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Review

Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs

Shrawan Baghel, Helen Cathcart, Niall J. O'Reilly*

Pharmaceutical and Molecular Biotechnology Research Centre (PMBRC), Waterford Institute of Technology, Waterford, Ireland

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ABSTRACT

Poor water solubility of many drugs has emerged as one of the major challenges in the pharmaceutical world. Polymer-based amorphous solid dispersions have been considered as the major advancement in overcoming limited aqueous solubility and oral absorption issues. The principle drawback of this approach is that they can lack necessary stability and revert to the crystalline form on storage. Significant upfront development is, therefore, required to generate stable amorphous formulations. A thorough understanding of the processes occurring at a molecular level is imperative for the rational design of amorphous solid dispersion products. This review attempts to address the critical molecular and thermodynamic aspects governing the physicochemical properties of such systems. A brief introduction to Biopharmaceutical Classification System, solid dispersions, glass transition, and solubility advantage of amorphous drugs is provided. The objective of this review is to weigh the current understanding of solid dispersion chemistry and to critically review the theoretical, technical, and molecular aspects of solid dispersions (amorphization and crystallization) and potential advantage of polymers (stabilization and solubilization) as inert, hydrophilic, pharmaceutical carrier matrices. In addition, different preformulation tools for the rational selection of polymers, state-of-the-art techniques for preparation and characterization of polymeric amorphous solid dispersions, and drug supersaturation in gastric media are also discussed.

Introduction

Oral drug delivery is the most commonly used route due to its ease of administration, high patient compliance, cost effectiveness, reduced sterility constraints, and flexibility of dosage form design.[1] When a drug is administered orally, it has to cross certain checkpoints (varies from drug to drug) within the biological system including dissolution in gastrointestinal fluids, permeation across the gut membrane, and first pass metabolism to finally reach its site of action via systemic circulation. Every checkpoint presents a potential bottleneck, of which dissolution in gastric fluid is of prime importance. Indeed, for most drugs, it is the main requirement to enable systemic circulation which determines the bioavailability. Taking into account the conceivable rate-constraining steps, Amidon et al. (1995) classified active pharmaceutical ingredients (APIs) into 4 groups on the basis of their solubility and permeability known as the Biopharmaceutical Classification System (BCS) as shown in Figure 1.[2] BCS involves mathematical analysis to experimentally determine solubility and permeability of drugs under specified conditions.[3] According to the US Food and Drug Administration, a drug is considered to be highly soluble when its highest clinical dose strength is soluble in ≤250 mL of aqueous media over a pH range of 1-7.5 at 37.5°C, and it is considered to be highly permeable if the absorption of an orally administered dose in humans is >90% when determined using mass balance or in comparison to an intravenous reference dose.[4] A biowaver (permission to skip *in vivo* bioequivalence studies) may be applied for certain drugs that pass specific *in vitro* solubility and permeability requirements. The following discussion is limited to BCS class II drugs (low solubility and high permeability).

* *Correspondence to:* Niall J. O'Reilly (Telephone: +353-51-306167; Fax: +353-51-302150).
E-mail address: noreilly@wit.ie (N.J. O'Reilly).

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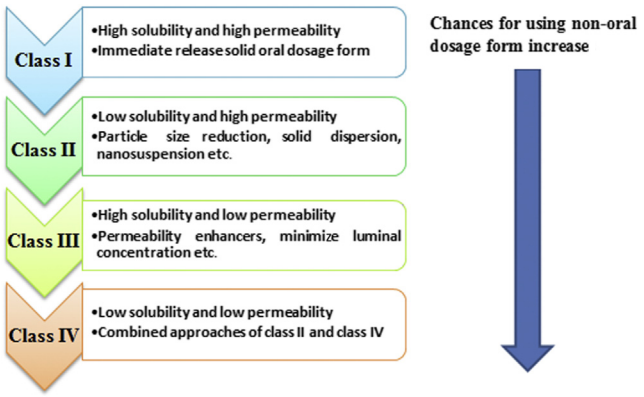

Figure 1. Biopharmaceutics classification system and formulation approaches for different classes of drugs.

Poor aqueous solubility is a matter of serious concern if the clinical dose of drug cannot dissolve in the available volume of gastrointestinal fluids. A well-known example is danazol which has an aqueous solubility of ~1 μg/mL at gastric pH and a dose of 200-600 mg/d.[5,6] To completely dissolve the lowest clinical dose of danazol at gastric pH, approximately 200 L of aqueous media would be required, which is obviously impossible *in vivo*. Furthermore, poorly water-soluble drugs will typically exhibit dissolution rate-limited absorption as they may pass their absorption site before complete dissolution. Therefore, there is great interest among formulation scientists to develop reliable, efficient, cost effective, and scalable methods to increase the aqueous solubility of BCS class II drugs. Common formulation strategies to tackle this challenge include pH adjustment, self-emulsifying drug delivery systems, particle size reduction, supercritical fluid (SCF) processing, inclusion complexes, cosolvency, micellar solubilization, hydrotrophy, solid dispersions, nanosuspensions, cocrystals, and nanocrystallization.[7-9] The choice of a particular method depends mainly on the physicochemical characteristics of drugs, carrier properties, and their expected use.[10]

The crystalline form of a drug offers the advantage of high purity and physical or chemical stability. However, the lattice energy barrier is a major constraint in the dissolution of crystalline drug molecules.[11] The amorphous state, on the other hand, exhibits a disordered structure in comparison to crystalline form and possesses higher free energy (thermodynamic driving force) leading to higher apparent water solubility, dissolution rate, and oral absorption.[12] Pure amorphous drugs are rarely used in formulation development because of their inherent physical or chemical instability. The solubility advantage of these systems can be retained by devising effective strategies to "kinetically stabilize" amorphous APIs. This has encouraged the development of amorphous solid dispersions (ASDs) products.

The concept of solid dispersions was first proposed by Sekiguchi and Obi in 1961.[13] On the basis of the distribution of the drug molecules in the carrier matrix, solid dispersions can be divided into 3 types: (1) Eutectic systems are mixtures of 2 compounds in a specific ratio and have a single melting point which is lower than the melting points of the individual components; (2) Solid solutions which are further divided into substitutional solid solutions (solute molecule replaces a solvent molecule), interstitial solid solutions (solute molecule is present in the interstices), and amorphous solid solutions having solute randomly distributed in an amorphous carriers; and (3) Microfine crystalline dispersions are crystalline dispersion of drugs in the carrier matrix.[14] The concept of solid dispersion has been successfully applied to oral formulations containing drugs with a high crystallization tendency (such as ivacaftor in Kalydeco) and also with a high drug loading (375 mg per tablet in Incivek; Table 1).[15] A wide range of pharmaceutical excipients such as carbohydrates, lipids, proteins, sugars (sucrose, xylitol), organic acids (succinic acid), surfactants (Spans®, Renex®), urea, pentaerythritol, and polymers have been investigated and used to kinetically stabilize the amorphous APIs.[16] Taking into consideration its most used form as shown in Table 1, solid dispersion can now be more narrowly defined as the dispersion of amorphous drug in a polymeric carrier matrix.[17] The following discussion is limited to a system that fits this more concise definition, that is, polymeric amorphous solid dispersions (PASDs). Information related to eutectic mixture or microfine crystalline dispersion can be found elsewhere.[18]

The main focus of the further discussion will be on how to engineer the thermodynamic properties of BCS class II drugs, different factors affecting the stability, and physicochemical properties of amorphous drug in solid dispersion; how different mechanisms are involved in stabilizing the amorphous form in polymer matrices; what should be considered for the rational selection of polymers and preparation techniques and latest characterization methods to develop a multidisciplinary approach toward the molecular level understanding of PASDs.

Amorphous State

To have a better understanding of the differences in the thermodynamic properties of crystalline and amorphous forms, consider a crystalline drug which, when heated, undergoes melting at temperature (T_m) as shown in Figure 2. On cooling the molten drug slowly, formation of an orderly system takes place as the molecules have sufficient time to move from their current location to a thermodynamically stable point on crystal lattice.[20] The molecules arrange themselves in a definite order, regenerating a crystalline structure. However, if the molten drug is cooled suddenly, then it may attain a supercooled liquid state (without undergoing crystallization), having a temperature lower than its T_m, which is in equilibrium with the molten drug.[21] On further cooling, the system remains in equilibrium until a glass transition temperature (T_g) is reached, below which it enters a nonequilibrium state (supercooled liquid state or lower viscosity rubbery state) and converts into the "frozen" glassy state of the drug.

A material in a glassy state behaves like a brittle solid, but without crystalline structure and having only short range order.[22] This transition is necessary because if the supercooled liquid state exists below the glass transition temperature, then a point comes whereby the crystals would have higher entropy compared to the supercooled liquid. The total entropy of the system would become negative before reaching absolute zero temperature, violating the third law of thermodynamics (entropy of perfect crystal is zero at 0 K).[23] The glass transition is a second order thermodynamic transition characterized by a step change in the heat capacity which is also associated with change in derivative of extensive thermodynamic properties such as volume, enthalpy, and entropy.[24] The amorphous state of a drug has a higher enthalpy, entropy, free energy, and volume as compared with the crystalline form which is responsible for its higher apparent solubility (as shown in Fig. 2). The relative increase in solubility of the amorphous form as compared with the crystalline form can be estimated by using the following equations (Eq. 1 and 2)[25]:

Table 1
FDA-Approved Solid Dispersion Products

Product Name	Drug	Polymers[a]	PASD Preparation Method[19]	Maximum Drug Loading Per Tablet/Capsule (mg)[b]	Dosage Form
Kalydeco	Ivacaftor	HPMCAS	Spray drying	150	Tablet
Zelboraf	Vemurafenib	HPMCAS	Coprecipitation	240	Tablet
Incivek	Telaprevir	HPMCAS	Spray drying	375	Tablet
Intelence	Etravirine	HPMC	Spray drying	200	Tablet
Novir	Ritonavir	PVP/PA	Melt extrusion	100	Tablet
Kaletra	Lopinavir	PVP/VA	Melt extrusion	200	Tablet

PA, pthalate acetate; VA, vinyl acetate.
[a] Information obtained from excipients list, patents, and other sources.
[b] Drug product label from US Food and Drug Administration (FDA) website.

