Amorphous Solid Dispersions: Analytical Challenges and Opportunities

*By Paul Harmon, Li Li, Patrick Marsac, Craig McKelvey, Narayan Variankaval, Wei Xu**

Single-phase amorphous solid dispersion formulations provide the potential for enhancing the bioavailability of water-insoluble compounds. This approach has been discussed for several decades, and has been the basis of several reviews articles and a large body of research[1, 2, 3, 4].

Amorphous solid dispersions have the potential to increase dissolution rates to promote higher effective drug solubility. However, solid dispersions of drugs are generally higher energy states than their crystalline counterparts, and while these higher energy states promote drug solubilization they also create a potential for physical instability.

This article focuses on amorphous formulation development, providing an overview of the current knowledge of the bioavailability enhancement mechanisms from solid dispersions, along with a description of analytical techniques and challenges associated with carrying out predictive in vitro dissolution experiments. This article also discusses practical analytical approaches to evaluate the physical stability risk associated with solid dispersions within the typical time frame for drug development.

Analytical techniques can lay the groundwork for understanding amorphous material property-bioperformance relationships with the goal of optimal amorphous formulation design. And analytical solutions can help mitigate the risk of solid-state transformations taking place during the shelf life of the material. Although there is no way to ensure this, certain fundamental properties of amorphous systems can be used to limit risk.

*All authors are employed at Pharmaceutical Research and Development, Merck and Co., Inc.

Bioavailability Enhancement in Dispersions

Amorphous solid formulations are formed by making single phase dispersions of poorly soluble drug molecules (typically 10–40 percent by weight) and preferably amorphous water soluble polymers, such as modified cellulosic, polymethacrylate, and/or vinyl pyrrolidone based polymers (ex,, HPMC-AS,[5] Eudragit polymers, and PVP-PVAc[6]). Upon contact with GI milieu, the water soluble polymer begins to dissolve bringing low solubiliFty drug molecules into solution. However, drug concentrations may be well beyond solubility limits, and nanoparticulate formation may also occur.

The impact of increased solubility and surface area on bioavailability has been illustrated by Amidon et al in their mathematical treatment of drug absorption from simple suspensions.[7] These authors derive an expression (see Equation 1) for a dissolution number, reflective of the relative dissolution rate based on an expression for simple diffusion.[8]

Equation 1

Dissolution rate ~ (SA)(D/h) [C_{sol}-C(t)]

In equation 1, SA is the surface area of the particle, D is the diffusion coefficient and h is the diffusion layer thickness, and the bracketed term is the concentration gradient driving the dissolution defined by the difference between the drug solubility limit, Csol, in the GI medium and the dissolved drug concentration in the lumen at any time, C(t).

These authors further derived an expression for fraction of drug absorbed (F) which highlights that F will be maximized when dissolution rates are fast. This simple concept provides a basis for understanding potential advantages of amorphous solid dispersions.

In the context of dissolution rate (e.g., Equation 1), solid dispersions can act by increasing the apparent solubility and/or increasing surface area (e.g., via in situ nanoparticle formation). C^{sol} is often simply the apparent solubility of the amorphous drug in the medium, which can be several to hundredfold higher than the solubility of the crystalline drug.[9]

Solid dispersions can thus increase effective permeation rates (and maximum absorbable dose) by increasing the absolute drug concentration in solution compared to crystalline materials. In contrast, conventional approaches to increase surface area via milling and/or wetting agents can only improve dissolution rate.

