studies to evaluate the crystallization tendency of compounds after solvent evaporation and under cooled melt preparation. They classified the compounds into three classes; class I-rapid crystallization, class II-intermediate crystallization and class III slow crystallization. RITO, ITRA, KETOCO, KETO, and IBU were classified as a class III-compounds, FLURBI was class II compound and CHLORP as class I (melt method)/class III (solvent method) compound (Van Eerdenbrugh et al., 2010 and Baird et al., 2010). As expected, the drug RITO, ITRA, KETO, IBU, FLURBI and CHLORP being class III compound, successfully inhibited crystallization in AGF SDM. This did not correlate for KETOC. Despite the slow crystallization tendency, the KETOC was partially crystalline in AGF SDM even at low DLs (10%). This can be attributed to the absence of solid-state hydrogen bonding between KETOC and AGF polymer. The presence of a crystalline drug in a 20 NAPROX-AGF SDM formulation even in the presence of solid-state hydrogen bonding can be explained as NAPROX is not a good glass former (Mahlin et al., 2011).

A study by Baird et al. (2010) showed that compared to low-MW compounds, compounds with high MW and complex structures were good glass formers (Baird et al., 2010). However, we did not observe any such relationship in our study. Drug melting and enthalpy of fusion (Table 5.2) did not show any specific correlation to the tendency of AGF SD to form an amorphous SD. Shibata et al. (2007) reported that the melting
temperature did not have an impact on the formation of amorphous SD. They used 20 different drugs and Crospovidone as a carrier for preparation of SDs (Shibata et al., 2007).

Thus, the mechanism of inhibition of crystallization by the AGF polymer includes:

1. The inherent ability of the AGF polymer to inhibit drug crystallization
2. AGF-drug solid- state hydrogen bonding
3. Solid-state AGF-drug acid base interactions
4. Anti-plasticizing effect of the AGF polymer

Thus, AGF polymer fits well into the category of other comparable polymers to inhibit drug crystallization in the SD prepared using the SDM method. The widely used carriers (HPMC, HPMCAS, PVP, PVP-VA, Eudragit E100, PAA, Crospovidone, Polyvinyl acetate) have been extensively investigated for their potential to inhibit the drug crystallization. The mechanism of inhibition of drug crystallization by these polymers has been previously established (Van Eerdenbrugh and Taylor, 2010; Kestur and Taylor, 2010; Shibata et al., 2007; Matsumoto and Zografi, 1999; Miyazaki et al., 2004). The results of our study are comparable to those reported by Van Eerdenbrugh and Taylor, (2010) because we performed XRPD analyses in at least a week old SDs (Van Eerdenbrugh and Taylor, 2010)
5.3.3. Comparisons of amorphous drug load of AGF SD versus comparable carrier SD

The DL of amorphous SD prepared using comparable carriers from the literature were compared with those of current AGF polymer SD irrespective of the method of preparation (Table 5.3). The amorphous DL capacity of the AGF polymer was much lower for some drugs (ITRA, KETO, and CHLORP). The maximum DL was lower for other drugs (NAPROX and NIMO) and equivalent for some drugs (IBU, KETOC, and RITO). The inhibition of crystallization of the drug in the presence of the polymer was not related to the MW and Tg of the polymer (Matsumoto and Zografi, 1999). Therefore, it is unlikely that the low Tg and comparatively low MW of the AGF polymer contributed to the low amorphous DL in AGF SD.

These findings can be only explained by the intermediate placement of the AGF polymer on the acid-base scale. Surprisingly, the slightly acidic AGF polymer was a weak inhibitor of crystallization of acidic drugs and therefore required more polymers to form the amorphous state of the drug. Exception is KETO. For neutral and basic drugs, on the other hand, the effect of AGF as an inhibitor of crystallization was comparable, except in KETOC. Our findings cannot explain the inhibition of crystallization of KETOC. Van Eerdenbrugh and Taylor, (2010) reported strong/moderate crystallization inhibition by the polymer similar to that reported in our study on the basis of the acidic/basic nature of the drug (Van Eerdenbrugh and Taylor, 2010). In summary, AGF, a novel carrier for preparation of amorphous SDs, is comparable to HPMC, HPMCAS, low viscosity HPC, and PVP polymers.
Table 5.3 Amorphous drug load of AGF SD versus comparable carrier SDs

<table>
<thead>
<tr>
<th>Solid dispersion</th>
<th>Amorphous DL</th>
<th>Detection technique</th>
<th>Reference</th>
<th>Amorphous DL in AGF SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU-HPMCK3</td>
<td>Between 10%-30%</td>
<td>PXRD, DSC</td>
<td>Chapter 3</td>
<td>Almost up to 20% DL</td>
</tr>
<tr>
<td>IBU-Kollidon</td>
<td>Up to 16% DL</td>
<td>PXRD, DSC</td>
<td>Xu et al., 2007</td>
<td>Almost up to 20% DL</td>
</tr>
<tr>
<td>IBU-PVPVA</td>
<td>Up to 50% DL</td>
<td>PXRD, DSC</td>
<td>Moneghini et al., 2008</td>
<td>Almost up to 20% DL</td>
</tr>
<tr>
<td>IBU-PVP</td>
<td>Up to 15% DL</td>
<td>PXRD, DSC</td>
<td>Yu et al., 2009</td>
<td>Almost up to 20% DL</td>
</tr>
<tr>
<td>Itraconazole-HPMC E5</td>
<td>Up to 40% DL</td>
<td>PXRD</td>
<td>Janssens et al., 2008</td>
<td>Almost up to 20% DL</td>
</tr>
<tr>
<td>ITRA-HPMC Coevaporates</td>
<td>Up to 40% DL</td>
<td>DSC</td>
<td>EL Maghraby and Alomrani, 2009</td>
<td>Almost 30% DL</td>
</tr>
<tr>
<td>ITRA-HPMCE5 SD</td>
<td>40% DL</td>
<td>DSC</td>
<td>Six et al., 2003</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>ITRA-PVP film</td>
<td>Up to 40% DL</td>
<td>DSC</td>
<td>Hong, 2009 (M Sc. Thesis)</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>ITRA-HPMCAS film</td>
<td>Up to 20% DL</td>
<td>DSC</td>
<td>Hong, 2009 (M.Sc. Thesis)</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>KETO-PVPK30 precipitate</td>
<td>Co Up to 50% DL</td>
<td>XRPD</td>
<td>Di Martino et al., 2004</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>KETO-PVP</td>
<td>Up to 58% DL</td>
<td>XRPD</td>
<td>Manna et al., 2007</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>KETO-Gelucire</td>
<td>Up to 33% DL</td>
<td>XRPD, DSC</td>
<td>Nagar et al., 2011</td>
<td>Almost up to 30% DL</td>
</tr>
<tr>
<td>RITO-PVPVA</td>
<td>Up to 20% DL</td>
<td>XRPD</td>
<td>Poddar et al., 2011</td>
<td>Up to 40% DL</td>
</tr>
<tr>
<td>Naproxen-HPMC</td>
<td>Up to 33% DL</td>
<td>DSC</td>
<td>Maheri-Esfanjani et al., 2012</td>
<td>Partially in 20% DL</td>
</tr>
</tbody>
</table>
Table 5.3 Amorphous drug load of AGF SD versus comparable carrier SDs (continued)

<table>
<thead>
<tr>
<th>Solid dispersion</th>
<th>Amorphous DL</th>
<th>Detection technique</th>
<th>Reference</th>
<th>Amorphous DL in AGF SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen-PVP</td>
<td>Up to 30% DL</td>
<td>XRPD</td>
<td>Nair et al., 2001</td>
<td>Partially in 20% DL</td>
</tr>
<tr>
<td>KETOC-PVPK25 SPRAYDRY</td>
<td>Up to 10% DL</td>
<td>XRPD</td>
<td>Van Den Mooter et al., 2001</td>
<td>10% DL</td>
</tr>
<tr>
<td>FLURBI-PVP</td>
<td>Up to 50% DL</td>
<td>DSC</td>
<td>Prajapati et al., 2010</td>
<td>10% DL but could be up to higher DL</td>
</tr>
<tr>
<td>FLURBI-HPMC</td>
<td>Up to 60% DL</td>
<td>PLM</td>
<td>Van Eerdenbrugh and Taylor, 2010</td>
<td>10% DL but could be up to higher DL</td>
</tr>
<tr>
<td>FLURBI-HPMCAS</td>
<td>Up to 50% DL</td>
<td>PLM</td>
<td>Van Eerdenbrugh and Taylor, 2010</td>
<td>10% DL but could be up to higher DL</td>
</tr>
<tr>
<td>FLURBI-PVP</td>
<td>Up to 75% DL</td>
<td>PLM</td>
<td>Van Eerdenbrugh and Taylor, 2010</td>
<td>10% DL but could be up to higher DL</td>
</tr>
<tr>
<td>CHLORP- HPMC/HPMCAS/PVP</td>
<td>Up to 75% DL</td>
<td>PLM</td>
<td>Van Eerdenbrugh and Taylor, 2010</td>
<td>Fully amorphous at 10%DL, can go up to high</td>
</tr>
<tr>
<td>NIMO-PVP</td>
<td>Up to 25% DL</td>
<td>DSC, XRPD</td>
<td>Oh et al., 2010</td>
<td>Almost up to 10% can go up to higher % DL</td>
</tr>
</tbody>
</table>

Note: PLM = Polarized light microscopy.
5.4. Summary and Conclusions

The AGF polymer inhibited the crystallization of all drugs (except KETOC), selected in our study at 10% DL. IBU, ITRA, KETO, and RITO were almost completely amorphous at 20% DL. RITO was amorphous at 30% DL and 40% DL in AGF SDs. The AGF polymer acted as an inhibitor of drug crystallization via its inherent ability to inhibit drug crystallization, by froming solid-state hydrogen bonds with the drug, by exerting anti-plasticizing effect, and by its intermediate acidic/basic characteristics.

The AGF polymer had a strong crystallization inhibition effect in the case of neutral and basic drugs (except KETOC). The crystallization inhibition effect was overall moderate for acidic drugs, which required a greater amount of the AGF polymer to maintain the drug in the amorphous form. The crystallization inhibition effect of the AGF polymer is comparable to that of HPMC, HPMCAS, and PVP polymers.
6.1. Introduction

The formation of an amorphous form of the drug is the predominant mechanism of dissolution enhancement in the glass solutions (reviewed by Saharan et al., 2009; reviewed by Chiou and Riegelman, 1971; reviewed by Leuner and Dressman, 2000). However, an amorphous form of the drug is a high-energy form and has a tendency to convert back to the crystalline form (Nazi, 2007).

A polymer tends to stabilize this amorphous form of the drug in the solid dispersions (SD) by (a) increasing the Tg of the SD to a value, which is greater than the Tg of the neat amorphous drug (Sakurai et al., 2012), (b) decreasing the molecular mobility of the drug (reviewed by Laitinen et al., 2012), (c) retarding the nucleation rate of the neat drug (Konno and Taylor, 2008), and (d) forming hydrogen bonds with the drug. Additionally, the solid solubility of the drug into the polymer and drug-polymer miscibility are equally important to stabilize the SD (reviewed by Laitinen et al., 2012).

Stabilization of the amorphous drug in the SD upon processing, aging, and storage, especially in the conditions of high heat and humidity, is difficult. Chiou (1977) prepared griseofulvin-PEG 6000 SD using the melting method. Griseofulvin precipitated out in an amorphous form while cooling from the melt. XRD scans showed amorphous griseofulvin in freshly prepared samples as expected. However, upon aging, the drug
converted back to its crystalline form. In addition, the pulverization process results in conversion of amorphous griseofulvin to its crystalline form (Chiou, 1977). Compaction of the amorphous SD, which results in phase separation has also been reported previously (Ayenew et al., 2012). The physical instability often results in a decrease in the dissolution of the SD, which compromises the performance of the formulation (Ford and Rubinstein, 1979; Suzuki and Sunada, 1998; Chokshi et al., 2007; Kanaujia et al., 2011).

Increase in temperature results in physical instability in SDs and consequent decrease in dissolution. The dissolution of the IBU microcapsules formulated with ethyl cellulose and a sodium alginate polymer decreased as the temperature increased from 40 °C to 50 °C to 60 °C. The investigators discussed that the physical instability led to the observed decrease in dissolution (Abed Al Rahman., 2006). Pan et al. (2000) reported a decrease in the potency of the drug in the piroxicam-PEG4000 SD upon storage at 25 °C and 37 °C for 10 weeks (Pan et al., 2000).

In some systems, the effect of humidity, however, is more pronounced than that of temperature because the rate of crystallization of the amorphous drug from the glass solution system increases linearly with an increase in humidity. On the other hand, the rate of crystallization of an amorphous drug from an amorphous SD increases in an Arrhenius manner with temperature (Yang et al., 2010). The furosemide-PVP SDs were physically stable at 40 °C/40% RH for 1 year. However, as soon as the SDs were exposed to 75% RH, rapid crystallization occurred (Doherty and York, 1989).

The combined effect of increase in temperature and humidity often expedite the process of physical instability. When the nifedipine-nicotinamide-HPMC SD was exposed to accelerated conditions for one month, the amorphous nifedipine converted to its
crystalline form. The dissolution was decreased and was observed in the order of Initial > 25 °C/60% RH > 30 °C/65% RH > 40 °C/75% RH (Suzuki and Sunada, 1998). Chokshi et al. (2007) prepared the solid solutions of poorly water-soluble drug with PVPK30. The drug crystallized back upon storage at 40 °C/75% RH for 1 month and slowed the dissolution (Chokshi et al., 2007).

Chemical stability of the amorphous drug from the amorphous SD is equally important to retain the original characteristics of the freshly prepared SD. The corticosteroid underwent oxidative degradation in a corticosteroid-PEG SD because of the presence of peroxides in PEG. This compromised the potency of the drug (Khalil et al., 1984). When soft gelatin capsules of IBU formulated with PEG 600 were stored at 40 °C/75% RH, PEG 600 esters were formed, which affected the chemical stability of IBU (Thorsteinsson and Liu, 2011 AAPS). The chemical stability of FUROS worsened in FUROS-PVP co-grounded SD (Adrjanowicz et al., 2011).

Considering the issue of physical and chemical stability associated with SDs, recently stability protocols are often included at the pre-formulation stage while evaluating the SD (Pan et al., 2000; Suzuki and Sunada, 1998; Chokshi et al., 2007; Sirnarong et al., 2009; Kanaujia et al., 2011).

The polymeric carriers often enhance the stability of the amorphous drug upon storage at ambient as well as at accelerated stability conditions. An amorphous API alone can convert back to its crystalline form within less than a minute to few days when stored at ambient stability conditions; on the other hand, the amorphous drug in the SD remained stable over a period of 9–22 months (Chyall et al., 2002; Ivanisevic, 2010). Further, most of the stability issues observed in the SD system were often attributed to the carrier
functionality itself. Some examples include but are not limited to- (a) significant adsorption of water vapor by PVP polymer leads to physical instability of the nifedipine-PVP SD upon storage at 21 °C/84% RH compared to that of nifedipine-HPMC SD (Sugimoto et al., 1982), (b) presence of PVP worsens the chemical stability of FUROS (Adrjanowicz et al., 2011), (c) water uptake by PEG leads to instability of the piroxicam-PEG SD upon storage (Pan et al., 2000), (d) peroxides present in PEG lead to oxidative degradation of corticosteroids (Khalil et al., 1984), (e) phenolic impurities in PVP and copovidone degraded the drug via free radical reaction (reviewed Bharate et al., 2010).

