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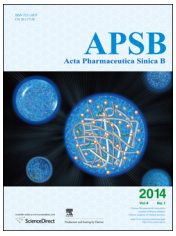

REVIEW

Fundamental aspects of solid dispersion technology for poorly soluble drugs

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Abstract The solid dispersion has become an established solubilization technology for poorly water soluble drugs. Since a solid dispersion is basically a drug–polymer two-component system, the drug–polymer interaction is the determining factor in its design and performance. In this review, we summarize our current understanding of solid dispersions both in the solid state and in dissolution, emphasizing the fundamental aspects of this important technology.

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1. Introduction

It is estimated that most compounds undergoing development at the present time are subjected to dissolution problems[1]. To meet this pharmaceutical challenge, various solubilization technologies have been developed including solid dispersions, nanocrystals, cyclodextrin complexes and lipid formulations. With accelerated increase in the number of FDA-approved products in recent years (Table 1), solid dispersion is now firmly established as a platform technology for the formulation of poorly-soluble drugs. Specifically, solid dispersion technology has been successfully applied to develop formulations with a high drug loading (*e.g.* 375 mg per tablet in Incivek) and/or containing drugs with a high tendency to crystallize (as indicated by the high melting point of 291 °C of ivacaftor in Kalydeco) (Table 1).

At least three methods of preparing solid dispersions have been successfully used in commercial production[2] (Table 1). These are melt extrusion, applicable to drugs with not-very-high melting points[3], spray drying, useful for drugs soluble in at least one volatile solvent[4], and co-precipitation, useful for drugs with high melting point and low solubility in common organic solvents[5]. The encouraging progresses should more-or-less ease previous concerns on solid dispersion regarding its drug loading, manufacturing, and stability issues[6].

Historically, the term "solid dispersion" was defined as a dispersion of drug in a solid matrix where the matrix was either a small molecule or polymer. The dispersed state has included many forms such as eutectic mixtures, crystalline/glass solutions, and amorphous/crystalline suspensions[7,8]. Taking account of its currently most-used form (Table 1), a solid dispersion can now be more narrowly defined as dispersion of drug in an amorphous polymer matrix where the drug is preferably in the molecularly dispersed state (*i.e.* as a glass solution to use the old term, Fig. 1A). The following discussion is limited to systems that fit this more limited definition.

Although other additives (particularly surfactants) are often included and products may be made using polymer mixtures, solid dispersions are mainly drug–polymer two-component systems. As discussed below, the drug–polymer interaction is fundamental to understanding the most important issues that arise in the design of a solid dispersion *viz.* the drug loading, stability of the system and its dissolution performance. The objective of this short review is to summarize our current understanding of solid dispersions in terms of this important factor. Other aspects related to solid dispersions can be found in a number of excellent reviews already in the literature[6,9–13].

2. Drug–polymer interactions in the solid state

2.1. Phase diagram and phase separation

A solid dispersion is a deceptively simple two component system where the drug and the polymer act as solute and solvent, respectively. Despite this apparent simplicity, these two-component systems can form multiple structures depending on their composition and sample processing history[14] (Fig. 1). When the drug loading is lower than the equilibrium solubility of drug in polymer, the drug is molecularly dispersed within the polymer matrix (Fig. 1A) and should form a thermodynamically stable, homogeneous solution. This is the most desirable structure of solid dispersion. However, for most drug–polymer pairs, this situation only appertains at very low drug loading and/or high temperature (see below). As temperature is decreased, the mixture becomes a supersaturated solution and the drug tends to precipitate out. This can result in a dispersion of crystalline drug particles in a polymer matrix, in which the drug concentration corresponds to its equilibrium solubility at that temperature (Fig. 1B). Alternatively, as drug crystallization is a slow process with a higher energy barrier compared to amorphous phase separation, an intermediate meta-stable structure may form in which amorphous drug aggregates are dispersed in a polymer matrix containing drug at its amorphous solubility at that temperature (Fig. 1C).

