Review

Physical stability of pharmaceutical formulations: solid-state characterization of amorphous dispersions

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A B S T R A C T

The acceptable stability of the drug formulations is one of the basic requirements for pharmaceutical development and commercialization. The increasing application of enabling delivery techniques poses even more challenge to the drug physical stability of pharmaceutical formulations. After a brief review of regulatory requirements and recent drug recalls due to physical instability, we discuss the physical stability of the solid-state drug in amorphous dispersions with focus on analytical techniques, amorphous molecular mobility, drug-excipient interaction, and the effect of water.

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1. Introduction

Drug stability, as one of the critical quality and performance attributes, needs to be evaluated during pharmaceutical development and controlled during clinical studies and marketing. Stability studies provide evidence on how the quality of a drug substance (DS) (also called active pharmaceutical ingredient, API) or a drug product (DP) varies with time under controlled temperature and relative humidity (RH). This helps to establish the retest date (for API) or shelf life (for DP) and their storage conditions.

Physical stability, along with chemical stability and microbiological stability, has been of industrial and regulatory interest for a long time [1,2]. Proper physical stability is required for a dosage form to ensure its intended performance during the shelf-life. Organoleptic physical changes, such as discoloration, even without altering drug potency, can affect the perceived effectiveness of a drug product and consumer confidence. Table 1 summarizes the major physical attributes of common pharmaceutical dosage forms.

Current regulatory stability guidelines, although mostly focusing on the chemical stability and related degradation products, have provided some general guidance on the physical attributes of DSs and DPs (Table 2). Compared to chemical stability, physical stability changes are often less quantitative and with poor predictability. Extrapolations from accelerated stability test conditions are often unreliable in predicting physical stability under ambient condition. Fundamental understanding of physical and chemical mechanisms behind any physical changes is essential to achieve robust drug formulation development. This should be part of the Quality by Design (QbD) drug-development strategy with the systematic evaluation of the drug substance, excipients, and manufacturing processes [3]. Physical changes of some pharmaceutical dosage forms may be attributed to the solid-state physical instability of DSs. In one example, the changes of tablet thickness and hardness were related to the dehydration-hydration cycle of a drug substance hydrate during manufacture [4].

Recent analysis of the 91 FDA recalls of small-molecule drugs due to physical defect or instability during the past two years (January 2011 to January 2013) [5] indicates that the majority of them were related to solid oral dosage forms, mostly tablets and modified release formulations (Fig. 1). The failure in dissolution-rate specification has been the prominent cause. The results are not particularly surprising, considering the market share of solid oral dosage forms and the relative technical challenges of modified release formulations. For injections, nearly 80% of these recalls were due to the appearance of particulates or crystals.

The novel drug-delivery technologies, such as controlled release, lipid-based formulations, solid dispersions, and nano-based systems, often bring increasing challenges of physical stability compared to conventional oral DPs. Supersaturated and disordered drug delivery systems are increasingly important formulation approaches to improve the dissolution rate and apparent solubility of poorly water-soluble compounds [6]. Their success depends on understanding solid-state characteristics, related manufacturing processes, packaging, and storage conditions. In this review, we discuss the solid-state analytical techniques and recent progress in the study of the physical stability of amorphous solid dispersions.

2. Solid-state analytical techniques

Various analytical techniques have been used to characterize solid-state pharmaceuticals [7]. There is no single characterization technique that can gather all the necessary information on a solid DS or DP. Due to the complexity of the solid-state analysis, especially the amorphous state, most of these techniques are used together to complement each other (Table 3). A selection of these solid-state analytical techniques is discussed briefly here with a focus on their applications in amorphous pharmaceutical systems. In vitro dissolution tests of amorphous solid dispersions, which can be significantly affected by many experimental factors [8], will not be discussed in this article.

