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REVIEW

# Characterization of amorphous solid dispersions

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**Abstract** The study of amorphous solid dispersions (ASDs) is currently one of the most exciting areas in pharmaceutics. Research has shown that ASDs offer unique advantages in improving the bioavailability of poorly water-soluble drugs over conventional delivery systems. The various formulations and manufacturing processes of ASDs affect their physicochemical stability, processability, and drug release characteristics. Therefore, the characterization of ASDs is critical in all stages of product development, including preformulation screening, formulation development, process scale-up, and commercial manufacturing. Proper characterization allows for the rational selection of formulation composition and manufacturing processing methods and allows for high-quality drug products. In this review, we present the most commonly used methods for characterizing the solid-state properties of ASDs, and we discuss their mechanisms, applications, advantages, and disadvantages. We also provide a brief overview of the methods used to characterize ASDs behavior in aqueous media. These methods are divided into three different categories: microscopic and surface analysis methods, thermal analysis methods, and spectroscopic methods. In addition, this article discusses a number of emerging techniques. Last, we discuss how these methods are applied at different stages in the ASDs product development life cycle.

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## Introduction

Combinatory chemistry and high-throughput screening in drug discovery have resulted in a higher percentage of drug candidates that have poor aqueous solubility and poor dissolution characteristics. Up to 90% of the drugs under investigation and up to 40% of marketed drugs are poorly water soluble (Williams et al. 2011). Oral delivery of these drug candidates is challenging.

A number of strategies have been developed to enable oral delivery of these poorly water-soluble drugs. These strategies include the use of salts, prodrugs, cocrystals, self-emulsifying formulations, and amorphous solid dispersions (ASDs) (Jain et al. 2015). Among these methods, the use of ASDs is demonstrably the most promising approach to improve the dissolution characteristics and absorption of poorly water-soluble drugs (He and Ho 2015).

The most common definition of ASD is "a molecular dispersion of one or more active ingredients in an inert carrier in the solid state prepared by the melting, solvent, or melt-solvent method" (Chiou and Riegelman 1971). The improvement in bioavailability using ASD is attributed to a combination of thermodynamic and kinetic factors.

In terms of thermodynamics, a significant increase in the dissolution rate and transient solubility of the API in an amorphous state occurs because the energy that would be required to disrupt the crystal lattice of crystalline drugs is not required to dissolve drugs in an amorphous state (Grohganz et al. 2014). In terms of kinetics, the

interactions between polymer and API molecules could delay or inhibit nucleation and crystal growth in the dissolution medium. As a result, the supersaturation of the drug could be maintained over an extended period of time to maximize drug absorption (Taylor and Zhang 2016).

As more and more commercial ASD products enter the marketplace, ASD is becoming the preferred approach to improve the dissolution rate and apparent solubility of poorly water-soluble drugs. Due to the complex physicochemical properties of ASDs, multifaceted analytical methods are needed to enable comprehensive characterization of the materials to help understand the relationship between the formulation and process variables and the in vivo performance of ASDs.

In an ASD, all components are mixed on a molecular level. The challenges of ASD characterization arise from the desire to characterize the interaction between the drug and the polymer, phase separation during storage, the dissolution process, and physical stability prediction (Vogt 2015). Many analytical techniques are now available to address these ASD characterization challenges. Fortunately, emerging sensitive technologies are providing more quantitative and qualitative information about the physicochemical properties of ASDs.

A combination of characterization techniques are commonly used to characterize ASDs at different stages of product development. Several review articles simply focus on one particular technique in ASD characterization, so they do not offer a complete picture of ASD research (Shen 2011; Baird and Taylor 2012; Hedoux 2016; Knopp et al. 2016; Thakral et al. 2016). In this paper, we offer a detailed discussion of the measuring principle, and we summarize the advantages and disadvantages of most classical methods. Last, we discuss the applications of different techniques to characterize ASDs at different product development stages.

The characterization of ASDs in solid state can be performed using a wide variety of analytical techniques. There is no single superior method that can provide the full structural information of an ASD. The best approach is to apply a combination of techniques to achieve a comprehensive understanding of the solid-state properties of ASDs. Generally, ASD characterization methods can be divided into two major categories: methods that characterize ASDs in solid state, and methods that characterize the behavior of ASDs in aqueous media.