As with all multi-component systems, a phase diagram is very useful to understand its structure under different conditions and to design a processing protocol to obtain a desired structure. By analogy with many small molecule–polymer systems described in the literature[15,16], a simplified drug–polymer phase diagram is shown in Fig. 2A. The curve of drug solubility in the polymer (solid curve) is particularly important not only to select the lower

Table 1 Examples of FDA-approved medicines that use solid dispersion technologies.

Product name	API	Polymer[a]	Maximum API dose per tablet or capsule (mg)[b]	API T_m (°C)[c]	Solid dispersion preparation method[e]	Year of approval[b]
Cesamet	Nabilone	PVP	1	160	—	1985
Sporanox	Itraconazole	HPMC	100	166	Spray drying on sugar beads	1992
Prograf	Tacrolimos	HPMC	5	128	Spray drying	1994
Kaletra	Lopinavir/ritonavir	PVP/VA	200/50	125/122	Melt extrusion	2005
Intelence	Etravirine	HPMC	200	265[d]	Spray drying	2008
Zotress	Everolimus	HPMC	0.75	115	Spray drying	2010
Novir	Ritonavir	PVP/VA	100	122	Melt extrusion	2010
Onmel	Itraconazole	HPMC	200	166	Melt extrusion	2010
Incivek	Telaprevir	HPMCAS	375	246	Spray drying	2011
Zelboraf	Vemurafenib	HPMCAS	240	272	Co-precipitation	2011
Kalydeco	Ivacaftor	HPMCAS	150	291	Spray drying	2012

[a]Best guess based on the inactive ingredient list, patents and other literature information.
[b]Information based on the drug product labels from the FDA website.
[c]From Merck index or otherwise specified.
[d]Decomposition temperature.
[e]From Brough and Williams[2].

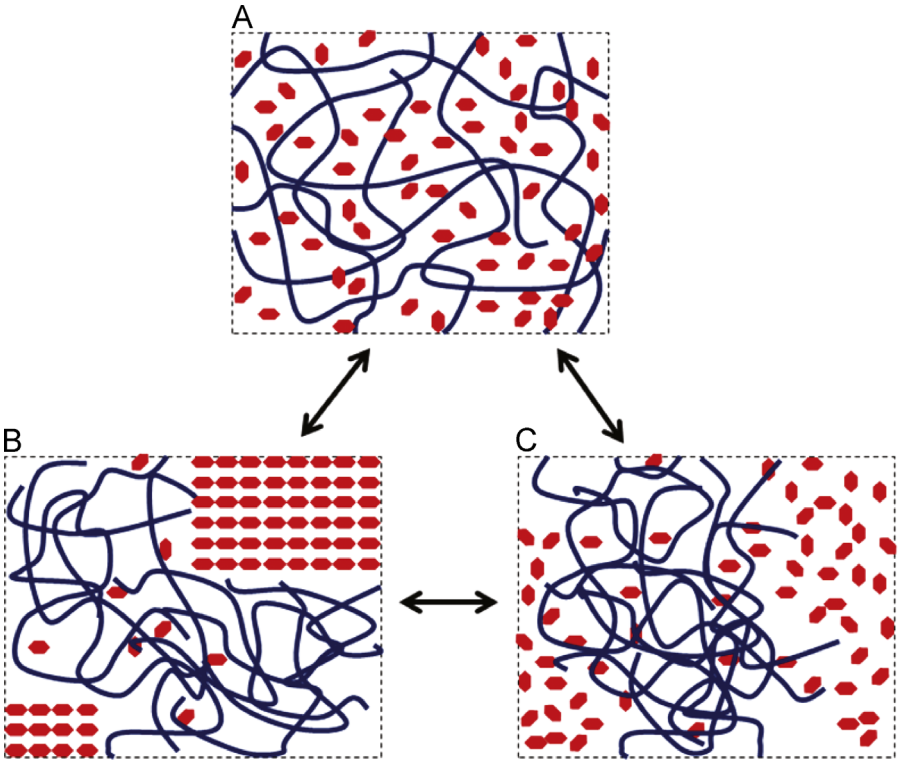

Figure 1 The three possible structures of a drug/polymer solid dispersion where hexagonal symbols represent drug molecules and curvy lines represent polymer chains. (A) The ideal structure of a solid dispersion where the drug is molecularly dispersed in the polymer matrix; (B) a drug–polymer system in which crystalline drug formation has occurred and (C) a drug–polymer system containing amorphous drug-rich domains dispersed in the polymer matrix.