Table 1
Major physical quality attributes of common dosage forms

<table>
<thead>
<tr>
<th>Physical attributes</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>All dosage forms</td>
</tr>
<tr>
<td>Odor</td>
<td>Oral dosage forms</td>
</tr>
<tr>
<td>Palatability</td>
<td>Oral dosage forms</td>
</tr>
<tr>
<td>pH</td>
<td>Solution, suspension, emulsion, semi-solid</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Solution, suspension, emulsion, semi-solid</td>
</tr>
<tr>
<td>Loss on drying/ Water content</td>
<td>Tablet, capsule, powder, lyophilized powder</td>
</tr>
<tr>
<td>Disintegration</td>
<td>Tablet, capsule, suppository</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Tablet, capsule, powder, lyophilized powder</td>
</tr>
<tr>
<td>Hardness</td>
<td>Tablet, suppository</td>
</tr>
<tr>
<td>Mechanical peel force</td>
<td>Topical formulations (i.e. cream, ointment, gel)</td>
</tr>
<tr>
<td>Friability</td>
<td>Transdermal patch</td>
</tr>
<tr>
<td>Particle size distribution</td>
<td>Tablet</td>
</tr>
<tr>
<td>In vitro release profile</td>
<td>Suspension, emulsion, inhalation, nasal aerosol/spray, liposome and other nanocarriers</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Solution, suspension, semi-solid, cream</td>
</tr>
</tbody>
</table>

Table 2
ICH guidelines related to drug physical quality

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Physical stability criteria and requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH Q1A(R2)</td>
<td>Appearance, physical attributes and functionality test (e.g., color, phase separation, resuspendability, caking, hardness, dose delivery per actuation, pH, dissolution)</td>
</tr>
<tr>
<td>ICH Q1B</td>
<td>Drug substance: any changes in physical properties (e.g., appearance, clarity, or color of solution)</td>
</tr>
<tr>
<td>ICH Q1E</td>
<td>Drug product: any changes in physical properties (e.g., appearance, clarity or color of solution, dissolution/disintegration for dosage forms, such as capsules)</td>
</tr>
<tr>
<td>ICH Q6A</td>
<td>Physical changes expected at the accelerated condition:</td>
</tr>
<tr>
<td></td>
<td>• softening of a suppository that is designed to melt at 37°C</td>
</tr>
<tr>
<td></td>
<td>• dissolution failure of gelatin capsule or gel-coated tablet due to cross-linking</td>
</tr>
<tr>
<td></td>
<td>Phase separation of a semi-solid dosage form occurs at the accelerated condition; testing at the intermediate condition should be performed</td>
</tr>
<tr>
<td>ICH Q11</td>
<td>Drug substance: a qualitative statement about the state and the color. Any change during storage should be investigated and appropriate action taken</td>
</tr>
<tr>
<td></td>
<td>Drug product: a qualitative description of the dosage form (e.g., size, shape, and color). Any change during manufacture or storage should be investigated and appropriate action taken. The acceptance criteria should include the final, acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate</td>
</tr>
<tr>
<td>ICH Q11</td>
<td>When physical properties are important with respect to in vivo performance or drug product manufacture, these can be designated as Critical Quality Attributes (CQAs)</td>
</tr>
</tbody>
</table>
2.1. Powder X-ray diffraction analysis

Powder X-ray diffraction analysis (PXRD) is an indispensable tool for the characterization and quality control of crystalline and amorphous materials [9]. PXRD under non-ambient conditions, such as computer-controlled variable temperature (VT-PXRD) and/or humidity, are powerful tools to study the physical stability of polymorphs, especially hydrate or solvate forms. In recent years, there were increasing applications of atomic pair-wise distribution functions (PDFs) for the local structural order analysis of non-crystalline pharmaceutical materials [10]. It is especially useful to detect the subtle differences of amorphous materials prepared by different methods, which can have a significant effect on their long-term physical stability [11]. With the advance of X-ray instrumentation, we also expect to see more applications of small-angle and wide-angle X-ray scattering (SAXS and WAXS) in the nanophase and structure characterization of pharmaceutical systems [12]. In particular, use of a synchrotron-radiation source provides unique capability, such as improved sensitivity to detect a small amount of crystalline material in predominantly amorphous samples [13] and simultaneous collection of SAXS and WAXS patterns to distinguish between amorphous, liquid crystalline and crystalline structures [14].