Table 1 shows the solid-state characterization methods. These methods can be classified based on their characterization level: the molecular level, the particulate level, and the bulk level. Molecular level methods characterize properties that can be detected between individual molecules. Particulate level methods characterize properties that can be detected through the analysis of particles. And, bulk level methods characterize properties that can be measured by using a relatively large amount of material (Chieng et al. 2011).

**Table 1** Classification of ASD characterization methods

| Molecular level | Particulate level | Bulk level |
|---|---|---|
| FTIR | Fluorescence spectroscopy | Density |
| Raman | PXRD | Contact angle |
| NIR | DSC | Flowability |
| SSNMR | MDSC | Karl Fischer titration |
| | TGA | |
| | PLM | |
| | SEM | |
| | TEM | |
| | XPS | |
| | AFM | |
| | Terahertz spectroscopy | |
| | Dielectric spectroscopy | |

Solution state characterization always includes not only the standard dissolution testing, which is covered by various regulatory guidance (e.g., USP, PhEur, JP), but also the solution-mediated phase transformation, recrystallization, and supersaturation that occur during the dissolution process. Characterizing the behavior of ASDs in aqueous media is the most challenging task in the study of ASDs. This paper focuses on solid-state characterization methods. However, a brief discussion of solution-state methods is also presented. Last, the conjunction method and new characterization techniques are also discussed.

## Methods used to characterize the solid-state properties of ASDs

In this review article, solid-state characterization methods are divided into three categories based on the mechanisms of analysis: (1) microscopic and surface analysis methods, (2) thermal analysis methods, and (3) spectroscopic methods. This section presents a detailed discussion of the methods in each category.

## Microscopic and surface analysis methods

Microscopy is a powerful solid-state characterization technique. It is a versatile, rapid, and nondestructive process for analyzing small samples for a wide range of physicochemical properties, such as particle size, particle morphology, crystallinity, surface properties, and even dissolution behavior and thermal behavior (Nichols 2006). In general, the microscopic and surface analysis methods employed in ASD characterization include polarized light microscopy (PLM), scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and

X-ray photoelectron spectroscopy (XPS). Table 2 summarizes the measurement time, sample status, application, advantages, and disadvantages of each technique.

### Polarized light microscopy (PLM) and hot-stage polarized light microscopy (HSPLM)

Among all the types of microscopy methods, PLM is one of the most useful for detecting small amounts of crystalline materials in ASDs. Solid forms can be distinguished by their optical properties when observed using plane polarized light and crossed polarizers, and this is especially true for crystalline and amorphous materials.

Amorphous solids are isotropic, which means their molecules are oriented randomly with no long-range order. As a result, they have no double refraction, are nonbirefringent, and do not exhibit any interference colors when observed between crossed polarizers. However, most crystalline solids are anisotropic, which means their molecules are packed in a regular, long-range, three-dimensional order. Therefore, crystalline solids show interference colors or polarization colors, which allows for rapid detection based on birefringence.

Telang et al. (2009) used PLM to observe the onset of crystallization in ASDs with different formulations, and they found that PLM is a more sensitive tool than XRPD for investigating drug recrystallization in physical stability studies. Combined with other analytical approaches, PLM can be used to assess the kinetics of drug crystallization, polymorphic transitions, and crystallization in solid state or in aqueous media (Cai et al. 2011; Raina et al. 2014).

Hot-stage polarized light microscopy (HSPLM) is another rapid and versatile method for observing the thermal behavior of samples using a polarized light microscope. In this method, the sample is heated in a furnace in which the heating or cooling rate can be accurately controlled. HSPLM is extensively applied in the initial formulation screening studies of ASDs.

During the process development of ASD, HSPLM is frequently applied to observe how the drugs interact with polymers in mixtures at elevated temperatures. Strong interactions (e.g., hydrogen bonding, ionic interaction) between the drug and excipients contributes to a lower drug melting point, improved stability of ASDs during storage, and enhanced dissolution performance (Li et al. 2014). During the heating process, the molten drug should be miscible with the polymer at a specific drug loading. During cooling, the drug should not recrystallize from the polymer–drug matrix.

