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EXPERT REVIEW

Physical Stability of Amorphous Solid Dispersions: a Physicochemical Perspective with Thermodynamic, Kinetic and Environmental Aspects

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ABSTRACT

Purpose Amorphous solid dispersions (ASDs) have been widely used in the pharmaceutical industry for solubility enhancementof poorly water-soluble drugs. The physical stability, however, remainsone of the most challenging issues for the formulation development.Many factors can affect the physical stability via different mechanisms, and therefore an in-depth understanding on these factors isrequired.

Methods In this review, we intend to summarize the physical stability of ASDsfrom a physicochemical perspective whereby factors that can influence the physical stability areclassified into thermodynamic, kinetic and environmental aspects.

Results The drug-polymer miscibility and solubility are consideredas the main thermodynamicfactors which may determine the spontaneity of the occurrence of the physical instabilityof ASDs. Glass-transition temperature,molecular mobility, manufacturing process,physical stabilityof amorphous drugs, and drug-polymerinteractionsareconsideredas the kinetic factors which areassociated with the kinetic stability of ASDs on aging. Storage conditions including temperature and humidity could significantly affect the thermodynamicand kineticstabilityof ASDs.

Conclusion When designing amorphous solid dispersions, it isrecommended that these thermodynamic, kinetic and environmental aspects should be completely investigatedand compared to establish rationale formulations for amorphous solid dispersions with high physical stability.

KEY WORDS amorphous solid dispersions · kinetic stability · physical stability · thermodynamic stability

ABBREVIATIONS

API	Active pharmaceutical ingredient
ASD	Amorphous solid dispersion
DSC	Differential scanning calorimetry
FDA	Food and drug administration
FT-IR	Fourier transform infrared spectroscopy
HPMCAS	Hydroxypropyl cellulose acetate succinate
MTDSC	Modulated temperature differential scanning calorimetry
NMR	Nuclear magnetic resonance spectroscopy
PC-SAFT	Perturbed-chain statistical associating fluid theory
PEG	Polyethylene glycol
PLGA	Poly lactic-co-glycolic acid
PVP	Polyvinylpyrrolidone
PVP K12	Polyvinylpyrrolidone (M_w = 3500)
PVPVA64	Vinylpyrrolidone-vinyl acetate copolymer[60:40]
T_g	Glass transition temperature
Vitamin E TPGS	D-α-tocopheryl polyethylene glycol succinate

INTRODUCTION

Amorphous solid dispersion (ASD) has been used as a classic drug delivery system for poorly water-soluble drugs for decades (1–7). Fundamentally it relies on the concept of dispersing drug molecules into polymeric carriers via pharmaceutical processes to form a homogeneous amorphous system. Within such dispersion system, drugs exist in the state of separated molecules, and thus the lattice energy that has to be overcome during dissolution could be completely avoided, and hence the

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dissolution rate can be enhanced (8–11). The application of ASDs has been successful as proved by ASD based medicines approved by FDA as shown in Table I (9).

Despite the successful commercialization of ASD based medicines, the main hurdle of using such system, the physical stability, remains substantially challenging for formulation scientists (12–15). Up to date, there have been many studies concerning the physical stability of ASDs since the concept was first introduced in 1961 (1). It has been reported that a number of factors, such as glass transition temperature (T_g) of amorphous drugs and polymers, molecular mobility of drugs, drug-polymer miscibility, solid solubility of drugs in the polymers, physical stability of amorphous drugs alone, fragility index of amorphous drugs, drug-polymer interaction, molecular weight of drugs, recrystallization temperature of amorphous drugs, storage environment (temperature and humidity) and preparation process, were related to and may significantly affect the physical stability of ASDs (16–24). Formulation design for ASDs are therefore guided under these factors. For instance, ASDs are recommended to be formulated with the drug loadings below the drug-polymer solubility (25). Meanwhile, it is also suggested that polymers with high glass transition temperatures should be used as the polymeric carriers for ASDs to enhance the physical stability of ASDs (26). When developing ASD formulations, such diverse suggestions may eventually raise the question as to selecting the polymers with high Tg or selecting the polymers that can offer high drug-polymer solubility. The two recommendations are certainly both correct, but they actually come from thermodynamic and kinetic concerns, respectively, which would influence the physical stability of ASDs by completely different mechanisms. The above mentioned stability-related factors that can thermodynamically or kinetically determine the physical stability, however, may not have been clearly distinguished (27–30). Therefore, under the great contributions that have already been made by previous studies, an overview on the physical stability of ASDs from the physicochemical perspective may further assist formulation design for ASDs (31,32). In this paper, we intend to review the physical stability of ASDs from the physicochemical perspective by classifying the physical stability-related factors into thermodynamic, kinetic and environmental aspects. Basically, ASDs can be considered as systems to be stored in the environment. Thermodynamics and kinetics of the physical stability of ASDs would therefore be influenced by the environment (temperature and humidity). The physical stability-related factors could accordingly be classified and summarized into thermodynamic and kinetic aspects. Thermodynamic factors are associated with the thermodynamic stability of ASDs, which can determine the spontaneity of the occurrence of the physical instability, such as phase separation or recrystallization (28). Kinetic factors are associated with the kinetic stability, which can be used to estimate or describe the rate of phase separation or recrystallization of ASDs, and hence understanding the kinetic factors could be useful to predict the shelf lives for ASD based medicines (33). Moreover, environmental aspect, referring to temperature and humidity, is exterior aspect that could only influence the physical stability of ASDs via affecting the thermodynamic and kinetic related factors.

The classification of the stability-related factors into different physicochemical aspects could be a novel and more fundamental way for understanding the physical stability of ASDs. Such classification could assist formulation scientists to group the numerous physical stability-related factors, which

Table I Approved Medicines Based on the Technologies of Amorphous Solid Dispersions

Product name	API	Polymeric carriers	Preparation process	Year of approval
Cesamet™	Nabilone	PVP	N.A.	1985
Sporanox®	Itraconazole	HPMC	Spray drying	1992
Prograf™	Tacrolimus	HPMC	Spray drying	1994
Gris-PEG™	Griseofluvin	PEG	Melt extrusion	2000
Cestor®	Rosuvastatin	HPMC	Spray drying	2002
Cymbalta®	Duloxetine	HPMCAS	N.A.	2004
Kaletra®	Lopinavir/ritonavir	PVP-VA	Melt extrusion	2005
Eucreas®	Vildagliptin/Metformin HCL	HPC	Melt extrusion	2007
Intelence®	Etravirine	HPMC	Spray drying	2008
Onmel™	Itraconazole	HPMC	Melt extrusion	2010
Fenoglide™	Fenofibrate	PEG/Polaxamer 188	Spray melt	2010
Novir®	Ritonavir	PVP-VA	Melt extrusion	2010
Incivo®	Telaprevir	HPMCAS	Spray drying	2011
Noxafil®	Posaconazole	HPMCAS	Melt extrusion	2013
Orkambi®	Lumacaftor/Ivacaftor	HPMCAS/SLS	Melt extrusion	2015

may simplify the application of these factors. Additionally in this review, not only all factors associated with the physical stability of ASDs are classified into different aspects, but also the classic theories or calculating models for these factors are introduced and discussed. It is expected that through this review, the strategy for developing ASDs might be clear and the process of formulation screening for ASDs could be shortened.

THERMODYNAMICS OF THE PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS

Thermodynamic viewpoint on the physical stability of ASDs are mainly derived from the concepts of liquid systems, in which miscibility and solubility are applied to describe mixing solutions and dissolving solids into solvents (34). Considering the preparation of ASDs as dissolving solvates in solvents, ASDs can therefore be thermodynamically stable if the drug loading of the ASD is below the solid solubility of the drug in the polymer (34). Unlike solubility, miscibility is the concept for describing the mixing proportions of two liquids to form single-phase solutions at certain temperature and pressure i.e. mixing water and phenol (33,35). Similarly, amorphous drugs and amorphous polymers could be considered as two liquids, and thus at certain temperature and pressure, thermodynamically stable ASDs could be formed if the drug to polymer ratio in the system is within the single-phase region as illustrated in Fig. 1 (34,36). Up to date, the prediction or calculation of miscibility and solid solubility has been carried out via theoretical models and experiments, and the details of these approaches are discussed in the following sections.