2.2. Thermal analysis

Thermal analysis techniques are widely employed for the characterization of solid-state pharmaceuticals. The most commonly used ones include differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), whereas other methods, such as isothermal microcalorimetry and dynamic mechanical analysis are also applicable. For amorphous drug and solid dispersions, the glass-transition temperature ($T_g$), miscibility between drug and excipients, molecular mobility of the drug, and the rate and the extent of drug crystallization can be obtained using high speed DSC,

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**Table 3**

<table>
<thead>
<tr>
<th>Analytical method</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polarized light microscopy (PLM)</td>
<td>Qualitative confirmation of presence of crystals</td>
</tr>
<tr>
<td>Thermomicroscopy (Hot-stage microscopy)</td>
<td>Appearance/form change with temperature</td>
</tr>
<tr>
<td>Powder X-ray diffraction (PXRD)</td>
<td>Crystallinity quantification, miscibility, crystallization kinetics</td>
</tr>
<tr>
<td>Small-angle X-ray scattering (SAXS) with Pairwise Distribution Function (PDF) analysis</td>
<td>Nanostuctures of the order of 1–100 nm</td>
</tr>
<tr>
<td>Karl-Fischer titration</td>
<td>Water content</td>
</tr>
<tr>
<td>FT-IR (ATR, DRIFTS)</td>
<td>Molecular level interaction, quantification</td>
</tr>
<tr>
<td>FT-Raman</td>
<td>Molecular level interaction, quantification</td>
</tr>
<tr>
<td>Near-infrared (NIR)</td>
<td>Quantification, solid form, molecular level interaction</td>
</tr>
<tr>
<td>Dielectric spectroscopy (DS)</td>
<td>$T_g$, molecular mobility and crystallization kinetics</td>
</tr>
<tr>
<td>Terahertz pulsed spectroscopy (TPS)</td>
<td>Crystallinity, polymorphs, surface mapping</td>
</tr>
<tr>
<td>Scanning electron microscopy (SEM)</td>
<td>Morphology of particulates</td>
</tr>
<tr>
<td>Differential scanning calorimetry (DSC/MDSC)</td>
<td>$T_g$ and other thermal events, crystallization kinetic, structure relaxation, miscibility, quantification</td>
</tr>
<tr>
<td>Isothermal microcalorimetry (IMC)</td>
<td>Crystallization kinetics, quantification, surface energy</td>
</tr>
<tr>
<td>Thermal gravimetric analysis (TGA)</td>
<td>Mass loss at elevated temperature (i.e., dehydration)</td>
</tr>
<tr>
<td>Solid-state NMR (SSNMR)</td>
<td>Molecular structure in solid, drug-carrier interactions, quantification</td>
</tr>
<tr>
<td>Dynamic vapor-sorption analysis (DVS)</td>
<td>Physical change and water content as a function of relative humidity and temperature</td>
</tr>
<tr>
<td>Inverse gas chromatography (IGC)</td>
<td>Surface energy and molecular mobility</td>
</tr>
<tr>
<td>Dissolution test</td>
<td>Surrogate for physical/quality changes</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Recent drug recalls by the US Food and Drug Administration (FDA) for reasons of physical defect or instability.
modulated DSC (MDSC) and other emerging thermal techniques [15].

There has been an increasing trend to combine thermal analysis with other analytical techniques to obtain real-time solid-state information of materials as a function of temperature change. Techniques, such as hot-stage microscopy, variable temperature molecular spectrometry, VT-PXRD, and variable temperature solid-state nuclear magnetic resonance (VT-SSNMR) are used to study thermal stability and phase transitions of solid pharmaceuticals. Nano-TA, as a local thermal analysis technique, takes advantage of the capabilities of atomic force microscopy (AFM) in high spatial resolution imaging. It enables a surface to be visualized at nanoscale resolution while, at the same time, investigating the thermal properties of the surface by applying heat locally via the probe tip and measuring the thermomechanical response. This technique has proved to be effective at the early detection of instabilities in amorphous solid dispersions and the quantifiable identification of the relative composition of phase-separated domains based upon their glass-transition temperatures [16].

2.3. Infrared spectroscopy

Fourier transform infrared spectroscopy (FT-IR), including ATR (attenuated total reflectance) and DRIFTS (diffuse reflectance infrared Fourier transform spectrometry), is a convenient, powerful analytical tool to probe the nature and the extent of interactions between drug molecules or with excipient molecules in solid dispersions. The changes in the oscillating dipole of the molecules due to the interactions present themselves as changes in the wave-number and bandwidth of the interaction groups compared to those in the individual components. FT-IR has been used to characterize different polymorphs, including hydrates and solvates. Changes in the IR spectra, such as new bands, a shift or a widening of the existing bands and a change in their intensity, can be used to study the tendency of amorphous drugs to crystallize in molecular dispersions with polymers [17,18].