limit of the processing temperature to obtain a molecular dispersion by melt extrusion, but also to understand the supersaturation level of such dispersions when they are cooled down (*e.g.*, to the storage temperature). The glass transition temperature T_g curve (dotted curve) is also important since the glass transition may freeze the system in a particular structure, a knowledge of which is essential to predicting the storage stability of a solid dispersion. Usually, the T_g curve obeys the Gordon–Taylor equation and T_g decreases continuously from that of the pure polymer to that of pure drug (Fig. 2A). However, the amorphous phase separation may complicate the T_g profile, as discussed below.

Ideally, a molecular dispersion should be kinetically-stable at its storage temperature as this is important for its dissolution profile (discussed in Section 3). Such stability can be achieved by carefully selecting polymer excipients, the polymer/drug ratio and the processing parameters. Indeed, many solid dispersions show no drug crystallization during characterization by thermal analysis and X-ray diffraction. However, it should be noted that such characterization methods are rather insensitive to crystal formation and can only detect 1–5% crystals in a given sample[9,17–19].

Alternative to drug crystallization, amorphous phase separation may also take place (Fig. 2B). This can occur very rapidly, especially when the drug/polymer composition falls into the spinodal zone[9,14,16] (not shown in Fig. 2B for simplicity) where there is no free energy barrier to separation. At least two situations can occur as shown in Fig. 2A and B. In Fig. 2A, the phase diagram applies to a system where the amorphous phase separation curve does not intersect with the glass transition temperature curve. In this case, amorphous phase separation can occur at temperatures below the whole glass transition temperature curve as in the case of the fenbufen/PVP system. In Fig. 2B, the phase diagram is for a system where the two curves intersect at pharmaceutically relevant temperatures as for example in the felodipine/poly(acrylic acid) system. In the field of polymer science, the intersection point of the two curves is known as the Berghmans' Point[16,20]. As temperature falls and amorphous phase separation proceeds, the compositions of the drug-rich and polymer-rich phases follow the phase line (shown as the dashed curve in Fig. 2B). When the temperature reaches that of the Berghmans' Point, the polymer-rich phase reaches its glass transition temperature, below which further phase separation does not occur. Consequently, the final solid dispersion is amorphous phase separated with the composition of the polymer matrix at Berghmans' Point, while the amorphous drug phase is almost pure drug, because the polymer–small molecule amorphous separation curve is usually highly asymmetric[15] as shown in Fig. 2B.

It should be emphasized that the phase diagrams shown in Fig. 2 do not represent the only possibilities because both assume that the drug and polymer are completely miscible above the drug melting point which may not always be the case. In addition, depending on the relationship between the drug–polymer interaction parameter and temperature (Eq. (4), see Section 2.3), amorphous phase separation can take place both when temperature decreases (below the upper critical solution temperature, or UCST, Fig. 2B) and when it increases (above the lower critical solution temperature, or LCST) (not shown).

Thermal analysis using differential scanning calorimetry (DSC) is often used to characterize solid dispersions but phase separation

in a solid dispersion is difficult to detect when the phase domains are small. Thus, when a drug melting event is absent and only one glass transition temperature T_g is observed, the solid dispersion is usually assumed to be a homogeneous solution when, in fact, it may contain segregated amorphous domains that are too small to be detected. For example, Qian et al.[21] demonstrated that a solid dispersion showing one T_g in thermal analysis has phase separated domains approximately 100 μm in size using confocal Raman microscopy. This is an interesting observation that needs to be confirmed in further studies. Another value in the literature[22] on the T_g detection size limit of amorphous phase domains is 30 nm, which was based on a single and inconclusive study of a block copolymer system[23] and therefore also should be used with caution. Nevertheless, one study[24] suggested that dynamic mechanical analysis (DMA) could detect amorphous phase domains as small as 10 nm and a method based on solid state NMR relaxation may be even more sensitive[25].

