Drug-excipient behavior in polymeric amorphous solid dispersions.

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ABSTRACT

Amorphous drug delivery systems are increasingly utilized to enhance aqueous solubility and oral bioavailability. However, they lack physical and/or chemical stability. One of the most common ways of stabilizing an amorphous form is by formulating it as an amorphous solid dispersion. This review focuses on polymeric amorphous solid dispersions wherein polymers are used as excipients to stabilize the amorphous form. A brief introduction to the basic concepts of amorphous systems such as glass transition temperature and the solubility advantage of amorphous systems is provided. Additionally, information on types of polymers used for the development of amorphous solid dispersions, their structural attributes and mechanisms of stabilization are presented here. Molecular aspects of drug-polymer miscibility and drug-polymer interactions are also discussed.

KEY WORDS: Amorphous, solid dispersion, miscibility, polymeric excipients, amorphous form stabilization, mechanism of stabilization

INTRODUCTION

Poor aqueous solubility of drugs has emerged as one of the major challenges in drug delivery. It has been reported that about 70 % of new chemical entities have aqueous solubility problems and consequently poor oral bioavailability and delivery problems (1). Formulation strategies, such as particle size reduction (2, 3), amorphous solid dispersions (ASDs) (4), co-crystal formation (5, 6), complexation employing cyclodextrins (7), co-solvents (8) and lipid formulations (9) have been used to improve aqueous solubility.

The crystalline form of a drug offers advantages in terms of high purity and physical/chemical stability compared to ASDs. However, constraints contributed by lattice energy must be overcome to allow solute molecules to dissolve. The amorphous state exhibits a disordered structure in comparison to the crystalline state and possesses higher free

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energy. Thus it offers enhanced apparent solubility, dissolution rate and oral bioavailability (10). Pure amorphous drugs are rarely developed alone into medicinal products because of their inherent physical/chemical instability. This has encouraged investigation of the stability of ASDs where advances have been made in recent years. ASDs are defined as solid systems consisting of a drug and carrier excipient(s) prepared using thermal and/or solvent based methods. A variety of excipients such as polymers and surfactants may be used to prepare and stabilize the amorphous form of a drug (11).

In the late 1960's, solid dispersions (SDs) emerged as a formulation strategy to improve apparent solubility by stabilizing amorphous forms of drugs (12). Solid dispersions have been classified based on the distribution of solute molecules within the carrier matrix as eutectic mixtures, solid solutions and microfine crystalline dispersions. Figure 1 shows a comprehensive classification system for SDs (13).

A eutectic system typically consists of two compounds which, when mixed in a particular proportion, forms a composition which has a single melting point that is lower than the melting points for the individual components.

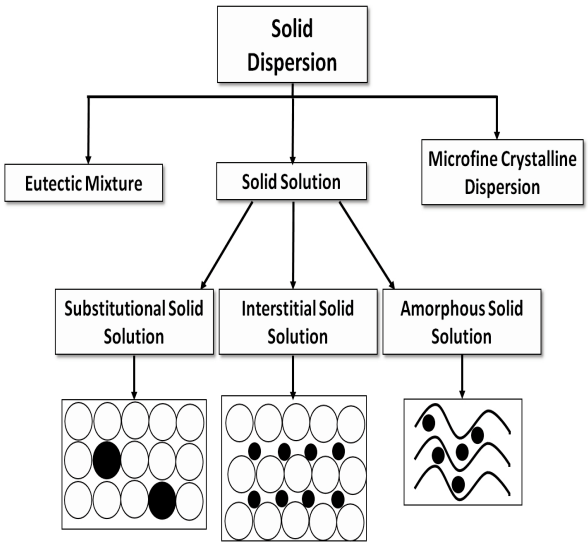


Figure 1 Classification of solid dispersions. (Reproduced with modification and permission from Reference 13).

Solid solutions are further classified into substitutional crystalline solid, interstitial solid and amorphous solid solutions. In substitutional crystalline solid solutions, a molecule of carrier/solvent is replaced by a solute molecule whereas an interstitial solid solution consists of dissolved solute molecules occupying interstices within the carrier matrix. Amorphous solid solutions consist of the drug molecularly, but irregularly, dispersed within the amorphous carrier. Microfine crystalline dispersions consists of a molecular dispersion of a crystalline drug in a carrier.

A wide range of pharmaceutical excipients have been used in the preparation of ASDs. Materials such as lipids, carbohydrates, proteins and surfactants have been used to kinetically stabilize an amorphous form of a drug (14). Small molecules such as meglumine (15), urea (16), sugars (17), amino acids (18) and organic acids (19) have also been investigated in the stabilizion of the amorphous form. Polymeric ASDs (PASDs) have shown considerable promise in the stabilization of amorphous forms providing significant increase in solubility and dissolution rate. Several products using this method have been commercialized to date, e.g., Novir®, Kaletra® and Sporana®.

This paper reviews the theoretical and technical aspects of PASDs and briefly describes the potential advantages of polymers as inert pharmaceutical excipients in ASDs. This review also discusses the molecular aspects of the generation and performance of PASDs.

Amorphous form

The amorphous form is ubiquitous in nature and plays an important role in material, biological and more recently pharmaceutical sciences. Amorphous forms are also known as glass, vitrified, disordered or frustrated systems (20).

The crystalline state is characterized by a long range order of molecular arrangements in the crystal lattice. In contrast, the amorphous form possesses only short range order in their molecular arrangement. Amorphous forms possess higher molecular mobility and increased thermodynamic properties, such as enthalpy and free energy, compared to the crystalline state (21, 22).

Excess thermodynamic properties of the amorphous state

Consider a crystalline form of a drug that melts at temperature T_m (23), see Figure 2, where the melting involves a change of state from solid to liquid. If the molten drug is cooled slowly, the molecules pack in an orderly manner and revert back to the crystalline form. In contrast, if the same molten drug is cooled rapidly, it may attain a temperature lower than T_m without crystallizing. Thus, the drug attains a super-cooled liquid state and is in equilibrium with the molten liquid state. The system on further cooling continues to be in equilibrium until glass transition temperature (T_g) is attained, where the system enters into a non-equilibrium state.

T_g is marked by a significant decrease in molecular mobility and viscosity. There is a sudden decrease in kinetic energy of the system. A steep change in the heat capacity at T_g, associated with change in the derivative of thermodynamic properties such as enthalpy, entropy and volume suggests the T_g to be a second order thermodynamic transition. T_g is a "thermodynamic necessity" of the system to prevent the "entropy crisis" of the supercooled liquid state. If the supercooled liquid state were to persist below T_g, then a stage would be attained wherein the crystal would possess higher entropy value than the supercooled liquid, and finally the entropy of supercooled liquid will attain a negative value, even before reaching absolute zero temperature. This infringes the third law of thermodynamics, which states that the entropy of a perfect crystal is zero at 0°K. The system avoids this entropy crisis by deviating to form the glassy state from the supercooled liquid state. This deviation occurs at T_g. The isoentropic point of the supercooled liquid and crystal is termed the 'Kauzmann temperature' (24) (T_K in Figure 2). T_K is believed to be a temperature of zero molecular mobility and approximates to "T_g-50°C" (25).

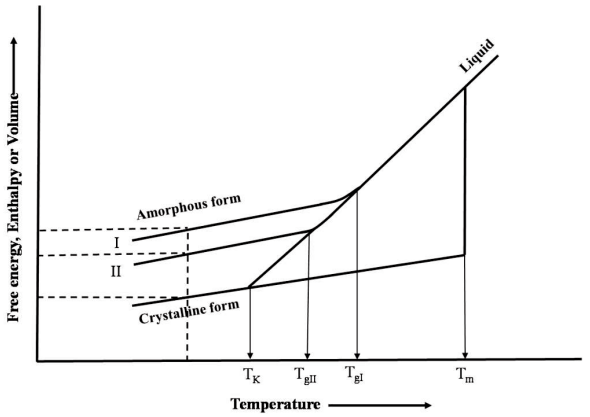


Figure 2 Plot of free energy, enthalpy or volume versus temperature. I and II represent two distinct amorphous forms having glass transition temperatures, T_{gI} and T_{gII} respectively. T_K denotes Kauzmann temperature while T_m the melting temperature (adapted from Reference 21).

These excess properties of the amorphous state are responsible for its higher solubility and reactivity. These properties also confer physical instability on the amorphous system has a tendcy to convert to a stable crystalline state. This process is referred to as devitrification (26).

Solubility advantage from amorphous systems

An amorphous form possesses a higher apparent solubility in comparison to its crystalline counterpart. Hancock *et al.* (27) proposed an equation to predict the theoretical increase of solubility gained from an amorphous system compared to its crystalline counterpart as shown in Equation 1.

$$\Delta G_T^{a,c} = -RT\ln\left(\frac{\sigma_T^a}{\sigma_T^c}\right) \qquad \text{Eq. 1}$$

Where; G is the difference in free energy, R is a gas constant, T is the given temperature, and (σ^a/ σ^c) is the solubility ratio of the amorphous and the crystalline form, respectively.

The increase in solubility of the amorphous drug, determined experimentally, remains lesser than theoretically predicted values in most cases. When an amorphous drug is added to the aqueous media, it shows a rapid increase in solubility, and appears as a 'peak' in the solubility curve. Subsequently, a decrease in the solubility is observed as the amorphous form devitrifies to the crystalline form. The appearance of a peak and subsequent decrease in the solubility curve of an amorphous system is known as the 'spring and parachute effect', and has been reported by several researchers (28, 29). The decrease in solubility can be explained by a devitrification mediated process which is caused by two simultaneously occurring phenomena: (i) crystallization of the drug due to supersaturation, and (ii) plasticization of undissolved amorphous drug by water and its subsequent devitrification. The latter phenomenon initiates from the surface of the particles and percolates into the bulk of the amorphous sample. Together these two phenomena manifest as a downward trend in the solubility curve for the amorphous drug.

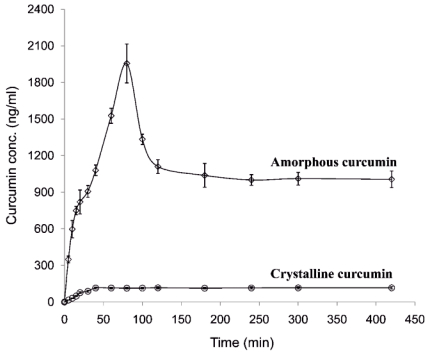


Figure 3 Comparison of dissolution profile of crystalline and amorphous curcumin. (Reproduced with modification and permission from Reference 29).

The solubility profile of amorphous and crystalline curcumin is shown in Figure 3 wherein the amorphous form of curcumin shows the 'spring and parachute effect'.

Although the initial apparent solubility of the amorphous form is noticeably higher, the conversion of the amorphous material to its crystalline counterpart creates considerable challenges during dissolution. Strategies have been devised to kinetically 'stabilize' the amorphous form so that the advantage of increasing solubility of these systems can be retained.