Nanoparticulates formed during initial dissolution of solid dispersions

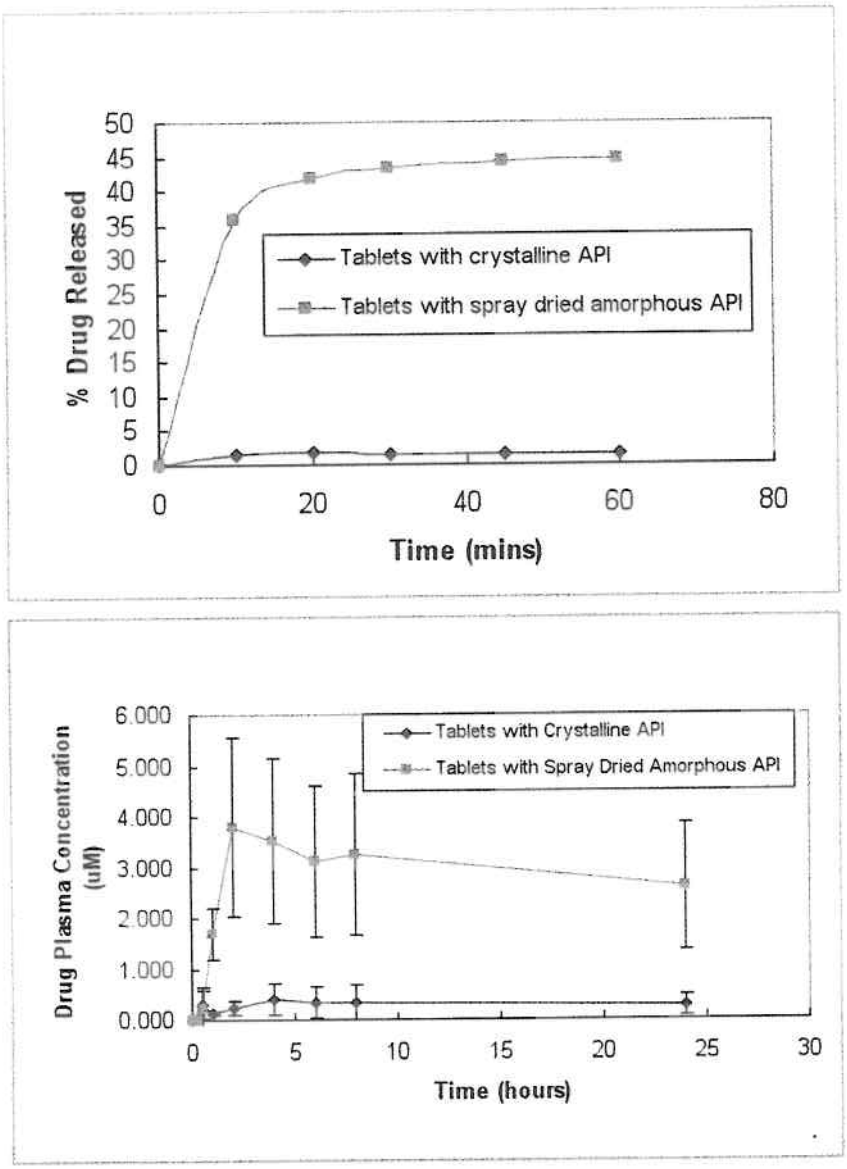


Figure 1. In vitro dissolution data (top) using Fassif as dissolution media and 1 µm filtration and animal model exposure data (bottom). (Dog study (N=3, 10mpk))

could be amorphous or crystalline, range in size from ~20–500 nm, and have varying degrees of polydispersity in both size and composition (drug only, drug-surfactant, drug-polymer aggregates, etc.).[10, 11] In all these cases, the total surface area of the drug particles can be much greater than the equivalent micronized crystalline active pharmaceutical ingredient (API) in conventional solid dosage forms. The nature of various drug species formed during in vitro dissolution of amorphous dispersions can be illustrated with a particle size continuum concept, and a detailed account can be found in Curatolo's publication.[11]

Table 1. Possible Analytical Procedures to Answer Questions

	Questions	Analytical methods
1.	Percentage of dose existing as particles <1 µm?	1 µm filtration/HPLC assay
2.	Percentage of dose dissolved molecularly?	HPLC assay or NMR on supernatant after ultracentrifugation at 80–100Krpm (~60,000g) for 15 minutes
3.	Is there a significant percentage of the dose in nanoparticulates?	Compare result 2 and result 1
4.	PSD of nanoparticulates?	Dynamic light scattering on undiluted samples post 1 µm filtration
5.	Crystallinity of nanoparticulates?	XRPD on collected solids after 1 µm filtration and ~60,000 g ultracentrifuge
6.	Composition of nanoparticulates? (do nanoparticulates involve polymer or surfactant?)	NMR technique to probe potential drug-polymer (or surfactant) interaction
7.	Dissolution rates of nanoparticulates?	Modeling and simulation of particle size impact on dissolution rate

Note: Typically data for questions 1 and 2 are obtained at several time points during three-hour dissolution in Fassif. Need for measurements 4–7 can be determined case by case.