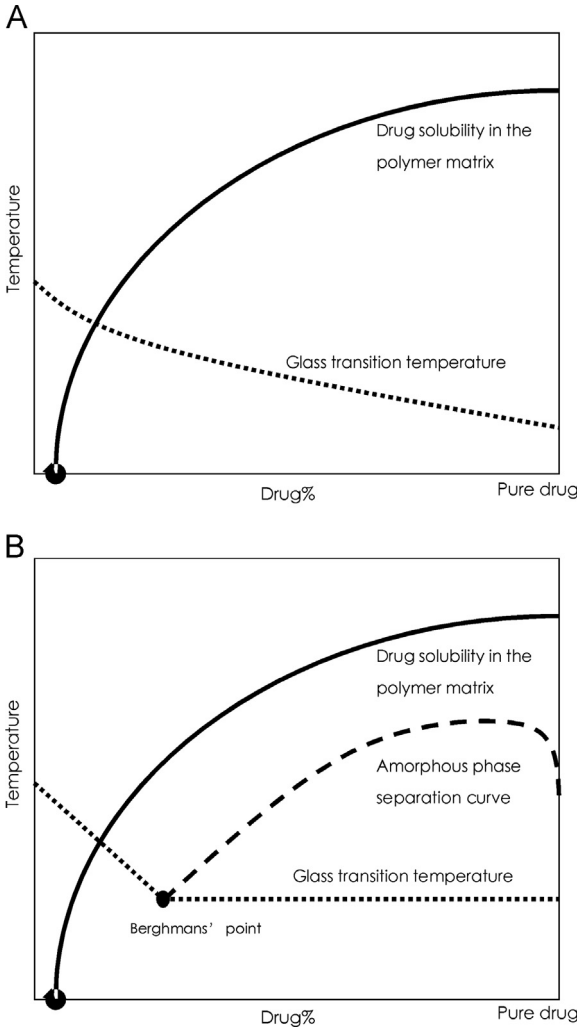

Figure 2 Possible temperature–composition phase diagrams for a drug–polymer solid dispersion showing (A) the situation where an amorphous phase separation curve does not interact with the glass transition temperature curve and (B) the situation where the amorphous phase separation curve interacts with the glass transition temperature curve.

2.2. *Storage stability and phase separation kinetics*

At normal storage temperatures and with a desirable drug loading (>20%), drug in most solid dispersions far exceeds its equilibrium solubility in the polymer matrix, which is difficult to experimentally measure but can be estimated (see Section 2.3). However, the dispersion can be stable kinetically if the phase separations are frozen below the glass transition temperature. Here we consider instability from the point of view of drug crystallization to illustrate why the rate of phase separation is slow at normal storage temperatures.

In a homogeneous drug–polymer solution, polymer chains are random coils that interpenetrate each other and extend through the whole system, while drug molecules are dispersed randomly among the polymer segments. It has been estimated that any continuous drug domain within the random coils is no larger than 2.5 nm[26], so that for a drug to form stable crystal nuclei a certain amount of polymer must diffuse away. The time for this diffusion to occur can be calculated from the polymer diffusion coefficient, the lower limit of which can be calculated on the basis of the following two assumptions (Fig. 3): (1) The medium through which the polymer diffuses essentially consists of pure drug (in reality, the medium contains other polymer chains and the viscosity is much higher than that in a pure drug domain); (2) The medium viscosity is close to that at the glass transition temperature *i.e.* viscosity $\sim 10^{12}$ Pa.s (again the storage temperature is usually below the glass transition temperature and the viscosity is much higher). With these assumptions and for a polymer about 10 nm in size, the diffusion coefficient of the polymer (the Rouse model[27]) is given by