$$\Delta G_T^{a,c} = -RT \ln \left(\sigma_T^a/\sigma_T^c\right) \quad (1)$$

$$\Delta G_T^{a,c} = \Delta H_T^{a,c} - T\Delta S_T^{a,c} \quad (2)$$

where (σ_T^a/σ_T^c) is the solubility ratio of the amorphous and crystalline forms; $\Delta G_T^{a,c}$, $\Delta H_T^{a,c}$, and $\Delta S_T^{a,c}$ are the difference in the free energy, enthalpy, and entropy, respectively; R is the universal gas constant; and T is the absolute temperature. In contrast, the experimentally determined apparent solubility of amorphous APIs remains lesser than the theoretically predicted values in most cases.[26] On adding an amorphous drug to the media, dissolution occurs rapidly which appears as peak followed by a decrease in solubility due to devitrification and is known as "spring and parachute effect," (Fig. 3) which creates considerable challenges during dissolution (discussed later).[27-30]

Polymers as Carrier Matrix

Polymers are chemically composed of repetitive structural units known as monomers which are linked with each other forming an extended structural framework. They can be classified on the basis of their origin as natural (e.g., starch, cellulose, and proteins), semisynthetic (e.g., hydroxypropyl methylcellulose [HPMC]), or synthetic polymers (e.g., polyvinylpyrrolidone [PVP]).[31] From the monomer perspective, they can be classified as homopolymers (1 type of monomer) such as methylcellulose or a copolymer (≥2 monomers) such as crospovidone. Polymers can be amorphous (polyacrylic acid), semicrystalline (poly L-lactic acid), or crystalline (polyethylene glycol). Due to their complex 3-dimensional structures with numerous interchain or intrachain cross links, incorporation of amorphous drugs into these cross-linked networks hinders their molecular mobility. This lowers the chemical potential of the amorphous drug and brings it closer to that of the crystalline form as shown in Figure 4.[32,33] As a result, polymers prevent devitrification thereby preserving the viability (solubility and stability) of the amorphous state over the shelf life of the product.[34] Various polymers have been studied and examined to prepare PASDs, and a comprehensive list is given in Table 2.

A number of factors, such as molecular mobility, thermodynamic properties, environmental stress, preparation methods, and conditions play a major role in the physical/chemical stability of the amorphous form (as mentioned in Table 3), and the following section will briefly review the effect of polymers on these factors along with the different mechanisms of stabilization as shown in Figure 5.

Crystallization Inhibition

Before developing the ASD-based formulation, it is important to estimate the suitability of a compound to form the amorphous phase. Glass forming ability (GFA) and fragility can provide a qualitative estimation of the tendency of a drug candidate to undergo devitrification and may clarify its suitability, on the basis of physical stability, for amorphous dosage forms.

GFA and fragility may be considered as an indicator of life expectancy of an ASD.[91] It has been suggested that crystallization is inversely related to the GFA of amorphous drugs, and GFA is defined as the ease with which materials can undergo vitrification on cooling.[92] Different methods are reported in the literature to measure the GFA of a drug compound such as reduced glass transition temperature (T_{rg}), cooling rate dependence, and the crossover point of the heating/cooling rate dependencies of the

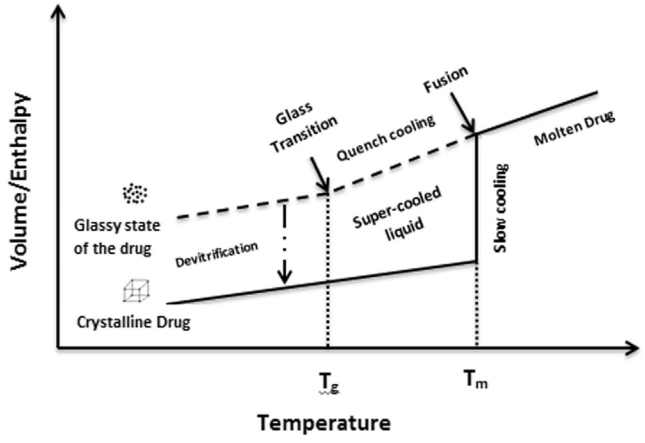

Figure 2. Enthalpy and volume of different state of drugs as a function of temperature; T_g and T_m are glass transition and melting temperature, respectively; diagram is not to scale.

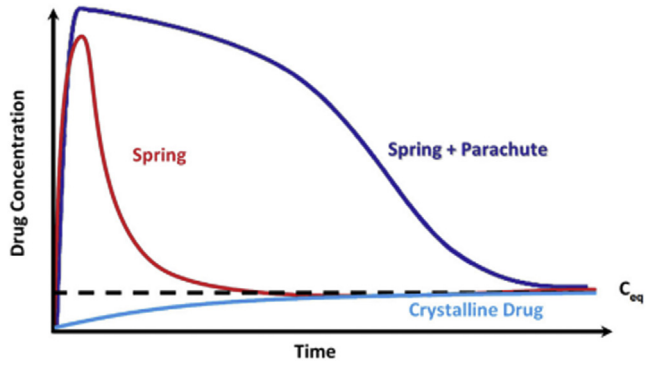

Figure 3. Drug profile based on the aqueous solubility of amorphous and crystalline form of the drug; reproduced with permission from Brough and William[19]; diagram is not to scale.

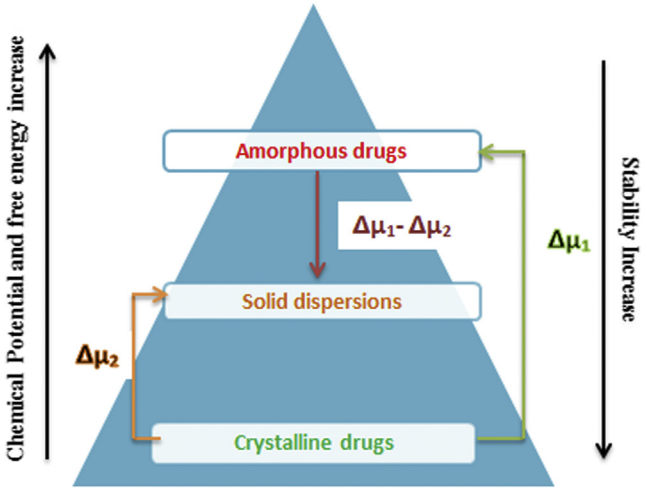

Figure 4. Energy pyramid of the crystalline form, amorphous solid dispersion, and amorphous form. μ is the chemical potential; diagram is not to scale.

crystallization temperature.[93] The kinetic behavior of a supercooled liquid can also be estimated by examining the sensitivity of the liquid structure to temperature change, known as "fragility" of the liquid, which is closely linked to its GFA.[94] It has been observed that strong "liquids" are good glass formers having higher viscosity at T_m and resistant to structural changes. Fragile liquids, on the other hand, are weak glass formers, exhibiting lower viscosity at T_m and allowing larger structural changes with change in temperature.[95] Fragility (m) of an amorphous drug can be calculated by measuring the dependence of T_g on the heating rate, q, in differential scanning calorimetry (DSC) measurements.[96] Other methods such as extrapolation of configurational entropy to 0 and observation of glass transition width are also mentioned in the literature.[97]

The crystallization of an amorphous drug is a 2-step process, although they occur simultaneously. The first step is nucleation which occurs at a lower temperature, and the second step is the crystal growth which requires higher temperature.[98] A supersaturated solution of drugs also favors crystallization. However, this is not the only requirement for the crystallization to start. A certain minimum amount of energy (known as energy of activation) is also required to overcome the high interfacial tension between small particles. Thus, nucleation may not start until a certain degree of supersaturation is reached to overcome the energy barrier. This range of supersaturated concentrations where no nucleation occurs is known as the *metastable zone*, and a smart choice of polymeric excipients can expand this region by causing an increase in the degree of supersaturation or decrease in interfacial energy.[98] Polymeric excipients that increase aqueous solubility (by inhibiting precipitation of the dissolved drug) can retard the nucleation rate by decreasing the free drug concentration available for nuclei/seed formation.[99] Polymer also increases the viscosity of the system which may alter the frequency of atomic/molecular transport at the surface of the nucleus.[100] Moreover, they have sufficiently high configurational entropy due to their large, complex, and flexible structures; their high molecular weights; and their ability to exist in many conformations. These significantly reduce the chance of drug recrystallization as it lowers the free energy of the ASD (Fig. 4).[101]

Antiplasticization

Antiplasticization is the reduction of plasticity or the hardening of a material.[102] In thermodynamics, it is described as a phenomenon which leads to an increase in T_g of the material which increases the free energy required by the amorphous drug to convert into the crystalline form. When 2 materials having different T_g's are mixed together, the final T_g of the mixture will be somewhere between the T_g's of both the materials.[103] Mixing a low-T_g amorphous drug with a high-T_g polymer at the molecular level leads to the formation of PASD with a T_g intermediate of these 2 components. In other words, the polymer undergoes plasticization whereas the T_g of the drug increases, and it undergoes antiplasticization. The resultant T_g of the final mixture can be calculated by using Gordon-Taylor equation (Eq. 3)[104]:

$$T_g = \frac{W_1 T_{g1} + K_G W_2 T_{g2}}{W_1 + K_G W_2} \quad (3)$$

where T_g, T_{g1}, and T_{g2} are glass transition temperatures of the drug-polymer mixture, the amorphous drug, and the polymer, respectively; W_1 and W_2 are the weight fraction of the drug and polymer, respectively, and K_G is a constant the value of which depends on the level of interaction between the drug and the polymer and can be calculated using the equation (Eq. 4) as shown:

$$K_G = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (4)$$

where ρ_1 and ρ_2 are the densities of amorphous drug and polymer, respectively. Other equations such as Fox,[105] Couchman-Karasz,[106] or Kwei[107] are also reported in the literature to estimate the resultant T_g of the PASD. Sathigari et al.[108] have studied the stabilization of amorphous efavirenz and reported that the stability of the amorphous drug in the solid dispersion having Plasdone S-630 as the carrier is due to the antiplasticizing effect of the polymer, which increases the viscosity of the system and decreases the diffusion of drug molecules (necessary to form crystalline lattice). However, sometimes, experimentally obtained T_g values deviate significantly from the theoretically predicted values as shown in Figure 6. This is due to the volume nonadditivity resulting from nonideal mixing of the drug and polymer.[109]