Miscibility Between Drug and Polymer

Prediction of drug-polymer miscibility is a useful tool for screening polymeric carriers and determining the drug loadings in formulation development of ASDs. The commonly reported approaches for predicting the drug-polymer miscibility include solubility parameter approach, molecular modelling and T_g evaluation of solid dispersions (37–40).

Solubility Parameter

Solubility parameter is defined as the square root of the cohesive energy density that is consumed to separate unit volume of molecules from condensed phase to infinite distance (41). The drugs and polymers with similar solubility parameters are considered to be miscible based on the concept of "likes dissolve likes" (42). Group contribution method is usually employed to calculate the solubility parameters of compounds with complex structure and high molecular weight (43). In this method, the compound with complex chemical structure could be divided into several small functional groups, and the solubility parameters of these small groups can be determined by evaporation method, and hence the solubility parameter of the intact compound can be calculated (42). For instance, in Fedors solubility parameter, chemicals are simply divided into small groups, and the solubility parameter is calculated by

$$\delta = (\Sigma E_{coh}/\Sigma V)^{1/2} \quad (1)$$

where δ represents solubility parameter, ΣE_{coh} represents the sum of cohesive energy of each group and ΣV represents the sum of the molar volume of each group (44). An example of group contribution method is given in this review to ease the

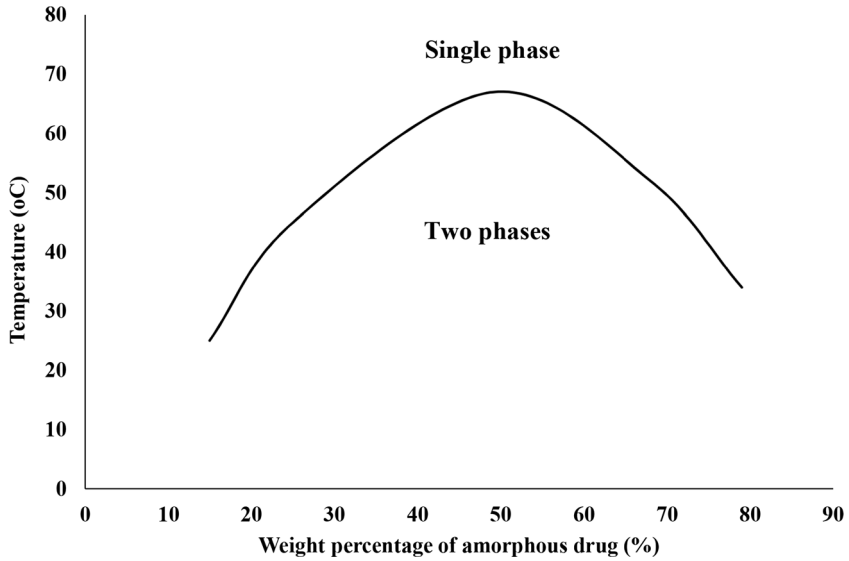


Fig. 1 Illustration of the drug-polymer miscibility.

understanding of this method, and fenofibrate is used as the model drug. As seen in the chemical structure of fenofebrate (Table II), the drug molecule is composed of several chemical groups, such as methyl group and carbonyl groups. Therefore, the intact structure could be divided into small chemical groups as listed in Table II. The cohesive energy and molar volume of these small groups can be achieved by direct determination using evaporation method or from published results. The solubility parameter of fenofibrate could accordingly be calculated by Eq. (1).

In addition to Fedors method, other group contribution approaches were also reported to be used to calculate the solubility parameter (45–47). For example, in Hansen solubility parameter method, total solubility parameter of chemicals are contributed by three components including dispersion force, hydrogen bonding and polar (electrostatic) force, as described in Eq. (2) (35,45):

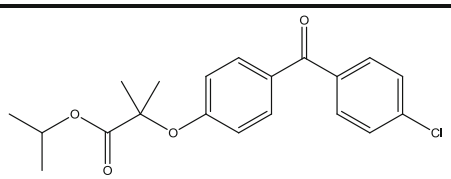
$$\delta^2 = \delta_d{}^2 + \delta_p{}^2 + \delta_h{}^2 \quad (2)$$

where $\delta_d{}^2$, $\delta_p{}^2$, and $\delta_h{}^2$ are the dispersion, polar and hydrogen bonding components of solubility parameters, respectively. Although the approaches of predicting solubility parameters are different, the calculated results of the same chemicals by different methods do not vary significantly, and therefore the miscibility results between drugs and polymers predicted using different solubility parameter methods are similar (43).

It was reported that, chemicals with a $\Delta\delta$ value (the difference of solubility parameter values between the drug and the polymer) less than 7.0 $MPa^{0.5}$ were considered to be miscible whereas chemicals with a $\Delta\delta$ value larger than 7.0 $MPa^{0.5}$ were considered to be immiscible, and the smaller the $\Delta\delta$ value, the higher the miscibility (43,48). This rule was reported to be useful for early stage formulation screening when developing ASD products (43). In one study, the researchers calculated the $\Delta\delta$ value between itraconazole and different polymers including Soluplus®, Eudragit® E PO and PVPVA64. The results showed that Eudragit® E PO had the highest $\Delta\delta$ value amongst the three polymers, and hence melt extrudates using Soluplus® and PVPVA64 presented better physical stability than the ASDs composed of Eudragit® E PO and itroconazole (38). The predicted results via solubility parameter for guiding the formulation development of ASDs, however, may not be reliable in some cases (49). For instance, it was reported that a binary system consisting of Vitamin E TPGS and Eudragit® E PO with a small $\Delta\delta$ value (0.8 $MPa^{0.5}$) was immiscible. In contrast, another binary system composed of Eudragit® E PO and tartaric acid was miscible and exhibited better physical stability despite of the large $\Delta\delta$ value (19.8 $MPa^{0.5}$) (49).

The reason for the discrepancy between the predicted miscibility and the real-time physical stability may be attributed to the interaction between the two types of compounds. Chemical entities are very likely to have high miscibility if

Table II Calculation of the Solubility Parameter of Fenofibrate Using Fedor's Group Contribution Method



Groups	Numbers of Groups	E_{coh} (kJ/mol)	V (cm^3/mol)
CH_3	4	4.71	33.5
C	1	1.47	-19.2
CO_2	1	18	18
O	1	3.35	3.8
Phenyl	2	31.94	71.4
CO	1	17.37	10.8
Cl	1	11.55	24
CH	1	3.43	-1

interactions i.e. hydrogen bonding or acid-base interaction can be formed between drugs and polymers (50). When strong interactions between chemicals occurs, the solubility parameter approach would be less accurate in predicting miscibility between drugs and polymers (50). Therefore, while applying solubility parameter to develop formulations, it is recommended to initially assess the potential interactions between components by using technologies such as infrared spectroscopy or solid state NMR (51–53).

Evaluation of Glass Transition Temperatures of Solid Dispersions

Another approach of assessing the drug-polymer miscibility relies on the application of MTDSC (modulated temperature differential scanning calorimetry) in testing the prepared ASDs (54). An amorphous solid dispersion with a single T_g that has a value in between the T_g values of the amorphous drug and the polymer is considered to be a homogeneous system, and the drug and the polymer are miscible in the system (39,55). As can be seen in Fig. 2, solid dispersion composed of felodipine and PVP-VA64 with 30% *w*/w drug loading shows the T_g value in between the T_g values of amorphous felodipine and PVP-VA64, and consequently the drug and the polymer in the solid dispersion are miscible. This approach is a direct indicator for the drug and the polymer being miscible in ASDs, and it is often served as the primary tool when investigating the miscibility between the drug and the polymer in ASDs (56).