2.4. Near-infrared spectroscopy

Near-infrared spectroscopy (NIR or NIRS), as a fast analytical method with little or no sample preparation, has been widely used in identification and qualification of pharmaceutical starting materials, intermediates and finished products. As a non-destructive method, it also constitutes one of the major techniques in process analytical technology (PAT) for many pharmaceutical applications [19]. The spectra are interpreted mostly by the use of chemometric models (i.e., partial least square regression analysis), which has to be qualified by a reference analytical method using analytical reference standards [20]. NIR has been used, along with other methods (Raman spectroscopy, DSC and ATR FT-IR) to determine drug concentrations and interactions in drug-polymer dispersions [21]. NIR imaging coupled with chemometrics has also been shown to be a powerful tool for the detection of trace drug crystallinity within amorphous solid dispersions [22].

2.5. FT-Raman

FT-Raman spectroscopy has been a practical tool in pharmaceutical laboratories in view of its many advantages. The intensity of Raman spectra obtained from drug compounds is generally stronger than that generated from most excipients. This provides good sensitivity for most drug formulations. As a non-destructive technique, which requires minimal or no sample preparation, FT-Raman has been established as a valid quantitative method for crystallinity and polymorph analysis. Sinclair et al. recently studied the solid-state physical stability and recrystallization kinetics of an amorphous drug in a tablet at a low concentration [23]. The predicted crystallinity had a direct correlation with the dissolution test results. Meanwhile, the confocal micro-Raman spectroscopy system, allowing collection of spectra from a sample volume smaller than 1 μm³, has proved to be a powerful tool in pharmaceutical development [24]. In conjunction with PXRD, it has been used to probe the state of the drug and if the drug is uniformly distributed at a microscopic level in the solid dispersion [25]. Micro-Raman mapping allows the size distribution and the spatial distribution of a drug in amorphous solid dispersions, such as the existence of both molecular-level and nano dispersions [26]. It is also used to evaluate the presence of trace crystallinity in amorphous samples [27] and change in polymorphic form in tablets of low drug contents [28] before and after stability tests.

2.6. Dielectric spectroscopy

With high sensitivity and a wide, accessible frequency range of molecular solicitation, the dielectric spectroscopy (DS) and thermally stimulated current (TSC) technique allow detection of motions that have a relaxation time of $10^{-3}$–$10^9$ s over a wide temperature range (~170 to 300°C). They have been used directly to characterize the time scale of intramolecular and molecular motions both above and below the glass transition temperature ($T_g$) of amorphous phases. TSC has been applied as an orthogonal method to DSC, to detect both glass-transition and beta-relaxation events in systems with weak calorimetric $T_g$ (i.e., strong glass-formers) [29]. The dielectric techniques directly probe the molecular motion by stimulating the different electrical dipolar groups with an applied electrical field. This allows clear differentiation between localized relaxing entities involved in secondary relaxation and the larger species involved in the dynamic glass-to-liquid transition [30]. The dielectric techniques have also been used to determine the kinetics of isothermal crystallization with real-time dielectric measurements. The isothermal crystallization of the amorphous sample can be monitored in situ in the dielectric cell as time elapses, without any temperature change during the entire experiment. In this case, the diminishing dielectric response of the amorphous part is recorded as the increase in degree of sample crystallinity with time [31].

2.7. Terahertz pulsed spectroscopy

Terahertz (THz) pulsed spectroscopy (TPS) is another novel non-destructive technique, which utilizes spectral information in the far-IR region of the electromagnetic spectrum and can probe long-range crystalline lattice vibrations and low-energy torsion and hydrogen-bonding vibrations of pharmaceutical materials. In contrast to spectra in other spectroscopic techniques, THz spectra are directly related to intermolecular vibrations within the lattice structure, rather than intramolecular vibrations. As THz spectra of amorphous materials exhibit no distinct spectral features, any recrystallization in amorphous solid dispersion may be monitored and qualified. When using in situ variable temperature TPS, distinct spectral changes with increasing temperature provided important information about both relaxation and crystallization processes [32]. In addition, THz pulsed imaging (TPI) has been used as a non-destructive technique to assess the coating quality of different solid oral dosage forms [33].