When a drug is dispersed in the polymer matrix, several homonuclear and heteronuclear interactions come into play. These interactions can be represented as the following:

1. D-D + P-P > 2(D-P)
2. D-D + P-P < 2(D-P)
3. D-D + P-P = 2(D-P)

where D and P represent drug and polymer, respectively. It is the relative strength of these interactions which defines the final volume of ASDs. In the first case, the homonuclear interactions are stronger than the heteronuclear interactions. Thus, when a solid dispersion is formed, there would be a net contraction in the volume. The second case represents stronger heteronuclear interactions causing a net expansion of the system. The third case is the ideal condition wherein there is no net increase or decrease in volume and volume additivity is perfect. Ideally, the drug and polymer should be completely miscible with each other, and the drug should be evenly dispersed in the polymer carrier. However, in most cases, the drug-polymer mixture is not ideal, and this nonideality in mixing causes deviation between experimental and theoretical T_g values. A stronger drug-polymer interaction is generally preferred resulting in favorable exothermic mixing with increased configurational entropy.[110] Crowley et al. have studied the nonideality of mixing and suggested that these deviations from predictions are due to the

Table 2
Examples of Different Polymers Used in the Formulation of Amorphous Solid Dispersions

Polymers[a]	Drugs Stabilized	Preparation Method	Comments	References
PVP based polymers				
Poly(vinylpyrrolidone) K17 (Povidone K17) (PVP K17) (MW: 10,000, T_g 126°C)	**Acetaminophen** (MW: 151.2, T_m 169.85°C, T_g 25.85°C)[a]	Spray drying	Polymer viscosity plays an important role in stabilizing the solid dispersion. No evidence of drug polymer interaction was found. Inverse relationship between polymer T_g and stabilization.	35
	Oridonin MW: 10,000, T_g 126°C	Gas anti-solvent technique	Significant increase in oral bioavailability of the amorphous drug (26.4 fold)	36
PVP K25 (MW: 25000, T_g 152.4°C)	**Indomethacin** (MW: 356.7, T_m 160.85°C, T_g 44.85°C)[a]	Spray drying/Film casting	In this study, the solubility of a drug-polymer dispersion was determined from the drug-polymer interaction and has been concluded that better solubility and higher drug-polymer interaction leads to improved physical stability of amorphous solid dispersion	37
	Piroxicam	Solvent evaporation	This study demonstrated that the PVP weight fraction and solvent evaporation has a significant effect on resistance to crystallization while the effect of polymer molecular weight was much smaller. Also, an increase in these three parameters led to an increase in H-bonding interaction.	38
	Naproxen (MW: 230.3, T_m 153°C, T_g -3°C)[b]	Spray drying	Different solvents used for spray drying have different effect on the drug-polymer interaction in the solid dispersion and the choice of an appropriate solvent leads to better dispersivity of drug in the polymer matrix.	39
PVP K30 (MW: 30000, T_g 160°C)	**Ezetimibe**	Solvent method	Thermal and spectroscopic analysis revealed that PVP K30 was effective in stabilizing amorphous ezetimibe and also causes faster drug release during *in vitro* dissolution testing, leading to improved oral bioavailability.	40
	Indomethacin (MW: 356.7, T_m 160.85°C, T_g 44.85°C)[a]	Spray drying	It has been concluded that solubility of a drug in polymer is determined by the drug-polymer interaction rather than the molecular weight of the polymer.	41
	Felodipine (MW: 384.3, T_m 146.85°C, T_g 44.85°C)[a]	Spray drying/Hot melt extrusion	Spray dried formulations were found to exhibit faster drug release profiles than melt extruded product, although in some cases melt extrusion offered improved stability. Antiplasticization is one of the factors responsible for improved stability.	42
	Telmisartan	Spray drying	The optimum pH-modulated solid dispersion formulation of Telmisartan/PVP K30/Na_2CO_3 at weight ratio of 2/0.5/3 showed improved dissolution rate (~3 fold)	43
PVP Vinyl acetate (PVP VA): 60/40 (Plasdone® S630) (MW: 45000-70000, T_g 106°C, T_m 140°C)	**Ketoconazole** (MW: 531.4, T_m 149.85°C, T_g 44.85°C)[b]	Hot Melt Extrusion	Raman mapping demonstrated full homogenous spatial distribution of ketoconazole in PVP VA. Spring and parachute effect was observed during dissolution experiments. The release of drug was carrier controlled initially and then burst release was observed leading to precipitation of amorphous drug.	44
	Itraconazole (MW: 705.7, T_m 167.85°C, T_g 57.85°C)[b]	Electrospinning method	Complete amorphization of drug was obtained using PVP VA *via* electro-spinning method. Better dissolution rate (>90% within 10 min) was observed as compared to the crystalline form of the drug. Also, this technique offered improved dissolution properties in comparison to spray dried microspheres of the drug and polymer.	45
	Dipyridamole (MW: 504.62, T_m 163°C, T_g 40°C)[d]	Solvent evaporation	H-bonding between the drug and polymer played an essential role in crystallization of amorphous drug in solid dispersions under conditions of 25°C and 50% RH. Drug-polymer interaction changes at 40°C and 75% RH which affects the crystallization rate of the drug in the dispersion.	46
Crospovidone (Polyplasdone® XL) (MW: >10000)	**Glipizide**	Rotary evaporation/ Fluid bed drug layering	No sign of phase separation or crystallization was observed. Antiplasticization and drug-polymer miscibility are the key players in stabilizing solid dispersion.	47
PEG based polymers				
Polyethylene glycol 4000 (PEG 4000) (MW: 4000, T_g ~45°C)	**Nifedipine** (MW: 346.3, T_m 172.85°C, T_g 46.85°C)[b]	Fusion/solvent method Fusion method	The polymer was capable of prohibiting drug crystallization in solid dispersion. Samples which are prepared at higher temperatures showed better dissolution profiles compared to the samples prepared at nifedipine melting point which may be due to improved drug-polymer mixing at higher temperatures.	48
PEG 8000 (MW: 8000, T_m 62°C)	**Curcumin** (MW: 368.4, T_m 176°C)	Solvent evaporation method	The polymer demonstrates poor capability to disperse the drug in the amorphous form, to inhibit crystal growth and to increase saturation solubility of the drug in water. It may be due to non-surface active property of the polymer.	49
PEG 8000 (MW: 8000, T_m 62°C)	**Curcumin** (MW: 368.4, T_m 176°C)	Solvent evaporation method	The polymer demonstrates poor capability to disperse drug in amorphous form, to inhibit crystal growth and to increase saturation solubility of drug in water. It may be due to non-surface active property of the polymer.	50
PEG 20,000 (MW: 20000, T_m 60-63°C)	**Carbamazepine** (MW: 236.3, T_m 190°C, T_g 61°C)[d]	Fusion method	Presence of intramolecular H-bonds causes high crystallization tendency of the amorphous drug. No drug-polymer interaction was found in the solid dispersion. Increased dissolution rate was due to the hydrophilic nature of the polymer.	51
Cellulose based polymers				
Methylcellulose (MW: 10000-220000, T_m 290-305°C)	**Carbamazepine** (MW: 236.3, T_m 190°C, T_g 61°C)[d]	Hot Melt Extrusion	Drug-polymer interaction and hydrophilic nature of the polymer improves the dissolution performance of the solid dispersion compared to the crystalline drug.	52

(*continued on next page*)

Table 2 (*continued*)

Polymers[a]	Drugs Stabilized	Preparation Method	Comments	References
Hydroxypropyl methylcellulose (HPMC) (MW: 10000-1500000, T_g 172°C)	**Tacrolimus** (MW: 804.02, T_m 142°C)	Solvent evaporation method	Drug-polymer interaction and antiplasticization plays a major role in the performance of the amorphous solid dispersion	53
	Valsartan (MW: 435.52, T_m 110°C, T_g 76°C[54])	Spray drying	HPMC increases the hydrophilicity of valsartan, improving the drug solubility by about 43-fold and leading to higher dissolution and bioavailability.	55
	Indomethacin (MW: 356.7, T_m 160.85°C, T_g 44.85°C)[b]/ **Itraconazole** (MW: 705.7, T_m 167.85°C, T_g 57.85°C)[b]/ **Griseofulvin** (MW: 352.8, T_m 216°C, T_g 88°C)[c]	Hot Melt Extrusion	It was concluded that high drug-polymer interaction were responsible for high dissolution rate and supersaturation of poorly water soluble drugs	56
	Quercetin (MW: 302.23, T_m 326°C)	Spray drying	H-bonding and antiplasticization are two main factors found to be responsible for high drug loading (50%) and stability of the solid dispersion. However, drug release in dissolution media was slow due to low wettability and poor water solubility of HPMCAS.	57
HPMC Acetate succinate (HPMCAS) (MW: 55000-90000, T_g 113°C)	**Itraconazole** (MW: 705.7, T_m 167.85°C, T_g 57.85°C)[b]	Film casting method	Drug loadings as high as 60% was found to be stable for 1 month at 40°C and 75% RH. This may be due to the high solubility of the drug in the polymer.	58
	NVS981P	Hot melt extrusion	Phase separation was observed even at 20% drug loading due to supersaturation of the polymer matrix with amorphous drug and irregular distribution of molecular mobility in the dispersion matrix	59
	Itraconazole (MW: 705.7, T_m 167.85°C, T_g 57.85°C)[b]	Spray drying/electro-spinning/electro-blowing	Electro-blowing method emerges as a promising manufacturing technique with higher stabilizing effect on solid dispersion compared to spray drying and shows 28-fold higher productivity than electro-spinning method.	60
HPMC Pthalate (HPMCP) (MW: 37900, T_g 143°C)	**Dutasteride** (MW: 528.53, T_m 249.7°C)[61]	Spray Drying	Highly effective in stabilizing and maintaining drug supersaturation leading to increased oral absorption of amorphous dutasteride.	62
	Mefanamic acid (MW: 241.3, T_m 231°C, T_g 51°C)[c]	Cryogenic grinding method	Intermolecular interaction, measured using ssNMR, between mefenamic acid and polymer leads to formation and high stability of the supersaturated solution.	63
Acrylate based polymers				
Ammonio methacrylate copolymer (Eudragit® E) (T_g ~55°C)	**Indomethacin** (MW: 356.7, T_m 160.85°C, T_g 44.85°C)[b]	Solvent evaporation	pH dependent solubility was observed. Solubility of polymer in dissolution media has a direct effect on achieving and maintaining drug supersaturation.	64
	Telmisartan (MW: 514.62, T_m 266.85°C, T_g 127.85°C)[65]	Mechanical activation method	Higher level of mixing between drug (slightly acidic) and polymer (slightly basic) leads to better dissolution profile compared to the pure drug.	66
Eudragit® RL	**Tadalafil** (MW: 389.4, T_m 302°C, T_g 147°C)	Freeze drying method	Poorly stable solid dispersion which may be due to the high difference in solubility parameter of drug and polymer (6.8MPa$^{1/2}$).	67
Polyacrylic acid (Carbomer or Carbopol 940) (MW: 450000, T_g 110°C)	**Carbamazepine** (MW: 236.27, T_m 191.5°C, T_g 53°C)[d]	Hot melt extrusion	High drug loading and better stabilization (12 months at 40°C and 75% RH) due to drug polymer interactions.	68
Miscalleneous polymers				
Chitosan (MW: 10000-1000000, T_g 203°C)	**Indomethacin** (MW: 356.7, T_m 160.85°C, T_g 44.85°C)[b]	Supercritical fluid/Hot melt extrusion	Drug-polymer interaction was independent of processing technique. Supercritical fluid based formulations performed better than HME formulations	69
Kollicoat® IR (MW: 45000, T_g 45°C)	**Fenofibrate** (MW: 360.83, T_m 80.85°C, T_g -17.15°C)[b]	Film freezing	Generated eutectic mixture with intermolecular H-bonding. Low T_g of the polymer causes rapid diffusion of the drug molecules, leading to drug crystallization and lower levels of supersaturation.	70
Soluplus® (MW: 90000-140000, T_g ~70°C)	**Carvedilol** (MW: 406.47, T_m 117°C, T_g 42°C)[b]	Solvent evaporation/ freeze drying/spray drying	Solid dispersion prepared using freeze drying method showed the highest saturation solubility.	71
Polyvinyl acetate phthalate (Sureteric®) (MW: 47000-60700, T_g 42.5°C)	**Ketoconazole** (MW: 531.4, T_m 149.85°C, T_g 44.85°C)[b]	Fusion method	X-ray diffraction analysis suggested complete miscibility of drug and polymer. However, thermal analysis revealed partial miscibility and it was concluded that the drug has limited miscibility in polymer.	72
Poloxamer 188 (Lutrol® F 127) (MW: ~10000-14000, T_m ~55°C)	**Nilvadipine**	Agitation granulation method	Using a higher viscosity grade polymer causes increase in dissolution rate. However, no change in apparent solubility was observed.	73