HSPLM is particularly useful to interpret or confirm the results acquired by differential scanning calorimetry (DSC), especially when overlapping events are observed on DSC thermal profiles. Liu et al. applied HSPLM to observe the in situ formation of cocrystal and salt between drug and other excipients at elevated temperature (Liu et al. 2012, 2017). New crystalline phase was observed during the heating process, which was attributed to the reaction between the drug and excipients. The HSPLM results corresponded well with the DSC data. Although PLM is a powerful tool for characterizing ASD, it is not an infallible method for detecting birefringence to distinguish amorphous from crystalline materials. Some crystalline materials are isotropic, so they do not show birefringence or interference colors (and the reverse is true for anisotropic materials). In addition, it is difficult to use PLM to quantify the degree of crystallinity in a crystal or a mixture. In general, to fully characterize the crystalline state of a sample, PLM should be used in combination with other techniques such as X-ray diffraction or DSC.

### Scanning electron microscopy (SEM) and energy dispersive X-ray microanalysis (EDX)

SEM is widely applied in the characterization of ASDs. SEM analysis uses a monochromatic electron beam to probe the surface and near-surface area of materials at a higher magnification and resolution than a traditional light microscope. Compared to light microscopy, SEM has the following three major advantages: (1) an upper magnification of about ×250,000, (2) a large depth of field, and (3) a lateral spatial resolution of 3 nm or higher.

SEM can be used to examine the effects of processing methods (e.g., spray drying, hot melt extrusion, electrospinning) on particle morphology (Bohr et al. 2012; Moffat et al. 2014; Ye et al. 2016). It can also be used to observe changes in the morphology of the ASD sample after dissolution or a physical stability study (Bruce et al. 2007; Priemel et al. 2013).

Energy dispersive X-ray microanalysis (EDX) is often combined with SEM to provide elemental information about the area probed by the electron beam. EDX analyzes the X-ray emission from the inner shells of atoms that have been ionized by the SEM beam. EDX analysis is ideal for the rapid and nondestructive elemental screening of samples.

### Transmission electron microscopy (TEM)

In addition to SEM, transmission electron microscopy (TEM) is a highly useful technique in the study of ASDs. It can produce both real-space images and electron diffraction patterns to identify crystalline drugs in ASDs (Marsac et al. 2010). Using TEM, Ricarte et al. (Ricarte et al. 2015) detected an overall 3% crystallinity in a spray-dried ASD based on hydroxypropyl methylcellulose acetate succinate (HPMCAS), which is below the practical lower detection

**Table 2** An overview of microscopic and surface analysis methods in ASD characterization

| Analytical method | Information | Advantages | Disadvantages | Sample destructiveness<br>Measurement time | Reference |
|---|---|---|---|---|---|
| PLM<br>(HSPLM) | • Crystallinity (Birefringence), Amorphous<br>• Crystalline morphology & size<br>• Polymorphic transitions<br>• Crystallization route | • High sensitive<br>• Small sample size<br>• Very little sample preparation<br>• Easy to use | • Semi-quantitative | (−)<br>Min-sec | Telang et al. (2009), Cai et al. (2011), Liu et al. (2012), Raina et al. (2014) |
| SEM<br>(EDS) | • Particle morphology and size<br>• Rapid measure surface crystal<br>• Chemical distribution map (EDS) | • High resolution<br>• Small sample size | • Require sample preparation (coating and vacuum setting) | (−)<br>Min-hour | Bruce et al. (2007), Bohr et al. (2012), Priemel et al. (2013), Moffat et al. (2014), Maniruzzaman et al. (2015) |
| TEM | • Identify crystalline<br>• Detect crystallinity degree<br>• Drug-polymer miscibility | • High resolution<br>• Small sample size<br>• Quantitative | • Tedious sample preparation<br>• Risk of electron beam damage for some samples | (−)<br>Hours | Marsac et al. (2010), Ma et al. (2013), Ricarte et al. (2015) |
| AFM | • Surface topography<br>• Phase separation<br>• Drug-polymer miscibility | • High resolution (nanoscopic)<br>• Small sample size | • Require sample preparation<br>• (smooth sample surface) | (−)<br>Hours | Lauer et al. (2011, 2013), Meeus et al. (2014) |
| XPS | • Surface chemical composition<br>• Drug-polymer interaction | • High sensitive<br>• Quantitative | • Limited testing area (1 μm)<br>• Require sample preparation (high vacuum setting) | (−)<br>Hours | Dahlberg et al. (2008), Stevens et al. (2014), Song et al. (2016a, b) |