Presence of the drug in the amorphous form in AGF SD was the predominant mechanism for the observed dissolution rate enhancement of IBU (Chapter 3). Detailed solution-state and solid-state characterization of the IBU SD have established the presence of IBU-AGF interactions in these systems. On the other hand, evaluation of hygroscopicity of the AGF polymer (Chapter 2) showed that AGF has good hygroscopicity. Therefore, we examined the stability of amorphous IBU from IBU-AGF SD upon exposure to ambient and accelerated storage conditions.

We performed an extensive literature search about the storage stability studies of IBU preparations at pre-formulations to the dosage form development stage. In these studies, % IBU that remained after the stability period was analyzed (Walker et al., 2011; Kianfar et al., 2011; Volonte et al., 2005; Thorsteinsson and Liu, 2011 AAPS). Some studies examined the dissolution of the samples at the end of the study period (Abed Al Rahman et al., 2006; Strouds et al., 2012).

The accelerated stability study of the IBU SD included physical characterization of the SD and dissolution studies at the end of the study period (Xu et al., 2007; Mallick et al.,
Few of these studies focused on the quantitation of isobutylacetophenone (IBAP) (a major IBU degradant) (OXI Liquid Suspension, Oxford PharmaScience Group PLC; Volonte et al., 2005). Therefore, the storage stability of the IBU AGF SD with respect to visual appearance, % weight gain, physical form stability, and chemical stability was examined.

The current investigation had the following objectives:

1) To perform stability study of IBU-AGF solid dispersions at ambient conditions 25 °C, 60% RH for 6 months and at accelerated conditions 40 °C, 75% RH for 3 months

2) To evaluate visual appearance and weight gain of the solid dispersions at the end of the study

3) To evaluate physical stability of amorphous IBU at the end of the study

4) To evaluate the chemical stability of the IBU with respect to IBAP content at the end of the study

For the solid dispersion to be utilized in a practical dosage form the following criteria should be satisfied:

1. The drug remains in the amorphous phase as shown by:
   a) An absence of the diffraction pattern signifying crystalline IBU

2. IBU does not significantly degrade chemically as shown by:
   a) An IBAP value is below the USP set specification of 0.1% of IBU
6.2. Materials and Experimental Methods

6.2.1 Materials

ACS grade ammonium nitrate and ACS grade sodium chloride were purchased from Fisher Scientific (Fair Lawn, NJ). Butylated hydroxytoluene (BHT) (99%) and IBAP were purchased from Sigma-Aldrich (St. Louis, MO). IBU was purchased from Spectrum (Gardena, CA). Formic acid was purchased from ACROS chemicals (NJ, USA). All HPLC-grade solvents were purchased from Fisher Scientific (Fair Lawn, NJ).

6.2.2 Stability study

Additional batches of IBU-AGF SDM and IBU-AGF MSD were prepared with 0.02% BHT, an antioxidant. The stability study of IBU AGF formulations was performed at 25 °C, 60% RH (2560) for 6 months and at 40 °C, 75% RH (4075) for 3 months according to ICH guidelines (Q1A (R2); WHO Stability Guidance 2009). The respective controlled stability conditions were 25 °C, 0% RH (2500) for 6 months and at 40 °C, 0% RH (4000) for 3 months.

Accurately weighed samples (~0.2–0.35 g for MSD, ~1 g for PM and SDM, 0.75–1 g for HPMCK3 SDM, and 0.3–0.5 g for blank polymer SDM samples) were placed in a clear bottle. The bottles were placed (open) in desiccators with either desiccant into it or the saturated salt solution specific to humidity conditions (60% RH or 75% RH). The saturated ammonium nitrate solution and the saturated sodium chloride solution were used to maintain 60% RH and 75% RH, respectively (Young et al., 1967). Then, the desiccators were closed airtight using vacuum grease. The desiccant silica gel was completely dried before use by drying overnight in an oven at 80 °C. The experiment was performed in triplicate. The temperature was monitored throughout the study period. At
the end of the study period (3 months for 4075/4000 and 6 months for 2560/2500), the samples were removed from the desiccators, observed for physical appearance, weight change, and evaluated for physical and chemical stability.

6.2.3 Conventional DSC

The method has been discussed previously (Chapter 3, section 3.2.6)

6.2.4 XRPD

The method has been discussed previously (Chapter 3, section 3.2.7)

RDC was calculated using the following equation

\[
RDC = \frac{I_{\text{sample}}}{I_{\text{drug}}} \]

\(I_{\text{sample}}\) - Peak height of the formulation under investigation at the same angle (2\(\theta\))

\(I_{\text{drug}}\) - Peak height of the neat drug with the highest intensity at the angle (2\(\theta\))

(Ryan, 1986; Ribeiro et al., 2003; Dalwadi et al., 2010).

Neat IBU diffraction peak at 22.4 (2\(\theta\)) was used for calculating RDC of the stability samples.

6.2.5 FTIR spectroscopy

The method has been discussed previously (Chapter 2, section 2.2.2)

6.2.6 HPLC instrumentation

HP1100LC (Hewlett Packard 1100 LC) system was equipped with a degasser (G1322A), a quaternary pump (G1311A), an autosampler (ALS G1313A), a column oven Colcomp (G1316A) and a variable wavelength detector (G1314A). Software Chemstation version
B.01.01 (Agilent Technologies) was used to control the instrument, for data processing, data acquisition and data analysis.

6.2.7 Mobile phase

Nanopure water and HPLC-grade acetonitrile (ACN) were first filtered separately under vacuum using a 0.45µm nylon membrane filter and then degassed using a helium sparge. The mobile phase consisted of 0.5% formic acid in water:ACN (35:65 v/v) was prepared.

6.2.8 Calibration curve

The calibration curve of IBU and IBAP were separately prepared in the mobile phase. A stock solution of IBU/IBAP was prepared by dissolving 25 mg of IBU/IBAP into 5–10 mL of ACN. The final volume was made up to 100 mL with the mobile phase. The stock solution was further diluted using the mobile phase to obtain various working concentrations of IBU and IBAP. The concentration range of standard curve was 2.5 to 25 µg/mL for IBU and 0.25 to 7.5 µg/mL for IBAP. The standard solutions were injected randomly and were analyzed using optimized chromatographic conditions to ensure that no residue was present between the runs, and there was sufficient wash time. The calibration curve was prepared using peak area versus IBU/IBAP concentration. The limit of detection (LOD) and the limit of quantification (LOQ) were determined as follows:

\[ \text{LOD} = \frac{3 \text{ SDV}}{x} \] \………………………………………………………………………………..6.2

\[ \text{LOQ} = \frac{10 \text{ SDV}}{x} \] \………………………………………………………………………………..6.3
SDV- Standard deviation of the response

x- Slope of the calibration curve

The selectivity, specificity and system suitability of the method were determined.

6.2.9 Accuracy and precision of the method using spiked samples

To determine the accuracy and precision of the developed method, placebo samples (prepared by dissolving 180 µg/mL of AGF in mobile phase) were spiked with 18 µg/mL of IBU and 12 µg/mL of IBAP. Four injections of this sample were injected randomly and analyzed using optimized chromatographic conditions.

6.2.10 Extraction efficiency

The working solutions of 10% IBU loaded SD (10 µg/mL), 10% IBU loaded PM (10 µg/mL concentration), and 20% IBU loaded SD (20 µg/mL concentration) were prepared. All formulations were pulverized. Then, 100 mg of this fine powder was placed in a 100-mL volumetric flask and dissolved in the mobile phase. After initial agitation using a stir bar and stir plate, the samples were bath-sonicated for 20 min to 1 h. We diluted 1-mL aliquots of this solution to 10 mL volume of mobile phase to obtain the working sample solution. The resulting solution was filtered using a 0.45 µm nylon syringe filter and assayed using an optimized HPLC method. We analyzed the precision, reproducibility, and accuracy of the IBU extraction process. Further, we performed DSC and FTIR spectroscopy of the solid remains after the extraction process.
6.3. Statistical Analysis

Minitab 16.0 (Minitab Inc.) software was used for statistical analysis. The statistical analysis of weight gain data was performed using ANOVA with a pairwise multiple comparison procedure. Differences were considered significant when \( p < 0.05 \). Tukey’s test for multiple comparisons was used to calculate the significant differences.

6.4. Results and Discussions

The stability study at the preformulation stage aimed to determine whether amorphous IBU from IBU-AGF SD remained physically and chemically stable upon storage at 25 °C/60% RH for 6 months and at 40 °C/75% RH for 3 months. The SDs prepared with BHT were included to investigate whether oxidative degradation of IBU would be inhibited by BHT, an antioxidant. BHT is usually added to the formulation up to 3% on a weight basis to be effective as an antioxidant (Motola et al., 1993). The SD at 10% DL was prepared with 0.02% BHT. 10 IBU AGF SD BHT formulation was found equivalent to 10 IBU AGF SD formulation (Appendix Figure G.2, Figure G.3, and Figure G.4).

The 20% SDs were included in the stability protocol to assess the effect of the stability conditions on the stability of the miscible (10% DL) versus immiscible (20% DL) SDs. The respective PMs were included as crystalline control samples. HPMCK3 SD and HPMCK3 PM were included to compare the AGF polymer to HPMCK3 in terms of the stabilization effect on amorphous IBU under stability conditions. Throughout the study period, the temperature was well-controlled. For a stability temperature at 40 °C, the mean temperature was 40.56 ± 0.60 °C over a period of 3 months. The variation in the
room temperature was ±2 °C over a period of 6 months. The conditions remained dry as indicated by desiccant indicators.

6.4.1. Visual appearance and weight gain

The AGF formulation became sticky and hard at 4075 stability condition (Appendix Table G.2). It is typical of the gum characteristics. The AGF polymer was expected to form a sticky hard mass upon exposure to 75% RH considering the moderate hygroscopicity of AGF. The SD formed with PVP VA became hard upon storage at 40 °C/75% RH (Kanaujia et al., 2011).

The color of the AGF SDM and AGF MSD formulation changed to light brown at 4000 stability condition. The color of the AGF SDM, AGF MSD and AGF PM turned to medium dark brown to dark brown at 4075 stability condition. A similar color change was observed at 4000 stability condition (Appendix Table G.2). An interesting observation is that the color change was not observed in 10 IBU AGF PM and neat AGF polymer at 40 °C. Thus, the formation of a SD, along with temperature and humidity excursion contributed to the polymer discoloration.

Discoloration is mostly caused by oxidative degradation of the phenolic compounds present in the AGF polymer itself. The phenolic compounds usually undergo thermal degradation and oxidative degradation upon heat treatment or aging. That results in discoloration (Neverova et al., 2011; Quinde-Axtell and Baik, 2006; Lee et al., 1990; Fabios et al., 2000). The possibility of thermal or oxidative degradation of the AGF
polymer is rare. Further studies are required to determine the degradation of the phenolic compounds.

Very few studies have reported color discoloration of drug delivery systems upon storage stability. The color of theophylline carboxymethyl chitosan hydrogel changed to brown at the end of a 6-month storage stability study at 25 °C/60% RH and 30 °C/65% RH (Yadav and Shivakumar, 2012).

BHT did not inhibit discoloration in 10 IBU AGF SD formulations, which suggested that BHT may not be able to prevent degradation of the phenolic compound. BHT was added in the 10 IBU-AGF SD formulations to prevent the degradation of IBU. The IBU-HPMCK3 SD and IBU HPMCK3 PM retained their white color even at accelerated conditions. This observation is similar to that of no visual changes observed in metformin hydrochloride-HPMC SD stored at 40 °C/75% RH for 6 months (Patil et al., 2010).

The samples stored at 2500 conditions were white and dry whereas those stored at 2560 conditions were white and non-sticky.

The IBU-AGF formulations absorbed a substantial amount of moisture when stored at 2560 and 4075 conditions (Appendix Table G.1). The absorbed moisture was in the order of MSD > SDM > PM. However, compared to the PM, the SDM did not show a significant increase in % weight gain at both 2560 and 4075 conditions. These findings are similar to those reported in a previous study of albendazole-PVP SD versus PM (Kalaiselvan et al., 2006).

The % weight gain was higher in IBU-AGF formulations than in IBU-HPMCK3 formulation. Although, both the neat AGF and the neat HPMCK3 polymer absorbed
nearly the same amount of moisture at 2560 conditions, % weight gain by the neat AGF polymer doubled as that of the neat HPMCK3 at 4075 conditions. These were expected findings considering that the AGF polymer was more hygroscopic than the HPMC polymer (Chapter 2; Cavinato et al., 2010).

The % weight gain for AGF based SDM formulations (4075) was between the % weight gain reported value of ~10% for PVPVA-based SD (Kanujia et al., 2011; Kubo et al., 2011) and ~20% for PVP-based SD exposed to 40 °C/75% RH (Kanujia et al., 2011). The % weight gain data suggest that compared to the neat AGF polymer, IBU AGF SDM formulations were less hygroscopic, which was further confirmed from the DDI data of AGF and 10 IBU AGF SDM (Appendix Figure G.1).

6.4.2. Physical stability

The stability samples were analyzed using DSC and XRPD to access the physical stability of the amorphous IBU upon storage at ambient condition and accelerated condition. The FTIR analysis was performed to investigate whether solid-state hydrogen bonding between IBU and the AGF polymer, a mechanism for the stability of IBU-AGF SD, changed over the stability study period.

6.4.2.1 DSC

The DSC endotherm indicated that the 10 IBU AGF MSD, 10 IBU AGF MSD BHT, and the 10 IBU HPMCK3 SDM formulations were stable at all the stability conditions (Figure 6.4, Figure 6.6, and Figure 6.8). The SDM formulations were stable at desiccant conditions irrespective of % DL. The melting endotherm appeared with a minute
intensity in 10 IBU AGF SDM and in 10 IBU AGF SDM BHT formulations (Figure 6.1, Figure 6.3) at 2560 and, 4075 conditions and in 20 IBU AGF SDM formulations at 4075 condition (Figure 6.2). Water acted as a plasticizer in SDM formulations, which converted amorphous IBU to its crystalline form; however, in a non-substantial amount. Contrary to the expectation, 20 IBU-AGF SDM formulations were physically stable at humid conditions although this formulation contained a small amount of the crystalline IBU.

DSC thermograms of the IBU AGF formulations exposed at 4075 conditions (irrespective of %DL) showed an observable thermal event above 120 °C. This thermal event could be due to absorbed water vapor because of the large quantity of absorbed moisture. However, absence of this thermal event in samples stored at 2560 conditions cannot be explained. Another possibility is that this thermal event indicates either degradation of the phenolic compound or hydrocarbon degradation. However, absence of this thermal event in the stability samples stored at 4000 stability condition where discoloration was observed can not be explained with the available data.
Figure 6.1 DSC thermograms of 10 IBU AGF SDM at stability conditions

Figure 6.2 DSC thermograms of 20 IBU AGF SDM at stability conditions
Figure 6.3 DSC thermograms of 10 IBU AGF SDM BHT at stability conditions

Figure 6.4 DSC thermograms of 10 IBU AGF MSD at stability conditions
Figure 6.5 DSC thermograms of 20 IBU AGF MSD at stability conditions

Figure 6.6 DSC thermograms of 10 IBU AGF MSD BHT at stability conditions
Figure 6.7 DSC thermograms of 10 IBU AGF PM at stability conditions

Figure 6.8 DSC thermograms of 10 IBU HPMCK3 SDM at stability conditions
6.4.2.2 XRPD

The RDC values of the stability samples are enlisted in the Table 6.1 and the corresponding XRPD diffractogram overlays are mentioned in the appendix (Appendix H). The RDC values were 0 or less at all the stability conditions compared to those at the initial condition for both SDM and MSD formulations. This suggests the stability of the amorphous IBU. These findings confirmed the above DSC findings.