$$D \cong \frac{kT}{6\pi\eta R} \sim 10^{-26}\ \mathrm{m^2/s} \quad (1)$$

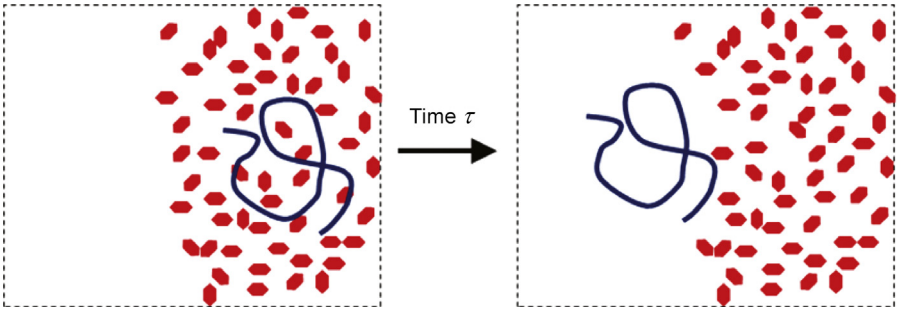

Figure 3 Schematic illustration of a solid dispersion in which a polymer chain is diffusing out of a drug domain.

and the time for the polymer to diffuse over a distance of its own size (~10 nm) is

$$\tau \cong \frac{R^2}{D} \sim 100 \text{ years} \quad (2)$$

Therefore, it is the high viscosity of the solid dispersion at the glass state that stabilizes the dispersion structure. However, at higher temperatures the viscosity of the drug–polymer mixture is much lower (*e.g.*, felodipine at 100 °C has a viscosity of approximately 10^2 Pa.s)[28], and the time scale for polymer diffusion can be as low as seconds. Thus, for systems at higher temperature in the molten state, the diffusion of both drug and polymer are fast and phase separation can occur quickly.

As water is a very effective plasticizer, the absorption of moisture significantly decreases the glass transition temperature of a solid dispersion and consequently enhances the mobility of drug and polymer. For example[29], after storage in a relative humidity of 53%, the glass transition temperature of poly(vinyl pyrrolidone) (PVP K-12) was reported to decrease from 170 °C to about 23 °C. Therefore, polymers that are resistant to the absorption of water, such as HPMCAS where the T_g remains >70 °C even after storage in a relative humidity of 75%, have become the first choice for the preparation of stable solid dispersions[9].

2.3. *The drug–polymer interaction parameter and phase diagram*

A drug–polymer phase diagram can be constructed using the Flory–Huggins polymer solution theory[9,14]. Taking the volume of a drug molecule as the unit lattice volume, the free energy change associated with mixing a polymer and small molecule is given by[27]

$$\frac{\Delta G}{KT} = \phi \ln \phi + \frac{(1-\phi)}{m} \ln(1-\phi) + \chi\phi(1-\phi) \quad (3)$$

where K is the Boltzmann constant, T is the absolute temperature, ϕ is the volume fraction of drug in the solid dispersion (*i.e.*, the drug loading), m is the volume ratio between polymer and drug, and χ is the Flory drug–polymer interaction parameter representing the difference between the drug–polymer contact interaction (Fig. 4, right) and the average self-contact interactions of drug–drug and polymer–polymer (Fig. 4, left). For example, hydrogen-bond formation between drug and polymer chains [*e.g.*, in the fenbufen/poly(vinylpyrrolidone) pair] may make it more energetically favorable for the drug and polymer to interact with each other rather than with themselves, resulting a negative interaction parameter.

The Flory drug–polymer interaction parameter χ is key to understanding the structures of solid dispersions and, according to the Flory–Huggins theory, is dependent only on temperature:

$$\chi = A + \frac{B}{T} \quad (4)$$

here A and B are constants independent of the drug loading and polymer molecular weight. It should also be noted that χ is dependent on the choice of unit volume[27]. Since the volume of a drug molecule is usually chosen as the unit lattice volume, care is needed when comparing interaction parameters between one polymer and different drugs.