Strategies for stabilizing amorphous forms

An amorphous form can be stabilized primarily by minimizing its molecular mobility which in turn prevents crystallization. The simplest approach is to store an amorphous form below its T_g. An empirical rule known as the 'T_g-50 °C rule recommends storage of the amorphous form at temperature 50°C below its T_g. This retards the molecular mobility of the amorphous state making it sufficiently stable to provide a practical shelf life (30). However, this strategy has limited applications as it affects stability during shelf life only. It has no effect on subsequent events during dissolution.

A more practical approach towards stabilizing the amorphous form is formulating an ASD wherein the amorphous drug is incorporated into a matrix of excipient(s). Various methods have been reported for achieving this including milling (31), fusion (32), hot melt extrusion (33), freeze drying (34), spray drying (35) and supercritical fluid precipitation (36). Formation of an ASD provides stability to the amorphous form both during shelf life and dissolution.

Polymers as stabilizers

Polymers consist chemically of repetitive structural units called monomers. Each monomer is covalently linked to another monomer forming an extended structural framework. They can be classified based on

their origin: a) natural polymers, e.g., cellulose derivatives, starch derivatives, gums, etc., and b) synthetic polymers, e.g., poly(vinlypyrollidone) and its copolymers, poly(ethyleneglycol) and poly(acrylate) (14).

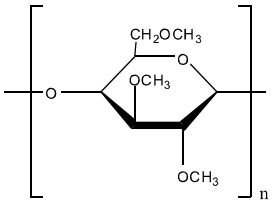
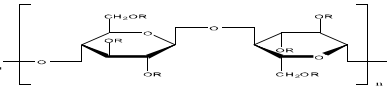
A polymer that consists of only one type of monomer to form a long chain is known as a homopolymer or simply a polymer. If the chain is composed of two different types of monomer units then it is known as a copolymer. Both homopolymers (e.g., methylcellulose, hypromellose) and copolymers (e.g., copovidone) are widely used as pharmaceutical excipients. From a structural perspective, polymers can be classified as amorphous, semi-crystalline or crystalline. Both polymer strength and stiffness increases with an increase in the degree of crystallinity as a result of greater intermolecular interactions (37).

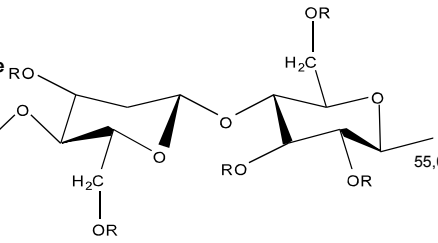
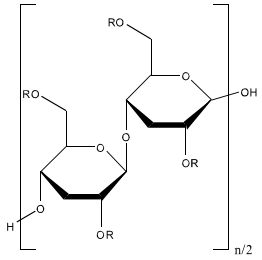
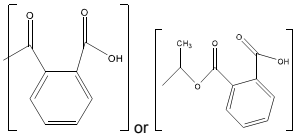
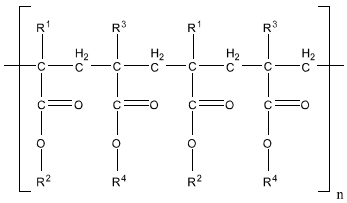
Owing to their complex structural properties, polymers form extensive inter- and intra-chain cross links, ultimately forming a network like structure. Incorporation of any heterogeneous molecule (amorphous drug) into these networks hinders the molecular mobility of the latter. As a result, polymer chains act as crystallization inhibitors, thereby preserving the viability of the amorphous form intact (38, 39). Various polymers have been investigated incorporating the amorphous drug into matrices in order to develop PSADs. A comprehensive list of these polymers is given in Table 1. Table 1 includes the polymer name, chemical structure, average molecular weight, T_m/T_g and number of hydrogen bond (H-bond) donors and acceptors.

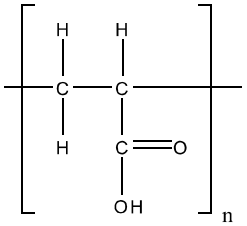
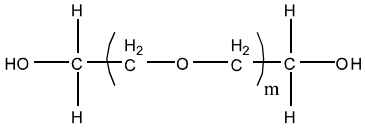
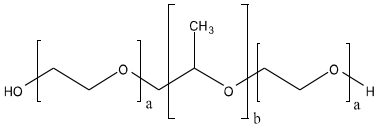
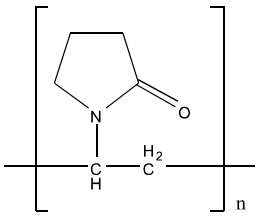
MECHANISMS FOR STABILIZING AMORPHOUS DRUG IN PASDs

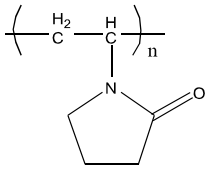
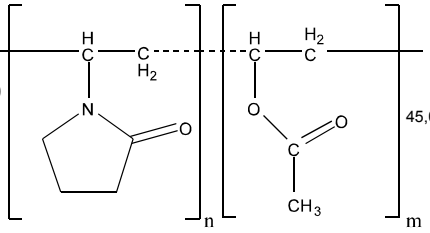
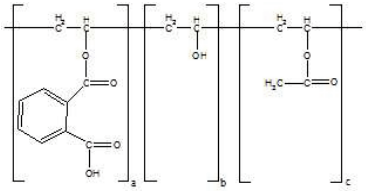
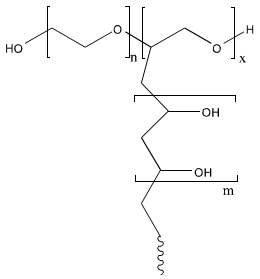
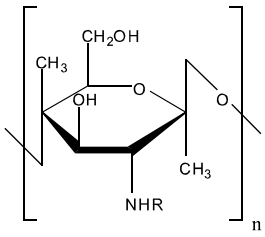
The amorphous form, because of its thermodynamic properties, less stable and is able undergo phase transformation to a stable crystalline form. As mentioned previously, the amorphous form can be stabilized by formulating it as a PASD. Figure 4 shows the energy landscape of a crystalline form, an amorphous form and a PASD. Formulation of an amorphous drug into a PASD lowers the free energy of the amorphous form closer to the energy level of crystalline form (62).

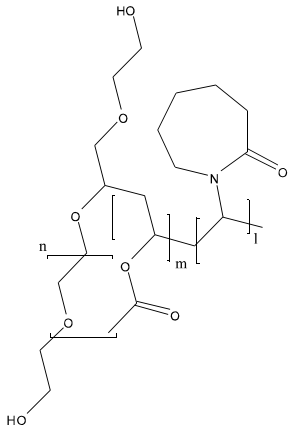
Table 1 Examples of various polymeric carriers employed in the formulation of PASDs[(a)]

Polymer	Chemical structure (representing monomeric unit)	Molecular weight (Da)	Melting point T_m (°C)	Glass transition T_g (°C)	Number of H-bond donors (H_D) /acceptors (H_A) per monomer unit[(b)]	Comments	Reference
CELLULOSE DERIVATIVES							
Methylcellulose		10,000-220,000	290-305	-	H_A = 5 H_D = 0	Slightly hygroscopic[(c)] GRAS listed	(31)
Hypromellose [Hydroxypropyl-methylcellulose (HPMC)]	 Where R = H, CH_3 or $CH_2CH(OH)CH_2$	10,000-1,500,000	190-220	170-180	H_A = 10 - 17 H_D = 0 - 7	Hygroscopic but stable, soluble in cold water and practically insoluble in hot water, GRAS listed	(40)

Polymer	Chemical structure (representing monomeric unit)	Molecular weight (Da)	Melting point T_m (°C)	Glass transition T_g (°C)	Number of H-bond donors (H_D) /acceptors (H_A) per monomer unit[b]	Comments	Reference
Hypromellose acetate succinate (HPMCAS)	 Where R = H, CH_3, $CH_3CH(OH)CH_2$, CH_3CO, or succinoyl	55,000-90,000	-	113±2	H_A = 10 - 28 H_D = 0 – 6	Hygroscopic and susceptible to hydrolysis upon exposure to moisture, listed in US FDA IIG	(41)
HPC (L-HPC)	Chemical structure same as HPMC Substitutions: Where R = H or CH_3 or $CH_2CH(OH)CH_3$	50,000-125,000	130-260	-	H_A = 10 - 16 H_D = 0 - 6	Hygroscopic but stable, GRAS listed	(42)
Hypromellose phthalate (HPMCP)	 Where R = H, CH_3, CH2CH(OH)CH_3, 	80,000-130,000	150	137 (for HP-50) 133 (for HP-55)	H_A = 28 H_D = 18	Hygroscopic, listed in US FDA IIG	(43)
POLYACRYLATES AND METHACRYLATES							
Ammonio methacrylate copolymer (Eudragit® E)	 Where R^1, R^3 = CH_3 R^2 = $CH_2CH_2N(CH_3)_2$ R^4 = CH_3, C_4H_9	-	-	-	H_A = 10 H_D = 0	-	(44)
Ammonio methacrylate copolymer, Type A (Eudragit® RL)	Chemical formula same as above Substitutions: Where R^1 = H, CH_3 R^2 = CH_3, C_2H_5 R^3 = CH_3 R^4 = $CH_2CH_2N(CH_3)_3^+ Cl^-$	-	-	-	H_A = 10 H_D = 0	-	(45)

Polymer	Chemical structure (representing monomeric unit)	Molecular weight (Da)	Melting point T_m (°C)	Glass transition T_g (°C)	Number of H-bond donors (H_D) /acceptors (H_A) per monomer unit[b]	Comments	Reference
Carbomer (Carbopol 940)		7×10^5 to 4×10^9	~260	100-105	$H_A = 2$ $H_D = 1$	Very hygroscopic, GRAS lited	(46)
POLY(ETHYLENE OXIDE) AND ITS DERIVATIVES							
Polyethylene glycol 4000 (PEG 4000)	 Where m= average number of oxyethylene groups	3,000-4,800	50-58	-	$H_A = 1$ $H_D = 0$	Non-hygroscopic, listed in US FDA IIG	(47)
Polyethylene glycol 8000 (PEG 8000)	Same as above	7,000-9,000	60-63	-	Same as above	Same as above	(48)
Polyethylene glycol 20,000 (PEG 20,000)	Same as above	-	Same as above	-	Same as above	Same as above	(49)
Poloxamer 407 (Lutrol® F 127)	 Where a = 101 and b = 56	9,840-14,600	52-57	-	$H_A = 1$ $H_D = 0$	Stable, hygroscopic only at > 80%RH , listed in US FDA IIG	(50)
VINYL POLYMERS AND ITS DERIVATIVES							
Povidone K17 (PVP K17)	 Where n = number of repeating monomer units	10000	-	-	$H_A = 2$ $H_D = 0$	Hygroscopic, GRAS listed	(51)
Povidone K25 (PVP K25)	Same as above	30000	-	-	Same as above	Same as above	(52)
Povidone K30 (PVP K30)	Same as above	50000	-	~160	Same as above	Same as above	(53, 54)