Surprisingly, the PMs stored at 4075 conditions showed enhanced physical stability compared to those stored in the initial storage conditions. Compared to the SDs stored at 2500 and 2560 conditions, those stored at 4000 and 4075 conditions showed enhancement in the physical stability. Increase in the % of amorphous drug in the SD
under accelerated conditions indicated stronger solid-state hydrogen bonding. Therefore, FTIR analysis of these stability samples was performed.

Table 6.1 RDC (XRPD) of IBU AGF formulations at stability conditions

<table>
<thead>
<tr>
<th>Formulations</th>
<th>INITIAL</th>
<th>2500 (6M)</th>
<th>2560 (6M)</th>
<th>4000 (3M)</th>
<th>4075 (3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT IBU</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NEAT AGF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 IBU AGF SDM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>0.076</td>
<td>0.020</td>
<td>0.0325</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>0.049</td>
<td>0.016</td>
<td>0.019</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>0.015</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>0.046</td>
<td>0</td>
<td>0.023</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 IBU AGF MSD BHT</td>
<td>0.018</td>
<td>0</td>
<td>0.022</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>0.105</td>
<td>0</td>
<td>0.101</td>
<td>0.010</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>0</td>
<td>0.015</td>
<td>0.017</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>0.273</td>
<td>0.1255</td>
<td>0.083</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note- IBU as a reference (2θ of 22.4°).
### 6.4.2.3 FTIR spectroscopy

Table 6.2 FTIR shifts in IBU major IR band (1708.7 cm\(^{-1}\)) in the stability samples

<table>
<thead>
<tr>
<th>Formulations</th>
<th>INITIAL</th>
<th>2500 (6M)</th>
<th>2560 (6M)</th>
<th>4000 (3M)</th>
<th>4075 (3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>1719.95</td>
<td>1717.3</td>
<td>1713.47</td>
<td>1718.97</td>
<td>1717.85</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>1713.92</td>
<td>1719.99</td>
<td>1720.65</td>
<td>1717.58</td>
<td>1718.16</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>1718.57</td>
<td>1720.07</td>
<td>1718.21 *</td>
<td>1711.17</td>
<td>1718.73</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>1719.8</td>
<td>1719.8</td>
<td>1709.8 *</td>
<td>SP</td>
<td>‡</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>1719.66</td>
<td>1719.65</td>
<td>1713.41</td>
<td>1718.53</td>
<td>1718.5 *</td>
</tr>
<tr>
<td>10 IBU AGF AGF BHT</td>
<td>1719.95</td>
<td>1719.4</td>
<td>1718.5 *</td>
<td>1718.6 *</td>
<td>‡‡</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>1710.26</td>
<td>1719 *</td>
<td>1718.5*</td>
<td>1711.34</td>
<td>1719.1 *</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>1732.1</td>
<td>1731.53</td>
<td>1712.8</td>
<td>1731.4 *</td>
<td>1722.8 *</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>1723.3 *</td>
<td>1714.5 *</td>
<td>1710.04</td>
<td>1715.6 *</td>
<td>1708.76</td>
</tr>
</tbody>
</table>

Note: *Less intense; ‡ No IR band; SP-Sample spilled.

Temperature and moisture have an effect on the strength and extent of the solid-state hydrogen bonding between the drug and polymer. With an increase in temperature, the drug-polymer hydrogen bonding tends to weaken (Six et al., 2003). Similarly, water tends to disrupt hydrogen bonding in the amorphous SDs (Crowley and Zografi, 2002).

The shifts in IR bands at 1708.7 cm\(^{-1}\) (IBU, C=O stretch) of stability samples are listed in Table 6.2. The hydrogen bonding remained unaffected in SDM and MSD formulation, except in 10 IBU-AGF MSD at 2560 stability condition. In PMs, the solid-state hydrogen bonding was formed between IBU and AGF polymer at all stability conditions, except at...
4000 conditions. This finding was similar to that observed in the HPMC samples, except for 10 IBU-HPMC PM at 4075 stability condition.

In this study, the retention or formation of solid-state hydrogen bonding interactions was observed at accelerated stability conditions. At higher temperature, the moisture may escape and more sites may become available for hydrogen bonding as evident from the larger shifts.

DSC, XRPD, and FTIR data showed that IBU-AGF SDM and IBU-AGF MSD formulations were physically stable at 10% and 20% DL under 2560 and 4075 stability conditions. Similarly, XRD indicated that IBU-Kollidon CL SD was amorphous at 25 °C/65% RH for 3 months (Xu et al., 2007). Shen et al. (2010) reported that IBU-SBA15 co-spray-dried SD was physically stable under accelerated conditions (40 °C/75% RH) for 12 months. The investigators did not observe an apparent diffraction peak, which represents IBU crystallinity (Shen et al., 2010) similar to that our study findings. IBU-Kaolin SD was physically stable (XRD, FTIR) upon storage for 10 weeks at 40 °C/75% RH (Mallick et al., 2008).

Solid-state hydrogen bonding remained intact in the SD and was attributed to the stability of the IBU SD. Drug-polymer hydrogen bonding plays a significant role in the stability of the SD (Taylor and Zografi, 1997; Xu et al., 2007). Hydrogen bonding in indoprofen-PVP SD protects the SD against phase separation when exposed to 40 °C/69% RH (Vasanthavada et al., 2005). The strong anti-plasticizing effect of AGF may stabilized the IBU-AGF SD in the current study.
Unlike the findings reported by Ivanisevic (2010), no differences were observed in the physical stability of miscible (10% DL) versus immiscible (20%) IBU-AGF SD. It is interesting to note that AGF has successfully stabilized amorphous IBU in the presence of the a small amount of crystalline IBU in 20% DL IBU AGF SDM formulation under accelerated stability conditions.

A small amount of crystalline drug was present in 10% DL SD stored at 25 °C/60% RH. This can be attributed to the hygroscopicity and moisture sorption tendency of the AGF polymer. At 60% RH, moisture uptake by the neat AGF polymer was ~10% (Appendix Figure G.1). Comparison of sorption data from Cavinato et al., (2010) with DDI data of AGF polymer (Chapter 2) indicated that moisture uptake by the neat AGF polymer was substantially lower than that by PVP (~21%) but was greater than that by the HPMCK3 polymer (~5% moisture uptake). The moisture uptake reduced upon SD formation (Appendix Figure G.1). However, there is a possibility that water acted as a plasticizer, which lowered the Tg of the SD and resulted in the observed increase in crystallinity.

The stabilization potential of AGF for amorphous IBU was comparable to that of HPMCK3 as shown by the results of solid-state characterization of the IBU-HPMCK3 SDM.

Contrary to our expectation, physical stability of amorphous IBU was enhanced when stored at 4000 and 4075 for both AGF- and HPMCK3-based SDs. This finding implied that the Tg of AGF SDs did not decrease substantially despite exposure to accelerated conditions. Further studies of Tg versus equilibrium moisture content similar to the ones performed by Cavinato et al. (2010) and Konno and Taylor (2008) should be performed for these IBU-AGF SD formulations.
6.4.3. Chemical stability

IBU is a widely used analgesic. It is included in WHO essential medicine list for adult and children (WHO Essential Med., 2011). Therefore, the degradation profile of IBU has been extensively studied (Farmer et al., 2004; Cory et al., 2010; Illes et al., 2013; Castell et al., 1987; Farmer et al., 2002). IBAP is the main degradation product of IBU as well as its major impurity (Higgins et al., 2001 Analytical Profile of Drug Substances and Excipients and Farmer et al., 2002). IBAP is known to cause adverse effects in the central nervous system (Gasco-Lopez et al., 1999). Further, IBAP was reported to be toxic to cultured fibroblasts in an in vitro assay (Castell et al., 1987). Therefore, the United States Pharmacopeia (USP) and British Pharmacopoeia (BP) have set limits for IBAP content in IBU raw material, bulk product, and dosage form (USP, 29th Edition and British Pharmacopoeia, 3rd Edition).

Therefore, while evaluating the chemical stability of IBU from IBU-AGF SD, a special attention was focused on determination of IBAP. Some of the physical-chemical characteristics of both IBU and IBAP are summarized in Table 6.3.
Table 6.3 The physio-chemical properties of IBU and IBAP

<table>
<thead>
<tr>
<th>Properties</th>
<th>IBU</th>
<th>IBAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td><img src="image1" alt="IBU Structure" /></td>
<td><img src="image2" alt="IBAP Structure" /></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>206.28</td>
<td>176.25</td>
</tr>
<tr>
<td>pKa</td>
<td>4.41</td>
<td>-</td>
</tr>
<tr>
<td>H Donor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>H Acceptor</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Log P</td>
<td>3.722</td>
<td>3.54</td>
</tr>
<tr>
<td>LogD (pH5.5)</td>
<td>3.72(pH 1)/3.58(pH4)/1.15(pH 7)</td>
<td>3.54 (pH5.5 and pH 7.4)</td>
</tr>
<tr>
<td>Solubility according to pH</td>
<td>Sparingly soluble (pH 1-7); Soluble (pH 8); Very soluble (pH 10)</td>
<td>-</td>
</tr>
</tbody>
</table>

6.4.3.1 Simultaneous determination of IBU and IBAP using reverse phase-HPLC

Many HPLC methods for determination of IBU have been reported in the literature. The USP states 2 HPLC methods for the quality control of IBU. The first method involves detection of impurities in the raw material at 214 nm where the individual impurity is specified not to exceed 0.3% and the sum of all the impurities should not exceed 1% based on peak area. The second method for assay of IBU includes detection of IBAP from bulk IBU at 254 nm where the content of IBAP is specified not to exceed 0.1% of IBU (USP, 29th Edition, Ibuprofen).
The BP described a similar method for the quality control of IBU raw material. It specifies 5 impurities, one of which is IBAP. The BP states that the area of the individual peak should not exceed 0.3% of the IBU peak area and the sum of areas of all these secondary peaks should not exceed 0.7% of the IBU peak area (BP, 3rd Edition). Further, the USP and BP mention that the IBAP levels should be controlled in pharmaceutical dosage forms. As per the USP, IBAP levels should not exceed 0.25% in IBU oral suspension and 0.1% in IBU tablet (weight basis) (USP, 29th Edition, Ibuprofen Tablet and Ibuprofen Oral Suspensions).

The USP IBU assay method was found very selective and specific for the quantitation of IBU and IBAP (Farmer et al., 2002; Truong, application note SI-01028). Therefore, we modified the USP IBU assay method to determine the IBU and IBAP content of the stability sample.

The main goal of the method development was to simultaneously assay IBU and IBAP with high sensitivity. The method was optimized using different mobile phases (ACN:phosphate buffer, pH 3.0, vs. ACN:formic acid-acidified water), different ratios of the organic and aqueous phases of the mobile phase (40:60 vs. 35:65 for formic acid-acidified water:ACN), different injection volume (20 µL vs. 50 µL), and different wavelength (222 nm vs. 254 nm vs. 214 nm).
Table 6.4 The optimized chromatographic conditions for the simultaneous determination of the IBU and IBAP

<table>
<thead>
<tr>
<th>Chromatic method</th>
<th>Optimized conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Isocratic</td>
</tr>
<tr>
<td>Analytical Column</td>
<td>Agilent Eclipse Plus C18 (4.6x150mm, 5µm) USP L1 ODS column</td>
</tr>
<tr>
<td>Mobile Phase</td>
<td>Water (acidified with 0.5% formic acid) : Acetonitrile (35:65 v/v)</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>Detection Wavelength</td>
<td>222 nm (0 to 6 min) and 254 nm (6 to 9 min)</td>
</tr>
<tr>
<td>Post Time (column equilibrium time)</td>
<td>3 min</td>
</tr>
<tr>
<td>Injection Volume</td>
<td>50 µl</td>
</tr>
<tr>
<td>Pressure</td>
<td>60-64 bar</td>
</tr>
</tbody>
</table>

The preliminary protocol included simultaneous detection of IBU and IBAP first at 254 nm and later at 222 nm. However, the HPLC assay had a limited sensitivity either for IBU (at 254 nm) or for IBAP (at 222 nm) (Figure 6.10 and Figure 6.11). The reason is that IBU has local absorption maxima at 222 nm whereas its degradation product IBAP has local minima at this wavelength (Kucera et al., 2005). On the other hand, IBAP has local absorption maxima at 258 nm (Kucera et al., 2005). An observation similar to that observed in our study was reported by Kucera et al. (2005) in that the sensitivity of IBU and IBAP was compromised at 2 respective wavelengths 219 nm and 258 nm. To overcome this issue, Kucera et al. (2005) successfully monitored the 2 wavelengths for determination of IBU and IBAP (Kucera et al., 2005). Cory et al. (2011) determined the
IBU and IBAP simultaneously the similar way to that of Kucera et al. (2005). Therefore, in this study, programmable switching of the wavelength to obtain greater sensitivity and selectivity for both IBU and IBAP was optimized.

The optimized chromatographic conditions are enlisted in Table 6.4. IBAP eluted at 7.1 min and IBU at 4.9 min.

![HPLC Chromatograms]

Figure 6.10 The HPLC chromatograms illustrating the sensitivity of detection at different wavelength I
Figure 6.11 The HPLC chromatograms illustrating the sensitivity of detection at different wavelength II

6.4.3.2 Calibration curve linearity

The linearity details are given in the Table 6.5. The $R^2$ values shows the excellent relationship between peak area and concentration for both IBU and IBAP.
Table 6.5 Calibration curve linearity details for IBU and IBAP

<table>
<thead>
<tr>
<th>Calibration parameter</th>
<th>IBU</th>
<th>IBAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration range (µg/ml)</td>
<td>2.5 to 25</td>
<td>0.25 to 7.5</td>
</tr>
<tr>
<td>Equation</td>
<td>Y=105.29X</td>
<td>Y=223.35X</td>
</tr>
<tr>
<td>Correlation coefficient $R^2$</td>
<td>0.9997</td>
<td>0.9999</td>
</tr>
<tr>
<td>LOD (µg/ml)</td>
<td>0.3918</td>
<td>0.1031</td>
</tr>
<tr>
<td>LOQ (µg/ml)</td>
<td>1.3063</td>
<td>0.3439</td>
</tr>
</tbody>
</table>

6.4.3.3 Selectivity and specificity of the method

The chromatograms obtained under optimum conditions (Figure 6.12) show that IBU and IBAP were well-separated within 9 min. No interference was observed from the AGF/HPMCK3 polymer present in the formulation. This was determined by injecting the blank (mobile phase) and samples of neat polymer, blank AGF SDM, and blank HPMCK3 SDM prepared in mobile phase (Figure 6.12). Determination of system suitability was performed for each analytical run by injecting 3 injections of the freshly prepared standard solutions. The retention time was determined. The retention time for IBU was between 4.9-5.1 min. The retention time for IBAP was between 7.0-7.4 min.
Figure 6.12 HPLC chromatograms illustrating the selectivity and specificity of the method
6.4.3.4 Accuracy and precision of the method from the spiked samples

The accuracy and precision results from the samples spiked with known amounts of IBU and IBAP in AGF polymer solution are shown in Table 6.6. The recovery and %RSD values indicate that this method was highly precise and accurate for determination of IBU and IBAP in the presence of the AGF polymer.