Molecular Modelling Prediction on Miscibility Between Drug and Polymer

Molecular modelling prediction is a method that employs quantum mechanical calculations combining with commercial software, i.e. Gaussian 09, to characterize the potential interactions between drugs and polymers (57,58). It is well known that interactions, such as hydrogen bonding between drugs and polymers, play important role in the miscibility between drugs and polymers (28). In molecular modelling method, dimeric structure of polymer and monomeric structure of drug are constructed by software, i.e. GaussView (59). The possibility of hydrogen bonding formation between drugs and polymers are assessed by calculating the binding energies from placing the drug molecule within the proximity of the dimeric structure of the polymer (40,60). If the binding energy level is comparable to the normal hydrogen bonding level, it is likely that H-bond might be formed between the drug and the polymer (61,62). Therefore, through molecular modelling, drug-polymer miscibility could be predicted before preparation

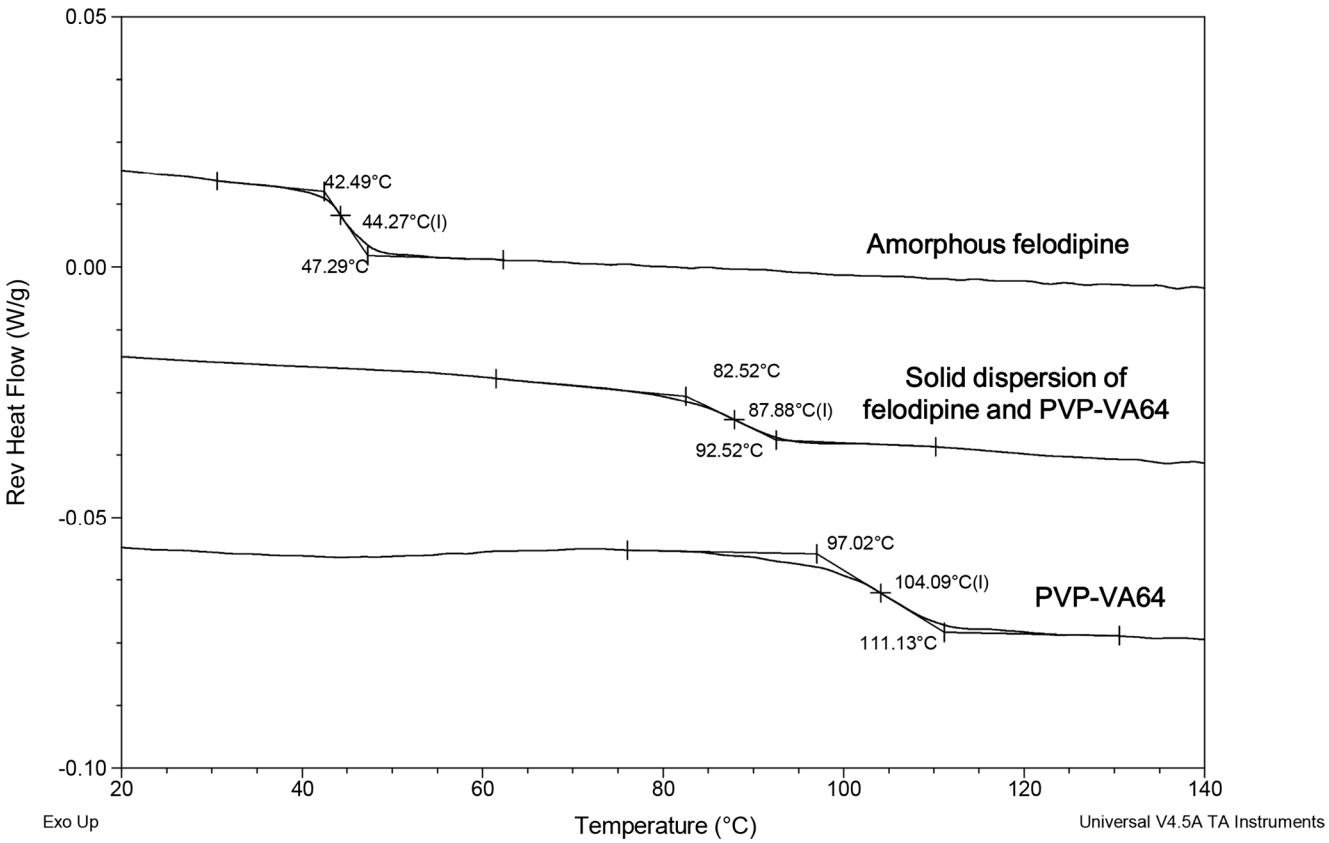


Fig. 2 MTDSC results of amorphous felodipine, PVP-VA64 and solid dispersion consisting of felodipine and PVP-VA64 with 30% *w*/w drug loading.

into ASDs. A typical research by Douroumis *et al.* reported the study of investigating into the miscibility between model drugs (such as propranolol HCl) and commercial polymers (such as Eudragit® L100 and Kollidon VA64) (40). It was concluded that some of the predicted drug-polymer interactions were in agreement with DSC studies and molecular modelling could be broadly applied when solubility parameter method or Flory-Huggins method had limitations (40). This method, although being useful for formulation development of ASDs, requires certain knowledge on quantum mechanical calculation.

Determination of Solid Solubility of Drug in Polymer

Melting Point Depression Approach

Melting point depression method was derived from Flory-Huggins lattice theory that was originally employed to assess the thermodynamics of polymer solutions (63,64). The method was further developed and modified to be applied in determining the solid solubility of drugs in polymers (65). The method requires a series DSC (differential scanning calorimetry) tests at low heating rate on drug-polymer physical mixtures with different ratios (66). Upon heating on a physical mixture of a crystalline drug and an amorphous polymer to equilibrium state, the solid–liquid chemical potential (calculated as partial differential of the free energy from Flory-Huggins model) change of the crystalline drug should be equivalent to the chemical potential change of the crystalline drug in liquid state and in the amorphous polymer phase (67). Such decreased chemical potential of the crystalline drug would cause a depression of melting point of the crystalline drug. Combined with Flory-Huggins model, the following relationship could be established (65,68):

$$\left(1/T^{mix}{}_M - 1/T^{pure}{}_M\right) = -R/\Delta H_{fus}\left[ln\Phi_{drug} + (1-1/m)\Phi_{polymer} + \chi\Phi_{polymer}{}^2\right] \quad (3)$$

where $T^{mix}{}_M$ is the melting temperature of the crystalline drug in the presence of the amorphous polymer, $T^{pure}{}_M$ isthe standard melting point of the pure drug, ΔH_{fus} is the heat fusion of the crystalline drug, m is the ratio of molar volume of polymer to that of the drug, and χ is the interaction parameter between the drug and the polymer. The interaction parameter (χ) can be achieved by the regression analysis using Eq. (3).

With the achieved interaction parameter (χ) value, combining Flory-Huggins lattice theory and the calculation of thermodynamic solubility, melting point depression method can be employed to predict the solid solubility of drugs in polymers using the following equations:

$$dlnS/dT = \Delta H_{fus}/\left(RT^2\right) \quad (4)$$

where S is the solubility of the compound at temperature T, ΔH_{fus} is the enthalpy of fusion of the compound. At a certain temperature, Eq. (4) can be rewritten into:

$$lnS = -\Delta H_{fus}/R\,(1/T_2 - 1/T_1) \quad (5)$$

where T_2 and T_1 represents $T^{mix}{}_M$ and $T^{pure}{}_M$ in Eq. (3), respectively. Therefore, according to Eq. (3) and Eq. (5), the solid solubility of drug in polymer, S_{drug}, can be calculated by:

$$lnS_{drug} = ln\Phi_{drug} + (1-1/m)\Phi_{polymer} + \chi\Phi_{polymer}{}^2 \quad (6)$$

where S_{drug} represents the solubility of drug in polymer at the temperature where solubility parameter is calculated, and in the melting point depression approach this temperature is the depressed meting point at standard atmospheric pressure (63,65,69).