MW, molecular weight (Da); Tg, glass transition; Tm, melting temperature; RH, relative humidity; HME, hot-melt extrusion.

[a] Handbook of pharmaceutical excipients, 6th edition, Pharmaceutical press.

[b] Data reported in literature.[74]

[c] Values obtained from previously published reports.[75]

[d] Values taken from literature.[76]; T_g and T_m represent glass transition and melting temperature, respectively; MW and RH represents molecular weight (Da) and relative humidity, respectively.

relative extent of heteromolecular to homomolecular interactions.[111] The conclusions were in accordance with the work carried out by Fule et al. who also concluded that intermolecular interaction between drug and polymer plays a great role in nonideality of mixing.[112]

Intermolecular Interaction

The drug molecules may interact with the polymer molecules via several weak forces such as H-bonding, van der Waals forces, electrostatic, ionic, or hydrophobic.[113] These intermolecular bonds

Table 3
Different Factors Affecting the Stability of Amorphous Drug in Solid Dispersion

Factors	Impact on the Stability of Amorphous Drugs
Glass transition temperature (T_g)	Stability increases with increasing T_g. Polymers increase the kinetic stability of amorphous drugs (antiplasticization effect)[77]
Structural relaxation/molecular mobility	Responsible for recrystallization. Rate of crystallization is higher at temperatures above T_g. Restriction of molecular mobility improves stability.[78]
Configurational entropy	Low configurational entropy favors crystallization.[79] Lower crystallization tendency of erythromycin-free base, for example, can be explained by its lower thermodynamic driving force for crystallization (H_{conf}) [80]
Configurational enthalpy	The greater thermodynamic driving force for crystallization (i.e., higher configurational enthalpy) causes increased nucleation rate of nifedipine as compared to felodipine.[81]
Gibbs free energy	Systems having lower Gibbs free energy are generally more stable.[82]
Humidity, mechanical stress, and temperature	Temperature significantly affects molecular mobility, and moisture may plasticize the material by lowering its T_g near to storage temperature: increases crystallization rate and decreases crystallization temperature.[83] Mechanical stress also causes significant differences in crystallization tendency.[84]
Preparation method (fusion or solvent evaporation method, freeze drying, supercritical fluid technology)	Different preparation methods induce different thermal histories and mechanical stresses leading to different degrees of drug-polymer mixing and drug mobility in the dispersion. Hence, variable solid-state stability of the solid dispersion can be obtained.[85-87]
Preparation conditions such as cooling rate, processing temperature, and time	Slow cooling of amorphous indomethacin increases its physical stability.[88] Different inlet temperature used in the spray-drying of naproxen led to the difference in dissolution profile and drug stability.[89] Different screw speed (residence time) in hot-melt extrusion affected the stability of fenofibrate formulations in stressed conditions.[90]

restrict the molecular mobility of the drug molecules in the polymer matrix and provide stability to the system. Khougaz et al. have reported on the role of specific drug-polymer interaction in stabilizing a solid dispersion.[114] They found that when amorphous MK-0591 was dispersed in different polymers such as PVP K-12 and PVP/vinyl acetate, the final T_g of the ASD was less than the T_g of the amorphous drug. However, the solid dispersion remained stable after 1 y of storage. This shows that antiplasticization is not the only factor responsible for a reduction in devitrification rate. Infrared (IR) spectra confirmed the presence of ion-dipole interactions between the PVP carbonyl group and the MK-0591 carboxylate group (COO^-Na^+) showing that that weak intermolecular forces also play an important role in stabilizing amorphous drugs in polymer matrix. Another interesting study was carried out by Meng et al.[115] which highlighted the importance of bond formation or drug-polymer interaction in the stability of amorphous curcumin as a model drug. They examined the ability of different polymers, such as PVP K90, Eudragit EPO®, HPMC, and PEG 8000, to interact with the model drug, curcumin, through stable bond formation. It was found that Eudragit® was the only 1 of the 4 polymers which stabilizes curcumin at the limit of miscibility during stability studies and also improved its dissolution performance. Interaction between curcumin and Eudragit® was verified using IR and Raman spectroscopy. It was concluded that a certain degree of interaction between a drug and a polymer is important for successful formulation of ASDs.

A study by Miyazaki et al. demonstrated the role of stereoselective interaction in the stability of amorphous nitrendipine (NTR) prepared by the melt quenching method.[116] They elucidated the effect of stereoselective drug-polymer interaction on the crystallization rate of ASD using PVP, HPMC, and HPMC pthalate (HPMCP) as model chiral polymers. The effect of chiral polymers, HPMC, and HPMCP on the crystallization inhibition of (+)-NTR was more effective compared to that of (−)-NTR at 50°C-70°C as shown in Figure 7. PVP, on the other hand, does not preferentially interact with any of the enantiomers and hence has no effect on the crystallization profile of NTR. This difference in crystallization profile or physical stability can be attributed to stereoselective interaction between drug and polymer. However, due to the weak nature of this interaction, the effect on the physical stability of ASD was minimal at 25°C.

The contribution of drug-polymer interaction in maintaining drug stability, higher drug solubility, and degree of superstation has further been emphasized by Shah et al.[117] using vemurafenib as the

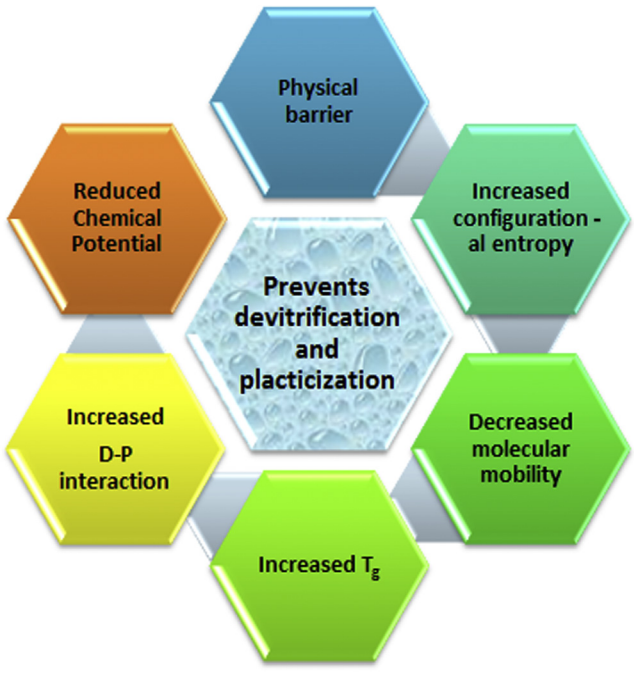

Figure 5. Different approaches for stabilizing the amorphous solid dispersion in a polymer matrix; D-P represents drug-polymer, and T_g represents glass transition temperature.

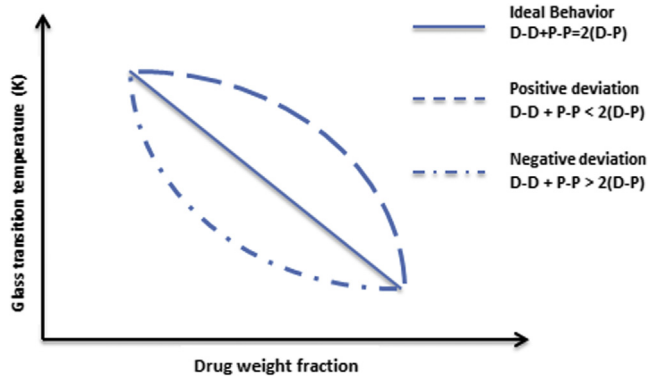

Figure 6. Deviation from ideal behavior as predicted by Gordon-Taylor equation; D represents drug, and P represents polymer; diagram is not to scale.