As shown by Lin and Huang[14], the χ–T relationship allows the whole phase diagram for a drug–polymer solid dispersion to be constructed including both the drug solubility temperature curve and the amorphous phase separation curve. As illustrated in detail by Lin and Huang[14], the χ–T relationship is obtained (Fig. 5) by fitting experimental melting point depression data (T_m~ϕ) to the following equation which is based on the Flory–Huggins theory (Eq. (5))[30–32].

$$\frac{\Delta H_m^0}{R}\left(\frac{1}{T_m^0} - \frac{1}{T_m}\right) = \ln\phi + \left(1 - \frac{1}{m}\right)(1-\phi) + \chi_{T_m}(1-\phi)^2 \quad (5)$$

Here ΔH_m^0 is the enthalpy of melting of pure drug crystals, R is the ideal gas constant, T_m^0 and T_m are the melting points of the pure drug crystals and drug crystals in the solid dispersion with drug volume faction of ϕ. Please note that the drug–polymer interaction parameter χ is temperature dependent and the value in Eq. (5) is that at the temperature T_m. When using Eq. (5), χ is usually assumed to be constant and, because the experimentally available T_m range is narrow, this assumption holds true and melting point depression data can give a good fit to Eq. (5). However, when Eq. (5) is used to estimate drug solubility at low temperatures such as at the storage temperature, the χ–T variation cannot be neglected (Fig. 5)[33] without overestimating drug solubility.

The accurate measurement of equilibrium melting points of drug crystals in solid dispersions also represents a considerable challenge. Currently, most researchers use the method developed by Tao et al.[32] where melting points are measured at different heating rates and extrapolated to zero heating rate to estimate the equilibrium value. In this method, the solid dispersion is prepared by intimate mixing of drug crystals and polymer *via* cryogenic

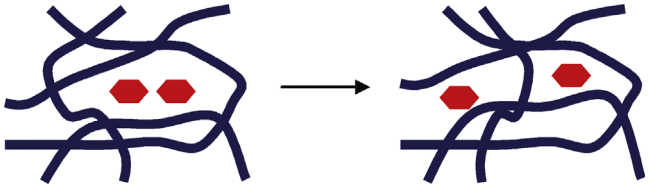

Figure 4 The Flory interaction parameter of drug molecules and polymer segments χ represents the energy difference between the inter-species (i.e., drug–polymer) contact interaction (right) and the average self-contact interactions (drug–drug and polymer–polymer) (left).

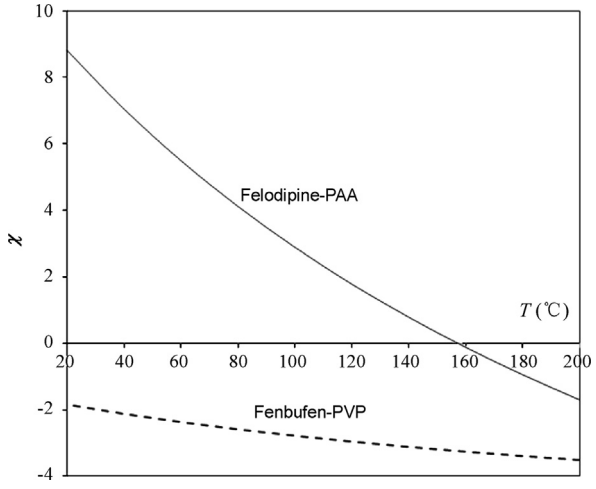

Figure 5 The predicted χ–T relationship (Eq. (4)) for the felodipine/poly(acrylic acid) and fenbufen–poly(vinyl pyrrolidone) drug polymer systems. The original melting point depression data used in the calculation are taken from Refs. 14 and 33.

milling. Alternatively, the sample may also be prepared by conventional methods (melt extrusion, spray drying, and co-precipitation) and then annealed at suitable temperature to generate drug crystals *in situ*[14]. One advantage of the direct mixing method is being able to avoid complications of drug crystal polymorphism.

3. Drug–polymer interactions in dissolution

The ultimate success of a solid dispersion is determined by its performance in dissolution after oral administration. The general strategy behind almost all solubilization technologies is the so-called "spring-and-parachute" concept[34]. For a solid dispersion, this means that the drug should first dissolve along with the soluble polymer matrix to create a supersaturated solution ("the spring") after which supersaturation is maintained long enough for drug absorption ("the parachute") to take place.