Melting point depression method has been used to assist the formulation development of ASDs in optimizing the ratios of drug to polymer and screening polymer candidates (70,71). Recently, a report from Tian *et al.* successfully applied Flory-Huggins lattice theory to draw a phase diagram for felodipine and three polymers to determine the maximum drug loading for each polymer (72). Inaccurate prediction by melting point depression method, however, was also reported (73). For instance, Yang *et al.* reported that felodipine-Eudragit® E PO dispersions with the estimated solid solubility of approximately 31% (*w*/w) showed significantly higher physical stability under different storage conditions than carbamazepine-Eudragit® E PO dispersions with the estimated solubility of 46% (w/w) (73). These results suggests that there could be limitations when using melting point depression method to calculate the solid solubility of drugs in polymers. Flory-Huggins lattice theory does not take into account the effect of molecular interactions, i.e. dipole-dipole interactions (64,74). In addition, the calculation of the interaction parameter, χ, is dependent on temperature, drug to polymer ratio and polymer molecular weight, and these factors varies significantly between different drugs and polymers (64,75). The assumptions and restrictions from the method may lead to unexpected results of physical stability of ASDs. It is therefore recommended that when using melting point depression method to develop ASD formulations, short-time physical stability studies under stressed conditions may be conducted to confirm the applicable drug loading.

Perturbed-Chain Statistical Associating Fluid Theory

Perturbed-chain statistical associating fluid theory (PC-SAFT) is a thermodynamic model in which each API molecule is considered as a chain of spherical segments, and it can interact with other segments via different types of interactions (76–78). Unlike Flory-Huggins lattice method, in PC-SAFT approach,

it involves almost all effective interactions between drugs and polymers, including repulsive interactions, van der Waals attractions, hydrogen bonding, and dipole-dipole interactions and charges (79). Due to the involvement of many aspects, PC-SAFT is more complex than Flory-Huggins method (melting point depression method). The advantage of PC-SAFT lies in the fact that all parameters in PC-SAFT have physical meanings and are not dependent on other variables. Besides, PC-SAFT parameters has been calculated for more than 400 compounds covering the fields of gases, solvate molecules and polymers (80).

The application of PC-SAFT approach in predicting drug/polymer solubility and miscibility is briefly summarised in this review. Thermodynamically, when a system composed of API and polymer reaches equilibrium, the solubility of the API in the polymer could be written by:

$$x_{API}^{L} = \frac{1}{\gamma_{API}^{L}} exp\left[-\frac{\Delta h_{API}^{SL}}{RT}\left(1-\frac{T}{T_{API}^{SL}}\right)-\frac{\Delta Cp_{API}^{SL}}{R}\left(ln\left(\frac{T_{API}^{SL}}{T}\right)-\frac{T_{API}^{SL}}{T}+1\right)\right] \quad (7)$$

where x_{API}^{L} is the solubility of API (mole fraction), γ_{API}^{L} is the activity coefficient of the API in the liquid API/polymer phase, R is the universal gas constant, T is the temperature in Kelvin, T_{API}^{SL}, Δh_{API}^{SL}, and ΔCp_{API}^{SL} are the melting temperature, the heat fusion and the difference in the solid and the liquid heat capacities of the API, respectively. It can be seen that values such as T_{API}^{SL}, Δh_{API}^{SL}, and ΔCp_{API}^{SL} could be easily determined by DSC. Consequently, if the activity coefficient value, γ_{API}^{L}, could be achieved, the solid solubility of the drug in the polymer should be able to be calculated using Eq.(7). The PC-SAFT approach is mainly applied for the calculation of the activity coefficient. In PC-SAFT, all molecules are treated as chains consisting of spherical segments with a certain value of diameter (Fig. 3). These chains could interact with each other. The number of segments (m^{seg}_i), the diameter of the segment (σ_i), and the interaction energy between two segments (u_i) are used to account for the interactions occurred between drug molecules and polymer molecules. In PC-SAFT, the residual of Helmholtz energy of a drug-polymer system is contributed by three types of energies including hard-chain contribution, van der Waals attraction and association, and can be calculated as the sum of repulsion of molecules. The repulsive interaction is the collective interactions that could be obtained by using m^{seg}_i, σ_i, and u_i. The activity coefficient is linked with the residual of Helmholtz energy via a few equations (details of these equations is discussed in Sadowski's publications). Therefore, with the known values of m^{seg}_i, σ_i, and u_i, the value of γ_{API}^{L} could be achieved, and hence the solid solubility of the drug in the polymer can be estimated.

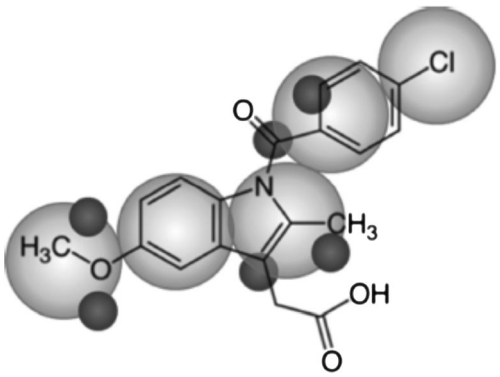


Fig. 3 The molecule of indomethacin described in PC-SAFT chain model composed of segments (grey sphere) and association sites (75).

The PC-SAFT approach has been applied in a few studies regarding the relationship between the predicted drug-polymer solubility and the physical stability of corresponding ASDs (75,81–83). In these studies, various polymeric carriers, such as PVP, PVPVA 64, HPMCAS, and PLGA were formulated with typical BCS II drugs (i.e. ibuprofen) into ACSs. The results showed that, under stressed humidity, formulations with the drug loadings below the drug-polymer solubility by PC-SAFT approach showed excellent physical stability. The consistency between the results from real-time physical stability and the predicted drug-polymer solubility verifies the PC-SAFT approach, demonstrating its effectiveness in estimating the solubility of drug in polymer.

Observation of Drug Dissolution in Polymer

The drug-polymer solubility could also be investigated visually by using polarized hot-stage microscopy (84,85). In this method, the physical mixtures with different ratios of crystalline drug and polymer are subjected to direct heating process on hot stage microscope. Birefringence from crystalline drug could be observed when temperature is below the melting point of the drug. At the temperature above the melting point of the drug and the T_g of the polymer, if birefringence disappears and a single liquid phase without boundary appears, the drug is considered to be dissolved in the polymer. Through testing a series of drug-polymer physical mixtures, the drug-polymer solubility may be obtained. This method that relies on observation, however, could only provide an approximation of drug-polymer solubility. Besides, inaccurate estimation on the drug-polymer solubility by this method may occur, due to the bubbles left by the melted drugs, which could be recognised as drug-polymer boundaries.

Thermal Approaches

Enthalpy Approach. The application of enthalpy approach to predict the solubility of drug in polymer is based on the principle that the fraction of the drug dissolved in polymer make no contribution to the melting endotherm associated with the

dispersed drug fraction (86). Accordingly, linear regression could be applied to estimate the relationship between the experimental values of melting enthalpy (dependent variables) and the drug concentrations (independent variables) in drug-polymer physical mixture (62). The solubility of the drug in the polymer, could be calculated as the x-intercept from the regression equation. In order to obtain an accurate drug-polymer solubility by this method, a fast heating rate (circa 400°C/min) has to be used to minimize the dissolution of the drug into the polymer while being heated, and hence the contribution from the exothermic drug dissolution to the melting endotherm can be reduced (87). It has been found that the faster the heating rate, the more accurate estimation of the drug solubility in polymer (87,88). With conventional DSC equipment, however, it is difficult to completely avoid the dissolution of the drug into the polymer on heating. This is because the maximum heating rate by conventional DSC may be less than 100°C/min, resulting in an inaccurate prediction (89).