Analytical Challenges

In vitro dissolution studies commonly used for conventional solid dosage formulation can often predict that solid dispersions will give better exposure than formulations containing crystalline API in an animal or human. Figure 1 shows a representative case of in vitro dissolution data.

The GI medium was modeled by fasted simulated intestinal fluid (Fassif). The target concentration (mg/ml) used is the anticipated dose (mg) divided by the GI volume (taken as 250–500 ml). Samples are taken over 0–3 hrs and filtered through a 1 µm filter (particle size of crystalline API was 15 µm) then assayed for drug content.

Minimum crystalline API was released into Fassif over 3 hours (see Figure 1, top), resulting in the C(t=3 hrs) value that is only around 2 percent of the target drug concentration. The amorphous dispersion dissolution data, in contrast, shows that 60 percent of the target dose passes through the 1 µm filter, and the resulting animal exposure is about tenfold greater (see Figure 1, bottom).

Ideally, biorelavent dissolution approaches could enable discrimination between different amorphous dispersions (utilizing different polymer systems, surfactants, drug loading levels, etc). To rank order the formulation performance requires a detailed understanding of what exactly is the nature of the drug passing through the 1 um filter; what fraction of the drug in the filtrate is actually molecularly dissolved; how much of the drug assayed is in the forms of nanoparticulates; whether the nanoparticulates are crystalline or amorphous; what their composition and size distribution is; and what the relative dissolution rates of the <1 µm particulate populations are.

These questions reveal the current analytical challenges associated with comparative in vitro dissolution testing of amorphous dispersions. Balancing resource expenditures, developmental timelines, and the depth of understanding required is a daunting task. Table 1 gives a brief overview of potential procedures and analytical solutions to some of these problems.

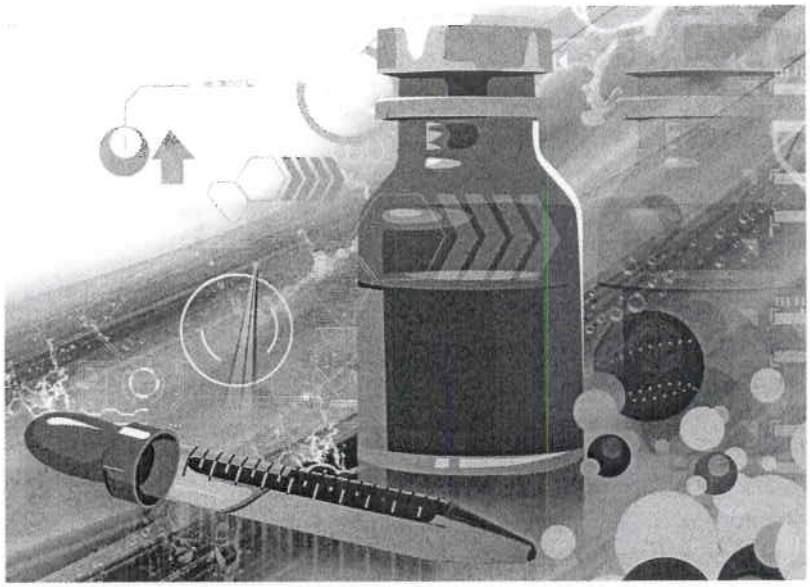
Physical Stability Risk Evaluation

Amorphous systems carry the liability of potential crystallization. As discussed above, substantial recrystallization of an amorphous dispersion could result in significant decreases in exposure of the drug in vivo.