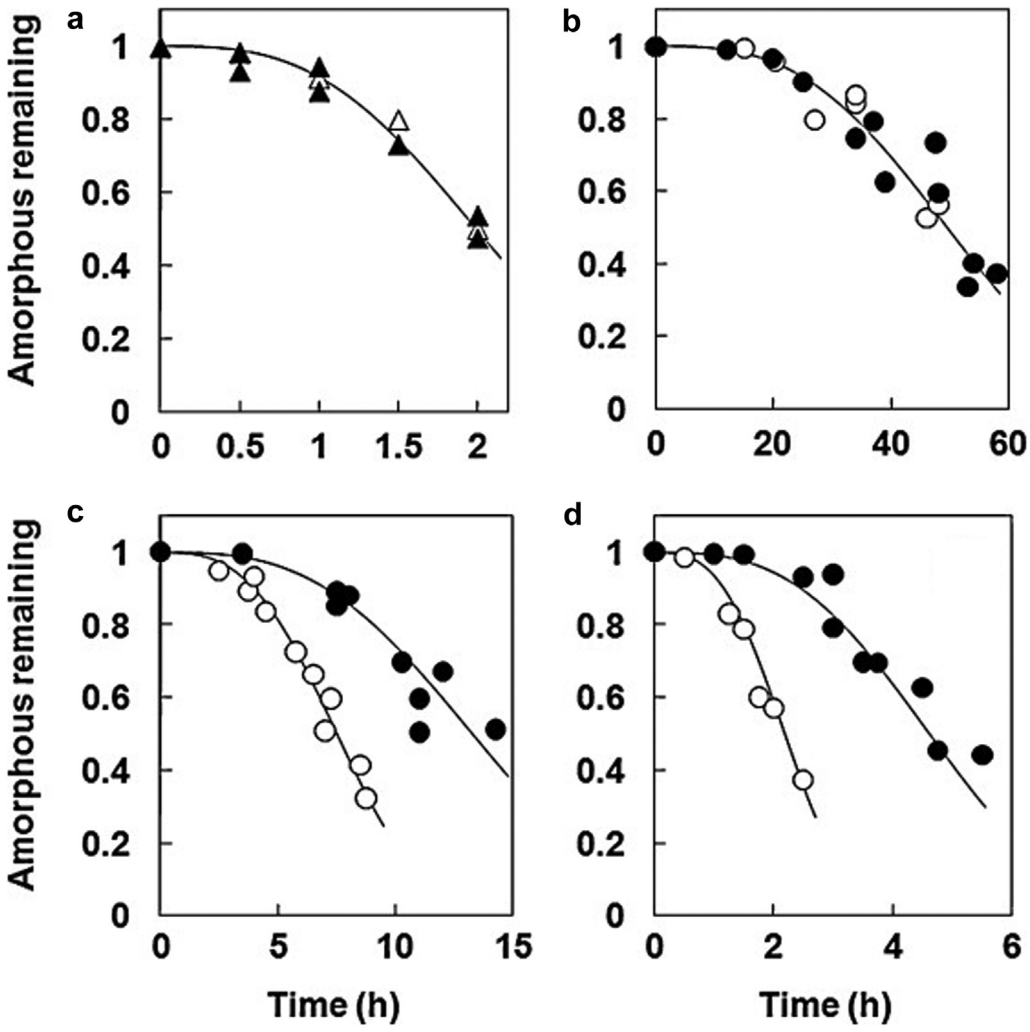

Figure 7. Crystallization rate of each nitrendipine enantiomer (a) and the enantiomers in amorphous solid dispersion with 10% PVP (b), 10% HPMC (c), and 10% HPMCP (d) at 60°C; Reproduced with permission from Miyazaki.[116] The lines represent the best fit to the Avrami model; closed symbols represent (+)-nitrendipine (NTR), and open symbols represent (−)-NTR enantiomer.

model drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), HPMCP, and Eudragit® L as model polymers. Amorphous solid dispersions were prepared by the solvent-controlled coprecipitation method. They demonstrated that HPMCAS can effectively interact with vemurafenib functional groups via H-bonding and other weak interactions in the PASD as compared to other polymers. This leads to a greater stability and a higher level of supersaturation maintenance. Indeed, Maniruzzaman et al.[118] further confirmed their role in stabilizing PASDs prepared using hot-melt extrusion process. Research findings showed the presence of H-bonding and intermolecular ionic interaction between polymer carboxylic groups and API amino functional groups which were confirmed by molecular modeling (Fig. 8) and X-ray photoelectron spectroscopy. They also demonstrated that the magnitude of the intermolecular interactions was dependent on the drug-polymer ratio and miscibility.

Reduction of Molecular Mobility of Amorphous Drug in PASD

The increased physical/chemical stability of amorphous drugs in PASD can be explained in terms of molecular mobility. An isolated metastable crystalline state of a drug may behave as if it is not affected by the stable crystalline form, until a polymorphic transition takes place. However, an amorphous drug may behave as if it always "identifies" the presence of the more stable crystalline state and gradually evolves toward it in a certain way which can be predicted from its thermal history and the extent of nonequilibrium. This is known as structural relaxation.[119] The molecular mobility of amorphous materials determines their physical stability and reactivity. Indeed, phase separation and crystallization involve diffusion and nucleation, both of which require sufficient molecular mobility. Different methods such as Kohlrausch-William-Watts method and Adam-Gibbs-Vogel equation are used to measure molecular mobility in terms of structural relaxation.[120,121] Polymer molecules, when used as a carrier for amorphous drug, have the capacity to restrict the molecular mobility of the amorphous API. Therefore, mechanistic investigation of reduced crystallization tendency due to restricted molecular mobility of amorphous drugs in PASD is essential to assess their stability. DSC,[122] solid-state nuclear magnetic resonance (ssNMR),[123] and dielectric spectroscopy[124] are commonly used to monitor molecular mobility in glass systems.

Knapik et al. have shown that the physical stability and water solubility of the amorphous drug (ezetimibe) were improved over 6 times when mixed within a PASD using Soluplus® as carrier.[125] DSC and dielectric spectroscopy analysis of amorphous ezetimibe have

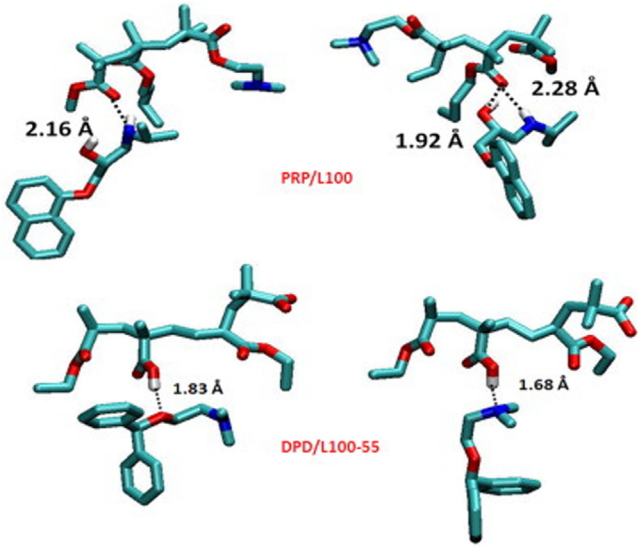

Figure 8. Molecular modeling of drug/polymers after energy optimization at the B3LYP 6-31G using Gaussian 09 software; PRP represents propranolol HCl, L100 represents Eudragit L100, and L100-55 represents Eudragit L100-55; Reproduced with permission from Maniruzzaman.[118]

led to the conclusion that the high molecular mobility, reflected in structural relaxation, is mainly responsible for its high crystallization tendency. This indicates that formation of a PASD in the Soluplus® matrix acts as physical barrier to the molecular motions of glass ezetimibe leading to improved stability. Mistry et al. have also shown that stronger drug-polymer interactions (ionic or H-bonding) reduce the molecular motion of amorphous ketoconazole which can potentially delay crystallization onset time and reduce crystallization extent.[126] In another interesting study conducted by Kothari et al.[127] it has been found that the relaxation time of the drug increases with an increase in polymer concentration. The improved stability results were attributed to the restriction of molecular mobility of amorphous drug.

Rational Selection of Polymers for PASDs

At an early developmental stage, with a limited drug supply, it is very important to characterize and correlate the physicochemical properties (such as chemical structure, molecular weight, T_m or T_g, melting enthalpy and entropy, viscosity of drug and polymer below and above T_g, structural flexibility, complexity and symmetry, functional groups contributing to bond formation, and so on) of drug and polymer for designing robust amorphous solid dispersion systems. As discussed previously, high T_g polymers at high concentrations are generally chosen to prepare ASDs owing to their antiplasticizing effect on the amorphous drug. However, at lower polymer weight fractions where no T_g differences (between amorphous drug and solid dispersion) are observed, usually drug-polymer interactions will determine their shelf life.[128] Increasing the molecular weight raises the T_g of polymers which favors antiplasticization of amorphous drugs.[129] Whereas at high molecular weight, the rise in T_g becomes insignificant as other factors such as viscosity come into play during the dissolution process. Viscosity of polymers increases with molecular weight which has significant effect on the dissolution properties.[130] Also, the polymer should have low melting point and solubility parameters similar to the drug. In addition, the extent of miscibility of an amorphous drug thei n polymer is also important as highly miscible systems are found to be more resistant to drug recrystallization.[131] The formation of a stable single phase or separate coexisting phases depends on the thermodynamic miscibility of the drug and polymer at the required condition. A change of conditions may cause phase separation of the homogenous single-phase system (Table 3). Therefore, conflicting requirements have to be met while choosing a suitable polymeric carrier. Different methods such as solubility parameter approach, Flory-Huggins theory, melting enthalpy approach, and molecular modeling as preformulation tools for the rational selection of polymers are discussed in the following sections.