Polymer	Chemical structure (representing monomeric unit)	Molecular weight (Da)	Melting point T_m (°C)	Glass transition T_g (°C)	Number of H-bond donors (H_D) /acceptors (H_A) per monomer unit[(b)]	Comments	Reference
Crospovidone (Polyplasdone® XL)		>10,000			$H_A = 0$ $H_D = 0$	Hygroscopic, GRAS/SA status	(55)
Copovidone PVP/VA: 60/40		45,000-70,000	140	~106	$H_A = 2$ $H_D = 0$	Low degree of hygroscopicity, GRAS/SA status	(56)
Polyvinyl acetate phthalate (Opaseal®, Sureteric®) Where a varies depending on mole percent with respect to b and c is acetyl content which is constant for the starting material		47,000-60,700	-	42.5	$H_{Aa} = 4$ $H_{Da} = 1$ $H_{Ab} = 1$ $H_{Db} = 1$ $H_{Ac} = 2$ $H_{Dc} = 0$	Non-hygroscopic, included in US FDA IIG	(57)
OTHER MISCELLANEOUS POLYMERS							
Kollicoat® IR		~45,000	-	-	$H_A = 2$ $H_D = 2$	Low degree of hygroscopicity	(58)
Chitosan hydrochloride (Chitosan) Where R= H or $COCH_3$		10,000-1,000,000	-	203	$H_A = 5\text{-}6$ $H_D = 3\text{-}4$	Hygroscopic	(59)

Polymer	Chemical structure (representing monomeric unit)	Molecular weight (Da)	Melting point T_m (°C)	Glass transition T_g (°C)	Number of H-bond donors (H_D) /acceptors (H_A) per monomer unit[b]	Comments	Reference
Soluplus®		90,000-140,000	-	~70	H_A = 3 H_D = 0	Drug Master File filed in USA	(60)

[a] Handbook of Phamraceutical excipients, 6th edition, Pharmaceutical press. [b] Values have been calculated based on Molinspiration program predictions (http://www.molinspiration.com/cgi-bin/properties). [c] The terminology used to represent hygroscopicity is based on hygroscopicity classification given by Callanhan *et al.* (61) GRAS: Generally recognized as safe; GRAS/SA: Generally recognized as safe/self affirmed, US FDA IID: United States Food and Drug Administration Inactive Ingredients Database.

Figure 5 shows the schematic representation of four different mechanisms that act simultaneously during the stabilization of a PASD. The intersection of the four circles can be termed the "sweet spot" representing the zone where all the four possible mechanisms interplay and serve as a zone of interest for the formulation of a stable PASD. These mechanisms are discussed in more detail in the following sections.

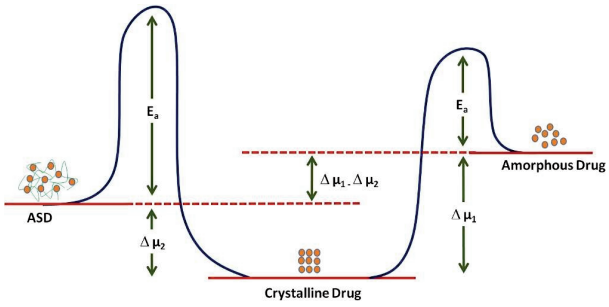


Figure 4 Comparison of energy landscapes of amorphous form, ASD and crystalline form. μ is the chemical potential while E_a is the activation energy barrier for crystallization. Diagram is not to scale.

Mechanism of incorporation of the drug into the polymer

The mechanism of stabilizing an amorphous drug as a PASD can be understood by looking at the interactions between the amorphous drug and polymeric excipients. The first step in

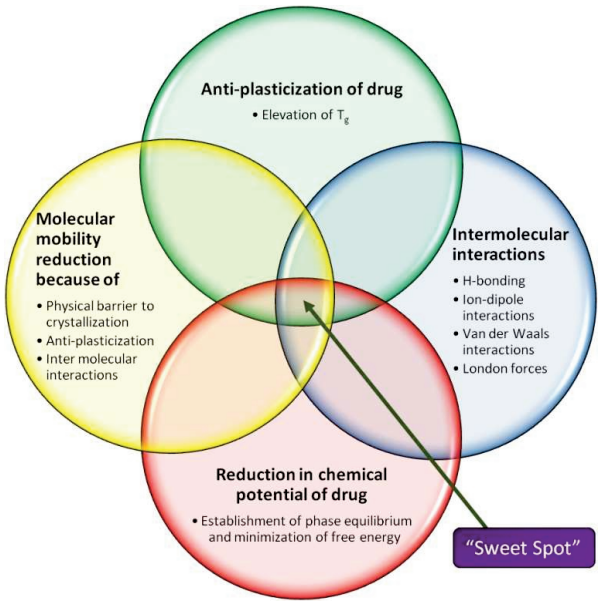


Figure 5 Interplay of various molecular mechanisms involved in the stabilization of PASD.

designing PASD is incorporating an amorphous drug into the matrix of a polymeric excipient(s). The incorporation of an amorphous drug in a polymer matrix results in intimate contact between the drug and the polymer. Drug molecules occupy void spaces between the polymer chains, thus making the polymer chains relatively flexible (63). The incorporation of a drug into a polymer matrix follows different steps, depending on how the PASD is formed. Figure 6 shows the schematic representation of the incorporation of a drug into the polymer using hot melt extrusion and spray drying, both commonly used processes in the pharmaceutical industry. Hot melt extrusion, also known as melt cooling, involves loosening the polymer chains by heat, followed by the incorporation of the drug molecules. The presence of the polymer usually lowers the melting point of the crystalline drug, known as 'melting point depression', discussed in detail later. The molten drug undergoes molecular association with polymer chains, governed by complementary chemical domains in the drug and the polymer. The drug molecules become incorporated into the polymer matrix, thus forming a PASD.

For spray drying, a solution of drug and polymer in a suitable solvent or solvent mixture is prepared. The solution of the polymer in the solvent loosens the cohesive inter- and intra-molecular interactions of the polymer chains and resulting in the formation of solvent-polymer interactions. Drug molecules that are dissolved in the solvent are incorporated into the loosened polymer chains. The solution containing polymer and drug is then spray dried to remove the solvent, thus forming the PASD.

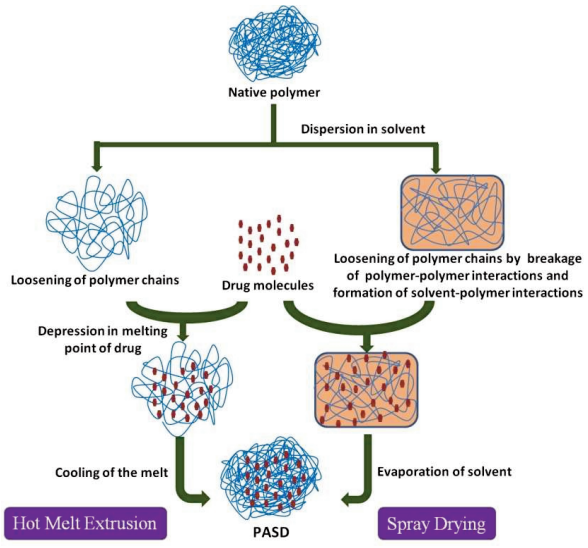


Figure 6 Schematic representation of formation of a PASD through hot melt extrusion and spray drying processes.

PASDs prepared by different methods do not necessarily exhibit the same physical properties. Dong *et al.* (64), performed a comparative evaluation of PASDs of Compound A in HPMCAS, prepared by hot-melt extrusion and solvent co-precipitation process. Powder X-ray diffractometry, thermal analysis and water vapor sorption analysis indicated that there were no significant differences between the PASDs prepared by either method. However, the PASD prepared by co-precipitation was more porous and had a larger specific surface area than the product prepared by hot-melt extrusion. Dissolution studies showed that the co-precipitated product had a faster dissolution profile, but slower, intrinsic dissolution rate, than the hot-melt extruded product. Both the products showed acceptable physical stability after storage at 40°C/75% RH for 3 months. The hot-melt extruded product was found to be more stable in an aqueous suspension.

Anti-plasticization

Anti-plasticization is widely used in the literature term for when the mechanical properties of a substance change into stiff and brittle when another substance is added (65). From a thermodynamic perspective, anti-plasticization can be explained as an increase in the T_g of the system. When a low T_g compound is mixed with a high T_g compound, the T_g of corresponding mixture would fall somewhere in between the T_g's of both components.

Mixing of an amorphous drug that has a low T_g with a high T_g polymer at the molecular level in a PASD leads to the development of a system with T_g intermediate to these two components. Hence, the T_g of the drug increases in comparison to its native amorphous state. Thus, the amorphous drug undergoes anti-

plasticization, whereas the T_g of the polymer decreases and it undergoes plasticization. Anti-plasticization decreases the molecular mobility of the drug, stabilizing the amorphous state. In terms of free volume, the energy required for the amorphous drug to reach the critical free volume increases, leading to its 'stabilization'. The T_g of the drug-polymer mixture can be predicted according to Fox (66) (Equation 2), Gordon-Taylor (67) (Equation 3), Couchman-Karasz (68) (Equation 4) or Kwei (24) (Equation 5).

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \quad \text{Eq. 2}$$

$$T_g = \frac{w_1 T_{g1} + K_{GT} w_2 T_{g2}}{w_1 + K_{GT} w_2} \quad \text{Eq. 3}$$

$$T_g = \frac{w_1 T_{g1} + K_{CK} w_2 T_{g2}}{w_1 + K_{CK} w_2} \quad \text{Eq. 4}$$

$$T_g = w_1 T_{g1} + w_2 T_{g2} + q w_1 w_2 \quad \text{Eq. 5}$$

Where; T_{g1} and T_{g2} are the glass transitions temperatures of drug and polymer, respectively, and w_1 and w_2 indicate their weight fractions. K_{GT}, K_{CK} and q are the constants which indicate a measure of interaction between two components. K_{GT} and K_{CK} may be expressed mathematically as shown in Equation 6 and 7.

$$K_{GT} = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad \text{Eq. 6}$$

Where; ϱ_1 and ϱ_2 are the densities of two components;

$$K_{CK} = \frac{\Delta C_{p1}}{\Delta C_{p2}} \quad \text{Eq. 7}$$

Where; C_{p1} and C_{p2} are the specific heat capacities of two components.

These equations can be used for the prediction of T_g for drug-polymer mixture and are useful tools for designing PASDs. It has been observed that experimental T_g values of PASDs deviate from theoretically predicted T_g values. The reasons for these deviations can be ascribed to 'volume non-additivity' and 'non-ideality in mixing' of drug and polymer systems (68).

When the drug is mixed with a polymer in a PASD, they interact with each other. This interaction can be represented as following:

(1) D-D + E-E > 2 (D-E)
(2) D-D + E-E < 2 (D-E)
(3) D-D + E-E = 2 (D-E)

Where; D and E indicate drug and excipient, respectively.