(+) or (−) indicate whether the analytical technique is sample destructive or non-destructive, respectively

limit of wide-angle X-ray scattering. When combined with EDX, TEM can be used to evaluate drug–polymer mixing status in ASD in the early stages of formulation and process development (Ma et al. 2013).

### Atomic force microscopy (AFM)

The main application of atomic force microscopy (AFM) in the study of ASDs is measuring the surface topography at sub-nanometer resolution. During AFM testing, a sharp probe tip usually made of silicon (Si) or silicon nitride ($Si_3N_4$) located on the underside of a flexible cantilever raster scans over the sample surface. The detailed working mechanism of AFM is presented in these review articles (Turner et al. 2007; Sitterberg et al. 2010).

Many characteristics of samples can be visualized directly using AFM, such as underlying molecular de-mixing mechanisms, mixture-specific separation rates, and bulk and surface evolution. These parameters are intrinsic and fundamental in the prediction of the long-term stability of an ASD (Lauer et al. 2011). Lamm et al. (2016) used AFM to evaluate the phase behavior and morphology of solid dispersions consisting of copovidone and TPGS 1000 prepared by hot-melt extrusion with various processing parameters and formulations. They concluded that AFM is a powerful technology for characterizing the effects of processing and composition on the phase behavior of the resulting extrudates. In summary, AFM is a robust method to study the phase behavior and molecular structure of ASDs, and it provides a novel analytical tool for the optimization of the ASD preparation process (Lauer et al. 2013; Meeus et al. 2014).

### X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS) is a surface analysis technique that can analyze the chemical composition of the surface of a substance based on atomic concentrations. The XPS spectrum is specific to the binding energies of most elements of interest in organic materials. The shift in the chemical bonding energy can be used to study drug and excipient interactions in ASDs. Specifically, XPS has excellent sensitivity in assessing the extent of protonation by measuring the shifts in the binding energy of selected atoms (Stevens et al. 2014). A discussion of the mechanism and basic theory of XPS analysis can be found in Lee and Flynn (2006).

As XPS instruments become more readily available, more applications of XPS in ASD characterization have been published. Dahlberg et al. (2008) used XPS to quantify the amount of drug present on the surface of ASDs prepared by spray drying and rotary evaporation. They found that the chemical surface composition directly influenced the wettability of the ASDs, which had a direct impact on dissolution performance and the physical stability in the solid state. XPS offers a rapid screening tool for the selection of carrier and drug loading in the early development of ASDs. Song et al. (Song et al. 2016a, b) applied XPS to investigate the acid–base interactions between the drug and excipient in ASDs. They used XPS to detect an increase in the binding energy of the basic nitrogen atoms in the drug, which indicated protonation of these nitrogen atoms.

### X-ray diffraction

X-ray diffraction has been described as the gold standard in characterizing pharmaceutical materials in the solid state. It has shown great promise for the fingerprinting, quantification, and even the modeling of amorphous pharmaceutical systems (Thakral et al. 2016). X-ray diffraction is generally categorized into single-crystal diffraction and powder X-ray diffraction.

Powder X-ray diffraction (PXRD) is more widely used than single-crystal diffraction for ASD solid characterization. It provides information on at least three important material attributes (de Araujo et al. 2017).

Table 3 summarizes the measurement time, sample status, application, advantages, and disadvantages of PXRD.

To understand the basic theory and working mechanism of powder X-ray diffraction, the readers are recommended to read these articles written by Dinnebier and Gilmore (Dinnebier 2008; Gilmore 2011).