For a marketed pharmaceutical product this would be a catastrophic quality failure. Equation 2 shows that the rate of nucleation, I, can be expressed in terms of the thermodynamic driving force for the formation of a critical size nucleus, ΔG^*, and the activation energy for crystallization, ΔG_a.[12]

Equation 2

$$I = A\exp\frac{-(\Delta G^{*} + \Delta G_{a})}{kT}$$



Pure amorphous drugs can crystallize over time assuming the compound has enough mobility to nucleate and grow. Although amorphous dispersions are nonequilibrium systems, it may be useful to visualize these within the framework of thermodynamic equilibria. (See Figure 2.)

Specifically, the addition of a miscible polymer may reduce the thermodynamic driving force for crystallization and increase the kinetic barrier to crystallization. If the chemical potential of the drug in the dispersion is higher than the crystalline drug, a thermodynamic driving force for crystallization will exist, in which case the only barrier to nucleation and crystal growth is the activation energy. SD1 and SD2 represent dispersions in which drug is present in the supersaturated state and below the solubility limit (of crystalline drug) in the polymer, respectively. SD solubility limit represents a dispersion in which the polymer is saturated with respect to the crystalline drug.

The need to develop a more complete understanding of nucleation and crystal growth drives continued research in the area of amorphous dispersions. Confidence around developing solid dispersions currently seems to rely on semi-empirical descriptors of physical stability.

These descriptors include the molecular mobility of the drug in the polymer matrix, the potential for specific interactions between the drug and the polymer (strength and extent of hetero interactions as compared to interactions between like species), molecular weight, hygroscopicity, glass transition temperature (Tg), nonisothermal crystallization temperature, rate of nucleation under isothermal conditions at elevated temperature, configurational entropy, and the thermodynamic driving force for crystallization among others.[13-16] Many of these descriptors are easily accessible while others require significant resource investment which is often not justified in today's fast paced drug development environment.

In this communication, several practical indicators of physical stability have been identified and are outlined in Table 2. Note: Table 2 is not comprehensive and does not replace real-time stability measurements. Instead, it is meant to provide the novice with a point of reference.

The sensitivity of crystallization during heating may provide some guidance as to the risk of crystallization over lengthy periods of time at

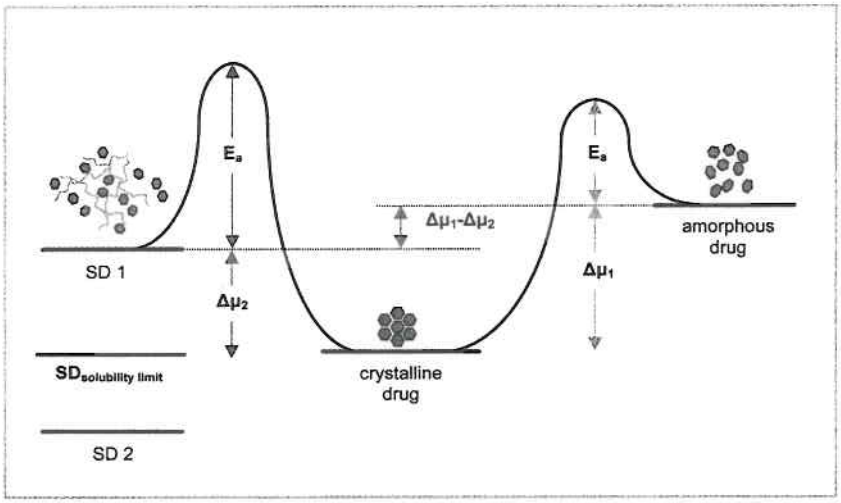


Figure 2. Schematic hypothetical energy cartoon showing the amorphous drug, crystalline drug, and several single phase amorphous solid dispersions (μ represents the chemical potential of the drug and E_a represents the activation energy barrier for crystallization).

moderate temperatures. It is best to assess this sensitivity using orthogonal techniques, such as DSC, and variable temperature techniques, such as XRPD, ssNMR, and optical microscopy among others. Under controlled experimental conditions, the increase in nonisothermal crystallization temperature may give some indication of the ability of miscible polymers to stabilize the drug.