2.8. Solid-state NMR

As a non-destructive and quantitative technique, solid-state NMR (SSNMR) provides detailed structural information about
solid-state pharmaceuticals based on dipolar correlation, spin diffusion, and relaxation measurements [34]. There was a good correlation between the crystallization rate of amorphous drugs and their molecular mobility measured by their enthalpy relaxation and $^1$H NMR relaxation times [35]. The observation of spin-diffusion effects with the 2D $^1$H–$^{13}$C cross-polarization heteronuclear correlation (CP-HETCOR) experiment was used to probe the association between the amorphous drug and polymer [36]. Proton-relaxation measurement using VT-SSNMR is a valuable addition to thermal analysis methods for predicting the physical stability of amorphous pharmaceuticals [37].

For drugs containing fluorine atoms in the structures, solid-state $^{19}$F-NMR has the advantage of higher sensitivity and shorter data acquisition time. Correlation time, a measure of rotational molecular mobility, can be calculated from the observed spin-lattice relaxation times. Using this method, the amorphous solid dispersion of flufenamic acid containing 20% polyvinylpyrrolidone (PVP) was shown to be more stable than that containing 20% hydroxypropylmethylcellulose (HPMC), as indicated by the difference in their molecular mobility [38].

2.9. Dynamic vapor-sorption analysis

With the advancement of fully automatic instruments, dynamic vapor sorption (DVS) analysis, especially water vapor sorption, has become a routine tool in the solid-state characterization of pharmaceutical materials. This fast, sensitive technique also has the advantage of small sample size and continuous monitoring. It is widely used to study both crystalline and amorphous solids. It provides information on amorphous content, surface property, phase transitions (i.e. crystallization, anhydrate-hydrate conversion, and deliquescence), critical RH, and other physical stability related phenomena [39]. The combination of water vapor sorption and a NIR spectroscopy probe can provide insights into the dynamics of physical changes, such as crystallization, as a function of RH [40].

2.10. Inverse gas chromatography

Inverse gas chromatography (IGC) has been used to study the surface properties of amorphous pharmaceutical systems, such as amorphous content, molecular mobility, glass transition, and crystallization [41]. It is especially useful to compare the batch-to-batch variations of amorphous solid dispersions or batches prepared by different methods. The surface structural relaxation of several model systems of drug-polymer dispersion was measured using IGC and compared to the bulk relaxation obtained by DSC method. The observation of the molecular mobility higher on the surface than in the bulk might have significant implication for understanding the physical and chemical stability of amorphous materials [42,43].

Recently, Miyanishi et al. studied the crystallization kinetics on the surface of nifedipine-PVP K-30 solid dispersion using IGC and to predict the physical stability at temperatures below the glass-transition temperature [44]. Surface crystallization was found to follow a two-dimensional mechanism for the growth of nuclei. The storage condition and the shelf life of the amorphous drug were estimated from the crystallization rates using the Avrami-Erofeev equation and the Arrhenius equation.

3. Physical stability of amorphous state

During the past two decades, the importance of amorphous state was widely accepted by the pharmaceutical community [45–47]. Crystalline DSs may be partly or totally converted to amorphous forms, either intentionally or unintentionally, during pharmaceutical manufacturing processes. The main objective for intentionally converting a poorly soluble crystalline DS to the amorphous form is to increase the dissolution rate and the apparent solubility, and potentially the bioavailability. However, this advantage may totally or partially get lost if the amorphous form converts to the stable crystalline form during manufacture, storage, or immediately after administration.

There have been significant amounts of research work on the thermodynamic and kinetic parameters (i.e. relaxation time, fragility index, enthalpy, entropy and Gibbs free energy) and their correlations with the observed physical stability of amorphous model drugs [48]. Compounds with high configurational entropy barriers and low molecular mobility are expected to show better stability [49]. In recent years, there has been significant progress in understanding the glass transition and molecular mobility in confined systems (e.g., amorphous state formed in liposomes) with the length scale of nanometers [50] and the surface molecular mobility of amorphous materials [43]. Meanwhile, some processing techniques, such as annealing [51] and surface coating [52], have been explored to increase the physical stability of amorphous drugs.

4. Physical stability of amorphous solid dispersions

Pharmaceutical dispersions are solid systems where the DS is mixed homogeneously with at least one matrix material (i.e. small-molecule excipients, polymers, or inorganic carriers) as a molecular solution, on the surface or in homogeneous amorphous particles. Solid dispersion technology represents an enabling approach to formulate poorly water-soluble drugs and also one of the biggest physical stability challenges of pharmaceutical formulations [53]. The recrystallization of amorphous DS in solid dispersions might lead to a loss in the dissolution rate and consequently reduced bioavailability. The assessment of formulation risk of an amorphous solid dispersion early in the development program can not only help in guiding development strategies but also point to critical design elements of the final dosage form [54].