Qi *et al.* modified the enthalpy approach and established a novel model to predict the solubility of drug in polymer (90). In that paper, it was assumed that the melting endotherm consisted of the energy associated with the drug dissolution in polymer and the energy of the drug melting. In that paper, the dissolution behavior of drug into polymer was dependent on the drug fraction in the drug-polymer physical mixture. According to the drug fractions, the drug-polymer mixing behaviors were divided into three areas: drug loading below the solubility of drug in polymer, polymer loading below the solubility of polymer in melted drug and the intermittent drug loading (Fig. 4) (90). The two x values at the corresponding interception points on the curve were the drug solubility in polymer (P_A) and the polymer solubility in molten drug (P_B), respectively. When predicting the solid solubility, this approach only involved the melting enthalpy and dissolution enthalpy of drugs, and the thermal test was nearly at equilibrium state due to the extremely slow heating rate used (90). Therefore the achieved solid solubility results could be considered as the thermodynamic solubility of the drug in the polymer. This approach, similar to the melting point depression method, however, may have its intrinsic limitation whereby the predicted solid solubility is only obtained at the temperature close to the melting point of the drug. Therefore there may be physical stability issues if the ASDs are designed based on the solubility predicted by such approach, since the solubility may decrease with decreasing temperature, leading to super-saturated systems at room temperature.

Thermal Acceleration Approach. Mahieu *et al.* reported another approach to estimate the drug solubility in polymer using thermal method (91). In this method, a super-saturated solid dispersion system consisting of indomethacin and PVP K12 was prepared using milling method. The solid dispersion was heated at 120°C in DSC for two hours to completely demix the drug from the solid dispersion, and then followed by re-scanning in DSC from room temperature to detect the T_g. An increased T_g value was detected in the milled samples compared with the T_g value in the fresh and untreated sample. Via Gordon-Taylor equation, the drug concentration in the heat-treated sample can be estimated using the T_g value from DSC re-scanning, and this drug concentration was considered as the solubility of indomethacin in PVP K12. The fundamental concept of this method lies in the fact that demixing of super-saturated ASDs occurs much faster than completely dissolving crystalline drugs into polymers (as illustrated in Fig. 5). Moreover, heat treatment at high temperature to ASDs can accelerate phase separation or recrystallization in ASDs and

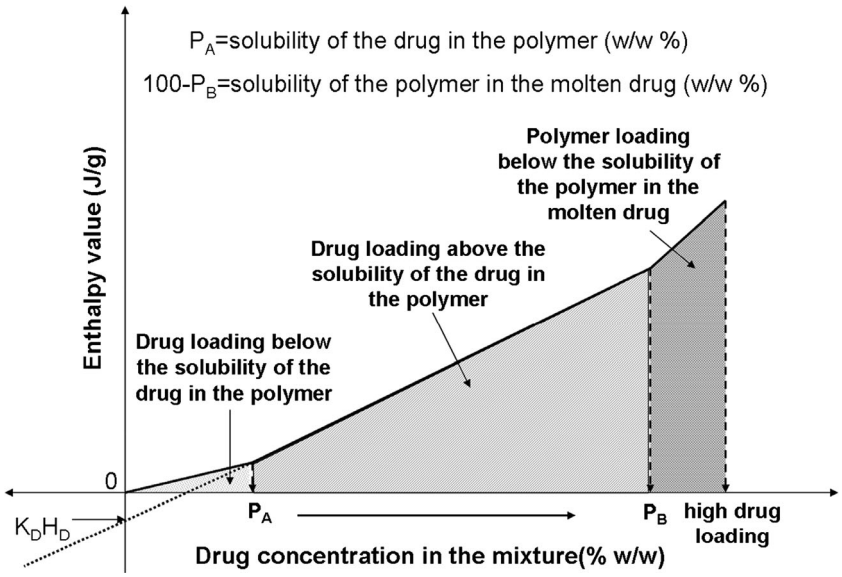


Fig. 4 Three possible regions of drug-polymer mixing behavior (90).

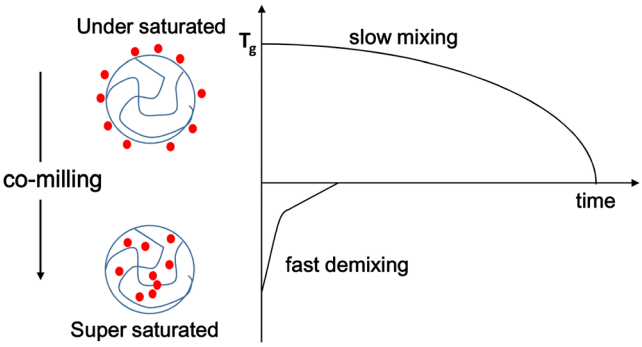


Fig. 5 Time evolutions of glass transition temperature of a drug/polymer mixture when reaching equilibrated state on annealing (redrawn figure from the paper by Mahieu *et al.*) (91).

hence the fraction of super-saturated drug in ASDs can re-crystallize out in short time. The remaining amount of drug in ASDs could therefore be considered as the dissolved drug in the polymer. The authors provide a practical approach for the determination of solid solubility in ASDs, and the method does not involve much assumption or complex calculation. Some restrictions, however, may also apply to this method. For instance, although milling method can be used to prepare solid dispersion consisting of drug and PVP, it may not be a general manufacturing process for preparing super-saturated ASDs containing other drug-polymer compositions, and hence limiting the broad application of this method (92).

KINETICS OF THE PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS

As mentioned above, although formulations with drug loadings above the drug solid solubility in polymers are thermodynamically instable, it is very likely that such formulations can be physically stable over a period of time. If this physically stable time period is longer than the common shelf life of a pharmaceutical product, the super-saturated ASD based products, can still be used clinically. Consequently, it is essential to understand the kinetic stability of ASDs as well as the factors that are associated with phase separation and recrystallization. It has been reported that factors including glass transition temperature of amorphous drugs and ASDs, molecular mobility of amorphous drugs, manufacturing process, physical stability of amorphous drugs and interactions between drugs and polymers, were linked with the kinetics of the physical stability of ASDs (18,93–98). These kinetic related factors are discussed in the following sections.

Glass Transition Temperature

The super-cooling method has been one of the most widely used methods for the preparation of amorphous material from its crystalline form (19,21,99,100). The relationship between the thermodynamic properties, such as enthalpy (H) or specific volume (V), and the temperature during the super-cooling process is shown in Fig. 6. For crystalline material at temperature below the melting point (T_m), the enthalpy increases slightly with increasing temperature (100). On increasing the temperature above the T_m, a discontinuous increase in both enthalpy (H) and specific volume (V) at T_m is observed, representing a first-order phase transition from crystalline state to liquid (99). As the melt suffers a rapid cooling process, the enthalpy (H) declines along the extrapolated liquid line, and the melt is formed into super-cooled liquid. As the super-cooled liquid is further cooled to the temperature below the T_g of the material, a break point could be observed at T_g, and the system is transformed into glass state with a significantly increased viscosity (99).

At the temperature below T_g, amorphous materials tend to approach the equilibrium (crystal) by releasing the extra enthalpy or configurational entropy, the process of which is defined as structural relaxation (101). During relaxation, amorphous materials could recrystallize at different rates depending on the storage temperature (101). Therefore, discrepancy between the glass transition temperature and the storage temperature can significantly affect the recrystallization rate of amorphous materials and hence increasing the T_g may improve the physical stability of ASDs due to the reduced recrystallization rate (102,103).