Consider both the thermodynamic and kinetic components of crystallization (see Figure 2) in terms of the glass transition temperature and the melting temperature. The ratio of the melting temperature to the Tg serves as an indicator of glass-forming ability[17, 18] and has been linked to physical stability of drugs in solid dispersions.[10]

Specifically, the melting temperature reflects the strength of the crystal lattice and is an indicator of the driving force for crystallization. Generally speaking, materials with high melting temperatures may have a higher risk for crystallization. The Tg can be thought of as a descriptor for mobility.

Materials with lower Tg may have more mobility at room temperature and therefore may represent a higher risk for crystallization. The higher this ratio the greater is the risk of crystallization.

Again, the polymer may act to alter both the thermodynamics and kinetics of crystallization (see Figure 2). If the drug and the polymer are miscible, the melting temperature of the drug may be reduced in the presence of the polymer and the glass transition temperature may be increased in the presence of a polymer. The ratio of Tm/Tg is reduced and therefore risk of crystallization is expected to be reduced.

The Tg of solid dispersions (in the absence of water) can be measured or predicted with little effort. Generally, only moderate changes in the Tg occur when small amounts of polymer are added to amorphous drugs and mixed on a molecular level to produce a single-phase dispersion (spray drying or hot-melt extruded for instance).[19]

However, it has been demonstrated that the addition of a small amount of polymer can drastically decrease the rate of nucleation as measured by optical microscopy.[20] It is reasonable to conclude that although the Tg is a very important descriptor of physical stability, it alone cannot describe the complicated dynamics of crystallization from amorphous solid dispersions, explaining the driver for much of the research around sub-Tg modes of molecular mobility.

Finally, hygroscopicity represents one of the most important properties of amorphous dispersions. In general, when amorphous dispersions show significant crystallization at a given water activity, water can be expelled from the dispersion and the weight of the sample then decreases during a typical dynamic moisture sorption experiment.

In such a case, the observed "smooth" asymptotic approach to the equilibrium water content at each water activity is replaced by a "choppy" weight gain profile and/or a reduction in weight with time. Although not as routine, several authors including Buckton[21] have described the use of the much more sensitive controlled RH calorimetry to monitor crystallization during exposure to moisture.

Increased water content leads to a decrease in the Tg. The Tg is easily measured as a function of water uptake for solid dispersions using hermetically sealed pans. Often a 10° C depression in Tg is observed for every 1 wt percent water uptake. Generally,

Table 2. Indicators of Physical Stability Risk/Associated Risk Assessment

Indicator (technique used to assess)	Risk Level
temperature at which nonisothermal crystallization is observed in the solid dispersion* (differential scanning calorimetry, variable temperature techniques such as XRPD, ssNMR, and/or microscopy)	Best case is when no crystallization is observed over reasonable timescales. In general, higher crystallization temperature suggests lower risk.
relative humidity where crystallization occurs over "short timescale" for the solid dispersion (dynamic vapor sorption, variable RH calorimetry, variable RH techniques such as XRPD)	Best case is when no crystallization occurs. Careful consideration has to be given to cases where crystallization is observed at RH<50–75 percent.
Tg-10°(expected wt. percent water uptake) (differential scanning calorimetry in hermetic pans, vapor sorption)	In general, the higher the water plasticized Tg, the lower is the risk of crystallization. Physical stability concerns can become significant when the moisture corrected Tg < 30°-50°C above RT.

*This indicator is not very useful when the amorphous phase crystallizes into hydrates.

when the Tg is 30–50° C above the storage temperature, the potential for crystallization is significantly reduced.

Conclusions

Amorphous solid dispersions present significant opportunities and challenges in drug development. Unlike conventional solid dosage forms that incorporate crystalline phases, amorphous dispersion is complex systems both in terms of understanding property-performance relationships and in terms of physical stability of the amorphous drug.