The physical stability of a solid dispersion depends on the molecular level interaction between the drug and the carrier. From a formulation stand-point, the following factors should be considered to achieve optimal physical stability:

1. the intrinsic solid-state phases and stability of the DS;
2. the physicochemical properties of the carrier, which include molecular weight, crystallinity, melting point or glass-transition temperature, hydrophilicity, hygroscopicity, hydrogen-bonding capability, acid or basic functional groups for ionic interaction, and impurity;
3. the drug load (or the weight ratio of drug to carrier) in the solid dispersion. Generally more physical stability can be achieved with lower drug loading. This will minimize interactions among drug molecules themselves to prevent drug recrystallization. It should be noted that the chemical instability induced by interaction with excipients is often inversely proportional to the drug loading where the worst chemical degradation is usually associated with the lower drug loading. The balance of physical and chemical stability should be evaluated, especially for chemically labile molecules; and,
4. manufacturing methods. The solid-phase transitions (i.e. crystallization of amorphous form) during manufacturing processes can have a significant effect on the performance of the solid dispersions and subsequent dosage forms [55]. The real time monitoring by PAT (i.e. NIR, Raman) can benefit both process development and in-process control.
4.1. Drug-polymer binary solid dispersions

There are two general approaches to model the physical stability of amorphous drug-polymer solid dispersions: thermodynamic and physicochemical. The thermodynamic approach is based on free energy, entropy, and enthalpy. The physicochemical approach focuses on chemical structure and intermolecular interactions, especially hydrogen bonding, as well as free volume, molecular mobility, and many others. In practice, both approaches complement each other.

The solubility and the miscibility of a drug in a polymer matrix are directly related to the stabilization of the amorphous drug in a solid dispersion, as miscible dispersions are likely more stable towards recrystallization [56]. The miscibility of various drugs with polymers was studied by coupling solution theories with experimental data. These approximations provided insight into the physical stability of drug-polymer mixtures and the thermodynamic driving force for crystallization [57].

DSC, PXRD, and SSNMR are the main analytical techniques for evaluating drug-polymer miscibility [58]. Intermolecular interactions between drug and polymer molecules, such as ionic or hydrogen bonds, can significantly increase the miscibility and the physical stability of the amorphous solid dispersions. The propensity to form hydrogen bonds can be predicted from the chemical structure of the drug and the polymer, while the nature of the hydrogen bonds might be confirmed by FT-IR, Raman and/or SSNMR [59]. It should be noted that miscibility depends on the temperature and the presence of other components, including water, and the miscibility range should be determined with consideration of these variables.

4.2. Multi-component solid dispersion systems

From a thermodynamics standpoint, multi-component systems may provide both an enthalpy advantage through stronger intermolecular interactions (hydrogen bonds, ion-ion, and ion-dipole forces) and an entropy advantage for amorphous state stabilization. Addition of another polymer or functional excipient (i.e. surfactants, organic acids, and organic bases) can also increase the performance of the solid dispersions, such as dissolution rate and/or processability [60].

Incorporating two different polymers increased both physical stability and oral absorption of poorly water-soluble drugs with low glass-transition temperature, compared with using one polymer alone [61]. Both anti-plasticizing effects (indicated by significant increases in the glass-transition temperature) and hydrogen bonding (indicated by spectroscopic methods) between polymer and drug molecules might be responsible for increasing the physical stability of the multi-component systems [62,63]. Multi-component solid dispersions containing additional functional excipients should be designed based on the assessment of individual components and their binary solid dispersions [64]. Physicochemical parameters (solubility parameter, hydrogen bond energy, LogP, pKa, and Tg of the dispersion as a surrogate for system mobility) might be used as thermodynamic and kinetic factors to examine their influences on the miscibility and the physical stability of the amorphous systems. A system possessing acid-base interaction and higher Tg is more likely to form amorphous dispersion with better physical stability [65].

Solid dispersions are often further processed to conventional dosage forms (i.e. tablets) where hardness, disintegration time and dissolution rate are important physical stability attributes. The drug/carrier ratio of the solid dispersion, excipients, and manufacturing processes can be optimized to produce the tablets that possess these properties and can also withstand storage conditions for stability [66].