Preparing ASDs using polymeric carriers with high T_gs can increase the T_g of ASD to a higher value in comparison to the T_g of pure amorphous drug. The T_g of the system can be predicted using Gordon-Taylor equation (104):

$$T_{gmix} = \left[\left(w_1 T_{g1}\right) + \left(K w_2 T_{g2}\right)\right] / \left[w_1 + \left(K w_2\right)\right] \quad (8)$$

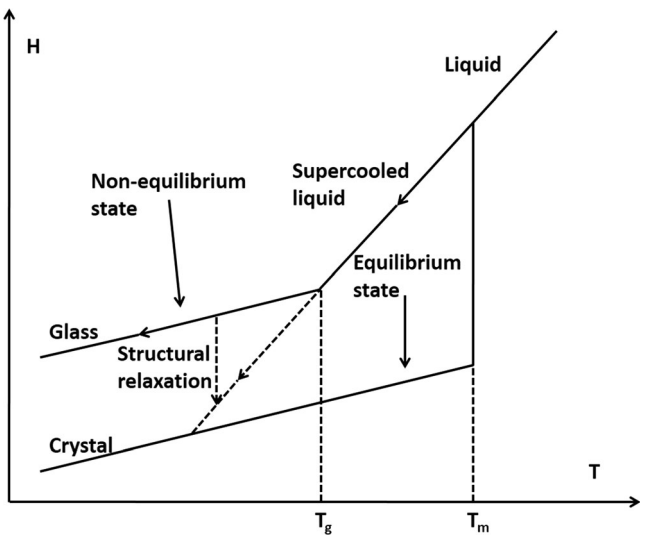


Fig. 6 Schematic depiction of the change in enthalpy (H) with temperature for a material undergoing super-cooling process (redrawn figure from the paper by Craig *et al.*) (99).

where T_{g1}, T_{g2} and T_{gmix} represent the T_g (in Kelvin temperature) of compound 1, 2 and the mixture, respectively, w_1 and w_2 represent the weight fractions of compound 1 and 2, respectively, and K represent a constant. K can be calculated by:

$$K \approx (\rho_1 T_{g1}) / (\rho_2 T_{g2}) \quad (9)$$

where ρ_1 and ρ_2 represent the true density of compound 1 and 2, respectively (104). T_g is highly associated with the molecular mobility of amorphous materials (this is discussed later in the paper), and the increased T_g value (compared with pure amorphous drug) can substantially reduce the molecular mobility of drugs in systems, resulting in a reduced recrystallization rate (105).

Molecular Mobility of Amorphous Drugs

As mentioned above, at the storage temperature lower than T_g, structural relaxation occurs in amorphous materials in the form of releasing extra enthalpy and configurational entropy. The time consumed by structural relaxation is defined as relaxation time. Molecular mobility is reciprocal to the relaxation time. The relaxation time, τ, can be calculated using the Adam-Gibbs model:

$$\tau = \tau_0 exp(C/(TS_c)) \quad (10)$$

where τ_0 is a constant, C is a material dependent constant, T is the absolute temperature, and S_c is the configurational entropy (106). Equation (10) can be rewritten into Adam-Gibbs-Vogel equation:

$$\tau = \tau_0 exp(D\,T_0/(T\,(1-T_0/T_f))) \quad (11)$$

where D is the strength parameter, T_0 is the temperature at which molecular mobility is zero, and T_f is the fictive temperature that can usually be replaced by the T_g value of the material as reported in literature (101,107,108).

Molecular mobility is linked with the recrystallization rate of amorphous materials, and hence it can affect the kinetics of phase separation and recrystallization of ASDs. Basically, there are two types of relaxations for amorphous materials, i.e. β- relaxation (local molecular mobility) and α-relaxation (global molecular mobility), which are defined at temperatures lower and higher than the T_g of the amorphous material, respectively (19). At the temperature below T_g, β-relaxation, characterized by the spinning of atoms in single molecule, is the major relaxation for small molecules. For polymeric molecules, β-relaxation refers to the vibration of polymer side chains (109,110). At the temperature above T_g, α-relaxation, characterized by the mobilization of intact molecule, is the dominant relaxation for both amorphous small molecules and polymers (β-relaxation still take place at this temperature) (109,110). It has been reported that α-relaxation and β-relaxation both contributed to the relaxation enthalpy of amorphous indomethacin that stored at room temperature for a certain time period (18,19). In addition, relaxations of drug and polymer in ASDs both make contributions to the physical instability of ASDs on aging (18,19,111–113). Amongst these studies, a profound research by Hancock first suggested a "T_g-50 K" rule for storing ASDs, which was achieved via the calculation of molecular mobility (18). In this study, molecular mobility of amorphous drug (indomethacin), polymer (PVP) and amorphous sugar (sucrose) were studied at different storage temperatures (18). It was found that no molecular mobility was detected for each material at the temperature 50 K lower than the individual T_g of each material, and excellent physical stability of amorphous materials was presented by all materials for over a period of years. Such results led to the classic theory that the storage temperature for ASDs should be at least 50 K lower than the T_g of the ASD to minimize molecular mobility of drug moleculesand to enhance the physical stability (18,34). Although the recommended "rule" of "T_g-50 K" is not universal for the storage of ASDs, it indeed demonstrates the correlation between the molecular mobility and the recrystallization rate of amorphous materials. This finding enlightens the formulation development of ASDs that the reduction of molecular mobility can substantially enhance the physical stability of ASDs (114).

Physical Stability of Amorphous Drugs

Several studies have reported that the physical stability of amorphous drugs alone also could affect the physical stability of ASDs (73,93,115). For instance, in a study regarding the "glass forming ability" of marketed amorphous drugs, instead of using experimental method i.e. DSC, the researchers applied *in silico* method to classify the marketed amorphous drugs into different categories based on the chemical space (115). The authors finally suggested that when developing ASD formulations, Class I drugs that had a high recrystallization tendency should be avoided to decrease the formulation risk (115). Similarly, Ng *et al.* prepared several drug-polymer ASDs containing different drugs including carbamazepine, felodipine, celecoxib and fenofibrate by spin coating method (93). It was confirmed that the more physically stable the amorphous drugs alone, the more physically stable the corresponding ASDs (93). In another paper, carbamazepine, felodipine, celecoxib and fenofibrate were formulated with Eudragit® EPO using hot melt extrusion (73). Amorphous drugs alone with higher physical stability also showed better physical stability of ASDs composed of these drugs (73). In the above two studies, typical preparation processes for solid dispersions including solvent evaporation (spin coating) and melting (hot melt extrusion) approaches were both employed. These results indicate that the physical stability of amorphous

drugs alone is consistent with the physical stability of ASDs and is independent of preparation processes.

Although the mechanism of such consistency has not been completely understood, it is likely that kinetic stability of ASDs are dependent on or strongly influenced by the kinetic stability of amorphous drugs alone. Compared with physically stable amorphous drugs, physically instable amorphous drugs intrinsically has a higher recrystallization rate which could only be reduced to a limited level even after being formulated with polymeric carriers. Whereas physically stable amorphous drugs in nature has a slow recrystallization rate that can be further slowed down when being formulated with polymers, leading to higher physical stability of ASDs. The mechanism of the physical stability of amorphous drugs alone, however, has not been fully disclosed, and it may be linked with various properties such as molecular weight, glass forming ability and recrystallization temperature of amorphous drugs as reported in the literature (116–118).

Manufacturing Process

As reported in literature, ASDs of the same components but prepared by different processes can present different physical stability (119–121). For example, in the paper by Yang *et al.*, felodipine-Eudragit® E PO solid dispersion systems were prepared by hot melt extrusion and spin coating, respectively (98). The spin coated ASDs with drug loadings up to 90% (*w*/w) only showed low level surface recrystallization after 12 months aging under 75% RH at room temperature. In contrast, hot melt extruded ASDs with 50% and 70% drug loading (aged under the same condition) showed high level surface recrystallization after 6 months as confirmed by SEM and AFM studies (98). Similarly, in the study by Weuts *et al.*, etravirine was prepared into ASDs with HPMC by both film casting and spray drying methods, and the spray dried samples showed higher physical stability than the corresponding film casted samples (119).