Depending on the type of solid dispersion, dissolution can occur in three possible ways (Fig. 6). When the drug loading is low, the drug and polymer in the solid dispersion dissolve rapidly (Fig. 6A) after which drug is continuously absorbed and can undergo precipitation in the presence of polymer and endogenous compounds such as bile acids, phospholipids and mucin. As described in detailed by Friesen et al.[9], various structures may form including free drug (the major species, if not the only species, being absorbed, so its concentration is what matters for absorption), drugs in bile salt/phospholipid micelles, amorphous drug nanoprecipitates with polymers, and possibly drug nanocrystals stabilized with polymers, all of which are in dynamic exchange with each other. Since such nanoparticles can escape filtration or centrifugation, the apparent solubility of a drug can be erroneously high. Nevertheless, with the proper choice of polymers, the free drug concentration can be maintained at the solubility of amorphous drugs[9,35]. However, it should be noted that, in theory, the highest concentration of free drug in the dissolution media is even higher, corresponding to the spinodal amorphous phase separation line, above which the drug forms amorphous aggregates spontaneously[36].

Solid dispersions generate a supersaturated drug solution when exposed to the aqueous environment of the gastrointestinal tract. Drugs in this state have a tendency to precipitate rapidly before being absorbed resulting in reduced bioavailability. A variety of polymer excipients have been evaluated for their ability to prolong the supersaturation and inhibit drug precipitation[37]. Fortunately, the polymers commonly used in the preparation of solid dispersions are generally the same ones that inhibit drug precipitation, specifically some cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) and hydroxypropylmethylcellulose acetate succinate (HPMCAS) and vinyl polymers such as poly (vinylpyrrolidone) (PVP) and poly(vinylpyrrolidone-co-vinyl