Solubility Parameter Approach

The experimental determination of the solubility of a drug in a polymer is challenging. However, qualitative estimation of drug-polymer miscibility can be performed using the solubility parameter approach. The solubility parameter is equal to the square root of the cohesive energy density (total attractive force within a condensed state material) (Eq. 5) as shown below[132]:

$$\delta = \sqrt{\text{CED}} = \sqrt{\Delta E_v / V_m} \tag{5}$$

where δ is the Fedor solubility parameter, CED is the cohesive energy density, ΔE_v is the energy of vaporization, and V_m is the molar volume. Similar values of cohesive energy density for drug and polymer indicate that lesser energy is required from external sources to break the interaction between the 2 similar molecules as the energy required will be compensated from the energy released by the interaction between 2 dissimilar molecules. It has been found that the cohesive energy also depends on the interactions between polar groups and hydrogen bonding. Better predictions of interaction can be made by using Hoftyzer and Van Krevelen Method as shown by the following equations (Eq. 6 and 7)[133]:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \tag{6}$$

$$\delta_d = \frac{\sum F_{\text{di}}}{V},\ \delta_p = \frac{\sqrt{\sum F_{\text{pi}}^2}}{V},\ \text{and}\ \delta_h = \sqrt{\sum \frac{E_{\text{hi}}}{V}} \tag{7}$$

where δ_d, δ_p, and δ_h(Eq. 6 and 7) are the contributions from the dispersive forces, polar forces, and hydrogen bonding, respectively; δ is the total solubility parameter; F_{di} is the molar attraction constant due to dispersive component; F_{pi} is the molar attraction constant due to polar component; E_{hi} is the hydrogen bonding energy; and V is the molar volume. Other methods for solubility parameter calculation, such as Hoy, Small, Dunkel, Hayes, and Di Benedetto, are also reported in the literature.[134] Generally, drug-polymer systems with lower $\Delta\delta$ values are predicted to be more miscible. Systems with $\Delta\delta < 7.0$ MPa$^{1/2}$ are found to be miscible whereas systems with $\Delta\delta > 10.0$ MPa$^{1/2}$ are likely to be immiscible.[135] Although widely used, this approach has certain limitations as well. The theoretical calculation of this approach is applicable for drug-polymer systems where van der Waal interactions play a major role, whereas for drug-polymer mixtures forming highly directional interactions such as H-bonds or long range forces such as ionic interactions, this method can yield erroneous results.[136]

Flory-Huggins Theory

Flory-Huggins (FH) theory is a well-known lattice-based theory which describes polymer-solvent miscibility on the basis of the Gibbs free energy change associated with the mixing of a polymer in a solvent.[137] Recently, this theory has been applied for assessing

drug-polymer miscibility using the melting point depression method to obtain FH interaction parameter, χ, and the modified FH equation by Nishi-Wang (Eq. 8) is shown below[138]:

$$-\left(\frac{1}{T_m}-\frac{1}{T_m^o}\right)\times\frac{\Delta H_f}{R}-\ln\Phi_d-\left(1-\frac{1}{m}\right)\Phi_p=\chi\Phi_p^2 \quad (8)$$

where T_m and T_m^o are the melting points of the drug-polymer physical mixture and pure drug, respectively; ΔH_f is the melting enthalpy of pure drug; Φ_d and Φ_p are the volume fraction of drug and polymer, respectively; and m is the ratio of the polymer volume to that of the drug. The slope of the line obtained by plotting the left hand side of the equation against Φ_p^2 will give the value of FH interaction parameter, χ. A negative value of χ will indicate stronger drug-polymer interaction than individual drug-drug or polymer-polymer interaction which predicts drug-polymer miscibility, whereas a positive value indicates that homonuclear interactions are preferred over heteronuclear which may lead to phase separation.[139-141]

Melting Enthalpy Method

The physical stability of ASD primarily depends on the drug solubility in the polymer at the storage temperature. Initial determination of drug solubility in a particular polymer can be used as a screening tool, that is, polymer(s) which solubilizes higher drug weight fraction can be used for further downstream processing of ASD. The most widely used method for the estimation of drug solubility in a polymer is by using the melting enthalpy of the crystalline drug in a drug-polymer system measured by hyper DSC.[142] This method is based on a simple principle that the fraction of drug dissolved in the polymer does not contribute to the melting endotherm. Therefore, by measuring the melting enthalpy of a series of drug concentrations in drug-polymer mixtures and extrapolating the plot to zero enthalpy, the solubility of a given drug in selected polymers could be estimated from the x-intercept of the plotted line as shown in Figure 9.

Molecular Simulation

Recent computational advances in the area of atomistic and molecular simulation have given us powerful tools to probe the molecular processes of different systems, thus permitting prediction of the thermodynamic behavior of amorphous solid dispersions that are not well characterized experimentally.[143] In silico predictive tools such as GROMACS all-atom field package, Monte Carlo simulations, Dreiding 2.21 force field measurement using Cerius 2 software, SYBYL/MMFF94 force field measurement, and Gaussian 09 software using density functional theory have been successfully used to PASD systems to understand glass transition, crystallization tendency, drug-polymer interaction, and stability.[144] These simulation tools in combination with FH theory have also been used to estimate the solubility of a drug in a lipid carrier.[145] Furthermore, Condensed-Phase Optimized Molecular Potentials for Atomistic Simulation Studies force field can predict the solubility parameter for drug-polymer systems.[146] Moreover, the density functional theory using B3LYP exchange correlation function gives a reasonable estimation of drug-polymer interactions (Fig. 8).[118] These findings demonstrate that in silico–based molecular modeling is a powerful preformulation tool that can enable formulation scientists to rationally select polymers to use for PASDs.[147]

Methods for Dispersing Amorphous Drugs in Polymers

Various preparation methods for solid dispersions have been reported in the literature (Table 2) including nanosuspension techniques, cryogenic techniques, cyclodextrin-based inclusion complex techniques, electrostatic spinning, electrostatic blowing, electrospraying film casting, hydrotrophy, and mechanical activation method.[148] These techniques rely on a solubilizing mechanism such as micellar solubilization, complexation, increased porosity, or decreased particle size, and it should be differentiated from polymer-based ASD. Binary systems are most commonly used for the preparation of ASDs due to simple formulation strategy, ease of scale-up, and lower cost of production.[149] Sometimes more complex ternary and quaternary systems have also been produced depending on the requirement of the formulation and the drug stability.[150] Surfactants may increase stability and solubility of ASDs, but they also increase the complexity of the process, and they are not always tolerated well in the body.[151] Furthermore, requirements such as intimate mixing at the molecular level should also be met while designing a suitable process. Care has to be taken to avoid demixing or phase separation while choosing the techniques. Generally, phase separation or recrystallization can be prevented by restricting the molecular mobility of amorphous drugs and polymers during preparation. Three different methods (Fig. 10) for preparing solid dispersion are discussed in this review. More information on preparation techniques can be found in a number of excellent review articles.[152]

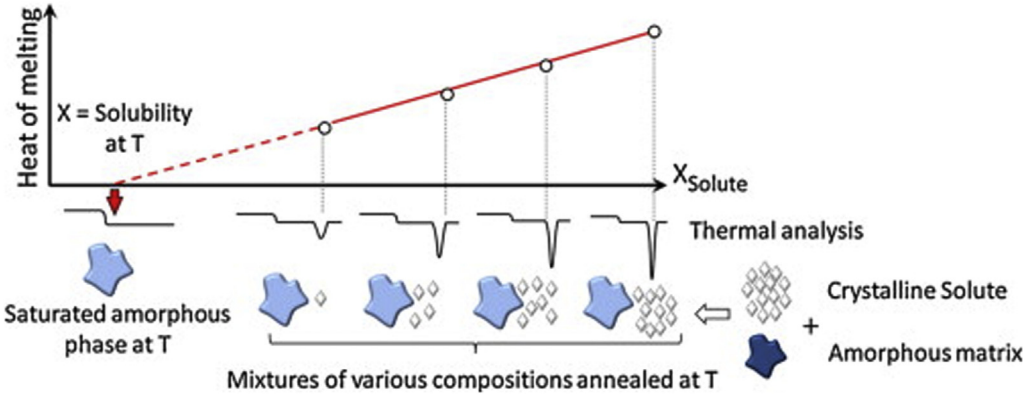

Figure 9. Melting enthalpy as a function of different drug loading in the drug-polymer physical mixture showing the fraction of unmixed drug contributing to the melting enthalpy; reproduced with permission from Amharar.[142]

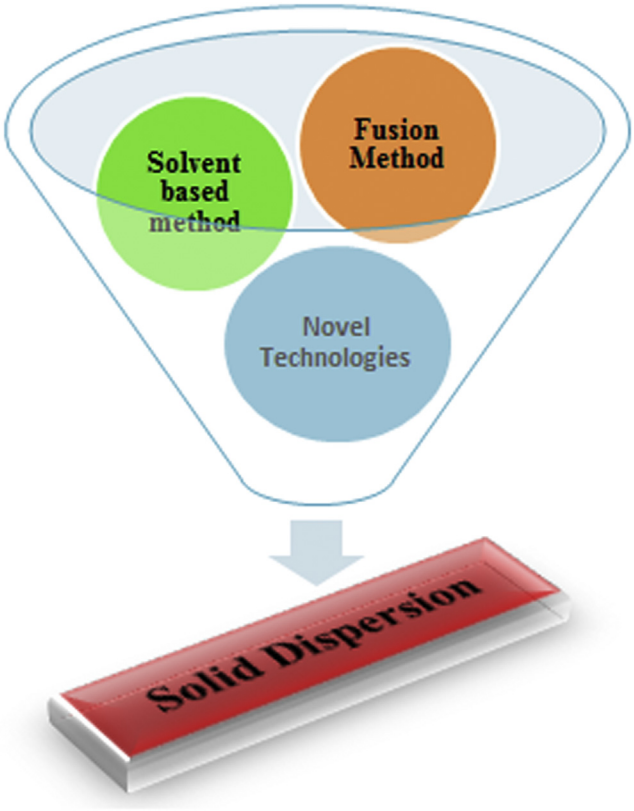

Figure 10. Different manufacturing techniques of solid dispersions.

Fusion Method

The fusion method, also known as the melt method, was first proposed by Sekiguchi and Obi in 1961.[153] A physical mixture of drug and polymer is heated to form a molten mixture which is then cooled and solidified with rigorous stirring. The resultant solid mass is then crushed, pulverized, and sieved to obtain the desired particle size. Although frequently used, there are a number of challenges in preparing solid dispersion using this method such as lack of drug-polymer miscibility at the heating temperature. The use of surfactants may avoid this problem.[154] Furthermore, drugs and polymers have to be thermally stable at the T_m, and consequently, lower processing temperatures are preferred.[155] Also, the fused mixture has to be stable against recrystallization and phase separation on aging over the shelf life of the products. Sheng et al. have reported that the supersaturation of amorphous drug in a felodipine-Eudragit formulation causes phase separation on aging.[156] Similar results have been reported by Save et al.[157] on slowly cooling the melt mixture of nifedipine-polyethylene glycol 6000 formulation.