Table 6.6 Accuracy and precision of the spiked samples

<table>
<thead>
<tr>
<th>Compound</th>
<th>Theoretical concentration</th>
<th>Ave % recovery ±Std dev</th>
<th>Accuracy (% relative error)</th>
<th>%RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU</td>
<td>18µg/ml</td>
<td>96.156±0.188</td>
<td>3.843</td>
<td>0.196</td>
</tr>
<tr>
<td>IBAP</td>
<td>12µg/ml</td>
<td>93.230±0.048</td>
<td>6.769</td>
<td>0.051</td>
</tr>
</tbody>
</table>

6.4.3.5 Extraction efficiency

The extraction of the SD and PM was performed with mobile phase as an extraction solvent. The samples were bath-sonicated for 20–30 min to extract the IBU from the IBU AGF samples. Pulverization of the HPMCK3 SDM samples did not yield a fine powder. Therefore, the HPMCK3 SDM sample required bath-sonication for 1 h for complete dissolution of the sample.

The solid remains after the extraction process were dried at room temperature and later in an oven at 45 °C. FTIR and DSC analyses were performed on the solid remain. The FTIR spectra of the solid remains after the extraction were similar to the FTIR spectra of the AGF polymer and showed absence of IBU-specific IR bands at 1708.7 cm$^{-1}$ and 2954 cm$^{-1}$ (Figure 6.13).
Figure 6.13 FTIR of the solid remains after the sample extraction

Figure 6.14 DSC of the solid remains after the sample extraction
DSC of the solid remains from the extraction shows the absence of IBU melting (Figure 6.14). This indicated absence of IBU in the remaining solids after extraction and that the solid remains were the polymer. Thus, results of FTIR spectroscopy and DSC suggested that the extraction solvent and the extraction process extracted 100% of IBU.

The results of extraction efficiency are shown Table 6.7. The % relative error and recovery values are the indication of the accuracy. The %RSD is the indication of the precision and repeatability of the method (USP 29 1225 Validation of Compendia Methods). The extraction of the IBU from the IBU-AGF formulations was precise and show good repeatability. Similar % RSD values were obtained for the extraction of IBU from pharmaceuticals (Matkovic et al., 2005).

The extraction recovery was 77% to 83%. The trend of reduced recovery from the heterogeneous nature of the formulation was evident. Thus, extraction recovery values and the % relative error indicated moderate accuracy. Similar low extraction efficiency because of formulation processing, the resulting encapsulation efficiency, and sample heterogeneity have been reported in a previous study (Cory et al., 2004).

In summary, the extraction process was found highly efficient and precise and showed good repeatability. However, the recovery of the extraction process was moderate because of the heterogeneous nature of the SD samples.
Table 6.7 Recovery, accuracy, and precision of the extraction process

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Theoretical concentration</th>
<th>Ave % extraction recovery±Std Dev</th>
<th>Accuracy relative error (%)</th>
<th>%RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF PM INITIAL</td>
<td>20 µg/ml</td>
<td>83.550±3.070</td>
<td>16.449</td>
<td>3.675</td>
</tr>
<tr>
<td>10 IBU AGF SDM INITIAL</td>
<td>15 µg/ml</td>
<td>77.966±2.559</td>
<td>22.033</td>
<td>3.282</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT 4075</td>
<td>20 µg/ml</td>
<td>66.467±3.184</td>
<td>33.532</td>
<td>4.790</td>
</tr>
</tbody>
</table>

6.4.3.6 Determination of IBU and IBAP in storage stability samples

The %IBU that remained at the end of the stability study period at different stability conditions is shown in Table 6.8. Most of the %IBU assay values were in the range of 60–115%, except for 3 samples, in which the %IBU assay were below 60%. For 2 samples, the %IBU content was above 115% (shown in bold). Under accelerated stability conditions (70 °C and 75% RH for 3 weeks) IBU tablets showed the IBU assay of 83% (Cory et al., 2010). The IBU tablet stored at 27 °C for 36 months showed the IBU assay value from 71.5% to 76.7% (Farmer et al., 2002).

However, no specific trend was observed in the %IBU value and stability conditions, %IBU assay and formulation type, or %IBU assay and polymer type.
Table 6.8 % initial IBU remained in stability samples

<table>
<thead>
<tr>
<th>Formulations</th>
<th>IBU actual conc µg/ml (INITIAL)</th>
<th>% INITIAL</th>
<th>2500 (6M) *</th>
<th>2560 (6M) *</th>
<th>4000 (3M) *</th>
<th>4075 (3M) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>16.163±1.068</td>
<td>100±6.608</td>
<td>102.18±5.719</td>
<td>102.18±5.719</td>
<td>81.996±1.24</td>
<td>105.6±6.339</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>17.953±1.167</td>
<td>100±6.504</td>
<td>95.893±7.702</td>
<td>101.450±2.245</td>
<td>66.098±13.634</td>
<td>84.353±0.742</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>16.003±6.635</td>
<td>100±5.060</td>
<td><strong>57.327±13.629</strong></td>
<td>83.600±6.080</td>
<td>74.265±7.887</td>
<td>68.4245±7.368</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>12.493±0.801</td>
<td>100±6.412</td>
<td>99.575±3.968</td>
<td>109.030±4.512</td>
<td>101.039±1.455</td>
<td><strong>56.097±14.875</strong></td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>14.088±5.459</td>
<td>100±38.75</td>
<td>114.555±44.959</td>
<td>102.214±43.085</td>
<td>SP</td>
<td><strong>130.689±60.255</strong></td>
</tr>
<tr>
<td>10 IBU AGF MSD BHT</td>
<td>21.734±3.981</td>
<td>100±18.317</td>
<td>77.723±22.394</td>
<td>73.553±10.458</td>
<td><strong>63.853±10.583</strong></td>
<td>78.060±12.877</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>17.011±0.971</td>
<td>100±5.708</td>
<td>103.586±5.541</td>
<td>80.640±27.522</td>
<td>112.406±2.224</td>
<td><strong>132.698±1.932</strong></td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>18.182±1.153</td>
<td>100±6.346</td>
<td>87.095±42.543</td>
<td>95.729±3.435</td>
<td>83.523±2.250</td>
<td>100.220±3.0923</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>19.491±0.433</td>
<td>100±2.221</td>
<td>93.246±2.498</td>
<td>75.383±1.823</td>
<td>79.043±1.681</td>
<td>98.693±1.174</td>
</tr>
<tr>
<td>NEAT AGF</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK AGF SDM</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NEAT HPMCK3</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK HPMCK3 SDM</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note- *% of initial IBU concentration remaining; SP-Sample spilled.
The % standard deviation of IBU assay values as high as 8.3% were reported in a stability study of IBU injectables diluted in different vehicles (Walker et al., 2011). Considering that we included SDs in our study, we expected the standard deviation up to 20%. However, few of the standard deviation values were >20% (Appendix Table G.3).

The poor chromatographic results of at least one of the samples from triplicate may result in an apparently higher value of standard deviation. The data were not discarded, but have been taken into the analysis. The poor chromatographic results of the stability samples, which yielded different % assay and standard deviation values have been mentioned in a previous study (Walker et al., 2011; Volonte et al., 2005). IBU degradation and heterogeneous nature of the SD samples have attributed to low %IBU content in our study. However, a clear distinction between these attributing factors could not be made. Overall, the findings were inconclusive.

Therefore, IBAP was used to evaluate IBU degradation instead of %IBU remained at the end of the stability period. A similar approach was followed by Cory et al., (2010). They assessed the degradation of IBU in the IBU tablet under accelerated conditions (70 °C, 75% RH and 3 weeks) from % total degradation rather the %IBU assay remained (Cory et al., 2010). The %IBAP values of IBU (content basis) are shown in Table 6.9.
Table 6.9 IBAP values (% of IBU) in stability samples

<table>
<thead>
<tr>
<th>Formulations</th>
<th>INITIAL</th>
<th>2500 (6M)</th>
<th>2560 (6M)</th>
<th>4000 (3M)</th>
<th>4075 (3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>0</td>
<td>1.4176*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>0</td>
<td>0.8565*</td>
<td>0</td>
<td>3.0986</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>0</td>
<td>0</td>
<td>0.7663*</td>
<td>1.6904*</td>
<td>0</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>0</td>
<td>0.7905*</td>
<td>0</td>
<td>SP</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF MSD BHT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>1.5546*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NEAT AGF</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK AGF SDM</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NEAT HPMCK3</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK HPMCK3 SDM</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note-*Below the quantification limit; IBAP is the % of IBU on a content basis; SP-
Sample spilled

The IBAP values (% of IBU) indicated no correlation between the IBAP concentration and the %IBU assay remained at the end of the stability period. The length of the study period (6 months vs. 3 months) was also not related to the observed %IBAP values. It is obvious that % IBAP values were 0 when the formulations were stored under humidity condition, especially at 4075 conditions (Table 6.9). The IBAP values were 0 at 2560 (except in the case of 10 IBU-AGF SDM).
BHT, completely prevented the degradation of IBU to IBAP with IBAP content equal to 0. Most of the standard deviations of IBAP concentration (µg/mL) were below the detection limit and few of them below the quantification limit.

The %IBAP value of one of the formulation stored at 4000 stability conditions (~3.1%) was very high. However, under accelerated conditions (70 °C/75% RH for 3 weeks) %IBAP values as high as 7.7% have been reported for branded IBU tablets (Cory et al., 2010).

Moreover, when IBAP was detected in the formulations, its content was well-above the USP specification of 0.1% of IBU on a content basis. In fact, IBAP was detected in some initial formulations, and it was well above the set specification of 0.1% of IBU.

A small amount of IBAP and other degradation products can be present in a bulk drug as well as in a new preparation (Volonte et al., 2005; Gasco-Lopez et al., 1999). IBAP has been detected in IBU gel formulation (Gasco-Lopez et al., 1999) and in freshly prepared compounded pediatric formulation (Volonte et al., 2005). This shows that formation of IBAP can be inhibited to below the set limit but cannot be completely eliminated even if the formulation is stored under ideal conditions. Our HPLC data of the initial samples as well as PM sample further attest the above observation.

The reason for the high levels of IBAP could be that IBU was present in an amorphous form in these formulations. Compared to the crystalline form, the amorphous form of a drug is usually highly prone to chemical degradation (Carstensen and Morris, 1993; Oberholtzer and Brenner, 1979).
The 4075 stability condition completely inhibited the IBAP formation. Similarly, the 2500 stability condition had higher %IBAP values than 2560 stability condition (except for 10 IBU-AGF MSD). Thus, formation of IBAP was lesser in humid conditions than in desiccant conditions at both temperatures. This could be because of the reorientation of IBU in the presence of water vapor, which makes IBU less susceptible to degradation (Humphrey et al., 2009 AAPS Abstract). To understand the mechanism underlying inhibition of IBAP formation in humid conditions, SEM of 20 IBU AGF SDM samples from 4000 and 4075 conditions was performed and the results were compared (Figure 6.15).

The SEM pictures showed that desiccant conditions completely exposed the IBU for degradation. However, at 4075 condition, the wet polymer mass coated the IBU and thus made it less susceptible for degradation.

Figure 6.15 SEM microphotographs of 20 IBU AGF SDM stored at accelerated condition  
Note-A-20 IBU AGF SDM at 4000; B-20 IBU AGF SDM at 4075.
The presence of a substantially higher %IBAP value at 4000 suggested that IBU degradation was most likely from thermal degradation. However, BHT prevented IBAP formation (IBU degradation). This suggests that IBU degradation could be also because of oxidative degradation. The possibility of degradation of phenolic compounds from the AGF polymer, which may further worsen IBU degradation at 40 °C cannot be completely denied. Phenolic impurities in PVP and copovidone degrade the drug via free radical reaction (reviewed Bharate et al., 2010).

Previously, Adrjanowicz et al., (2011) implied hydrogen bonding between FUROS and PVP as one of the reasons of chemical instability of FUROS (Adrjanowicz et al., 2011). However, in our study, solid-state IBU-AGF hydrogen bonding was not related to chemical degradation of the amorphous IBU.

AGF can compete with IBU as a substrate for oxidation and thus reduce the oxidative degradation of IBU. However, our findings were contrary to this assumption. The reason being that AGF requires a stronger oxidizing agent than environmental air or the passage of oxygen for oxidation (Borisov et al., 2004; Mudarisova et al., 2010).

Thus, IBU SD formulations were chemically stable at 2560 and 4075 stability conditions. However, at 4075 stability condition, a significant discoloration of the polymer was observed; therefore, the 2560 would be the optimum stability condition to store these SDs. The 10 IBU-AGF SDs prepared with BHT were chemically stable at 2500 stability condition.

In this study, HPMCK3 was superior to AGF polymer in protecting amorphous IBU against chemical degradation. This is evident from the %IBAP value of 0 and %IBU value from 75% to 100%. No discoloration was observed in HPMCK3 polymer.
Thus, the enhanced physical and chemical stability of the amorphous IBU from the SD at accelerated stability conditions compared to that at ambient stability conditions observed in this study cannot be attributed to experimental uncertainty. These findings are contrary to those reported in previous studies in which the SD was physically stable at 25 °C/60% RH but rarely at 40 °C/75% RH. The studies that reported this finding are - Shah et al. (2013), Suzuki and Sunada (1998), Thorsteinsson and Liu (2011 AAPS), and Janssens et al. (2008).

Storage of IBU AGF SDM at 2500 would be desirable for physical stability of the AGF polymer and amorphous IBU. On the other hand, the 2560 stability condition was optimum for chemical stability of the amorphous IBU from the amorphous SD. The 10 IBU AGF SDM with 0.02% BHT was chemically stable at 2500 conditions. Thus, the IBU AGF formulation prepared with an antioxidant can be stored at 2500 to prevent physical and chemical degradation of the polymer and amorphous IBU. Further, storage of the IBU AGF SD at room temperature and ambient humidity (35%) is expected to provide chemical and physical stability.

Although, the stability study performed here was more of a screening study, further stability studies using closed vial and Activ-vial (complete prevention of moisture) would be useful. Further, a study in which headspace oxygen is removed and replaced with nitrogen to prevent oxidative degradation of the drug or the polymer (or of phenolic compound), if any, should be performed. Oxidative and thermal degradation of the phenolic compound, the most probable reason of polymer discoloration, needs to be evaluated.
6.5. Summary and Conclusions

This study aimed to evaluate the physical and chemical stability of the IBU-AGF SD upon exposure to 25 °C/60% RH for 6 months and to 40 °C/75% RH for 3 months. Physical appearance indicated that the IBU-AGF SD stored at 40 °C changed the color of the SDs to light medium to dark brown. The % weight gain data suggested that IBU-AGF SDM absorb lesser moisture than the neat AGF polymer upon exposure to humid conditions. The IBU AGF miscible (10% DL) and immiscible (20% DL) SDs were XRPD-amorphous upon exposure to the accelerated conditions. Solid-state hydrogen bonding was retained in these SDs. This was the mechanism of physical stability of the SDs at accelerated stability conditions. Contrary to our expectation, the SDs showed enhanced physical stability at 40 °C/75% RH.

The HPLC method for the simultaneous determination of IBU and IBAP with the highest sensitivity was developed by switching the wavelength. The calibration curves for both IBU and IBAP showed good linearity. Complete extraction (100%) of the IBU was achieved using mobile phase as an extraction solvent. Although the SD samples were heterogeneous, most of the %IBU assay values were ~80–115% at 2500 and 2560 stability conditions. This finding indicated that IBU was chemically stable if stored under these stability conditions. IBU degradation contributed to the observed decrease in %IBU assay values. IBAP (% of IBU) was undetected in most of the sample. Addition of BHT completely prevented IBU degradation. This suggests that the IBU-AGF SD should be formulated with an antioxidant.