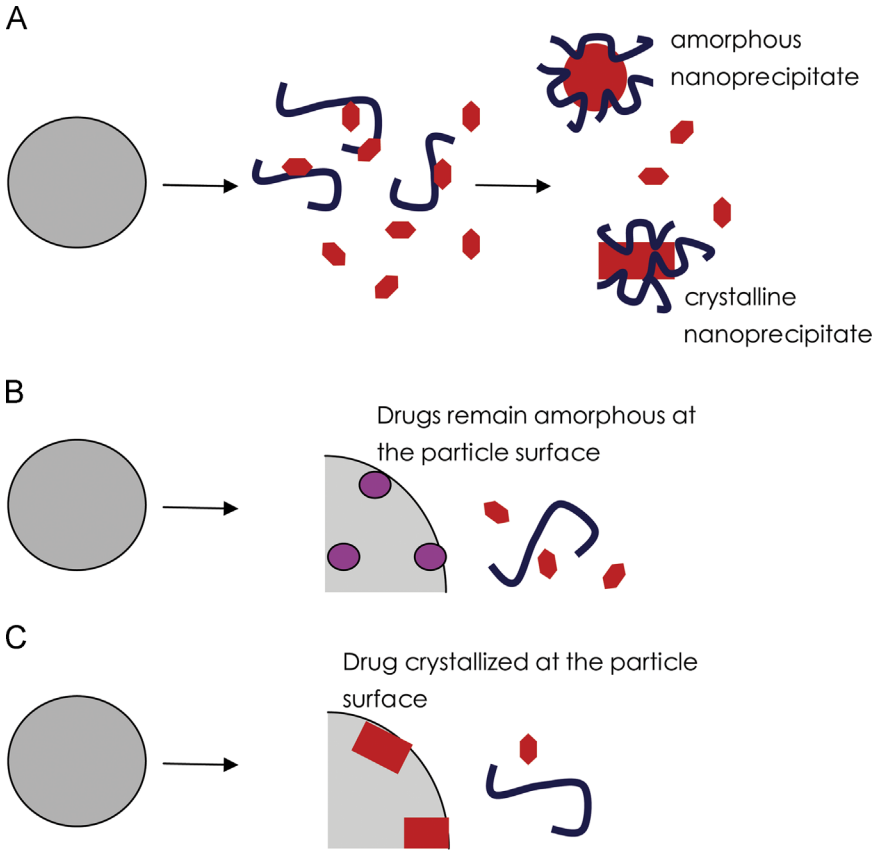

Figure 6 Three possible scenarios of drug dispersion from solid dispersions. (A) Particles dissolve rapidly and release drug into a highly supersaturated solution; subsequently drug precipitates as amorphous and/or crystalline particles onto which polymer adsorbs as a stabilizer; (B) drug and polymer are gradually released while drug remains amorphous in the undissolved particles; and (C) drug and polymer are gradually released but drug is present as crystals in the undissolved particles especially near their surfaces. The free drug concentration is dependent on the solubility of either amorphous or crystalline drug which in turn depends on the drug/polymer ratio, polymer dissolution rate and drug crystallization rate.

acetate) (PVPVA). These polymers are able to maintain a supersaturated drug concentration *in vivo* for an extended period of time to allow optimal absorption.

The mechanism of how polymers prolong drug supersaturation is still not fully understood despite considerable research but is generally believed to result from a polymer–drug interaction. Drug precipitation (or crystallization) takes place in two stages *viz.* nucleation and crystal growth. The polymers in solid dispersions may interfere with one or both of these processes by interacting with the drug or changing the properties of the medium[38,39]. Thus some polymers are known to suppress the nucleation process[40] while others adsorb on the surface of crystals to block the access of solute molecules ("the poisoning effect") thus preventing or retarding crystal growth[41,42].

The polymer–drug interactions may mainly be the result of hydrogen bond formation and/or hydrophobic interactions. For example, studies have shown that HPMC is effective in inhibiting nucleation of drugs rich in hydrogen-bond acceptors[43–45] in a concentration dependent manner[40]. This ability to delay nucleation may be because hydrogen bonds between drug molecules and polymers not only increase the nucleation activation energy but also reduce crystal growth[46–48].

Hydrogen bonding is not the only type of interaction that influences drug precipitation/dissolution in solid dispersions. Studies have also shown that the higher the lipophilicity of a polymer the more it is able to inhibit/retard nucleation and/or crystal growth[49–51]. This is because a polymer with a higher lipophilicity adsorbs more effectively onto crystal surfaces to enhance the inhibition of further drug attachment[52,53]. However, there is an upper limit to polymer lipophilicity above which the inhibition effect is lost[54]. In addition, other factors such as steric hindrance to adsorption, polymer rigidity and distribution of functional groups in the polymer may play a significant role in the polymer–drug interaction. For example, polymers with relatively rigid structures can adsorb onto crystal surfaces more easily to inhibit drug precipitation[54,55].

In the scenario described above, the dissolution of the solid dispersion is fast and complete and the supersaturated solution around the solid dispersion determines the concentration of free drug. In contrast, solid dispersion particles may dissolve slowly either because of high drug loading or the nature of the polymer resulting in a more sustained release profile. As water continuously penetrates into solid dispersion particles, phase separation eventually occurs. If drug crystallization is still inhibited by the polymer matrix in this situation, the drug may form amorphous aggregates (Fig. 6B) and the free drug concentration in the dissolution media will be equal to the solubility of amorphous drugs. However, if the drug is present in a crystalline state in the solid dispersion particles (Fig. 6C), the free drug concentration in the solution decreases to that of the solubility of drug crystals, *i.e.*, the dissolution advantage of the solid dispersion is lost[35,56,57].

4. Summary

As an increasing proportion of drugs undergoing development are poorly water-soluble, solubilization technologies have become an essential feature in bringing them successfully to market. The solid dispersion is one such technology which in recent years has led to the approval of a large number of products, suggesting it is now the preferred technology for drug solubilization. However, despite considerable progress in understanding the nature of solid dispersions, many aspects of their behavior remain to be clarified such as the kinetics of phase separation in the solid state and in solution, and even such simple questions as how polymer molecular weight affects the drug crystallization rate. Research is also needed into the use of solid dispersions in conjunction with controlled release technologies such as the osmotic pump.

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