Such phenomenon has occurred in other studies, the underpinning mechanism, however, has not been disclosed yet (120,122). It is likely that different preparation processes may generate different super-saturation levels for ASDs. Therefore, kinetically, ASDs with low super-saturation level would exhibit better physical stability (123). This was reported in the study, where super-saturation levels of ASDs prepared by hot melt extrusion were assessed using milling method (Fig. 7) (123). The mechanism of this approach was based on the theory that milling can accelerate phase separation of super-saturated ASDs. In the paper, super-saturated ASDs were prepared by hot melt extrusion, and the extrudates were milled using ball milling for 5 min. It was found that 70% (*w*/w) extrudates without milling only showed low level phase separation and crystallization, and even after being aged under 75% RH at room temperature for 10 months, the crystallinity of the sample was still under 2.5% (w/w) (estimated using MTDSC). On the contrary, freshly prepared and milled 70% (w/w) extrudates showed high level phase separation and recrystallization, approximately 25% (w/w). In addition, 50% (w/w) milled extrudates also showed phase separation and recrystallization (the crystallinity was circa 5% w/w) after being aged under the same condition for 2 months. By subtracting the amount of recrystallized drug in 50% and 70% (w/w) milled extrudates, the remained drugs in both systems were the physically stable drugs. Surprisingly, the amount of the thermodynamically stable drugs in both systems (50% and 70% w/w) were close, circa 45% (w/w), and this value was higher than the predicted solubility values using three theoretical models (123). Furthermore, crystallinity in both milled systems did not increase on further aging under 75% RH at room temperature up to 6 months. These results indicate that manufacturing process may be capable to reduce

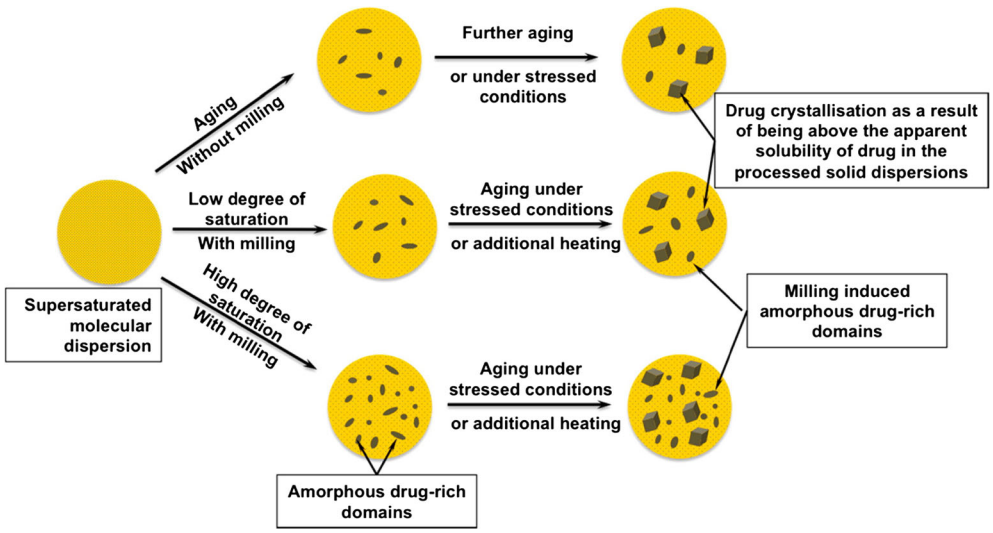


Fig. 7 Illustration of the measurement of process related solid solubility in hot melt extrudates using milling method (123).

super-saturation levels for ASDs, which might create an "apparent" drug-polymer solubility that is higher than the thermodynamic solubility. Therefore, this increased "apparent" drug-polymer solubility can guarantee the physical state of ASDs for a certain time length. Results from this research are also useful for the formulation scientists while developing ASD medicines: when the formulation show poor physical stability, it could be potentially helpful to move to another processing technique.

Interactions Between Drug and Polymer

Drug-polymer interaction in ASDs has been suggested as one of the key factors contributing to the physical stability of ASDs (69,124). The mechanism of the physical stability enhancement via drug-polymer interaction is mainly attributed to two reasons. Firstly, the drug-polymer interactions, such as hydrogen bonding and acid-base interaction, can reduce the molecular mobility of drugs in ASDs, leading to an enhanced physical stability of ASDs (8,101,125). Secondly, the drug-polymer interactions have been reported to be associated with the drug-polymer miscibility and the drug solubility in polymer (65). In this review, we consider the drug-polymer interaction as the kinetic factor due to the reason that the restriction on molecular mobility via drug-polymer interactions may be the dominant mechanism for the enhanced physical stability (126).

One of the common drug-polymer interactions is hydrogen bonding that is likely to be formed amongst the amine groups (proton donors), carbonyl groups (proton acceptors), and hydroxyl groups (proton donors and accepters). Drugs and polymers containing the above groups tend to form hydrogen bonding in ASDs, which can be characterized using solid state NMR and FT-IR (22,127,128).

Acid-base interaction is another drug-polymer interaction which is also responsible for the enhanced physical stability of ADSs in some case studies (129,130). Similar to the mechanism of hydrogen bonding, acid-base interaction can slow down the phase separation and recrystallization rate by reducing the molecular mobility. However, this interaction may not be generalized when developing ASD formulations, since the acid-base interaction is dependent on the chemical properties of drugs and polymers.

Despite of the effect on reducing molecular mobility, hydrogen bonding may not always be favorable for kinetic stability when using hydrophilic carriers i.e. PVP or PVPVA64 in ASDs (93,131,132). Aged upon exposure to high humidity, ASDs prepared with hydrophilic polymers are likely to absorb moisture (93,133). As illustrated in Fig. 8, the hydrogen bonding between drug and polymer can be disrupted by the moisture absorption since water molecules can act as both strong hydrogen bonding donor and acceptor (93). Consequently, in these systems, phase separation followed by recrystallization is prone to occur. For instance, Qi *et al.* found that phase separation was detected in felodipine-PVP ASDs within 24 h aged under high humidity (23). Therefore, the formulation strategy of using hydrogen bonding acceptor

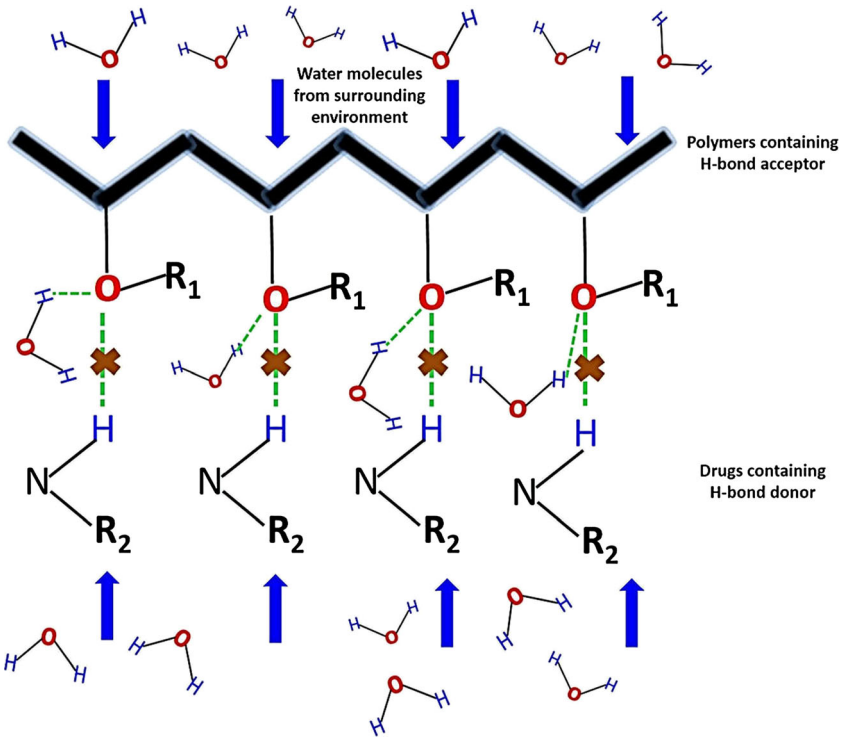


Fig. 8 Illustrated mechanism of hydrogen bonding disruption in ASDs by absorbed water molecules.

polymers should be applied carefully, and short time physical stability study under stressed humidity is highly recommended for formulation screening.