Hot-melt extrusion method is the modern version of the fusion method in which intense mixing of the components is induced by the extruder. Compared with the traditional fusion method, melt extrusion offers the potential to shape the molten drug-polymer mixture into implants, pellets, or oral dosage forms.[158] This method requires complete miscibility of the drug and polymer in the molten state. Solubility parameter phase diagrams can be used to predict miscibility and to rationally select the compatible polymer. This technique offers several advantages such as (1) solvent free method; (2) fewer processing steps as there is no compression of ingredients and no need to dry products which makes this technique simple, continuous, and efficient; and (3) thorough mixing at high shear rate and temperature causes the particles to deaggregate and creates a uniform distribution of fine drug particles in the polymer matrix and molecular level dispersion.[159] Furthermore, compared with the traditional fusion method, this technique offers the possibility of continuous manufacture, which makes it suitable for large-scale production. Some examples of commonly used polymeric materials which are used in hot-melt extrusion include HPMC, HPMCAS, PVP, PVP–vinyl acetate, and polyethylene oxide (Table 2).[160]

Solvent Method

The solvent method involves the preparation of a solution of both drug and polymer in a single solvent followed by removal of the solvent to yield a solid dispersion. This technique enables molecular level mixing which is preferred to increase the solubility and stability of the product. The main advantage of this method is that the thermal decomposition of drug and polymer can be prevented as low temperatures are typically required to evaporate organic solvents. However, formulation scientists face two challenges when using this approach. The first challenge is to mix the drug and the polymer in one solvent which can be difficult if they have significant polarity differences. Sometimes surfactants are used to improve drug or polymer solubility in particular solvents. However, their amount in final dosage form is often significant which reduces the drug loading capacity and may also cause problems if they are not well tolerated in the body. Also, the need to evaporate a large amount of the solvent makes the process expensive. The second challenge is the phase separation which may occur during removal of the solvent. Vacuum drying is frequently used to dry the solution. Sometimes fast drying is achieved by a rotary evaporator. Higher drying temperatures are preferred which reduces the time available for phase separation. However, the high molecular mobility of drugs and polymers at elevated temperatures may accelerate phase separation.[161]

Spray drying has emerged as a popular processing technology for developing solid dispersions of drugs.[162] It is used to convert a solution or suspension into a dry powder in a single step. This technique provides a better control of process variables, producing powders with desired size, shape, density, flow properties, and crystalline forms.[163] Evaporation of solvent occurs at a very fast rate in spray drying, causing a sudden rise in viscosity which leads to the entrapment of drug molecules in the polymer matrix.[164] Drugs with poor aqueous solubility may be spray dried into very small particles provided that they are soluble in certain solvents suitable for spray drying. The nature of the solid particles formed also depends upon chemical properties of the drug, and spray drying may produce amorphous material, crystalline forms, imperfect crystals, or metastable crystals.[165] Indeed, Mahlin et al.[166] and Baird et al.[167] have worked on the different drug compounds and showed that generating an amorphous form depends on the chemical nature of the drugs rather than on the process variables. However, the stability of the amorphous form depends on the process variables.[168] Spray drying offers great control of the powder characteristics and due to cheaper manufacturing costs, ease of scale-up, and continuous batch manufacture, it has become the most popular solvent-based production method.[169]

SCF Method

SCFs possess the properties of both liquid and gas. Under supercritical conditions, materials have liquid-like solvent properties and gaslike viscosity, diffusivity, and thermal conductivity. Although the solvent properties are beneficial for drug/polymer solubilization, the gaslike properties significantly enhance the mass transport characteristics of the fluids. This method is mostly applied using

supercritical carbon dioxide (CO_2) either as a solvent for drug and polymer or as an antisolvent.[170] The polymer and drug are dissolved in supercritical CO_2 and sprayed through a nozzle into low-pressure region causing adiabatic expansion of the CO_2 and rapid cooling. Thus, this technique allows the production of drug particles with a greatly reduced particle size. This technique is known as rapid expansion of supercritical solution (RESS). Current SCF methods have demonstrated the potential to create nanoparticulate suspensions of particles with 5-2000 nm diameters.[171] Because this technique is not dependent on the use of organic solvents and the small amount of the residual CO_2 trapped inside the polymer poses no danger to patients, this technique is referred to as environment friendly. Furthermore, the ability of CO_2 to plasticize and swell polymers can also be exploited. However, the low solubility of most pharmaceutical compounds in CO_2 limits the practical application of this approach.[172] Several methods of SCF processing have been developed to address individual aspects of these shortcomings and to improve the solubility. These methods include precipitation with a compressed antisolvent,[173] solution-enhanced dispersion by SCF,[174] supercritical antisolvent processes,[175] gas antisolvent recrystallization,[176] and aerosol supercritical extraction system.[177]

Characterization of PASDs

The nature of ASDs and the inherent risk of recrystallization require in-depth characterization of these formulations. Quality by Design principles demand a thorough understanding of the processes taking place at a molecular level. No single characterization technique can give the full picture, and a suite of complementary methods is often required (Fig. 11). A brief selection of the available literature will be discussed here.

X-Ray Powder Diffraction

Powder x-ray diffraction is an indispensable tool for the characterization of amorphous solid dispersions.[178] Moes et al.,[179] Zhao et al.,[180] and Al-Obaidi et al.[181] have reported the use of this technique to confirm the presence of amorphous state of the drug in solid dispersion. Recent advancements in X-ray powder diffraction (XRPD) instrumentation and software can provide useful information under nonambient conditions, such as XRPD equipped with variable temperature (VT) or humidity control which can provide an insight into molecular behavior of amorphous drugs in solid dispersion under stressed conditions.[182] Zhu et al.[183] have studied the crystallization kinetics of a naproxen solid dispersion at different temperatures by *in situ* small-angle X-ray scattering/wide-angle X-ray scattering. Furthermore, atomic pairwise distribution function has gained importance to detect the degree of amorphization induced into crystalline drugs.[184] Nollenberger et al.[185] have used pairwise distribution function analysis to show that subtle changes at the molecular level of polymer structure can have a significant effect on the release characteristics of the final product.

Thermal Analysis

The most widely used thermal analysis (TA) methods are DSC and thermogravimetric analysis. However, other methods such as dynamic mechanical analysis and isothermal microcalorimetry are also used for routine analysis in the pharmaceutical industry. An insight into processes occurring at a molecular level in the solid dispersion such as glass transition, crystallization, polymorphic transition, molecular mobility, structural relaxation, and miscibility between drug and polymer can be obtained using DSC and other emerging TA techniques.[186] Mahajan et al.[187] have applied this technique to quantify the amorphous content in carvedilol tablets by carrying out T_g and heat capacity analysis. Furthermore, the higher sensitivity of Fast-Scan DSC offers the advantage of separating the overlapping thermal events.[188] The information regarding viscoelastic properties of polymers, relaxation transitions, and miscibility in binary or ternary systems can be obtained by using differential mechanical thermal analysis.[189]

With the advent of more sophisticated instruments in the past few years, it is now possible to perform real-time solid-state characterization as a function of change in temperature. The molecular orientation and structural relaxation of amorphous drugs in solid dispersions and their interaction with polymers can now be studied in greater detail with the use of techniques such as VT molecular spectroscopy, VT-XRPD, and VT-ssNMR. Nano-TA, a localized TA technique, when combined with atomic force microscopy can provide high resolution images of the thermal behavior of amorphous drugs. In nano-TA based atomic force microscopy, a miniature heater having topographic resolution of approximately 5 nm is placed on top of the microfabricated silicon-based probe enabling the measurement of thermal properties at a nanometer scale.[190]

Spectroscopy

Fourier transformed IR spectroscopy, combined with attenuated total reflectance and/or diffuse reflectance, and Raman spectroscopy are the 2 very efficient techniques among the vibrational spectroscopic methods.[191,192] These techniques have been used for a range of pharmaceutical applications including polymorph identification, phase transition, recrystallization stability, evaluation of different manufacturing methods for solid dispersions, phase separation, and nature and extent of drug-polymer interaction.[193,194] These techniques offer information on structural and molecular conformation in the solid state by probing band vibrations. Furthermore, Raman spectroscopy is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. Also, an insight into the crystal packing may be obtained by studying low-energy lattice vibration associated with different crystal packing arrangements.[195] Furuyama et al.[196] have used Raman spectroscopy as a mapping technique to distinguish between the crystalline and the amorphous form of troglitazone in solid dispersions. Sinclair et al.[197] applied FT Raman spectroscopy to measure the recrystallization kinetics of an amorphous solid dispersion of the drug ibipinabant. It is also used to detect the presence of trace crystallinity which would otherwise go undetected by XRPD or high-sensitivity DSC.[198]

Water Vapor Sorption

Water vapor sorption has been frequently used to study the behavior of amorphous and crystalline material in the presence of moisture. Theoretical approaches such as predicting the additivity of the moisture sorption isotherm of the individual components or using ternary FH interaction theory can be used to interpret the moisture sorption data which may provide an insight into drug-polymer-water interactions.[199] When combined with other techniques such as DSC, fourier transformed IR spectroscopy, and nuclear magnetic resonance (NMR), it can provide various information on molecular level attributes such as surface properties, degree of amorphization, phase transitions, critical relative humidity for glass transition and crystallization, and physical stability of freshly prepared and aged materials.[200-202] Dynamic vapor sorption combined with near IR spectroscopy can provide an insight into the desorption behavior of amorphous materials before and during crystallization, as a function of temperature and relative humidity.[203]