The AGF was comparable to HPMCK3 in that both these polymers protected IBU against physical and chemical instability upon exposure to 40 °C/75% RH for 3 months.
However, discoloration of the polymer at 40 °C was observed in the AGF polymer but not in HPMCK3. Finally, this study provides preliminary results about storing the SDs as well the AGF polymer at room temperature and at desiccant conditions.
CHAPTER 7

CONCLUSIONS

The advanced amorphous SD processing and evaluation techniques have established the significance of the carrier for preparation of SDs. Most of the recent studies have comprehensively and retrospectively evaluated the well-established carriers such as HPMC and PVP. Novel carriers for SDs, such as Soluplus and Solumer, have attracted the attention of many investigators. The GRAS designated, larch arabinogalactan (FiberAid grade) (AGF) is an amorphous polymer with low Tg and OH functional groups. This provides an opportunity to evaluate AGF as a carrier for preparation of amorphous SDs. Therefore, we performed a comprehensive evaluation of the AGF polymer as a carrier for SDs.

Characterization of the AGF polymer provided evidence of its suitability as a carrier for SDs. The interesting findings were its Tg, ~82 °C and degradation temperature, 185 °C. AGF has very low viscosity and good hygroscopicity. The flow properties of the AGF polymer were similar to those of the HPMCK3 polymer. HPMCK3 was selected as the control polymer for this study.

AGF polymer successfully formed amorphous SDs and enhanced IBU dissolution using a modified water-in-oil emulsion solvent evaporation method (MSD) and a modified solvent evaporation method (SDM). Extensive solid-state characterization of these SDs using DSC, XRPD, SEM, TMA, and FTIR spectroscopy showed formation of amorphous IBU to ~20% DL. Solid-state hydrogen bonding was the mechanism underlying the loss in IBU crystallinity. IBU AGF polymer was miscible at 10% DL in the AGF SD. The
dissolution enhancement from the IBU-AGF SD was significantly greater than that from neat IBU. $^1$H-NMR indicated the presence of solution-state interactions.

Solid-state characterization of IBU-HPMCK3 SDM showed the presence of amorphous IBU at 10% DL and partially crystalline IBU at a 30% DL. This finding was similar to that reported for the IBU-AGF SDM system. The dissolution enhancement of 10 IBU-AGF SDM was greater than that for the 10 IBU-HPMCK3 SDM.

ITRA-AGF SDM and KETO-AGF SDM were prepared at 10%, 20%, and 30% DLs. The dissolution rates of these SDM formulations was significantly higher than those of their respective neat drugs. We compared dissolution enhancement of the ITRA-AGF SDM, KETO-AGF SDM, and IBU-AGF SDM. The observed dissolution enhancement in terms of $R_{DRT}$ was in the order of KETO-AGF SDM > ITRA-AGF SDM > IBU-AGF SDM.

The solubilizing power of the AGF polymer for these drugs, on the other hand, was in the order of ITRA > IBU > KETO. The drug polymer miscibility in the AGF SD was in the order of KETO ≥ ITRA > IBU. Formation of the amorphous drug and solubility enhancement because of the AGF polymer were the predominant mechanisms underlying the increase in dissolution of these poorly water-soluble drugs.

The solid-state evaluation of the SDM of additional poorly water-soluble drugs were performed. The selected drugs had different physiochemical properties. The results showed that in addition to the glass forming ability of the individual drug, the ability of the AGF polymer to inhibit drug crystallization was pivotal. The solid-state drug-AGF hydrogen bonding, drug-AGF solid-state acid-base interactions, anti-plasticizing effect of the AGF, and inherent ability of AGF to inhibit drug crystallization governed the crystallization inhibition by AGF polymer.
The stability of IBU-AGF SDs after storage at 25 °C/60% RH (6 months) and at 40 °C/75% RH (3 months) showed that amorphous IBU was physically stable. Solid-state hydrogen bonding was associated with the physical stability of the amorphous IBU exposed to ambient and accelerated stability conditions. IBU was chemically stable. IBAP, the major degradation product of IBU, was not detected in most of the samples. The ability of the AGF polymer to stabilize amorphous IBU physically was equivalent to that of HPMCK3. HPMCK3 polymer was superior to AGF polymer for chemical stabilization of the IBU-AGF SD. Further, AGF polymer exhibited discoloration at accelerated stability conditions.

Future studies should be performed with a focus on the evaluation of the dosage forms of these amorphous drugs-AGF SDs. The precipitation inhibition ability of the AGF polymer should also be studied. This is a mechanism which can improve absorption and bioavailability. The studies will be designed to prepare ternary SDs with the HPMCE5 polymer, a commonly used polymer for preparation of SDs. Additional studies will be performed to develop a USP excipient monograph. The modification to the AGF polymer to induce desired degree of hydrophobicity will be investigated.

Thus, we comprehensively evaluated the AGF polymer as a carrier for preparation of SDs. The studies included:

(a) Characterization of the relevant properties of the neat AGF polymer with its prospective use as a carrier for SDs;

(b) Evaluation of the solid-state and solution-state interactions, solubility, and dissolution enhancement of the SD of AGF and a poorly water-soluble drug IBU;
(c) Comparison of IBU-AGF SD with IBU-HPMCK3 SD with respect to solubility, dissolution enhancement, and solid-state characteristics;

(d) Comparison of the ITRA-AGF SDs, KETO-AGF SDs, and IBU-AGF SDs with respect to solid solubility, equilibrium solubility, and dissolution enhancement;

(e) Evaluation of the mechanism inhibition of drug crystallization by AGF polymer by evaluating and comparing AGF SDs of additional 9 poorly water-soluble drugs prepared by solvent evaporation method;

(f) Evaluation of the physical and chemical stability of the amorphous IBU-AGF SD at 25 °C/60% RH (6 months) and at 40 °C/75% RH (3 months).

The progression of the studies indicated AGF polymer as a novel carrier for SDs. AGF has the following advantages:

1) It is a better polymer for the dissolution enhancement. This is especially beneficial for highly potent, low dose poorly water-soluble drugs.

2) It is a better polymer when the initial dissolution rate enhancement is desired at high polymer loadings.

3) Physical mixture with AGF can offer dissolution enhancement for some drugs like ketoprofen.

4) It could be a better alternative to PVP. PVP is a highly hygroscopic polymer which leads to processing, handling, and physical instability issues.

5) It could be a better alternative to the HPMC class polymers, which pose an obstacle in dissolution enhancement, because of the high solution viscosity especially at a high polymer load.
6) Further, the modification of this polymer similar to that of HPMC, however, to induce the desired hydrophobicity could open an entire new area in the field of pharmaceutical excipients.
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APPENDIX A

AGF POLYMER CHARACTERIZATION DATA (CHAPTER 2)

Figure A. 1 TGA spectrum of AGF polymer in the presence of air

Figure A. 2 GPC chromatogram of NEAT AGF polymer

Note- PL-GPC 50 Plus- RI w/ PD2020 light scattering detector (system)

1x PLaquagel-OH Mixed-M 8μm 300x7.5mm (P/N: PL1149-6801) (Column); 0.2M NaNO₃, 0.01M NaH₂PO₄ (Mobile Phase); PEO narrow standard with a molecular weight of 126,500 g/mol.
Figure A. 3 Effect of shear rate on the viscosity of the AGF solutions at 25 °C and 70 °C.

Table A. 1 Post compression evaluation of AGF compacts

<table>
<thead>
<tr>
<th>Compression force (LB)</th>
<th>Compression force (kN)</th>
<th>Weight (mg)</th>
<th>Thickness (mm)±SD</th>
<th>Diameter (mm)±SD</th>
<th>Hardness kp±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>4.44</td>
<td>399.33±19.49</td>
<td>3.53±0.2103</td>
<td>22.69±0.02</td>
<td>1.6±0.26</td>
</tr>
<tr>
<td>1500</td>
<td>6.67</td>
<td>454.93±16.59</td>
<td>3.76±0.03</td>
<td>22.77±0.02</td>
<td>2.83±0.70</td>
</tr>
<tr>
<td>2000</td>
<td>8.89</td>
<td>439.03±48.83</td>
<td>3.38±0.43</td>
<td>22.81±0.05</td>
<td>4.86±0.89</td>
</tr>
<tr>
<td>2500</td>
<td>11.12</td>
<td>437.7±31.29</td>
<td>3.27±0.24</td>
<td>22.78±0.05</td>
<td>5.76±1.25</td>
</tr>
<tr>
<td>3000</td>
<td>13.34</td>
<td>458.93±27.92</td>
<td>3.27±0.24</td>
<td>22.77±0.01</td>
<td>7±0.55</td>
</tr>
<tr>
<td>3500</td>
<td>15.56</td>
<td>455.2±13.28</td>
<td>3.27±0.14</td>
<td>22.78±0.06</td>
<td>8.16±0.73</td>
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<tr>
<td>4000</td>
<td>17.79</td>
<td>465.43±30.10</td>
<td>3.15±0.13</td>
<td>22.78±0.05</td>
<td>10.6±1.91</td>
</tr>
</tbody>
</table>
Table A. 2 Post compression evaluation of HPMCK3 compacts

<table>
<thead>
<tr>
<th>Compression force (LB)</th>
<th>Compression force (kN)</th>
<th>Weight (mg)</th>
<th>Thickness (mm)±SD</th>
<th>Diameter (mm)±SD</th>
<th>Hardness kp±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>4.44</td>
<td>483.13±12.27</td>
<td>3.10±0.17</td>
<td>22.97±0.05</td>
<td>13.36±0.15</td>
</tr>
<tr>
<td>1500</td>
<td>6.67</td>
<td>471.3±14.92</td>
<td>3.55±0.03</td>
<td>23.04±0.02</td>
<td>19.46±2.91</td>
</tr>
<tr>
<td>2000</td>
<td>8.89</td>
<td>500.06±3.00</td>
<td>3.55±0.01</td>
<td>23.09±0.06</td>
<td>29.66±1.30</td>
</tr>
<tr>
<td>2500</td>
<td>11.12</td>
<td>499.26±8.95</td>
<td>3.43±0.02</td>
<td>23.13±0.06</td>
<td>36.5±2.64</td>
</tr>
<tr>
<td>3000</td>
<td>13.34</td>
<td>493.53±5.82</td>
<td>3.32±0.06</td>
<td>23.13±0.02</td>
<td>39.93±3.13</td>
</tr>
<tr>
<td>3500</td>
<td>15.56</td>
<td>502.8±1.47</td>
<td>3.33±0.01</td>
<td>23.13±0.12</td>
<td>40.9±0.56</td>
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<tr>
<td>4000</td>
<td>17.79</td>
<td>491.26±3.12</td>
<td>3.25±0.00</td>
<td>23.11±0.07</td>
<td>39.2±2.68</td>
</tr>
</tbody>
</table>
APPENDIX B

SOLID-STATE AND DISSOLUTION DATA OF IBU-AGF SDs PREPARED USING VARIOUS METHODS (CHAPTER 3)

Table B. 1 Design of an experiment for IBU AGF SDs preparation using different methods

<table>
<thead>
<tr>
<th>Method</th>
<th>IBU drug load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent deposition (SOLDEP)</td>
<td>10%</td>
</tr>
<tr>
<td>Physical hot mix (HM)</td>
<td>10%,20%,30%</td>
</tr>
<tr>
<td>Solvent evaporation with water as a solvent (SEWS)</td>
<td>10%</td>
</tr>
<tr>
<td>Freeze drying (FRZDR)</td>
<td>10%,20%,30%</td>
</tr>
<tr>
<td>Spray drying (SPRDY)</td>
<td>10%</td>
</tr>
<tr>
<td>Innerphase solid dispersions (IPSD)</td>
<td>10%,20%,30%</td>
</tr>
<tr>
<td>Microsphere solid dispersion (MSD)</td>
<td>10%,20%,30%</td>
</tr>
<tr>
<td>Modified solvent evaporation (SDM)</td>
<td>10%,20%,30%</td>
</tr>
</tbody>
</table>

Solvent deposition (SOLVDEP)- The method described by Williams et al. (2005) was modified. Briefly 400 mg of IBU was dissolved into HPLC-grade acetone. Accurately weighted AGF polymer was added to it and mixed using a stirring rod. The stirring continued until the entire ethanol evaporated. The samples were completely dried by placing them in an oven at 45 °C (overnight).
Physical hot mixes (HM)- The method described by Williams et al. (2005) was modified. Accurately weighed IBU was placed in a glass beaker. Then the beaker was heated in a silicone oil bath until the IBU melted completely. Then accurately weighed AGF polymer was mixed with this molten IBU (using geometric dilution) with a stirring rod for 20 min. These physical hot mixes were allowed to cool down at room temperature for 24 h.
Figure B. 2 DSC thermograms of IBU AGF HOT MIX solid dispersions

Figure B. 3 XRPD diffractograms of IBU AGF HOT MIX solid dispersions

Note - NEAT IBU; 10 IBU AGF HM; 20 IBU AGF HM; 30 IBU AGF HM.
Solvent Evaporation using water as a solvent (SEWS)- A method described by Al-Hamidi et al. (2010) was modified. Briefly, 0.2 g of IBU was dissolved into 10 mL ethanol/acetone. Then, 0.9 mg of AGF was dissolved an equal volume of nanopure water. The drug solution was added to the polymer solution while stirring. After evaporation of the solvents at room temperature, dried SDs were obtained.

Figure B. 4 DSC thermograms of IBU AGF SEWS solid dispersions

Freeze drying (FRZD)- IBU AGF freeze-dried SD samples with 10%, 20%, and 30% DL were prepared. We heated 10 mL of nanopure water at 90 °C. Accurately weighed AGF polymer was added to it and stirred using a magnetic stir bar. Accurately weighed IBU was added to this hot AGF polymer solution and stirred for 1 min. This thin inner phase was immediately transferred into the glass culture tube. These culture tubes were immediately placed on dry ice until the solution solidified completely. These samples
were freeze-dried for 48 h at -45 °C using Freeze-drier Freezone- 1 Liter Benchtop (Labconco, Kansas City, MO)

Figure B. 5 DSC thermograms of IBU AGF FRZD solid dispersions

Spray drying (SPRDY)- Spray-dried 10% IBU-AG SD were prepared with 10% solid load. The AGF polymer, 8.5 g, was dissolved in nanopure water while stirring. Further, 1 g of IBU was added to the aqueous polymer solution and stirring continued. Once the drug dispersed well in the solution, 0.5 g of carbosil was added to it. The spray drying was performed using a BUCHI minispray dryer B-290 (Buchi Corp, Newcastle, DE). The inlet temperature was set at 185 °C and the outlet temperature at 60 °C. The aspirator volume was 85%, airflow rate was 40 mm, and the feed rate was 9 mL/min. The spray-dried SDs were separated using the high-performance cyclone separator, collected, and weighed. This spray-dried SD was stored in a desiccator (SRPDY 60 °C). Another
sample of 10% IBU AG SD was prepared using an inlet temperature of 220 °C and an outlet temperature of 83 °C with a feed rate of 6 mL/min (SRPDY 90 °). The yield was 60% .

Figure B. 6 DSC thermograms of IBU AGF SPRDY solid dispersions
Figure B. 7 XRPD diffractogram of IBU AGF SPRDY 90°C solid dispersion

Note-NEAT IBU; 10 IBU AGF SPRDY 90 °C; NEAT AGF.

**Inner phase solid dispersion (IPSD)**- The Inner phase of the microsphere preparation (Chapter 3, section 3.2.3) was poured onto the liner and air dried for 1 h (instead of emulsifying in oil phase). Later, this inner phase SD was dried completely in an oven at 45 °C.
Figure B. 8 DSC thermograms of IBU AGF IPSD solid dispersions.