In the first case, the interaction between the individual components, i.e., D-D and E-E is stronger than the interaction between the drug and excipient (D-E). Thus, when a PASD is formed, there would be a net contraction in the volume. In the second case, D-D and E-E are weaker than D-E and thus a net expansion is obtained. The third case indicates the ideal situation wherein there is no net increase or decrease in volume and perfect volume additivity is found (26, 68).

Non-ideality in mixing is another reason for deviations between experimental and predicted T_g values. It can be predicted by determining excess enthalpy, entropy and free energy of mixing using Equation 8.

$$-\Delta H^E = \Delta H_m^G - \Delta H_m^{SCL} = w_1 \int_{T_{g-\exp}}^{T_{g1}} \Delta C_{p1} dt + w_2 \int_{T_{g-\exp}}^{T_{g2}} \Delta C_{p2} dT \quad \text{Eq. 8}$$

Where; ΔH^E is the enthalpy of mixing of a mixture, whose T_g has deviated from ideal behavior assuming that the mixing is non-thermal. $\Delta H_m{}^G$ and $\Delta H_m{}^{SCL}$ are the enthalpies of mixing of glass and supercooled liquid states, respectively. ΔC_{p1} and ΔC_{p2} are specific heat capacity changes at absolute T_g for drug and polymer, respectively. w_1 and w_1 are the weight fractions of drug and polymer, respectively.

$T_{g\text{-}exp}$ is the experimentally observed T_g of the mixture.

When the entropy changes on mixing are in excess of those corresponding to a regular solution (i.e., the entropy change is purely combinatorial) there is an excess entropy of mixing which is calculated according to Equation 9.

$$-\Delta S^E = \Delta S_m^G - \Delta S_m^{SCL} = w_1 \int_{T_{g-exp}}^{T_{g1}} \Delta C_{p1} d\ln T + w_2 \int_{T_{g-exp}}^{T_{g2}} \Delta C_{p2} d\ln T \quad \text{Eq. 9}$$

The excess entropy of mixing (ΔS^E) is related to the difference in the entropy of mixing in the glass ($\Delta S_m{}^G$) and the supercooled liquid states ($\Delta S_m{}^{SCL}$) and is the difference between entropy of the mixture at $T_{g\text{-}exp}$ and the theoretical entropy of the mixture at a temperature that represents the theoretically predicted T_g of a randomly mixed system. The relative contribution of ΔH^E and ΔS^E to the excess free energy of mixing, ΔG^E can be calculated by following Equation 10.

$$\Delta G^E = \Delta H^E - T_{g-exp}\Delta S^E \quad \text{Eq. 10}$$

Crowley *et al.* (70) reported the non-ideality of mixing in some PASDs including indomethacin (IMC), ursodeoxycholic acid (UDCA) and indapamide (IDP), prepared using PVP (70). Negative deviations were observed in IMC/PVP and UDCA/PVP PASDs, where the T_g of the binary mixture was found to be lower than predicted values at PVP concentrations greater than 50%. Similarly, positive deviation was observed in IDP/PVP PASDs, where the T_g of the binary mixture was found to be higher than the predicted T_g in intermediate dispersion compositions of 30-80% w/w PVP. Figure 7 shows the positive and negative deviations of these three dispersion systems. These deviations from predictions were explained based on the relative extent of hetero-molecular to homo-molecular interactions. IMC/PVP and UDCA/PVP dispersions experienced negative deviation at high PVP compositions, as the level of drug-PVP interaction was less than the sum of drug-drug and PVP-PVP interactions at these compositions. However, stronger IDP-PVP interactions relative to the homo-molecular interactions were responsible for positive deviation from predicted T_g values.

Inter-molecular interactions

Besides anti-plasticization, drug-excipient interactions also contribute towards 'stabilization' of a PASD. Several studies have shown the formation of ion-dipole interactions and intermolecular H-bonding between drugs and polymers.

Makiko *et al.* (71) reported the role of specific interactions in stabilizing solid dispersions. They examined the effects of different substituents on benzodiazepines (nitrazepam, nimetazepam, diazepam and medazepam) in ASDs with phosphatidylcholine. It was found that nitrazepam was the only one of the four which remained stable at the limit of miscibility after one year of storage. Nitrazepam was also the only compound with an H-bond donor group. Interactions between nitrazepam and phosphatidylcholine were verified using infrared spectroscopy (IR). Specific interactions were not observed with the other three benzodiazepines. It was concluded that some interaction between a drug and a carrier was necessary for a solid dispersion to stabilize.

Another interesting study was carried out by Taylor *et al.* (72) which highlighted the importance of chemical interactions between amorphous IMC and PVP. ASDs, of IMC with PVP were prepared by a solvent evaporation technique and studied using vibrational

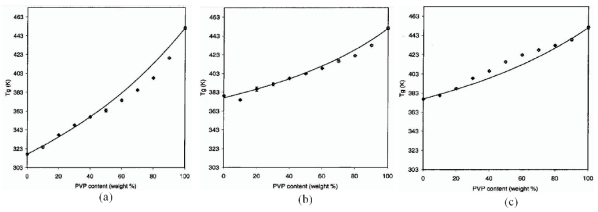


Figure 7 Deviation of experimental T_g from predicted T_g for amorphous drug/PVP dispersions (a) IMC/PVP system, (b) UDCA/PVP system and (c) IDP/PVP system. Solid lines represent predicted T_g values using the Couchman-Karasz version of the Gordon-Taylor equation (reproduced with permission from Reference 70).

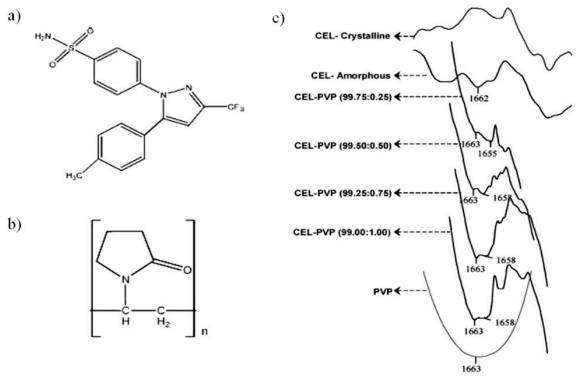


Figure 8 chemical structures of (a) celecoxib and (b) PVP. (c) FTIR spectra indicating the molecular interactions of CEL and PVP (reproduced with permission from Reference 75).

spectroscopy. The investigation confirmed the existence of drug-polymer interactions even at lower concentrations of PVP where anti-plasticization had little effect on stabilization. This study highlighted the changes in stretching vibrations of IMC and PVP. The authors suggested that interactions between PVP and IMC were mainly H- bonding interactions. PVP can act as a proton acceptor (through either the O or N atoms of the pyrrole ring) and IMC has only one proton donor site, the OH group of the carboxyl acid function. IR spectra of the carbonyl region for IMC, PVP and solid dispersions, confirmed the presence of H-bonding interactions between IMC and PVP in ASDs.

These conclusions were in accordance with the work carried out by Yoshioka *et al.* (72), who concluded that the inhibition could not be explained solely by the antiplasticizing effect of the polymer. Moreover, in solution PVP was found to interact with numerous organic molecules and it was reported that the mechanism of crystallization inhibition is related to the extent of interaction between drug and polymer.

The contribution of drug-polymer interaction has further been highlighted in a study by Khougaz and Clas (74). They demonstrated that the onset of crystallization relative to amorphous MK-0591 increased in all SDs even where T_g of the polymer blend (PVP K-12 and PVP/VA) was less than T_g of drug. This counter-intuitive finding led to the conclusion that anti-plasticization alone cannot explain crystallization inhibition. They demonstrated an ion-dipole interaction between PVP and the COO^-Na^+ moiety of MK-0591 based on an increase in the intensity of the carbonyl stretching in the amide group of PVP observed in the IR spectrum. This contributed to the stabilization of the ASD.

Another study highlighting the role of molecular interaction in the stability of celecoxib(CEL)-PVP amorphous systems was carried out by Gupta *et al.* (75). Amorphous solid dispersions of celecoxib in PVP were prepared using a solvent evaporation method. The authors demonstrated that molecular interactions play an important role in the stabilization of amorphous forms. This was confirmed by computational simulation, Differential Scanning Calorimetric (DSC) and Fourier Transform Infrared (FTIR) spectroscopy. DSC analysis showed that the T_g values for CEL-PVP binary systems of varying PVP composition exhibited a positive deviation from predicted T_g values based on the Gordon-Taylor/Kelley-Bueche equation. The positive deviation from expected T_g values was attributed to intermolecular interactions between CEL and PVP. This was further confirmed by FTIR analysis.

FTIR studies confirmed the formation of H-bonding between -NH_2 groups of CEL and

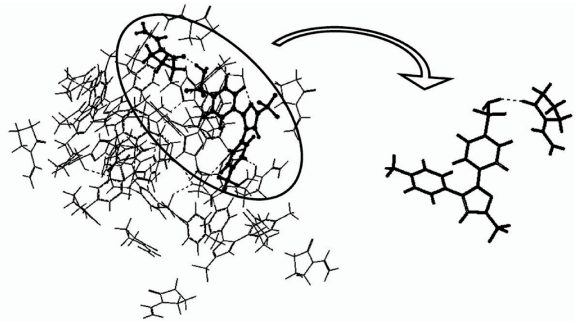


Figure 9 Stereoview of intermolecular association between CEL and PVP, the monomeric unit of PVP. The H-bonding is represented by dotted lines between the interacting groups of CEL and PVP (reproduced with permission from Reference 75).

–C=O groups of PVP. Figure 8 shows the chemical structure of PVP and CEL and the FTIR spectra of the corresponding PASD. The appearance of a band at 1662 cm^{-1} for amorphous CEL was attributed to the alteration of intermolecular H-bonding of CEL in the crystalline and amorphous forms. Spectral shifts from 1662-1655 cm^{-1} at low PVP content (0.25% w/w to 1.00% w/w) implied that CEL-PVP binary amorphous systems consisted of CEL-CEL as well as CEL-PVP in H-bonded states. Computer simulations of CEL and N-vinyl-2-pyrrolidone (NVP), the monomeric unit of PVP, also favored interactions between –C=O group of NVP and $–NH_2$ group of CEL, as shown in Figure 9.

In some cases, studies of H-bonding interactions are not possible because of the chemistry of the system. Vippagunta *et al.* (76) concluded that fenofibrate did not exhibit specific interactions with polyethylene glycol (PEG), irrespective of the number of H-bond donating groups present. The absence of specific chemical interactions between ketoconazole and PVP K25 was reported by Van den Mooter *et al.* (77). Nevertheless, the majority of the drugs contain H-bonding sites and thus exhibit specific directional H-bonding interactions that contribute to their stabilization in ASDs.