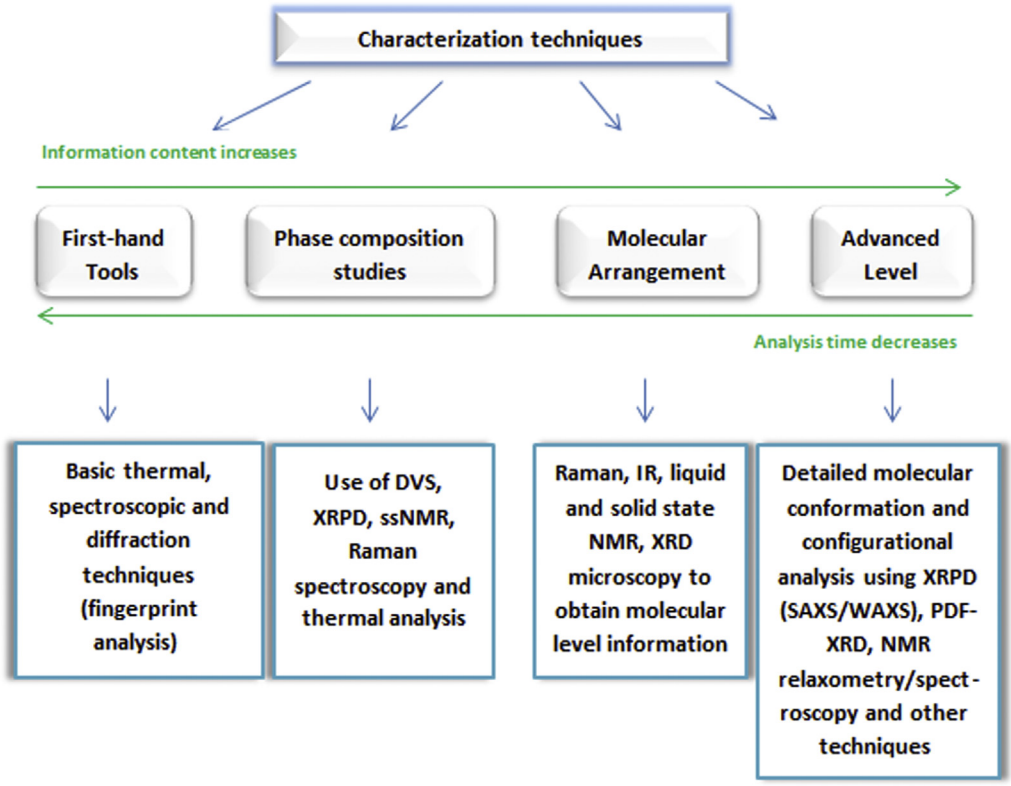

Figure 11. Solid-state characterization tools for polymeric amorphous solid dispersions. SAXS, small-angle X-ray scattering; WAXS, wide-angle X-ray scattering; PDF, pair-wise distribution function; DVS, dynamic vapor sorption; XRPD, X-ray powder diffraction; ssNMR, solid-state nuclear magnetic resonance; XRD, X-ray diffraction.

Solid-State Nuclear Magnetic Resonance

ssNMR is nondestructive technique which provides qualitative and quantitative information about amorphous solid dispersions. It provides detailed 1-dimensional and 2-dimensional structural information based on NMR relaxometry/spectroscopy/imaging techniques.[204] By correlating the relaxation time with the length scale of the spin diffusion, predictions can be made about drug-polymer domain size in solid dispersions. For example, values of the spin-lattice relaxation time, T_1, ranging between 1 and 5 s correspond to a domain size of approximately 20-50 nm. In addition, $T_{1\rho}$ (spin-spin relaxation time) values between 5 and 50 ms will suggest the length scale of approximately 2-5 nm. Reliable predictions can be made based on these relaxation time measurements. A single value of ^{1}H T_1 and $T_{1\rho}$ obtained from the amorphous solid dispersions will suggest Dmain size is smaller than 2-5 nm. Different $T_{1\rho}$ values but same T_1 value will indicate a domain size of about 5-20 nm. Domain size larger than 20-50 nm will give different values of T_1 and $T_{1\rho}$ for drug and polymer. This method is much more sensitive as compared with DSC which has a sensitivity of about 20-30 nm and domain size smaller than this will give single T_g values. Thus, ssNMR relaxometry will provide a better understanding of drug-polymer intimacy in the solid dispersion which helps in improving the stability of amorphous solid dispersions and preventing phase separation over the shelf life of the product.[205] Information regarding phase composition and molecular mobility of the polymers in solid dispersions can be obtained by ^{1}H transverse magnetization relaxation T_2 measurements.[206] ^{13}C cross-polarization magic angle spinning NMR experiments were used to probe the recrystallization of amorphous troglitazone in solid dispersion prepared by different methods where no difference was observed in the XRPD pattern.[207] NMR microimaging technique is a valuable addition to analytical methods to study water penetration and polymer mobilization kinetics.[208]

Inverse Gas Chromatography

Inverse gas chromatography is still an emerging technology and has been used to analyze surface properties of amorphous solid dispersions.[209] It is used to examine molecular mobility, amorphous transition or recrystallization, and molecular relaxation which is especially useful in detecting batch-to-batch variation of amorphous solid dispersions prepared by the same or different methods.[210] Furthermore, the study of higher molecular mobility on the surface of the material than in the bulk will provide an insight into moisture interaction and recrystallization of amorphous drugs.[211] Hasegawa et al.[212] have used inverse gas chromatography to study the structural relaxation at the surface of solid dispersions and found that structural relaxation occurs faster at the surface than in the bulk due to higher molecular mobility at the surface. Predictions regarding physical stability of amorphous products can be made by investigating the crystallization kinetics on the surface of solid dispersions.[213]

Dissolution Behavior of PASDs

The most widely used method to predict *in vivo* performance of a formulation is dissolution. However, it is challenging to establish an accurate *in vitro–in vivo* correlation because the dissolution kinetics may not be predictive of the complex nature of supersaturation generation and maintenance (Fig. 12) or fully consider the driving

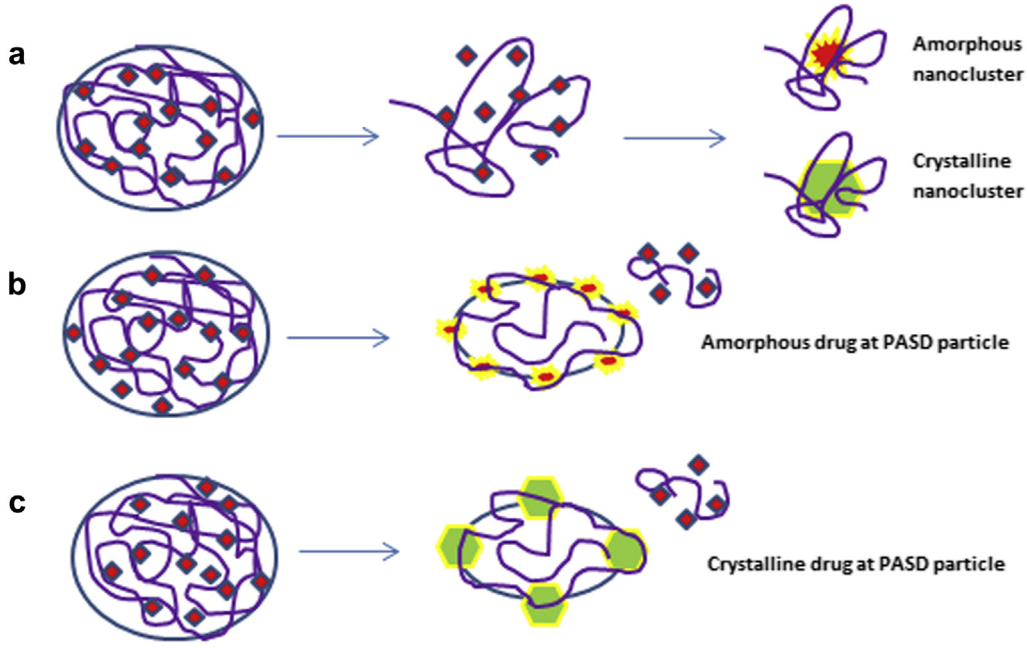

Figure 12. Dissolution behavior of polymeric amorphous solid dispersions. (a) First case; (b) second case; (c) third scenario.

force for absorption via solubilizing power of such drug delivery systems.[214] This holds true for PASDs because several different complex processes occur simultaneously during their dissolution.[215]

Increased efforts from academic and industrial researchers have pushed the understanding of drug-polymer interaction in aqueous media.[216] The general solubilization mechanism of PASDs is the so-called "spring and parachute" concept.[217] The drug first dissolves along with the soluble polymer matrix to generate a supersaturated solution (spring) followed by decline in drug concentration in the media due to either absorption or precipitation (parachute) as shown in Figure 3. Three different scenarios are possible for dissolution behavior of PASD as shown in Figure 12.[43] In the first case (Fig. 12a), PASD particles dissolve rapidly generating a highly supersaturated solution followed by the formation of drug nanoclusters (amorphous or crystalline) within the polymer matrix. The second case (Fig. 12b) represents the gradual release of drug and polymer while drug remains amorphous in the undissolved particles. In the third scenario (Fig. 12c), the drug and polymer are released gradually; however, the drug may undergo crystallization mainly at the surface of undissolved PASD particles due to plasticizing effect of water. It is important to mention here that the free drug concentration in the dissolution media is dependent on the aqueous solubility of the crystalline or amorphous drug which in turn depends on many factors including, but not limited to, drug crystallization rate, drug-polymer interaction, and drug-polymer ratio. The success of the PASD depends on the ability of the polymer to maintain supersaturation long enough without precipitation to facilitate drug absorption. The mechanism of how the polymer delays supersaturation is not completely understood and needs further research. However, as discussed previously, it is generally believed that drug-polymer interactions play a major role in inhibiting crystallization either by interfering with the nucleation process or by inhibiting crystal growth.

Conclusions

The emerging pharmaceutical scenario of drug discovery has shifted the major portion of newer drugs from hydrophilicity to lipophilicity. In consequence, a large number of drugs in the development pipeline are poorly water soluble presenting significant challenges to formulation scientists. Amorphous solid dispersions have provided an attractive alternative for overcoming solubility limitations by the use of altered "molecular architecture," bestowing the amorphous drug with high-energy and thermodynamic properties which, on the other hand, also drives them toward devitrification and limits their commercial applicability. A better understanding of thermodynamics and molecular level processes such as glass transition, molecular mobility, fragility, devitrification, and molecular interactions of drug and polymer is crucial for designing efficient and stable amorphous drug delivery systems. The molecular engineering of the amorphous drugs using polymers as carriers gives better control in stabilizing the solid dispersion products. A better control over both the solid-state stability and supersaturation generation and maintenance will lead us to delivery systems having desirable and predictable properties and a practical option to solubilize the "difficult to solubilize" drugs.

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