Figure B. 9 XRPD diffractograms of IBU AGF IPSD solid dispersions.

Note - NEAT IBU; 10 IBU AGF IPSD; 20 IBU AGF IPSD; NEAT AGF.
Table B. 2 FTIR shifts in major IBU and AGF IR bands in IBU AGF solid dispersions

<table>
<thead>
<tr>
<th>Formulation</th>
<th>IBU 1708.7 cm(^{-1}) (C=O)</th>
<th>IBU 2954 cm(^{-1}) (OH)</th>
<th>AGF 1590 cm(^{-1}) (COO(^{-}))</th>
<th>AGF 3308 cm(^{-1}) (OH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT IBU</td>
<td>1708.7</td>
<td>2954</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NEAT AGF</td>
<td>-</td>
<td>-</td>
<td>1590</td>
<td>3308</td>
</tr>
<tr>
<td>10 IBU AGF SOLDEP</td>
<td>1714.02</td>
<td>2953.1*</td>
<td>1594.38</td>
<td>3329.31</td>
</tr>
<tr>
<td>10 IBU AGF HM</td>
<td>1714.02</td>
<td>2955.75</td>
<td>1587.93</td>
<td>3310*</td>
</tr>
<tr>
<td>30 IBU AGF HM</td>
<td>1714.03</td>
<td>2954.76</td>
<td>NO BAND</td>
<td>NO BAND</td>
</tr>
<tr>
<td>10 IBU AGF SEWS ETHANOL</td>
<td>1710.55</td>
<td>2954.58</td>
<td>1564</td>
<td>3343.7</td>
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<tr>
<td>10 IBU AGF SEWS ACETONE</td>
<td>1710.98</td>
<td>2954.68</td>
<td>-</td>
<td>3339</td>
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<tr>
<td>10 IBU AGF FRZD</td>
<td>1718.91</td>
<td>2953.78</td>
<td>1588.32</td>
<td>3319.81</td>
</tr>
<tr>
<td>20 IBU AGF FRZD</td>
<td>1712.46</td>
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<td>3320.26</td>
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<td>30 IBU AGF FRZD</td>
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<td>10 IBU AGF SPRDY Y 60 °C</td>
<td>1718.91</td>
<td>2953.78</td>
<td>1588.32</td>
<td>3319.81</td>
</tr>
<tr>
<td>10 IBU AGF SPRDY 90 °C</td>
<td>1712.46</td>
<td>2954.85</td>
<td>1587.46</td>
<td>3320.26</td>
</tr>
<tr>
<td>10 IBU AGF IPSD</td>
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<td>2954.38</td>
<td>1590</td>
<td>3306</td>
</tr>
<tr>
<td>20 IBU AFG IPSD</td>
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<td>2954.85</td>
<td>1593.8</td>
<td>3307.13</td>
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<tr>
<td>30 IBU AGF IPSD</td>
<td>1717.56</td>
<td>2954.70</td>
<td>1598.7</td>
<td>3301.47</td>
</tr>
</tbody>
</table>

Note-* Less intense
Table B. 2 FTIR shifts in major IBU and AGF IR bands in IBU AGF solid dispersions (continued)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>IBU 1708.7 cm$^{-1}$ (C=O)</th>
<th>IBU 2954 cm$^{-1}$ (OH)</th>
<th>AGF 1590 cm$^{-1}$ (COO$^-$)</th>
<th>AGF 3308 cm$^{-1}$ (OH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF MSD</td>
<td>1719.97</td>
<td>2953.27</td>
<td>1586.72</td>
<td>3296.42</td>
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<tr>
<td>20 IBU AGF MSD</td>
<td>1718.63</td>
<td>2953.1*</td>
<td>1590.88</td>
<td>3316.85</td>
</tr>
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<td>30 IBU AGF MSD</td>
<td>1719.08</td>
<td>2954.09</td>
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<tr>
<td>10 IBU AGF SDM</td>
<td>1716.01</td>
<td>2954.14</td>
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<td>3294.51</td>
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<tr>
<td>20 IBU AGF SDM</td>
<td>1717.4</td>
<td>2954.88</td>
<td>1588.14</td>
<td>3305.8*</td>
</tr>
<tr>
<td>30 IBU AGF SDM</td>
<td>1716.51</td>
<td>2954.81</td>
<td>1595.5*</td>
<td>3305*</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>1733.6</td>
<td>2933.3</td>
<td>-</td>
<td>-</td>
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<td>1709.76</td>
<td>2954.90</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10 IBU AGF PM</td>
<td>1710.4</td>
<td>2953.1*</td>
<td>1588.96</td>
<td>3291.53</td>
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<tr>
<td>20 IBU AGF PM</td>
<td>1709.37</td>
<td>NO BAND</td>
<td>NO BAND</td>
<td>NO BAND</td>
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<tr>
<td>30 IBU AGF PM</td>
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<td>2953.1*</td>
<td>1592.12</td>
<td>3272.46</td>
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<td>1709.83</td>
<td>NO BAND</td>
<td>-</td>
<td>-</td>
</tr>
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<td>1709.19</td>
<td>2954.2</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Note: * Less intense
Figure B. 10 SEM microphotographs of IBU AGF solid dispersions (porous versus non porous)

Note-A-10 IBU AGF SPRDY 90 °C (porous); B-10 IBU AGF FRZD (non porous); C-10 IBU AGF MSD (porous); D-10 IBU AGF SDM (porous); E-10 IBU AGF PM (porous).
Figure B. 11 Mean *in vitro* dissolution profiles of 10 %DL IBU AGF SDs prepared using different methods

Note-IBU dissolution from MSD, SDM, FRZD, IPSD was significantly higher than NEAT IBU. Dissolution profiles of MSD and SDM statistically equivalent. Both profiles statistically higher than the dissolution profiles of FRZD, IPSD, HM, SPRDY, SOLDEP. Dissolution profiles of FRZD and IPSD statistically equivalent.
Figure C. 1 Equilibrium solubility of IBU AGF coground mixture (2:8 drug to polymer ratio)
Table C. 1 % Encapsulation efficiency and % yield of IBU-AGF MSDs

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Encapsulation efficiency</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF MSD</td>
<td>85.965±3.346</td>
<td>67.00 ± 4.82</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>85.875±3.049</td>
<td>58.83 ± 11.47</td>
</tr>
<tr>
<td>30 IBU AGF MSD</td>
<td>80.920±7.334</td>
<td>62.00 ± 4.26</td>
</tr>
<tr>
<td>40 IBU AGF MSD</td>
<td>53.186</td>
<td>-</td>
</tr>
<tr>
<td>50 IBU AGF MSD</td>
<td>48.298</td>
<td>-</td>
</tr>
<tr>
<td>60 IBU AGF MSD</td>
<td>51.242</td>
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</tr>
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<td>75 IBU AGF MSD</td>
<td>30.978</td>
<td>-</td>
</tr>
<tr>
<td>10 IBU HPMCK3 MSD</td>
<td>2.48%</td>
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</tr>
<tr>
<td>30 IBU HPMCK3 MSD</td>
<td>4.32%</td>
<td></td>
</tr>
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</table>

Figure C. 2 Mean *in vitro* dissolution profiles of IBU-AGF MSDs in PB pH 7.2
Figure C. 3 DSC thermograms of 10 IBU AGF SD prepared by SDM method and revised SDM method

Figure C. 4 DSC thermograms of 30 IBU AGF SD prepared by SDM method and revised SDM method
Figure C. 5 XRPD diffractograms of IBU AGF MSDs demonstrating solid-state miscibility.
Table C. 2 \(^1\)H chemical shifts (ppm) of IBU proton in IBU AGF formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Doublet (H1)</th>
<th>Multiplet (H2)</th>
<th>Doublet (H3)</th>
<th>Doublet (H4&amp;H6)</th>
<th>Doublet (H5&amp;H7)</th>
<th>Quartet (H8)</th>
<th>Doublet (H9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT IBU</td>
<td>0.7522 (6)</td>
<td>1.6894 (1)</td>
<td>2.3560 (2)</td>
<td>7.0905 (4)</td>
<td>7.1481 (4)</td>
<td>3.4647 (1)</td>
<td>1.2649 (3)</td>
</tr>
<tr>
<td>10 IBU AGF SDM</td>
<td>0.5424 (6)</td>
<td>1.4959 (1)</td>
<td>2.1283 (2)</td>
<td>6.8806 (4)</td>
<td>6.8808 (4)</td>
<td>3.5819 (1)</td>
<td>1.0553 (3)</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>0.5273 (6)</td>
<td>1.4815 (1)</td>
<td>2.1206 (2)</td>
<td>6.8431 (4)</td>
<td>6.9135 (4)</td>
<td>3.5468 (1)</td>
<td>1.0405 (3)</td>
</tr>
<tr>
<td>30 IBU AGF SDM</td>
<td>0.6144 (6)</td>
<td>1.5766 (1)</td>
<td>2.2178 (2)</td>
<td>6.9549 (4)</td>
<td>7.0165 (4)</td>
<td>3.7146 (1)</td>
<td>1.1275 (3)</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>0.5251 (6)</td>
<td>1.4707 (1)</td>
<td>2.1288 (2)</td>
<td>6.8637 (4)</td>
<td>6.9168 (4)</td>
<td>3.2287 (1)</td>
<td>1.0382 (3)</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>0.7555 (6)</td>
<td>1.7179 (1)</td>
<td>2.3591 (2)</td>
<td>7.0940 (4)</td>
<td>7.1471 (4)</td>
<td>3.5646 (1)</td>
<td>1.2687 (3)</td>
</tr>
<tr>
<td>30 IBU AGF MSD</td>
<td>0.7511 (6)</td>
<td>1.7221 (1)</td>
<td>2.3452 (2)</td>
<td>7.0875 (4)</td>
<td>7.1427 (4)</td>
<td>3.5089 (1)</td>
<td>1.2637 (3)</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>0.7486 (6)</td>
<td>1.7109 (1)</td>
<td>2.3524 (2)</td>
<td>7.0727 (4)</td>
<td>7.1423 (4)</td>
<td>3.5038 (1)</td>
<td>1.2614 (3)</td>
</tr>
<tr>
<td>20 IBU AGF PM</td>
<td>0.7629 (6)</td>
<td>1.7391 (1)</td>
<td>2.3667 (2)</td>
<td>7.0765 (4)</td>
<td>7.1570 (4)</td>
<td>3.4095 (1)</td>
<td>1.2760 (3)</td>
</tr>
<tr>
<td>30 IBU AGF PM</td>
<td>0.7550 (6)</td>
<td>1.7089 (1)</td>
<td>2.3587 (2)</td>
<td>7.0936 (4)</td>
<td>7.1487 (4)</td>
<td>3.4926 (1)</td>
<td>1.2680 (3)</td>
</tr>
</tbody>
</table>
APPENDIX D

INTRINSIC DISSOLUTION RESULTS (CHAPTER 3)

Experimental Methods

A stationary disk system described by Viegas et al. (2001) was used to generate an intrinsic dissolution rate (IDR) data for IBU, IBU-AG PM, and IBU-AG MSD formulations. A few modifications were made to the method. Using IDR dies and a Carver Press (model 3912 Carver Inc.), 130 mg of the sample was compressed at a compression force of 4000 LB for 1 min to obtain non-disintegrating compacts (51612 LB per square inch). After compression, air was blown over the die surface to get rid of loose powder particles. The exposed smooth surface area of the compact was 0.5 cm².

The dissolution medium, was 500 mL of 0.1 N HCl at 37 °C. Adhesive tape was placed onto the threaded shoulder of the die to seal this side of the die. Then, this assembly was immersed in the dissolution media with the help of a pair of tongs. The average time to place the die into the dissolution vessel was less than 30 s. The distance between the surface of the compacts and the bottom of the vessel was 0.75 inches.

The USP Apparatus 2 paddles at 15 rpm were used to stir the dissolution media for proper mixing. The dissolution experiments were performed using a Vankel VK 7010 dissolution apparatus (Cary, NC). To de-aerate, the medium was filtered under vacuum at ~45 °C using a 0.45-µm nylon membrane filter while stirring. Then, the medium was allowed to equilibrate to set dissolution bath temperature. Finally, the medium was sparged with helium for 15 min (avoiding turbulence).
At appropriate time intervals, 5 mL of samples were collected and replaced with fresh media. Each sample was filtered through a 0.45-µm membrane filter, and the drug was analyzed using an Agilent/HP 8453 UV-Vis spectrophotometer (λ<sub>max</sub> = 222 nm). Each experiment was performed in triplicate. Analysis was performed to calculate IDR.

Results

The results of IDR are summarized in Table D.1. The inverted die stationary disk method was used; however, the pellet showed chipping after 6 min. Therefore, times points up to 4 min were included to calculate IDR. However, the experiments were not reproducible. We encountered random chipping of the pellet and bubble formation on the surface of the pellet in the middle of the experiment. Therefore, these were the best results obtained using this method.

Table D. 1 Mean intrinsic dissolution rate of IBU-AG MSDs and IBU AG PMs

<table>
<thead>
<tr>
<th>Formulation</th>
<th>IDR mg/min sq cm</th>
<th>Observations within 4 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT IBU</td>
<td>0.07±0.00</td>
<td>-</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>0.41±0.05</td>
<td>-</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>0.34±0.03</td>
<td>Bubbles and uneven surface in one of the triplicate</td>
</tr>
<tr>
<td>30 IBU AGF MSD</td>
<td>0.27±0.02</td>
<td>-</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>0.32±0.06</td>
<td>Bubbles and uneven surface in one of the triplicate</td>
</tr>
<tr>
<td>20 IBU AGF PM</td>
<td>0.36±0.05</td>
<td>Bubbles in one of the triplicate</td>
</tr>
<tr>
<td>30 IBU AGF PM</td>
<td>0.23±0.05</td>
<td>Bubbles with two of the triplicate</td>
</tr>
</tbody>
</table>
Table E. 1 Comparisons of experimental Tg values of drug-AGF SDMs

<table>
<thead>
<tr>
<th>Thermal Transitions (°C ) of Formulations</th>
<th>IBU</th>
<th>KETO</th>
<th>ITRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT DRUG</td>
<td>-45.15 (Tg)</td>
<td>-3.15 (Tg)</td>
<td>58.23 (Tg)</td>
</tr>
<tr>
<td>10 AGF SDM</td>
<td>78.14 °C (Tg)</td>
<td>77.11 (Tg)</td>
<td>67.30 (Tg)</td>
</tr>
<tr>
<td>20 AGF SDM</td>
<td>58.03 (Tm) and 83.88 (Tg)</td>
<td>75.33 (Tg)</td>
<td>64.18 (Tg)</td>
</tr>
<tr>
<td>30 AGF SDM</td>
<td>63.67 (Tm);79.54 (TgI);124.49 (TgII)</td>
<td>71.91 (Tg); 91.44 (Tm )</td>
<td>72.56 (Tg);133 (Tm )</td>
</tr>
<tr>
<td>AGF</td>
<td>82 (Tg)</td>
<td>~82 (Tg)</td>
<td>~82 (Tg)</td>
</tr>
</tbody>
</table>

Figure E. 1 TMA spectra of ITRA-AGF SDMs
Figure E. 2 TMA spectra of KETO-AGF SDMs

Table E. 2 % Drug release at 15 min and corresponding RDR$_{15\text{min}}$

<table>
<thead>
<tr>
<th>Formulations</th>
<th>IBU (RDR$_{15\text{min}}$)</th>
<th>KETO (RDR$_{15\text{min}}$)</th>
<th>ITRA (RDR$_{15\text{min}}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT DRUG</td>
<td>8</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td>10 SDM</td>
<td>94 (11.75)</td>
<td>87 (48.33)</td>
<td>18 (12.87)</td>
</tr>
<tr>
<td>20 SDM</td>
<td>66 (8.25)</td>
<td>99 (55)</td>
<td>20 (14.28)</td>
</tr>
<tr>
<td>30 SDM</td>
<td>12 (1.5)</td>
<td>23 (12.77)</td>
<td>17 (12.14)</td>
</tr>
<tr>
<td>10 PM</td>
<td>52 (6.5)</td>
<td>75 (41.66)</td>
<td></td>
</tr>
</tbody>
</table>

Note- RDR$_{15\text{min}}$ in the bracket.
Table E. 3 % Drug release at 30 min and corresponding RDR₃₀min

<table>
<thead>
<tr>
<th>Formulations</th>
<th>IBU (RDR₃₀min)</th>
<th>KETO (RDR₃₀min)</th>
<th>ITRA (RDR₃₀min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT DRUG</td>
<td>27</td>
<td>3.3</td>
<td>1.6</td>
</tr>
<tr>
<td>10 SDM</td>
<td>100 (3.7)</td>
<td>93 (28.18)</td>
<td>23 (14.3)</td>
</tr>
<tr>
<td>20 SDM</td>
<td>71 (2.6)</td>
<td>93 (28.18)</td>
<td>22 (13.75)</td>
</tr>
<tr>
<td>30 SDM</td>
<td>17 (0.62)</td>
<td>30 (9)</td>
<td>19 (11.8)</td>
</tr>
<tr>
<td>10 PM</td>
<td>57 (2.1)</td>
<td>93 (28.1)</td>
<td></td>
</tr>
</tbody>
</table>

Note- RDR₃₀min in the bracket.