4.3. Surface solid dispersion

There has been increasing interest in the solid complexes of drugs with porous inorganic materials in the past decade. Their high-energy surface and polar function groups can interact with drug molecules through ionic or hydrogen bonding to stabilize the amorphous drug molecules in the pores and on the surface. Acid-base interaction and/or hydrogen bonding were responsible for the amorphization and physical stability when Neusilin, an amorphous synthetic magnesium aluminometasilicate, and a crystalline acidic drug containing the carboxyl moiety were milled together [67]. The similar acid-base interaction and stabilization effect have also been reported with other basic inorganic carriers [68].

4.4. Effect of process attributes

The stability and the performance of amorphous DDSs depend on not only the formulation components, but also the manufacturing methods and process parameters [42]. Preparation of amorphous solid dispersions for poorly water-soluble compounds remains a challenge, especially at the production scale.

For solid drug-polymer dispersions, the influence of polymer properties (i.e. Tg, hydrophilicity, solubility, and hydrogen-bonding ability) needs to be considered to select the most suitable manufacturing process [69]. For example, solid dispersions prepared using the melt-extrusion method usually have a lower water content, which can lead to better physical and/or chemical stability [70].

For the spray drying of drug-polymer solid dispersions, process parameters (i.e. nozzle configuration, nitrogen flow rate, pump speed, temperature, solvent type and drug concentration) can have a significant effect on product morphology, stability and dissolution properties.

4.5. Effects of water on solid-state physical stability

It has been realized that water can have a significant effect on the physical and chemical stability of amorphous pharmaceutical materials [71–73]. Amorphous materials are usually more hygroscopic than their crystalline counterparts, primarily because of a different mechanism of water uptake. While crystalline materials adsorb water on the surface, water in amorphous materials is absorbed and distributed throughout the bulk resulting in a higher water uptake. The plasticizing effect of water molecules (Tg ~ 136 K or -137°C) can significantly lower the glass-transition temperature of most amorphous drugs, even at a very low level of water content. The understanding of interactions of water with pharmaceutical solids is crucial to water-based manufacturing processes or prediction of the stability and the shelf life of the solid dosage form. Analytical techniques that have been used to investigate the roles of water in the physical stability of solid dosage formulations include DVS analysis, NIR, MDSC and VT-PXRD.

As in all stability programs, temperature and RH are two critical environment factors. For amorphous materials, these stresses can cause not only solid-phase change but also morphology change, such as agglomeration or sintering. Amorphous drug recrystallization may happen at high temperature or elevated RH due to increasing molecular mobility [74]. This should be taken into consideration when designing a stability study or reviewing study results [75]. Recrystallization kinetics of amorphous solid dispersions stored at controlled temperature and RH can be measured using DSC. In the case of efavirenz-PVP dispersions, temperature was found to affect recrystallization in an Arrhenius manner, while the recrystallization rate constant was shown to increase linearly with RH [76].
At elevated RH, some amorphous drug-polymer solid dispersions might lose their miscibility and form separate drug-rich and polymer-rich amorphous phases followed by crystallization of the drugs. When an amorphous solid dispersion containing a hydrophobic drug and hydrophilic polymer is subjected to atmospheric water, drug crystallization can occur via one of two routes [77]:

- crystallization from the plasticized one-phase solid dispersion;
- or, crystallization from a plasticized drug-rich amorphous phase in a two-phase solid dispersion.

In the former case, the polymer can inhibit crystallization to a greater extent than the latter scenario, where the polymer concentration in the drug phase is reduced as the result of phase separation [78]. An amorphous solid dispersion with a less hydrophobic polymer, stronger drug-polymer interactions, and low hygroscopicity is more likely to resist water-induced phase separation [18].

To extend the shelf lives of solid oral DPs containing water-sensitive amorphous solid dispersions, proper protection packaging may also be required. The prediction of water effects on long-term physical stability of DPs (i.e. crushing strength of tablets stored in blister packages) can be based on knowledge of drug-water sensitivity, water permeability of the packaging and RH of storage conditions [78]. The threshold RH, at which physical attributes of the drug (i.e., tablet hardness, dissolution rate) become problematic, takes into consideration of the initial water content of dosage form [80].

EMEA/CHMP/CVMP/D97/175/2009 Rev2. Guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations.

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