Alteration of chemical potential of a drug

Chemical potential, also known as partial molar free energy, is a form of potential energy that can be absorbed or released during a chemical reaction (79). All systems tend to reduce their chemical potential to the state of lowest potential energy. A drug in its native amorphous state has a higher chemical potential compared to its crystalline state which acts as a driving force for crystallization. The chemical potential of the amorphous drug can be lowered by mixing it with a polymer. In a binary blend, thermodynamic criterion for two phases at equilibrium is that the chemical potentials of the components should be equal in two coexisting phases represented in Equation 11.

$$\Delta\mu_1^a = \Delta\mu_1^b \qquad \Delta\mu_2^a = \Delta\mu_2^b \qquad \text{Eq. 11}$$

Where; 1 and 2 represent the two components, and a and b represent the phases.

If the drug and polymer form a miscible amorphous system, the chemical potential of the drug in such a system is less than the pure amorphous drug. The reduction in chemical potential results from the increased entropy in a mixture. Additionally, if the strength and/or extent of enthalpic interactions are greater in the mixture than the sum of the interactions in the pure components, the drug chemical potential is further reduced. Hence, an ideal solid dispersion will be in chemical equilibrium or phase equilibrium such that the total sum of chemical potentials is zero and the free energy of the system is at minimum (80).

Reduction in molecular motions of drug

The stabilization of the amorphous drug in PASDs can also be explained in terms of molecular mobility. Amorphous systems by virtue of their short range order possess excess properties such as enthalpy, entropy and free energy relative to the crystalline state (81). Due to their thermodynamic instability they tend to approach equilibrium over extended periods of time when stored at a temperature close to T_g. The excess enthalpy and entropy of amorphous forms present in entrapped frozen molecules is lost gradually on storage at temperatures close to T_g for a specified period of time. As a result there is a reduction in the molecular mobility, enthalpy, entropy, and free volume as a

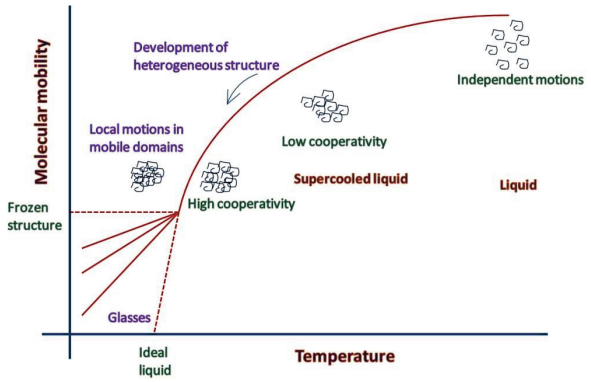


Figure 10 Events taking place during glass formation. Local motions in glass leading to structural relaxation.

function of storage time. This phenomenon is known as structural relaxation (82). Figure 10 represents a sequence of events in terms of molecular mobility that happens during glass formation.

Lost or relaxed enthalpy can be measured with time and it reflects the molecular mobility of the unstable glassy amorphous system (83). Quantification of enthalpy relaxation in molecular PASDs is a good marker for the extent of stabilization as it reflects the molecular mobility. The latter is one of the major reasons behind the instability of amorphous systems. Hence, mechanistic investigation of PASDs is essential to assess their stability. Differential scanning calorimetry (DSC) is commonly used for the determination of enthalpy relaxation (84, 85).

Polymer molecules when mixed with an amorphous drug have the capacity to reduce the molecular motions of the latter. Kakumanu *et al.* (86) carried out enthalpy relaxation studies using DSC to measure the effect of various polymeric excipients on the structural relaxation of amorphous celecoxib. Poly(vinylpyrrolidone) (PVP) K30, PVP K17 and hydroxypropylmethylcellulose (HPMC) K100LV were selected as the polymers. The dispersions of celecoxib and various excipients were prepared by solvent evaporation under vacuum. DSC analysis suggested that the addition of polymeric excipients affected the rate of enthalpy change. The reason for the change in enthalpy relaxation rate was explained in terms of anti-plasticizition effect. This indicates that the addition of polymeric excipients reduces the molecular motions and the extent of enthalpy relaxation. Figure 11 represents a plot of enthalpy recovered versus time for CEL and CEL dispersions with various excipients.

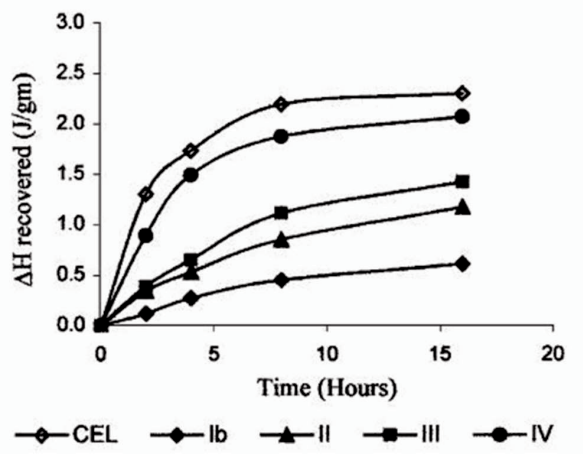


Figure 11 Enthalpy recoveries of CEL and CEL dispersions. Key: (Ib) is CEL + PVP K30, (II) is CEL + PVP K17, (III) is CEL + HPMC and (IV) is CEL + Trehalose. (reproduced with permission from Reference 85).

Bhattacharya *et al.* (87) prepared amorphous solid dispersions of sucrose with PVP and sorbitol using lyophilization. The solid dispersions were characterized for molecular motions and their implications on stability were explored further. Molecular motions were studied using dielectric spectroscopy. Preliminary DSC studies indicated negligible change in calorimetric T_g values. However, dielectric analysis showed that the addition of polymer increased the relaxation times of sucrose, for both global and local molecular motions. Similarly, PVP increased the onset of crystallization, as shown by an increase in dielectric loss due to relaxation associated with crystallization. The findings were confirmed using DSC. The results were attributed to the inhibition of molecular motions of amorphous sucrose by PVP.

MOLECULAR ASPECTS INVOLVED IN DEVELOPMENT OF PASDs

Miscibility

Solubility is defined as an equilibrium thermodynamic parameter at which the chemical potential of the solute in the solid phase is the same as that of liquid phase for regular small molecule solid solutions. A similar definition can be applied to PASDs provided that, the temperature of the system is above the T_g of the polymer. The solubility at temperatures below and close to the T_g is the 'apparent' solubility. However, measurable miscibility in the case of a drug/polymer dispersion is associated with the meta-stable equilibrium state and requires that the drug remains in the supercooled liquid state (a liquid

at a temperature above T_g and below T_m), without crystallization within the experimental time frame. This can only be achieved when both of the components of the binary mixture form a single amorphous phase. In order to form a single phase, the two liquids should be thermodynamically miscible. The system is perturbed during the preparation stage and the system must re-equilibrate at the post-processing conditions. The system may remain as a single phase or become metastable/ unstable. Thermodynamics dictates that metastable/unstable systems tend to phase separate. However, owing to slow dynamics, the dispersion may be sufficiently kinetically stable for its intended use. Formation of a single amorphous phase of the drug with the excipient is most commonly assessed from the formation of a single T_g in DSC. However, systematic study using advanced techniques show the homogeneity of PASD (88-90).

The extent of mixing is also governed by the nature and magnitude of the interactions between the drug and the polymer. The magnitude of enthalpic interactions in each of the pure amorphous components (cohesive or homo-molecular interactions) relative to the enthalpic interactions in the blend (adhesive or hetero-molecular interactions) essentially determines the miscibility of components (91). The relative strength of these interactions depends upon the chemistry of the drug and the polymer.

Tools to assess miscibility of components

Solubility parameter as a predictor of miscibility

The use of solubility parameters to predict miscibility can be applied to low molecular weight materials and polymers. Hildebrand (92) proposed the solubility parameter as a square root of the cohesive energy density (CED). CED represents the total attractive forces within a condensed state material and can be defined as the amount of energy required to completely remove a unit volume of molecules from their neighbours to infinite separation. Further, CED can be used to predict the solubility of one material into another material. Similar values of CED for two materials indicate the likelihood of miscibility, as both materials possess similar interactions. Thus, the overall energy needed to facilitate mixing should be small, as the energy required to break the interactions within the components should be compensated by the energy released due to the interactions between unlike molecules.

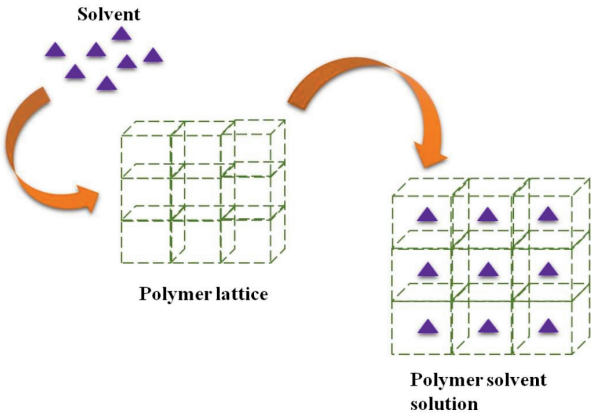


Figure 12 Schematic illustration of Flory-Huggins theory.

Greenhalgh *et al.* (93) reported such types of interactions and possible incompatibilities in solid dispersions of hydrophobic drugs with hydrophilic carriers. They used the 'Hildebrand solubility parameters' as a means to interpret such interactions. A trend between the differences in drug/excipient solubility parameters and immiscibility was reported. Incompatibilities were evident when large solubility parameter differences existed between the drug and the carrier. Table 2 represents various drug/excipient systems, their miscibility and their corresponding solubility parameter values.

Despite their ease of application, using the 'Hildebrand solubility parameters' to accu-rately predict the phase diagram, and the specific level of interaction between drugs and excipients, remains limited. They only provide information about the overall cohesive energy in materials, but little information on relative strengths of various types of forces *viz* dispersion, polar and H-bonding.

Table 2 Solubility parameters as indicator of miscibility between drug and excipient (reproduced with permission from Reference 93).

DRUG/CARRIER SYSTEM	DESCRIPTION	δ $(MPa)^{0.5}$	δ
Ibuprofen/PVP	Forms a 1:1 drug: polymer complex in the solid state	20.9/22.5	1.6
Ibuprofen/Lutrol F68	Forms a eutectic system. Eutectic composition contained 30-35% w/w Ibuprofen	20.9/19	1.9
Ibuprofen/Maltose	Immiscible when both components are molten at 1% and 99% w/w	20.9/38.9	18
Ibuprofen/Sorbitol	Immiscible when both components are molten at 1% and 99% w/w	20.9/38.2	17.3
Ibuprofen/Xylitol	Immiscible when both components are molten at 25% w/w, 50% w/w, 75% w/w and 99.9% w/w, Ibuprofen	20.9/37.1	16.2

δ $(MPa)^{0.5}$ represents the solubility parameter (Mega Pascals)

δ represents the difference in solubility parameter between the drug and excipient

Improved predictive qualities can be obtained using 'Hansen partial solubility parameters' (94). These can be predicted by various group contribution methods that involve consideration of contribution of each functional group to the cohesive energy of the molecule. Methods such as, 'Hoftyzer and Van-Krevelen', 'Hoy' and 'Fedors' (95) provide specific numerical values to each functional group that provides theoretical estimates of solubility parameters (96, 97). One practical hurdle of calculating Hansen parameters using group contribution methods is the limited data available for different structural groups which limits its application to complex molecules such as polymers.