Table E. 4 % Drug release at 120 min and corresponding RDR₃₀min

<table>
<thead>
<tr>
<th>Formulations</th>
<th>IBU (RDR₁₂₀min)</th>
<th>KETO (RDR₁₂₀min)</th>
<th>ITRA (RDR₁₂₀min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT DRUG</td>
<td>41</td>
<td>8.4</td>
<td>2.6</td>
</tr>
<tr>
<td>10 SDM</td>
<td>100 (2.4)</td>
<td>99 (11.78)</td>
<td>27 (10.38)</td>
</tr>
<tr>
<td>20 SDM</td>
<td>93 (2.26)</td>
<td>98 (11.66)</td>
<td>23 (8.46)</td>
</tr>
<tr>
<td>30 SDM</td>
<td>32 (0.78)</td>
<td>50 (5.95)</td>
<td>21 (8)</td>
</tr>
<tr>
<td>10 PM</td>
<td>74 (1.8)</td>
<td>100 (11.90)</td>
<td></td>
</tr>
</tbody>
</table>

Note- RDR₁₂₀min in the bracket.
Figure F.1 Mass spectrum of propranolol free base extracted from propranolol HCl

Note-Method-Column Zorbax SB-C18, 2.1*30mm.3.5µm; 4min gradient 5%-100% water/ACN/0.1% formic acid.
Table F. 1 RDC of DRUG-AGF SDM and %RC of DRUG AGF PM I

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Formulations</th>
<th>% RC by DSC</th>
<th>RDC by XRPD</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITO</td>
<td>10 RITO AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-128.68 °C)</td>
</tr>
<tr>
<td></td>
<td>20 RITO AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(XRPD peak at 22.1° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>30 RITO AGF SDM</td>
<td>NA</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 RITO AGF PM</td>
<td>≥100</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>TIOCO</td>
<td>10 TIOCO AGF SDM</td>
<td>NA</td>
<td>0.031</td>
<td>(Tm-84.24 °C)</td>
</tr>
<tr>
<td></td>
<td>10 TIOCO AGF PM</td>
<td>83.968</td>
<td>0.045</td>
<td>(XRPD peak at 20.4° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td>FUROS</td>
<td>10 FUROS AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-228.34 °C)</td>
</tr>
<tr>
<td></td>
<td>10 FUROS AGF PM</td>
<td>NA</td>
<td>NA</td>
<td>(XRPD peak at 6° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td>KETOC</td>
<td>10 KETOC AGF SDM</td>
<td>NA</td>
<td>0.169</td>
<td>(Tm-150.51 °C)</td>
</tr>
<tr>
<td></td>
<td>10 KETOC AGF PM</td>
<td>87.349</td>
<td>NA</td>
<td>(XRPD peak at 19.9° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td>PROPFB</td>
<td>10 PROPFB AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-95.86 °C)</td>
</tr>
<tr>
<td></td>
<td>20 PROPFB AGF SDM</td>
<td>NA</td>
<td>NA</td>
<td>(XRPD peak at 10.9° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>10 PROPFB AGF PM</td>
<td>92.39</td>
<td>0.228</td>
<td></td>
</tr>
<tr>
<td>NAPROX</td>
<td>10 NAPROX AGF SDM</td>
<td>NA</td>
<td>0.053</td>
<td>(Tm-155.53 °C)</td>
</tr>
<tr>
<td></td>
<td>20 NAPROX AGF SDM</td>
<td>NA</td>
<td>0.44</td>
<td>(XRPD peak at 22.25° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>10 NAPROX AGF PM</td>
<td>≥100</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>FLURBI</td>
<td>10 FLURB AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-117.43 °C)</td>
</tr>
<tr>
<td></td>
<td>10 FLURB AGF PM</td>
<td>≥100</td>
<td>NA (?)</td>
<td>(XRPD peak at 6.49° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td>NIMO</td>
<td>10 NIMO AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-126.77 °C)</td>
</tr>
<tr>
<td></td>
<td>10 NIMO AGF PM</td>
<td>≥100</td>
<td>NA</td>
<td>(XRPD peak at 20.2° 2θ used to calculate RDC)</td>
</tr>
</tbody>
</table>

Note- RDC(XRPD) and %RC (DSC) of neat drug as a reference.
Table F. 1 RDC of DRUG-AGF SDM and %RC of DRUG AGF PM I (continued)

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Formulations</th>
<th>% RC by DSC</th>
<th>RDC by XRPD</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHLORP</td>
<td>10 CHLORP AGF SDM</td>
<td>NA</td>
<td>0.015</td>
<td>(Tm-127.30 °C and 130.84 °C). (XRPD peak at 6.7° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>10 CHLORP AGF PM</td>
<td>≥100</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Note- RDC(XRPD) and %RC (DSC) of neat drug as a reference.

Table F. 2 RDC of DRUG-AGF SDM and %RC of DRUG AGF PM II

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulations</th>
<th>% RC by DSC</th>
<th>RDC by XRPD</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU</td>
<td>10 IBU AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-76.56 °C) (XRPD peak at 22.3° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>20 IBU AGF SDM</td>
<td>NA</td>
<td>0.219</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 IBU AGF SDM</td>
<td>NA</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 IBU AGF PM</td>
<td>95.25</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ITRA</td>
<td>10 ITRA AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-169.92°C) (XRPD peak at 20.4° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>20 ITRA AGF SDM</td>
<td>NA</td>
<td>0.099</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 ITRA AGF SDM</td>
<td>NA</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 ITRA AGF PM</td>
<td>81.043</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>KETO</td>
<td>10 KETO AGF SDM</td>
<td>NA</td>
<td>0</td>
<td>(Tm-96.53 °C) (XRPD peak at 22.6° 2θ used to calculate RDC)</td>
</tr>
<tr>
<td></td>
<td>20 KETO AGF SDM</td>
<td>NA</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 KETO AGF SDM</td>
<td>NA</td>
<td>0.148</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 KETO AGF PM</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Note- RDC(XRPD) and %RC (DSC) of neat drug as a reference (data obtained from Chapter 3 and Chapter 4).
Table F. 3 Diffraction peaks indicative of drug crystallinity of the selected neat drugs

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Diffraction peaks representing crystallinity (at 2θ)</th>
<th>References where similar XRPD pattern reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITO</td>
<td>8.59°, 13.74°, 16°, 19.4°, 19.9°, 21.6°, 22.1°, 25.2°</td>
<td>Poddar et al., 2011</td>
</tr>
<tr>
<td>TIOCO</td>
<td>10.8°, 14.50°, 17.54°, 20.40°, 23.53°, 25.44°, 27.1°</td>
<td>-</td>
</tr>
<tr>
<td>FUROS</td>
<td>12°, 18.1°, 19°, 23.9°, 24.8°, 28.4°</td>
<td>Chaulang et al., 2009</td>
</tr>
<tr>
<td>KETOC</td>
<td>7.21°, 11.95°, 17.44°, 18.6°, 19.94°, 20.34°, 21.01°, 23.6°, 24°, 27.4°</td>
<td>Kumar P et al., 2011</td>
</tr>
<tr>
<td>PROPFB</td>
<td>7.6°, 10.9°, 14.3°, 15.2°, 20.6°, 24.2°, 24.5°</td>
<td>-</td>
</tr>
<tr>
<td>NAPROX</td>
<td>6.6°, 12.6°, 16.7°, 18.94°, 20.25°, 22.25°, 23.69°, 28.35°</td>
<td>Javadzadeh et al., 2010</td>
</tr>
<tr>
<td>FLURBI</td>
<td>7.3°, 10.92°, 20.74°, 21.53°, 23.79°, 25.5°, 30.14°</td>
<td>Ranjha et al., 2010</td>
</tr>
<tr>
<td>NIMO</td>
<td>6.54°, 12.8°, 17.3°, 20.2°, 24.8°, 24.7°</td>
<td>Pan et al., 2009</td>
</tr>
<tr>
<td>CHLORP</td>
<td>6.7°, 11.8°, 19.5°, 20°, 21.6°, 23.8°</td>
<td>Yeo et al., 2003</td>
</tr>
</tbody>
</table>
Table F. 4 FTIR major IR band assignments of the selected neat drugs

<table>
<thead>
<tr>
<th>Selected drugs</th>
<th>Major IR bands observed in the current study</th>
<th>Reference where similar IR band assignment reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITO</td>
<td>3325 cm$^{-1}$ (amide stretching vibration); 2958 cm$^{-1}$ (hydrogen bonding within the RITO molecule); 1702 cm$^{-1}$ (ester linkage); 1660 cm$^{-1}$ (C=C stretching vibration of aromatic ring)</td>
<td>Sinha et al., 2010; Poddar et al., 2011</td>
</tr>
<tr>
<td>TIOCO</td>
<td>1627 cm$^{-1}$ (C=N stretching vibration); 1119 cm$^{-1}$ (C-O-C stretching vibration)</td>
<td>El-Halim et al., 2013</td>
</tr>
<tr>
<td>FUROS</td>
<td>3399.47 cm$^{-1}$ (OH stretch); 3282.76 cm$^{-1}$ (N-H stretch); 1676.31 cm$^{-1}$ (N-H bending); 1561.80 cm$^{-1}$ (C=O stretch); 1261.1 cm$^{-1}$ (S=O asymmetric stretch).</td>
<td>Raval et al., 2010</td>
</tr>
<tr>
<td>KETOC</td>
<td>1645 cm$^{-1}$ (C=O stretch); 1243 cm$^{-1}$ (C-O stretch of cyclic ether); 1031 cm$^{-1}$ (C-O stretch of aliphatic ether)</td>
<td>Kumar P et al., 2011</td>
</tr>
<tr>
<td>PROPFB</td>
<td>~3270 cm$^{-1}$ (N-H stretch)</td>
<td>Crowley et al., 1999</td>
</tr>
<tr>
<td>NAPROX</td>
<td>1726 cm$^{-1}$ (C=O stretch); 1394 cm$^{-1}$ (COO$^{-1}$ stretch); 1682 cm$^{-1}$, 1604 cm$^{-1}$ and 1504 cm$^{-1}$ (skeletal stretching vibration of the aromatic ring C-C vibration); 1175 cm$^{-1}$ (C-O absorption)</td>
<td>Rezvani et al., 2012; Wei et al., 2004</td>
</tr>
<tr>
<td>FLURBI</td>
<td>2934 cm$^{-1}$ (OH stretch); 1694 cm$^{-1}$(C=O stretch); 1215 cm$^{-1}$ (C-F stretch)</td>
<td>Akhlaq et al., 2011; Shah et al., 2009</td>
</tr>
<tr>
<td>NIMO</td>
<td>1693 cm$^{-1}$ (C=O stretch);1647 cm$^{-1}$ (C=C stretch); 1522 cm$^{-1}$(NO$_2$)</td>
<td>Papadimitriou et al., 2009</td>
</tr>
<tr>
<td>CHLORP</td>
<td>3070 cm$^{-1}$ (C-H stretch); 3000 cm$^{-1}$-2800 cm$^{-1}$(C-H, CH2 and CH3 vibrations); 1709 cm$^{-1}$ (C=O stretch); 1664.69 cm$^{-1}$ (COO$^{-1}$ stretch)</td>
<td>Tudor et al., 1993; Chesalov et al., 2008</td>
</tr>
</tbody>
</table>
APPENDIX G

AMBIENT AND ACCELERATED STABILITY STUDY DATA (CHAPTER 6)

Figure G. 1 DDI of NEAT AGF and 10 IBU AGF SDM

Figure G. 2 XRPD diffractograms of 10 IBU AGF SDM and 10 IBU AGF SDM BHT

Note - NEAT IBU; NEAT AGF; 10 IBU AGF SDM; 10 IBU AGF SDM BHT.
Figure G. 3 XRPD diffractograms of 10 IBU AGF MSD and 10 IBU AGF MSD BHT

Note - NEAT IBU; NEAT AGF; 10 IBU AGF MSD; 10 IBU AGF MSD BHT.