ENVIRONMENTAL EFFECTS ON THE PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS

Unlike thermodynamic and kinetic aspects that can directly affect the physical stability of ASDs, environmental aspect is indirect influence that could only affect the physical stability of ASDs via affecting the thermodynamic and kinetic factors. Seeing ASDs as systems stored in the normal environment, accordingly the environmental factors are composed of temperature and humidity (134–136).

As discussed above, molecular mobility of amorphous materials is associated with temperature in an exponential relationship (18). According to the relationship of Eq. (10) and Eq. (11), the increase of temperature may cause orders of magnitude increase of molecular mobility, leading to a substantially accelerated rate of phase separation and recrystallization of ASDs. Humidity can influence the physical stability through the absorbed water molecules in ASDs. The physical stability can therefore be reduced by moisture uptake through the plasticizing effect and potential of destroying drug-polymer hydrogen bonding, offered by the water molecules (137–139). Recently in a research, a novel mechanism of water induced physical instability of ASD was introduced, and in the research, poloxamer 188 was applied as the polymeric carrier in the ASD (16). It was found that physical instability of the ASD was attributed to the drug recrystallization process within absorbed water. Poloxamer 188 was highly hygroscopic and hence a high level water absorption in the system was established to the extent that drugs were found to be dissolved in the absorbed water. Therefore, on aging the ASD started losing water progressively, leading to the recrystallization of the dissolved drugs.

Despite the fact that both factors can affect the physical stability of ASDs, the dominant environment factor, however, has not been revealed yet. The selection of the main physical stability related environmental factor is vitally important, because this would determine the storage condition for ASDs. A report by Tian *et al.* studied the effect of temperature and humidity on the physical stability of hot melt extruded cinnarizine and Soluplus® (72). Samples were stored at 40°C and 60°C under dry condition, and at 25°C under the humidity of 75% RH and 94% RH, respectively. It was found that humidity and temperature showed similar effect on the physical stability of cinnarizine-Soluplus® system with 20% (*w*/w) drug loading, but with increased drug loading, samples stored under high humidity presented poorer physical stability. In another study regarding the effect of temperature and humidity, the authors used four model drugs including felodipine, carbamazepine, celecoxib and fenofibrate, to formulate with Eudragit® E PO using hot melt extrusion (73). Melt extrudates were stored under controlled temperature and humidity, and it was found that samples aged under high humidity (75% RH, 25°C) showed higher level crystallization than samples aged at high temperature (0% RH, 40°C). These results can be applied to the ASDs of all four model drugs with both low (10% w/w) and high (70% w/w) drug loadings (73).

From the results of the two reported studies, it may be unacceptable to make the conclusion that humidity has more significant influence on the physical stability of ASDs than temperature. This is because the effect of temperatures was not completely eliminated in both studies. At room temperature (25°C), the contribution from molecular mobility of drugs to the physical instability in ASDs cannot be neglected. These studies, however, still provide useful information that moisture proof should be significantly taken into consideration when developing formulations of ASDs.

In the study regarding the physical stability of ASDs, a polymer blend ASD system was developed to enhance the physical stability of ASDs against stressed humidity (140). The authors took advantage of immiscible polymer blend system to purposely design a phase separated solid dispersion. The hypothesis was that when hydrophobic acid-soluble polymer (i.e. Eudragit® E PO), hydrophilic polymer (i.e. PVP-VA64) and drugs were extruded together, phase separation would occur due to the two types of polymers being immiscible (140). Moreover, asymmetry drug distribution in the system could be generated. This was because hydrophilic polymers that can form hydrogen bonding with the drugs were able to dissolve more drug molecules than the hydrophobic polymers. Therefore, after co-extrusion of the polymer blend and the drug, a phase separated solid dispersion was formed, having a microstructure similar to "emulsion". In the solid state "emulsion", hydrophobic polymers containing small amount of drugs could be the continuous phase (outer phase) and the hydrophilic polymers containing large amount of drugs could be the separated phase. Via the "emulsion" structure, such polymer blend system could effectively block the moisture penetration into the solid dispersions as the outer or continuous phase was completely hydrophobic (the design is illustrated in Fig. 9). Therefore the physical stability of the solid dispersions could be enhanced. Unlike the conventional formulation strategy of using homogeneous solid dispersions, this study provides an insightful formulation strategy of using immiscible for ASDs to improve the physical stability. It is highly likely that, by optimising the ratio of hydrophobic polymers and hydrophilic polymers, the solid "emulsion" ASDs as illustrated in Fig. 9 could be achieved (140).

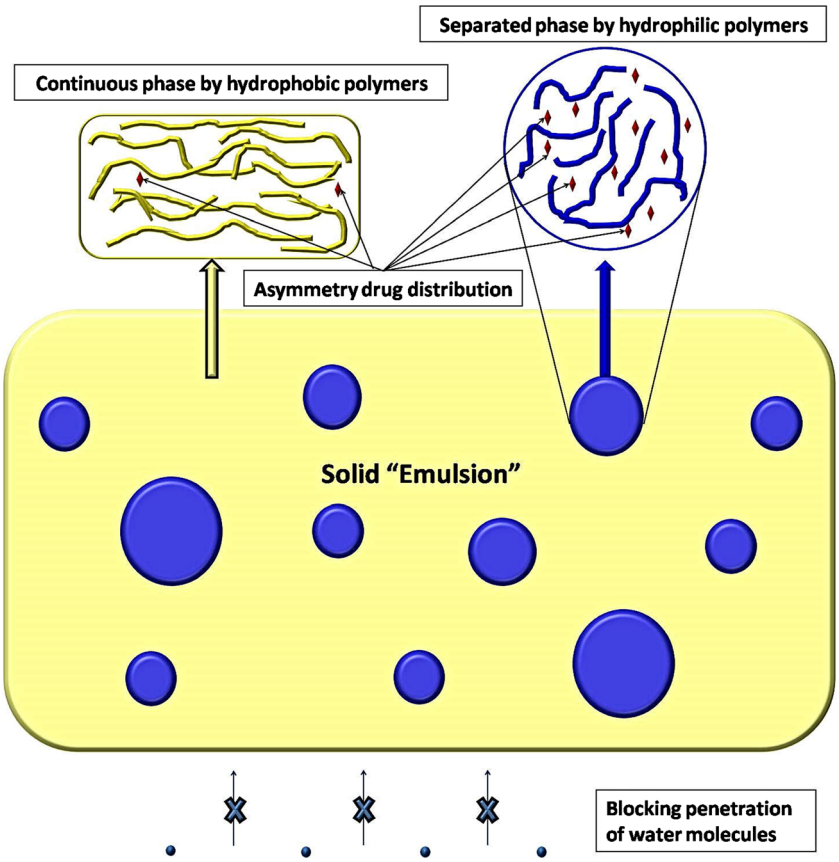


Fig. 9 Mechanism of the improved physical stability against stressed humidity by polymer blend solid dispersions (modified figure from the paper by Qi *et al.*) (140).

CONCLUSION

In this review, the physical stability of ASDs are discussed and summarized from a physicochemical perspective and factors that can affect the physical stability are accordingly divided into thermodynamic, kinetic and environmental aspects. The formulation development of ASDs, therefore, may be conducted by following such perspective. For instance, given a specific drug, one may try to screen the polymeric carriers that have the highest drug solubility using theoretical models. Subsequently, the formulation scientists may further use different preparation process to formulate the drug into ASDs and compare the physical stability of different formulations. If possible, the influence of manufacturing process on the supersaturation levels of ASDs should be assessed to approximate the maximum drug loading that can be used. Meanwhile, the physical stability of the amorphous drug alone and other physical characterisation of the amorphous drug should be investigated to predict the kinetics of the physical stability of ASDs. If given a group of drugs to be developed into ASDs, the comparison of physical stability of amorphous drugs alone is recommended to be carried out to estimate the physical stability of ASDs composed of these drugs, and hence screening the suitable drug candidates. Finally, when designing the packing, moisture proof materials should be applied to avoid the moisture uptake by ASDs.

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