Flory-Huggins theory

Solution models involving small molecules and solvents are inadequate to describe how small molecules mix into the polymers. The Flory-Huggins lattice theory provides an explanation of the thermodynamics of polymer solutions (98, 99). In the case of polymer solutions, the free energy of the mixture is more accurately described in terms of volume fraction of the material rather than mole fraction. This is because entropy of mixing for large molecular weight materials is significantly reduced due to the limited number of possible configurations of two components of the binary mixture (100, 101). The Flory-Huggins lattice theory takes molecular size into account when predicting the entropy of mixing.

Consider a large molecular weight polymer mixed with a small molecular weight solvent. Flory-Huggins theory defines a hypothetical "lattice" in the space (see Figure 12). The size of each position in the lattice may be described by the molecular volume of a solvent molecule or any other convenient volume. Each component of the mixture will occupy several adjacent positions in the lattice and the number of lattice positions required to accommodate each component is equal to the ratio of molecular volume of each component to that of the lattice cell.

The Flory-Huggins model can be applied to describe the thermodynamics of drug-polymer systems by considering an amorphous drug as similar to a solvent. Following this rationale, and after the addition of the Flory-Huggins interaction parameter, χ to account for the enthalpy of mixing, the free energy of mixing of a drug-polymer system, G_M can be described using Equation 12.

$$\frac{\Lambda G_M}{RT} = n_{drug} \ln \Phi_{drug} + n_{polymer} \ln \Phi_{polymer} + n_{drug} \Phi_{polymer} x \qquad \text{Eq. 12}$$

Where; n_{drug} and $n_{polymer}$ denote the number of moles of drug and polymer respectively. Φ_{drug} and $\Phi_{polymer}$ denote the volume fraction of the drug and polymer, respectively. R denotes gas constant and T denotes absolute temperature of the system. The application of above equation to a drug-polymer system enables the evaluation of thermodynamic parameters related to mixing of drug and polymer.

Most of the experimental techniques for prediction of interaction parameters, such as vapour pressure reduction, inverse gas chromatography and osmotic pressure depression are not applicable to drug-polymer blends because of their viscous and non-volatile character. Methods applicable to drug-polymer systems are: 1) *a priori* estimates using solubility parameters and 2) melting point depression (102).

Estimation of Flory-Huggins interaction parameter using solubility parameter

Solubility parameter differences have been proposed as a means to predict miscibility in pharmaceutical systems. The interaction parameter (χ) can be estimated from solubility parameters, δ as shown in Equation 13.

$$x = \frac{V_{site}}{RT}\left(\delta_{drug} - \delta_{polymer}\right)^2 \qquad \text{Eq. 13}$$

Where; V_{site} denotes the volume of the hypothetical lattice.

The relationship shown in Equation 13 assumes that enthalpic interactions between unlike species are equal to like species. This assumption is reasonable for systems containing van der Waals type interactions, but not for systems with specific directional interactions. Many drugs and pharmaceutical polymers are known to involve specific interactions and hence solubility parameter estimates of the interaction parameter can be inaccurate for such systems.

Estimation of Flory-Huggins interaction parameters using melting point depression

When a mixture of a drug and a polymer is subjected to thermal analysis such as DSC, the melting point of the drug system is generally observed at temperatures lower than the melting point of the drug alone, provided the two components are miscible. This phenomenon has been introduced previously in this paper and is known as 'melting point depression'.

Melting point depression is a manifestation of the reduced thermodynamic activity of the drug, in the presence of the polymer relative to the activity of the pure drug. Systematic explanation of the reason behind melting point depression can be explained by the reduction in vapour pressure of the drug and increased entropy (S) after mixing. The melting point is the temperature at which vapour pressure of solid equals the vapour pressure of liquid and addition of non-volatile substance decreases the vapour pressure of solid and as a result the melting point decreases. Moreover, it is obvious that polymer molecules do not interfere with molecular interactions of drug in the crystalline state, but in turn they increase the entropy of the liquid state after melting. Hence, ΔS increases for a solid, melting into an impure liquid (polymer molecules in molten drug) compared to a pure liquid. At the melting point (T_m), the change in free energy of transformation from solid to liquid (ΔG) equals zero. Hence, solving the equation ΔG = ΔH - TΔS and assuming the value of ΔG=0 at T_m, yields T = ΔH/ΔS. If ΔS increases, melting temperature should decrease (63).

Melting point depression arises because the chemical potential of the drug in solid and liquid phase must be identical at the melting point. The drug in amorphous molecular solid dispersion possesses a chemical potential equal to that of the crystalline drug at a temperature lower than the fusion temperature of the pure drug, thus resulting in depression of the melting point. This approach has been reported to be useful to estimate the interaction parameter in drug-polymer systems. The prediction of the interaction parameters between drug and polymer using melting point depression data is shown in Equation 14.

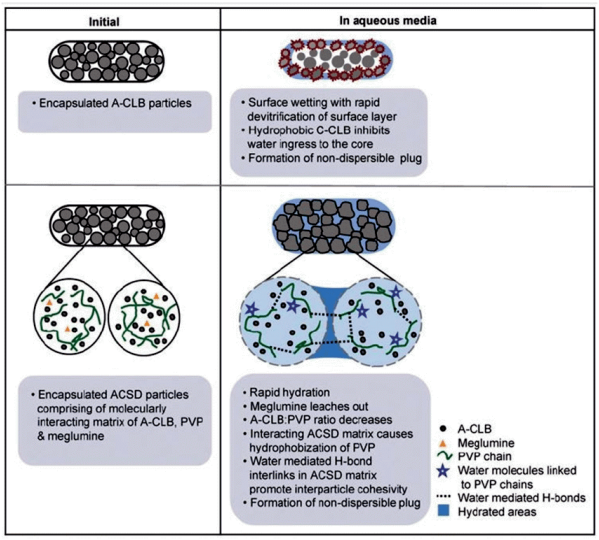


Figure 13 Schematic representation of the phenomenon occurring during dissolution of encapsulated amorphous celecoxib (A-CLB) and amorphous celecoxib solid dispersion (ACSD) (reproduced with permission from Reference 107).

$$\left(\frac{1}{T_M^{mix}}-\frac{1}{T_M^{pure}}\right)= \frac{-R}{\Delta H_{fus}}\left[\ln\Phi_{drug}+\left(1-\frac{1}{m}\right)\Phi_{polymer}+x\Phi_{polymer}\right]^2 \quad \text{Eq. 14}$$

Where; T_M^{mix} is the melting temperature of the drug in the presence of the polymer, T_M^{pure} is the melting temperature of the drug in the absence of the polymer, ΔH_{fus} is the heat of fusion of the pure drug, and m is the ratio of the volume of the polymer to that of the lattice site (defined here by the volume of the drug).

The slope of a linear plot, $(1/T_M^{mix} - 1/T_M^{pure}) * (\Delta H_{fus}/-R) - \ln(\Phi_{drug}) - (1 - 1/m)\Phi_{polymer}$ *vs.* $[\Phi_{polymer}]^2$, gives the interaction parameter, χ. Marsac *et al.* (102) determined the miscibility of nifedipine in PVP K12 using melting point depression data obtained from DSC measurements. For these systems, melting point depression is usually kinetically favourable because of the low melting point of the polymer being around 60°C. At the melting temperature of the drug, the polymer is molten, and therefore the drug can easily interact and equilibrate with the polymer in the liquid state. The interaction parameter determined using Equation 14 was found to be -3.8 for nifedipine in the presence of PVP K12 which indicated mutual miscibility of the two components. This observation was consistent with experimental observations.

ROLE OF DRUG-CARRIER INTERACTIONS DURING PRODUCT PERFORMANCE

Amorphous solid dispersions are expected to maintain sustained supersaturation levels in the aqueous environment of gastrointestinal tract during the dissolution process. However, the dissolution of drug from a PASD is influenced by parameters such as the particle size of the PASD (103), type of polymer (104), drug load, interaction strength of the drug/polymer complex, compaction pressure during tabletting (105), aqueous solubility of components, drug miscibility in the polymer and the drug recrystallization tendency. Furthermore, in a dosage form, solid-liquid interfacial phenomena can become the rate controlling step for drug release. These multiple factors simultaneously influence drug release from a PASD (106). Literature reports indicate that some PASD based drug products exhibited poor dissolution performance, thus limiting their commercial application. This deviation from the desired performance can be attributed to any of the above mentioned factors.

In a study carried out by Puri *et al.* (107), release profiles of CEL from its ASD comprising of amorphous celecoxib, PVP and meglumine (7:2:1, w/w) were compared with crystalline CEL, in powder and capsule form. Although, the powder displayed 28- to 50-fold higher dissolution efficiency at 60 minutes (DE_{60}), the DE_{60} of the encapsulated powder was drastically reduced due to the formation of a non-dispersible plug. Rapid hydration followed by leaching out of meglumine and formation of water mediated H-bond interlinks in the ASD matrix were found to be the reasons behind increased interparticle cohesivity. Figure 13 represents the schematic representation of the phenomena occurring during dissolution of encapsulated amorphous CEL (A-CLB) and the ASD of amorphous CEL with PVP and meglumine (ACSD). These conclusions should be considered when formulating an ASD.

CONTRIBUTION OF POLYMERIC CARRIERS TO PROCESSIBILITY

PASDs must be developed into convenient dosage forms such as capsules or tablets for clinical use and successful commercialization. However, manufacturing of PASDs offers numerous challenges with respect to polymer properties such as hygroscopicity, tackiness and aging (108). As a result of advances in manufacturing technologies, many products based on ASD platform have been commercialized (shown in Table 3).

Some of the technologies now in use are hot melt extrusion, spray drying and supercritical fluid technology. Hot melt extrusion is a fast continuous manufacturing process which allows the processing of amorphous drugs and has the advantage of short thermal exposure. Spray drying, either using a conventional spray dryer or a fluidized bed spray dryer has facilitated development of PASDs.

Table 3 List of commercial amorphous solid dispersions

PRODUCT	DRUG	DISPERSION POLYMER	MANUFACTURER
Cesamet®	Nabilone	PVP	Eli Lilly and Company
Certican®	Everolimus	HPMC	Novartis
Gris-PEG®	Griseofulvin	PEG 6000	Pedinol/Valeant Pharmacueticals
Intelence®	Etravirine	HPMC	Tibotec/ Johnson & Johnson
Isoptin SR-E®	Verapamil	HPC/HPMC	Abbott
Kaletra®	Lopinavir Ritonavir	PVP/VA	Abbott
Nivadil®	Nivaldipine	HPC/HPMC	Fujisawa Pharmaceuticals Co., Ltd.
Prograf®	Tacrolimus	HPMC	Fujisawa Pharmaceuticals Co., Ltd.
Rezulin®*	Troglitazone	PVP	Pfizer, Inc.
Sporanox®	Itraconazole	HPMC	Janssen Pharmaceuticals, Inc.