Figure G. 4 Mean in vitro dissolution profiles of 10 IBU AGF SDM and 10 IBU AGF SDM BHT

Note - Basket method; 270 mesh size basket; 900ml 0.1N HCl; 100 rpm.
Table G. 1 % Weight gain by stability samples at ambient and accelerated stability conditions

<table>
<thead>
<tr>
<th>Formulations</th>
<th>2560 (6M)</th>
<th>4075(3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>11.138±1.978</td>
<td>14.888±3.44</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>14.960±1.295</td>
<td>14.482±0.933</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>18.287±1.487</td>
<td>13.976±1.812</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>31.416±5.418</td>
<td>33.325±4.496</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>28.413±1.744</td>
<td>24.327±1.627</td>
</tr>
<tr>
<td>10 IBU AGF MSD BHT</td>
<td>38.267±1.083</td>
<td>36.105±1.492</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>13.691±1.399</td>
<td>18.707±0.443</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>12.315± 1.339</td>
<td>12.079±0.356</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>10.100±0.290</td>
<td>11.749±0.596</td>
</tr>
<tr>
<td>AGF POLYMER</td>
<td>15.2±2.376</td>
<td>21.284±0.552</td>
</tr>
<tr>
<td>BLANK AGF SDM</td>
<td>18.257±2.587</td>
<td>21.305±0.433</td>
</tr>
<tr>
<td>HPMCK3 POLYMER</td>
<td>16.706± 3.06</td>
<td>13.578±0.805</td>
</tr>
<tr>
<td>BLANK HPMCK3 SDM</td>
<td>27.296±6.00</td>
<td>25.438±0.763</td>
</tr>
</tbody>
</table>

Note-% weight gain in g
Table G.2 Physical appearance of the stability samples at accelerated stability conditions

<table>
<thead>
<tr>
<th>Formulations</th>
<th>4000 (3M)</th>
<th>4075 (3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>20 IBU AGF SDM</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>10 IBU AGF MSD BHT</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>White, Dry, Free flowing</td>
<td>Light brown, Sticky, Hard</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>White, Dry, Free flowing</td>
<td>White, Non-sticky</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>White, Dry, Free flowing</td>
<td>White, Non-sticky</td>
</tr>
<tr>
<td>AGF POLYMER</td>
<td>White, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>BLANK AGF SDM</td>
<td>Light brown, Dry, Free flowing</td>
<td>Dark brown, Sticky, Hard</td>
</tr>
<tr>
<td>HPMCK3 POLYMER</td>
<td>White, Dry, Free flowing</td>
<td>White, Non-sticky</td>
</tr>
<tr>
<td>BLANK HPMCK3 SDM</td>
<td>White, Dry, Free flowing</td>
<td>White, Non-sticky</td>
</tr>
</tbody>
</table>

Note-All initial samples were white colored, dry, free flowing
Table G. 3 Actual IBU concentrations (µg/ml) of stability samples

<table>
<thead>
<tr>
<th>Formulations</th>
<th>INITIAL</th>
<th>2500 (6M)</th>
<th>2560(6M)</th>
<th>4000(3M)</th>
<th>4075(3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 IBU AGF SDM</td>
<td>16.163±1.068</td>
<td>15.985±0.207</td>
<td>16.476±0.178</td>
<td>13.442±0.398</td>
<td>17.048±2.149</td>
</tr>
<tr>
<td>10 IBU AGF SDM BHT</td>
<td>19.283±0.975</td>
<td>11.131±3.096</td>
<td>16.160±1.951</td>
<td>13.342±0.853</td>
<td>13.242±2.048</td>
</tr>
<tr>
<td>10 IBU AGF MSD</td>
<td>12.493±0.801</td>
<td>12.446±1.060</td>
<td>13.597±0.335</td>
<td>12.568±0.975</td>
<td>7.008±2.239</td>
</tr>
<tr>
<td>20 IBU AGF MSD</td>
<td>14.088±5.459</td>
<td>14.518±1.089</td>
<td>12.844±0.619</td>
<td>SP</td>
<td>16.248±0.356</td>
</tr>
<tr>
<td>10 IBU AGF MSD BHT</td>
<td>21.734±3.981</td>
<td>16.953±5.559</td>
<td>15.720±0.82</td>
<td>12.530±4.576</td>
<td>16.624±0.045</td>
</tr>
<tr>
<td>10 IBU AGF PM</td>
<td>17.011±0.971</td>
<td>17.585±0.064</td>
<td>13.867±5.229</td>
<td>19.140±0.878</td>
<td>22.562±1.022</td>
</tr>
<tr>
<td>10 IBU HPMCK3 SDM</td>
<td>18.182±1.153</td>
<td>16.150±8.510</td>
<td>17.389±0.903</td>
<td>15.497±0.074</td>
<td>18.199±0.654</td>
</tr>
<tr>
<td>10 IBU HPMCK3 PM</td>
<td>19.491±0.433</td>
<td>18.407±0.552</td>
<td>14.697±0.643</td>
<td>14.963±1.032</td>
<td>19.234±0.348</td>
</tr>
<tr>
<td>PURE AGF</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK AGF SDM</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PURE HPMCK3</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BLANK HPMCK3 SDM</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note-SP-Sample Spilled
APPENDIX H

DIFFRACTOGRAMS OF STABILITY SAMPLES (CHAPTER 6)

Figure H. 1 XRPD diffractograms of 10 IBU AGF SDM stability samples

Note-NEAT IBU; 10 IBU AGF SDM INITIAL; 10 IBU AGF SDM 2500; 10 IBU AGF SDM 2560; 10 IBU AGF SDM 4000; 10 IBU AGF SDM 4075.
Figure H. 2 XRPD diffractograms of 20 IBU AGF SDM stability samples

Note- NEAT IBU; 20 IBU AGF SDM INITIAL; 20 IBU AGF SDM 2500; 20 IBU AGF SDM 2560; 20 IBU AGF SDM 4000; 20 IBU AGF SDM 4075.

Figure H. 3 XRPD diffractograms of 10 IBU AGF SDM BHT stability samples

Note- NEAT IBU; 10 IBU AGF MSD BHT INITIAL; 10 IBU AGF SDM BHT2500; 10 IBU AGF MSD BHT2560; 10 IBU AGF MSD BHT 4000; 10 IBU AGF MSD BHT 4075.
Figure H. 4 XRPD diffractograms of 10 IBU AGF MSD stability samples

Note - NEAT IBU; 10 IBU AGF MSD INITIAL; 10 IBU AGF MSD 2500; 10 IBU AGF MSD 2560; 10 IBU AGF MSD 4000; 10 IBU AGF MSD 4075.

Figure H. 5 XRPD diffractograms of 20 IBU AGF MSD stability samples

Note - NEAT IBU; 20 IBU AGF MSD INITIAL; 20 IBU AGF MSD 2500; 20 IBU AGF MSD 2560; 20 IBU AGF MSD 4000; 20 IBU AGF MSD 4075.
Figure H. 6 XRPD diffractograms of 10 IBU AGF MSD BHT stability samples

Note-NEAT IBU; 10 IBU AGF MSD BHT INITIAL; 10 IBU AGF MSD BHT 2500; 10 IBU AGF MSD BHT 2560; 10 IBU AGF MSD BHT 4000; 10 IBU AGF MSD BHT 4075.

Figure H. 7 XRPD diffractograms of 10 IBU AGF PM stability samples

Note-NEAT IBU; 10 IBU AGF PM INITIAL; 10 IBU AGF PM 2500; 10 IBU AGF PM 2560; 10 IBU AGF PM 4000; 10 IBU AGF PM 4075.
Figure H. 8 XRPD diffractograms of 10 IBU HPMCK3 SDM stability samples

Note-NEAT IBU; 10 IBU HPMCK3 SDM INITIAL; 10 IBU HPMCK3 SDM 2500; 10 IBU HPMCK3 SDM 2560; 10 IBU HPMCK3 SDM 4000; 10 IBU HPMCK3 SDM 4075.

Figure H. 9 XRPD diffractograms of 10 IBU HPMCK3 PM stability samples

Note-NEAT IBU; 10 IBU HPMCK3 PM INITIAL; 10 IBU HPMCK3 PM 2500; 10 IBU HPMCK3 PM 2560; 10 IBU HPMCK3 PM 4000; 10 IBU HPMCK3 PM 4075.
APPENDIX I

ABBREVIATIONS USED

ACN- Acetonitrile
AFM- Atomic force microscopy
AG- Larch arabinogalactan
AGF- Larch Arabinogalactan FiberAid grade
ANOVA- Analysis of variance
aw- Water activity
BCS- Biopharmaceutical classification system
BHT -Butylated hydroxytoluene
CSD- Closed cycle spray drying
CK- Couchman-Karasz
CMC- Carboxy methyl cellulose
Da- Dalton
DDI- Dynamic dew point isotherm
DL-Drug load/Drug loads
DMA- Dynamic mechanical analysis
DSC- Conventional differential scanning calorimetry
DQ- Dihydroquercitin
E100- Eudragit 100

EM- Eutectic mixture

EMs- Eutectic mixtures

EVA- ethylene vinyl acetate copolymer

f₂- Similarity factor

FRZD- Freezedried

FTIR- Fourier transform infra red

g- Gram/Grams

GI- Gastrointestinal

GPC- Gel permeation chromatography

GRAS- Generally recognized as safe

h- Hour/Hours

HM- Hot Mix

HME- Hot melt extrusion

HPMC- Hydroxypropylmethylcellulose

HPMCAS- Hydroxypropylmethylcellulose acetate succinate

HPC- Hydroxypropylcellulose

HP-β-CD- Hydroxypropyl-β-cyclodextrin

HPLC- High performance liquid chromatography
IBAP- Isobutylacetophenone

IBU- Ibuprofen

10 IBU AGF SDM- 10% IBU loaded AGF solid dispersion prepared with modified solvent evaporation method

20 IBU AGF SDM- 20% IBU loaded AGF solid dispersion prepared with modified solvent evaporation method

30 IBU AGF SDM- 30% IBU loaded AGF solid dispersion prepared with modified solvent evaporation method

10 IBU HPMCK3 SDM- 10% IBU loaded HPMCK3 solid dispersion prepared with modified solvent evaporation method

30 IBU HPMCK3 SDM- 30% IBU loaded HPMCK3 solid dispersion prepared with modified solvent evaporation method

10 IBU AGF MSD- 10% IBU loaded AGF microsphere solid dispersion

20 IBU AGF MSD- 20% IBU loaded AGF microsphere solid dispersion

30 IBU AGF MSD- 30% IBU loaded AGF microsphere solid dispersion

10 IBU AGF PM- 10% IBU loaded AGF physical mixture

20 IBU AGF PM- 10% IBU loaded AGF physical mixture

30 IBU AGF PM- 30% IBU loaded AGF physical mixture

10 IBU HPMCK3 PM- 10% IBU loaded HPMCK3 physical mixture
30 IBU HPMCK3 PM- 30% IBU loaded HPMCK3 physical mixture

IDR- Intrinsic dissolution rate

IPSD- Innerphase solid dispersion

ITRA- Itraconazole

10 ITRA AGF SDM- 10% Itraconazole loaded AGF solid dispersion prepared by modified solvent evaporation method

20 ITRA AGF SDM- 20% Itraconazole loaded AGF solid dispersion prepared using modified solvent evaporation method

30 ITRA AGF SDM- 30% Itraconazole loaded AGF solid dispersion prepared using modified solvent evaporation method

10 ITRA AGF PM- 10% Itraconazole loaded AGF physical mixture

20 ITRA AGF PM- 20% Itraconazole loaded AGF physical mixture

30 ITRA AGF PM- 30% Itraconazole loaded AGF physical mixture

kD- Kilodalton

KETO- Ketoprofen;

10 KETO AGF SDM- 10% Ketoprofen loaded AGF solid dispersion prepared using modified solvent evaporation method

20 KETO AGF SDM- 20% Ketoprofen loaded AGF solid dispersion prepared using modified solvent evaporation method
30 KETO AGF SDM- 30% Ketoprofen loaded AGF solid dispersion prepared using modified solvent evaporation method

10 KETO AGF PM- 10% Ketoprofen loaded AGF physical mixture

20 KETO AGF PM- 20% Ketoprofen loaded AGF physical mixture

30 KETO AGF PM- 30% Ketoprofen loaded AGF physical mixture

LB- Pounds

LOD- Limit of detection

LOQ- Limit of quantification

mPa s- Millipascal-second

MW- Molecular weight

LC-MS- Liquid chromatography mass spectroscopy

LS- Light scattering

Min- Minute/Minutes

mDSC- Modulated differential scanning calorimetry

MCC- Microcrystalline cellulose

NA-Non-applicable

NCE- New chemical entities

NMR- Nuclear magnetic resonance

PEO- Polyethylene oxide

PEG- Polyethylene glycol
PAA- Polyacrylic acid

PM- Physical mixture

PMs- Physical mixtures

PVP- Poly vinylpyrrolidone

PVP-CL- Poly vinly pyrrolidone cross linked

PVPVA- Poly vinly pyrrolidone-vinyl acetate

PSSA- Poly-styrene sulfonic acid

PSSA- Poly (styrene sulfonic acid); PVP-Poly( vinylpyrrolidone)

RC- Relative crystallinity

RDC- Relative degree of crystallinity

RH- Relative humidity

SD- Solid dispersion

SDs- Solid dispersions

SEC- Size exclusion chromatography

SEM- Scanning electron microscopy

Tg- Glass transition temperature

Tgs- Glass transition temperatures

TGA- Thermogravimetric analysis

TMA- Thermomechanical analysis
Tm-Melting Temperature

SPRDY- Spray-dried

SEWS- Solvent evaporation with water as a solvent

MSD-Microspheres solid dispersion

MSDs-Microspheres solid dispersions

10 MSD- 10% IBU loaded microspheres solid dispersion

20 MSD- 20% IBU loaded microspheres solid dispersion

30 MSD- 30% IBU loaded microspheres solid dispersion

SDM-Solid dispersion prepared by modified solvent evaporation method

SDMs-Solid dispersions prepared by modified solvent evaporation method

10 SDM- 10% drug loaded solid dispersion prepared by modified solvent evaporation method

20 SDM- 20% drug loaded solid dispersion prepared by modified solvent evaporation method

30 SDM- 30% drug loaded solid dispersion prepared by modified solvent evaporation method

PM-Physical mixture/Physical mixtures

10PM- 10% drug loaded physical mixture

20PM- 20% drug loaded physical mixture

30PM- 30% drug loaded physical mixture
RDR $^{15\text{ min}}$ - Relative drug release with respect to respective neat drug at 15 min

RDR $^{30\text{ min}}$ - Relative drug release with respect to respective neat drug at 30 min

RDR $^{120\text{ min}}$ - Relative drug release with respect to respective neat drug at 120 min

TMA- Thermomechanical Analysis

s- Second/seconds

vs- Versus

XRPD- X-ray powder diffraction

XRD- X-ray diffraction

2500- 25 °C and 0% RH stability condition

2560- 25 °C and 60% RH stability condition

4000- 40 °C and 0% RH stability condition

4075- 40 °C and 75% RH stability condition

3M- 3 months

6M- 6 months

CHLORP- Chlorpropamide

FLURBI- Flurbiprofen

FUROS- Furosemide

KETOC- Ketoconazole

NAPROX- Naproxen
NIMO- Nimodipine

PROPFB- Propranolol free base

PROPHCl- Propranolol hydrochloride

RITO- Ritonavir;

TIOCO- Tioconazole

10 CHLORP AGF SDM- 10% Chlorpropamide AGF solid dispersion prepared by modified solvent evaporation method

10 FLURBI AGF SDM- 10% flurbiprofen AGF solid dispersion prepared by modified solvent evaporation method

10 FUROS AGF SDM- 10% furosemide AGF solid dispersion prepared by modified solvent evaporation method

10 KETOC AGF SDM- 10% Ketoconazole AGF solid dispersion prepared by modified solvent evaporation method

10 NAPROX AGF SDM- 10% Naproxen AGF solid dispersion prepared by modified solvent evaporation method

10 NIMO AGF SDM- 10% Nimodipine AGF solid dispersion prepared by modified solvent evaporation method

10 PROPFB AGF SDM- 10% Propranolol free base AGF solid dispersion prepared by modified solvent evaporation method

10 RITO AGF SDM- 10% Ritonavir AGF solid dispersion prepared by modified solvent evaporation method
10 TIOCO AGF SDM- 10% Tioconazole AGF solid dispersion prepared by modified solvent evaporation method

10 CHLORP AGF PM- 10% Chlorpropamide AGF physical mixture

10 FLURBI AGF PM- 10% Flurbiprofen AGF physical mixture

10 FUROS AGF PM- 10% Furosemide AGF physical mixture

10 KETOC AGF PM- 10% Ketoconazole AGF physical mixture

10 NAPROX AGF PM- 10% Naproxen AGF physical mixture

10 NIMO AGF PM- 10% Nimodipine AGF physical mixture

10 PROPFB AGF PM- 10% Propranolol free base AGF physical mixture;

10 RITO AGF PM- 10% Ritonavir AGF physical mixture

10 TIOCO AGF PM- 10% Tioconazole AGF physical mixture
ACKNOWLEDGEMENTS FOR PERFORMING ANALYSES

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