In vitro dissolution experiments carefully designed for amorphous dispersions can help in understanding bioperformance and potentially shorten the time to identify a clinical formulation for an insoluble compound with adequate bioavailability. There is ample scope to design consistent biorelevant dissolution experiments so as to establish in vitro/in vivo correlations and also to enable comparisons of various formulation choices early in drug development. This remains a key challenge in pharmaceutical development.

A clinical formulation also requires robust physical stability to be launched as a product. Substantial recrystallization of the drug during the intended shelf life of the drug product may have a substantial impact on product performance by reducing bioavailability. A thorough understanding of the factors responsible for physical instability of an amorphous drug dispersed in a polymer can help in mitigating the risk of recrystallization.

At the present time, a combination of empirical descriptors and real-time stability testing are typically used to assess the physical stability risk of an amorphous dispersion formulation throughout the development cycle. Pharmaceutical scientists may often face the challenge at the early stage of the development program to make a decision on an amorphous dispersion formulation that has some physical stability risk at accelerated conditions but little real time data under realistic packaging conditions. The key challenge in the near future lies in being able to quantitatively characterize the risk of physical instability of an amorphous dispersion using limited experimentation and time.

References

1. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersion. *Eur J Pharm Biopharm Sci.* 2000;50(1):47–60
2. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci.* 1999;88(10):1058–1066.
3. Chiou WL, Riegelman S. Pharmaceutical Applications of Solid Dispersion Systems. *J Pharm Sci.* 1971;60(9):1281-1302.
4. Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Adv Drug Delivery Rev.* 2001;48(1):27–42.
5. Miyajima M, Yamaguchi Y, Tsunematsu T, Oda T. US patent 4983593, 1991.
6. Goertz HH, Klimesch RG, Laemmerhirt K, Lang S, Sanner A, Spengler R. US Patent 4801460, 1989.
7. Oh DM, Curl RL, Amidon GL. Estimating the fraction of dose absorbed from suspensions of poorly soluble compounds in humans: A mathematical model. *Pharm Res.* 1993;10(2):264–270.
8. Noyes AA, Whitney WR. The rate of dissolution of solid substances in their own solutions. *J Am Chem Soc.* 1897;19:930–934.
9. Yalkowsky, S. Solubility and solubilization in aqueous media. New York, NY: Oxford University Press; 1999;92–95
10. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. *Mol Pharmaceutics.* 2008;5(6):1003–1019.
11. Curatolo W, Nightingale JA, Herbig SM. Utility of hydroxylpropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. *Pharm Res.* 2009;26(6):1419–1431.
12. Mullin JW. Crystallization. 4th ed.,Oxford: Reed Educational and Professional Publishing Ltd; 2001.
13. Adam G, Gibbs JH. On temperature dependence of cooperative relaxation properties in glass-forming liquids. *J Chem Phy.*1965;43(1):139–146.
14. Ediger MD. Supercooled liquids and glasses. *J Phy Chem.* 1996;100(31):13200–13212.
15. Hancock BC, Shamblin SL. Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry. *Thermochimica Acta.* 2001;380(2):95–107.
16. Andronis V, Yoshioka M, Zografi G. Effects of sorbed water on the crystallization of indomethacin from the amorphous state. *J Pharm Sci.* 1997;86(3):346–351.
17. Turnbull D. On the relation between crystallization rate and liquid structure, *J Phys Chem.* 1962;66(4):609–613.
18. Turnbull D, Cohen MH, Modern aspects of the vitreous state, Ed. Butterworths, London: J. D. Mackenzie, 1960;38–62.
19. Gordon M, Taylor JS. Ideal co-polymers and the second-order transitions of synthetic rubbers. *J Appl Chem.* 1952;2:493–500
20. Marsac PJ, Konno H, Taylor LS. A comparison of the physical stability of amorphous felodipine and nifedipine systems. *Pharm Res.* 2006;23(10):2306–2316.
21. Buckton G, Darcy P, Mackellar A, The use of isothermal microcarlorimetry in the study of small degrees of amorphous content of powders. *Int J Pharm.* 1995; 117(2):253–256.