*Withdrawn in 2000 due to adverse drug reactions

The polymeric carriers that are used in manufacturing of PASDs largely contribute to their processing. Suitability of a manufacturing process is greatly influenced by the type of polymer used for the preparation of the PASD.

Work carried out by Chokshi *et al.* (109). Is a good example of a systematic experimental protocol for the selection of polymers and the assessment of their suitability for use in the hot melt extrusion manufacture of a PASD. Indomethacin was used as a model drug together with polymers such as Eudragit® EPO, PVP-VA, PVP K30 and Poloxamer 188. These drug-polymer systems were characterized for their thermal and rheological properties as a function of drug concentration. Solubility parameters were used as initial screening tools for the selection of the most useful polymers. Further evaluation of various binary mixtures using DSC provided an estimate of T_g and T_m. The extrusion temperatures were set at 10 to 20°C above the T_g or T_m to assure proper material flow in the extruder. Rheological evaluation was performed to obtain the parameters: zero rate viscosity (viscosities at low shear rates, whose values are generally constant) and activation energy (energy required to initiate the flow) which are useful in evaluating the extrudability and predicting the miscibility of the drug/polymer blends. The understanding of thermal and rheological properties of the various drug/polymer mixtures assisted in establishing the processing conditions for hot melt extrusion, as well as, providing insights into the properties of the final extrudates.

During high speed continuous manufacturing operations, various properties of the material such as T_g, moisture content, hygroscopicity and mechanical properties play a significant role. An understanding of the contribution of polymer carriers to these properties would help in efficient large scale product development. An understanding of how polymer carriers contribute to these properties could help in developing efficient large scale product manufacturing. Research shows that during the preparation of PASDs, the influence of variables such as moisture, temperature and drug loading varies from polymer to polymer (110, 111). Therefore judicious selection of formulation components, especially the choice of polymers and manufacturing technology, can aid the efficient development and manufacturing of PASDs.

CONCLUSION

PASDs provide a potential advantage in stabilizing the amorphous form of a drug. Polymers play an important role in stabilization through various mechanisms including anti-plasticization, specific intermolecular interactions, alteration of chemical potential and reduction in molecular mobility of the amorphous drug. Molecular aspects of miscibility and interaction between drug and polymer should be considered when formulating PASDs. Proper selection of the polymer, composition of the PASD, and the method of preparation can aid in formulating a stable amorphous system. However, challenges such as poor stability as a result of hygroscopicity, deviations from expected dissolution behavior, and poor processability may limit their utility as a viable formulation strategy. Careful control of these parameters can help in harnessing the benefits of the amorphous state by converting them to successful commercial products.

REFERENCES

1 Che E, Zheng X, Sun C, Chang D, Jiang T, Wang S. Drug nanocrystals: a state of art formulation strategy for preparing the poorly water-soluble drugs. Asian J Pharm Sci, 7(2): 85-95, 2012.

2 Elamin AA, Ahlneck C, Alderborn G, Nyström C. Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure. Int J Pharm, 111(2): 159-170, 1994.

3 Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, Toguchi H, Liversidge GG, Higaki K, Kimura T. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Controlled Release, 111(1): 56-64, 2006.

4 Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today, 12(23): 1068-1075, 2007.

5 Smith AJ, Kavuru P, Wojtas L, Zaworotko MJ, Shytle RD. Cocrystals of quercetin with improved solubility and oral bioavailability. Mol Pharm, 8(5): 1867-1876, 2011.

6 Aakero¨y CB, Forbes S, Desper J. Using cocrystals to systematically modulate aqueous solubility and melting behavior of an anticancer drug. J Am Chem Soc, 131(47): 17048-17049, 2009.

7 Kimura K, Hirayama F, Arima H, Uekama K. Effects of aging on crystallization, dissolution and absorption characteristics of amorphous tolbutamide-2-hydroxypropyl-beta-cyclodextrin complex. Chem Pharm Bull, 48(5): 646-650, 2000.

8 Yalkowsky SH, Rubino JT. Solubilization by cosolvents I: Organic solutes in propylene glycol-water mixtures. J Pharm Sci, 74(4): 416-421, 1985.

9 Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nature Rev Drug Discovery, 6(3): 231-248, 2007.

10 Zhang M, Li H, Lang B, O'Donnell K, Zhang H, Wang Z, Dong Y, Wu C, Williams III RO. Formulation and Delivery of Improved Amorphous Fenofibrate Solid Dispersions Prepared by Thin Film Freezing. Eur J Pharm Biopharm, 2012.

11 Broman E, Khoo C, Taylor LS. A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water soluble drug. Int J Pharm, 222(1): 139-151, 2001.

12 Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci, 60(9): 1281-1302, 1971.

13 Qiu Y, Chen Y, Geoff G, Zhang Z. Developing Solid Oral Dosage Forms - Pharmaceutical Theory and Practice. Academic Press, 2009.

14 Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 50(1): 47-60, 2000.

15 Gupta P, Bansal AK. Spray drying for generation of a ternary amorphous system of celecoxib, PVP, and meglumine. Pharm Dev Technol, 10(2): 273-281, 2005.

16 Goldberg AH, Gibaldi M, Kanig JL, Mayersohn M. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures IV: Chloramphenicol—urea system. J Pharm Sci, 55(6): 581-583, 1966.

17 Van Drooge D, Hinrichs W, Frijlink H. Anomalous dissolution behavior of tablets prepared from sugar glass-based solid dispersions. J Controlled Release, 97(3): 441-452, 2004.

18 Löbmann K, Grohganz H, Laitinen R, Strachan C, Rades T. Amino acids as co-amorphous stabilisers for poorly water soluble drugs-Part 1: Preparation, stability and dissolution enhancement. Eur J Pharm Biopharm, 2013.

19 Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III: Experimental evaluation of griseofulvin-succinic acid solid solution. J Pharm Sci, 55(5): 487-492, 1966.

20 Kaushal AM, Gupta P, Bansal AK. Amorphous drug delivery systems: molecular aspects, design, and performance. Crit Rev Ther Drug, 21(3): 133, 2004.

21 Shah B, Kakumanu VK, Bansal AK. Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids. J Pharm Sci, 95(8): 1641-1665, 2006.

22 Cui Y. A material science perspective of pharmaceutical solids. Int J Pharm, 339(1): 3-18, 2007.

23 Ediger M, Angell C, Nagel SR. Supercooled liquids and glasses. J Phys Chem, 100(31): 13200-13212, 1996.

24 Kwei T. The effect of hydrogen bonding on the glass transition temperatures of polymer mixtures. J Polym Sci: Polym Lett Ed, 22(6): 307-313, 2003.

25 Torquato S. Glass transition: Hard knock for thermodynamics. Nature, 405(6786): 521-523, 2000.

26 Gupta P, Bansal AK. Devitrification of amorphous celecoxib. AAPS PharmSciTech, 6(2): E223-E230, 2005.

27 Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res, 17(4): 397-404, 2000.

28 Babu NJ, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. Cryst. Growth Des., 11: 2662-2679, 2011.

29 Pawar YB, Shete G, Popat D, Bansal AK. Phase behavior and oral bioavailability of amorphous curcumin. Eur J Pharm Sci, 47: 56-64, 2012.

30 Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci, 86(1): 1-12, 1997.

31 Onoue S, Sato H, Kawabata Y, Mizumoto T, Hashimoto N, Yamada S. In vitro and in vivo characterization on amorphous solid dispersion of cyclosporine A for inhalation therapy. J Controlled Release, 138(1): 16-23, 2009.

32 Law D, Krill SL, Schmitt EA, Fort JJ, Qiu Y, Wang W, Porter WR. Physicochemical considerations in the preparation of amorphous ritonavir-poly (ethylene glycol) 8000 solid dispersions. J Pharm Sci, 90(8): 1015-1025, 2001.

33 Lakshman JP, Cao Y, Kowalski J, Serajuddin AT. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Mol Pharm, 5(6): 994-1002, 2008.

34 Yang W, Tam J, Miller DA, Zhou J, McConville JT, Johnston KP, Williams RO. High bioavailability from nebulized itraconazole nanoparticle dispersions with biocompatible stabilizers. Int J Pharm, 361(1): 177-188, 2008.

35 Ambike AA, Mahadik K, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low T g drug: *in vitro* and *in vivo* evaluations. Pharm Res, 22(6): 990-998, 2005.

36 Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm, 301(1): 199-208, 2005.

37 Patrick J. Martin's physical pharmacy and pharmaceutical sciences. Lippincott Williams and Wilkins, 2010.

38 Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. Eur J Pharm Biopharm, 70(2): 493-499, 2008.

39 Rawlinson CF, Williams AC, Timmins P, Grimsey I. Polymer-mediated disruption of drug crystallinity. Int J Pharm, 336(1): 42-48, 2007.

40 Miyazaki T, Aso Y, Yoshioka S, Kawanishi T. Differences in crystallization rate of nitrendipine enantiomers in amorphous solid dispersions with HPMC and HPMCP. Int J Pharm, 407(1): 111-118, 2011.

41 Kennedy M, Hu J, Gao P, Li L, Ali-Reynolds A, Chal B, Gupta V, Ma C, Mahajan N, Akrami A. Enhanced bioavailability of a poorly soluble VR1 antagonist using an amorphous solid dispersion approach: a case study. Mol Pharm, 5(6): 981-993, 2008.

42 Ambike AA, Mahadik K, Paradkar A. Stability study of amorphous valdecoxib. Int J Pharm, 282(1): 151-162, 2004.

43 Wang L, Cui FD, Hayase T, Sunada H. Preparation and evaluation of solid dispersion for nitrendipine-carbopol and nitrendipine-HPMCP systems using a twin screw extruder. Chem Pharm Bull, 53(10): 1240-1245, 2005.

44 Liu H, Wang P, Zhang X, Shen F, Gogos CG. Effects of extrusion process parameters on the dissolution behavior of indomethacin in Eudragit® E PO solid dispersions. Int J Pharm, 383(1): 161-169, 2010.

45 Huang J, Li Y, Wigent RJ, Malick WA, Sandhu HK, Singhal D, Shah NH. Interplay of formulation and process methodology on the extent of nifedipine molecular dispersion in polymers. Int J Pharm, 420(1): 59-67, 2011.

46 Jachowicz R, Czech A. Preparation and evaluation of piroxicam-HPMCAS solid dispersions for ocular use. Pharm Dev Technol, 13(6): 495-504, 2008.

47 Xie Y, Xie P, Song X, Tang X, Song H. Preparation of esomeprazole zinc solid dispersion and study on its pharmacokinetics. Int J Pharm, 360(1): 53-57, 2008.

48 Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ, Krill SL, Qiu Y. Ritonavir–PEG 8000 amorphous solid dispersions: *In vitro* and *in vivo* evaluations. J Pharm Sci, 93(3): 563-570, 2004.

49 Janssens S, Denivelle S, Rombaut P, Van den Mooter G. Influence of polyethylene glycol chain length on compatibility and release characteristics of ternary solid dispersions of itraconazole in polyethylene glycol/hydroxypropylmethylcellulose 2910 E5 blends. Eur J Pharm Sci, 35(3): 203-210, 2008.

50 Nepal PR, Han HK, Choi HK. Enhancement of solubility and dissolution of Coenzyme Q_{10} using solid dispersion formulation. Int J Pharm, 383(1): 147-153, 2010.

51 Li S, Liu Y, Liu T, Zhao L, Zhao J, Feng N. Development and in-vivo assessment of the bioavailability of oridonin solid dispersions by the gas anti-solvent technique. Int J Pharm, 411(1): 172-177, 2011.

52 Ayenew Z, Paudel A, Van den Mooter G. Can compression induce demixing in amorphous solid dispersions? A case study of naproxen-PVP K25. Eur J Pharm Biopharm, 2012.

53 Balani P, Wong S, Ng W, Widjaja E, Tan R, Chan S. Influence of polymer content on stabilizing milled amorphous salbutamol sulphate. Int J Pharm, 391(1): 125-136, 2010.

54 Muela S, Escalera B, Peña M, Bustamante P. Influence of temperature on the solubilization of thiabendazole by combined action of solid dispersions and co-solvents. Int J Pharm, 384(1): 93-99, 2010.

55 Shibata Y, Fujii M, Sugamura Y, Yoshikawa R, Fujimoto S, Nakanishi S, Motosugi Y, Koizumi N, Yamada M, Ouchi K. The preparation of a solid dispersion powder of indomethacin with crospovidone using a twin-screw extruder or kneader. Int J Pharm, 365(1): 53-60, 2009.

56 Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersions containing ibuprofen. Int J Pharm, 361(1): 125-130, 2008.

57 Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. J Pharm Sci, 2012.

58 Janssens S, Anné M, Rombaut P, Van den Mooter G. Spray drying from complex solvent systems broadens the applicability of Kollicoat® IR as a carrier in the formulation of solid dispersions. European Journal of Pharmaceutical Sciences, 37(3): 241-248, 2009.

59 Portero A, Remunan-Lopez C, Vila-Jato J. Effect of chitosan and chitosan glutamate enhancing the dissolution properties of the poorly water soluble drug nifedipine. Int J Pharm, 175(1): 75-84, 1998.

60 Liu X, Lu M, Guo Z, Huang L, Feng X, Wu C. Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. Pharm Res, 29(3): 806-817, 2012.

61 Callahan J, Cleary G, Elefant M, Kaplan G, Kensler T, Nash R. Equilibrium moisture content of pharmaceutical excipients. Drug Dev Ind Pharm, 8(3): 355-369, 1982.

62 Qian F, Huang J, Hussain MA. Drug–polymer solubility and miscibility: Stability consideration and practical challenges in amorphous solid dispersion development. J Pharm Sci, 99(7): 2941-2947, 2010.

63 Stukalin EB, Douglas JF, Freed KF. Plasticization and antiplasticization of polymer melts diluted by low molar mass species. J Chem Phys, 132: 1-11, 2010.

64 Dong Z, Chatterji A, Sandhu H, Choi DS, Chokshi H, Shah N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. Int J Pharm, 355(1–2): 141-149, 2008.

65 Anderson S, Grulke E, DeLassus P, Smith P, Kocher C, Landes B. A model for antiplasticization in polystyrene. Macromol, 28(8): 2944-2954, 1995.

66 Fox GT., Bull Am Phys Soc, 1:123, 1956.

67 Gordon M, Taylor JS. Ideal copolymers and the second-order transitions of synthetic rubbers. i. non-crystalline copolymers. J Appl Chem, 2(9): 493-500, 2007.

68 Couchman P, Karasz F. A classical thermodynamic discussion of the effect of composition on glass-transition temperatures. Macromol, 11(1): 117-119, 1978.

69 Shamblin SL, Taylor LS, Zografi G. Mixing behavior of colyophilized binary systems. J Pharm Sci, 87(6): 694-701, 1998.

70 Crowley KJ, Zografi G. Water vapor absorption into amorphous hydrophobic drug/poly (vinylpyrrolidone) dispersions. J Pharm Sci, 91(10): 2150-2165, 2002.

71 Makiko F, Junko H, Hideaki K, Mitsuo M. The solid dispersion of benzodiazepins with phosphatidylcholine. The effect of substituents of benzodiazepins on the formation of solid dispersions. Chem Pharm Bull, 39(11): 3013-3017, 1991.

72 Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in

amorphous molecular dispersions. Pharm Res, 14(12): 1691-1698, 1997.

73 Sekikawa H, Arita T, Nakano M. Dissolution behavior and gastrointestinal absorption of phenytoin-polyvinylpyrolidone and dicumarol-beta-cyclodextrin. Chem Pharm Bull, 26: 118-126, 1978.

74 Khougaz K, Clas SD. Crystallization inhibition in solid dispersions of MK-0591 and poly (vinylpyrrolidone) polymers. J Pharm Sci, 89(10): 1325-1334, 2000.

75 Gupta P, Thilagavathi R, Chakraborti AK, Bansal AK. Role of molecular interaction in stability of celecoxib-PVP amorphous systems. Mol Pharm, 2(5): 384-391, 2005.

76 Vippagunta SR, Wang Z, Hornung S, Krill SL. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. J Pharm Sci, 96(2): 294-304, 2006.

77 Van den Mooter G, Wuyts M, Blaton N, Busson R, Grobet P, Augustijns P, Kinget R. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur J Pharm Sci, 12(3): 261-269, 2001.

78 Gunawan L, Johari G, Shanker RM. Structural relaxation of acetaminophen glass. Pharm Res, 23(5): 967-979, 2006.

79 Job G, Herrmann F. Chemical potential-a quantity in search of recognition. Eur J Phys, 27(2): 353, 2006.

80 Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. Pharm Res, 23(10): 2417-2426, 2006.

81 Westrum E, McCullough J. Thermodynamics of crystals. Phys Chem Org Solid State, 1: 89-102, 1963.

82 Bansal SS, Kaushal AM, Bansal AK. Enthalpy relaxation studies of two structurally related amorphous drugs and their binary dispersions. Drug Dev Ind Pharm, 36(11): 1271-1280, 2010.

83 Surana R, Pyne A, Rani M, Suryanarayanan R. Measurement of enthalpic relaxation by differential scanning calorimetry-effect of experimental conditions. Thermochim Acta, 433(1): 173-182, 2005.

84 Hancock BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm Res, 12(6): 799-806, 1995.

85 Craig DQ. A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behavior of polyethylene glycols. Thermochim Acta, 248: 189-203, 1995.

86 Kakumanu VK, Bansal AK. Enthalpy relaxation studies of celecoxib amorphous mixtures. Pharm Res, 19(12): 1873-1878, 2002.

87 Bhattacharya S, Suryanarayanan R. Molecular Motions in Sucrose-PVP and Sucrose-Sorbitol Dispersions: I. Implications of Global and Local Mobility on Stability. Pharm Res, 28(9): 2191-2203, 2011.

88 Rumondor AC, Ivanisevic I, Bates S, Alonzo DE, Taylor LS. Evaluation of drug-polymer miscibility in amorphous solid dispersion systems. Pharm Res, 26(11): 2523-2534, 2009.

89 Ivanisevic I, Bates S, Chen P. Novel methods for the assessment of miscibility of amorphous drug-polymer dispersions. J Pharm Sci, 98(9): 3373-3386, 2009.

90 Qian F, Huang J, Zhu Q, Haddadin R, Gawel J, Garmise R, Hussain M. Is a distinctive single T_g a reliable indicator for the homogeneity of amorphous solid dispersion? Int J Pharm, 395(1): 232-235, 2010.

91 Painter PC, Graf JF, Coleman MM. Effect of hydrogen bonding on the enthalpy of mixing and the composition dependence of the glass transition temperature in polymer blends. Macromol, 24(20): 5630-5638, 1991.

92 Hildebrand JH. Solubility. J Am Chem Soc, 38(8): 1452-1473, 1916.

93 Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci, 88(11): 1182-1190, 1999.

94 Hansen CM. Hansen solubility parameters: a user's handbook. CRC, 2007.

95 Fedors RF. A method for estimating both the solubility parameters and molar volumes of liquids. Polym Eng Sci, 14(2): 147-154, 2004.

96 Krevelen DWv, Nijenhuis Kt. Properties of polymers. Elsevier, 2009.

97 Barton AF. Handbook of solubility parameters and other cohesion parameters. CRC, 1991.

98 Flory PJ. Thermodynamics of high polymer solutions. J Chem Phys, 9: 660-661, 1941.

99 Young RJ, Lovell PA. Introduction to polymers. CRC, 2009.

100 Flory PJ. Principles of polymer chemistry. Cornell University Press, 1953.

101 Huggins ML. Thermodynamic Properties of Solutions of Long-chain Compounds. Ann NY Acad Sci, 43(1): 1-32, 1942.

102 Marsac PJ, Li T, Taylor LS. Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm Res, 26(1): 139-151, 2009.

103 Ford JL, Elliott PN. The effect of particle size on some *in vitro* and *in vivo* properties of indomethacin-polyethylene glycol 6000 solid dispersions. Drug Dev Ind Pharm, 11(2-3): 537-549, 1985.

104 Akbuga J, Gürsoy A, Yetimoglu F. Preparation and properties of tablets prepared from furosemide-PVP solid dispersion systems. Drug Dev Ind Pharm, 14(15-17): 2091-2108, 1988.

105 Sjökvist E, Nyström C. Physicochemical aspects of drug release. XI. Tableting properties of solid dispersions, using Xylitol as carrier material. Int J Pharm, 67(2): 139-153, 1991.

106 Hideshi S, Hisakazu S. Some factors influencing the dissolution of solid dispersions with nicotinamide and hydroxypropylmethylcellulose as combined carriers. Chem Pharm Bull, 46(6): 1015-1020, 1998.

107 Puri V, Dantuluri AK, Bansal AK. Investigation of atypical dissolution behavior of an encapsulated amorphous solid dispersion. J Pharm Sci, 100(6): 2460-2468, 2011.

108 Serajuddin A. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci, 88(10): 1058-1066, 1999.

109 Chokshi RJ, Sandhu HK, Iyer RM, Shah NH, Malick AW, Zia H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion processs as a means to manufacture solid dispersion/solution. J Pharm Sci, 94(11): 2463-2474, 2005.

110 Lamm MS, Simpson A, McNevin M, Frankenfeld C, Nay R, Variankaval N. Probing the Effect of Drug Loading and Humidity on the Mechanical Properties of Solid Dispersions with Nanoindentation: Antiplasticization of a Polymer by a Drug Molecule. Mol Pharm, 9(11): 3396-3402, 2012.

111 Marsac PJ, Rumondor ACF, Nivens DE, Kestur US, Stanciu L, Taylor LS. Effect of temperature and moisture on the miscibility of amorphous dispersions of felodipine and poly(vinyl pyrrolidone). J Pharm Sci, 99(1): 169-185, 2010.