The first use of PXRD is to examine changes in the crystallinity and polymorphism of ASDs after manufacture or during stability studies. Because PXRD operates on bulk powders, it is very useful for the overall quantitative analysis of the crystalline content of a batch of ASD. A number of examples for the application of PXRD in the analysis of residual crystalline content in ASDs have been reported (Rumondor et al. 2009a, b, c, d; Takeuchi et al. 2015).

Amorphization generally results in broad, diffuse scattering signals, while the signals for crystal materials are sharp Bragg reflections. For a mixture of amorphous and crystalline materials, the degree of crystallinity is the ratio of integrated crystalline intensity to the total integrated amorphous and crystalline intensity. The typical detection limits for crystalline content are in the 1–5% (w/w) range, depending on the reflection methods (Vogt 2015).

The second use of PXRD in the study of ASDs is the direct characterization of miscibility and amorphous structure with the total scattering pair distribution function (PDF). The PDF is obtained through an inverse Fourier transform of the reduced total scattering structure function F(Q), which is the subtracted, corrected, and normalized background diffracted intensity that includes both Bragg and diffuse scattering. The detailed theory and general

**Table 3** A brief summary of PXRD in ASD characterization

| Analytical method | Information | Advantages | Disadvantages | Sample destructiveness<br>Measurement time | Reference |
|---|---|---|---|---|---|
| PXRD (scattering pair distribution function, PDF) | - Polymorph screening<br>- Amorphous identification<br>- Detect crystallinity degree<br>- Recrystallization kinetic<br>- Drug-polymer miscibility (PDF)<br>- Microstructure of ASD (PDF) | • Small sample size<br>• Very little sample preparation<br>• Easy to use<br>• Qualitative and quantitative | • Less sensitive (> 5% crystallinity)<br>• No chemical structure information | (−)<br>Mins | Telang et al. (2009), Cai et al. (2011), Liu et al. (2012), Raina et al. (2014) |

(+) or (-) indicate whether the analytical technique is sample destructive or non-destructive, respectively

application of PDF in PXRD are presented in (Young and Goodwin 2011; Egami and Billinge 2012).

Nollenberger et al. (2008) applied PDF to show that subtle changes in the polymer structure at the molecular level have a significant impact on the drug release profile of ASDs. Newman et al. (2008) developed a method that uses PXRD coupled with PDF to assess the miscibility between amorphous drugs and polymers. They found that the PDF method is more sensitive than DSC for detecting phase separation. However, due to the inherent limitations of conventional copper-anode X-ray laboratory sources, the PDF analysis data may not be reliable and may generate ambiguous and potentially incorrect results (Nunes et al. 2005; Dykhne et al. 2011).

The development of high-energy X-rays produced by synchrotron radiation allowed the use of short wavelengths to achieve a higher detection range. Araujo et al. (2017) used synchrotron X-ray diffraction and PDF to investigate the local chemical structure and ionic drug–polymer interactions in a lapatinib ASD prepared with hypromellose phthalate (HPMCP) and hypromellose (HPMC-E3). Based on the total PDF results, they found that the drug did not pack in the same way in these two formulations due to the different interactions between the drug and polymer carriers.

Recent developments in PXRD can also provide useful information under non-ambient conditions, such as PXRD equipped with variable temperature and humidity control, which provides new insights into the crystallization kinetics of amorphous drugs in ASDs (Zhu et al. 2013). Furthermore, when PXRD is used in conjunction with other techniques, such as second-harmonic generation microscopy, the sensitivity of PXRD for detecting drug crystallinity increases dramatically (Newman et al. 2015).

## Thermal analysis methods

The thermal analysis method is an indispensable and well-established routine tool for the characterization of ASD. The basic process of thermal analysis is measuring a material's response (e.g., changes in energy, temperature, mass) to a change in the temperature of the sample. Thermal analysis methods are normally used to monitor endothermic processes (e.g., glass transition, melting, solid–solid phase transition) and exothermic processes (e.g., crystallization, chemical degradation). Commonly used thermal analysis methods include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), modulated differential scanning calorimetry (MDSC) and micro-nano thermal analysis. Table 4 summarizes the measurement time, sample status, application, advantages, and disadvantages of each technique.

### Thermogravimetric analysis (TGA)

TGA is one of the oldest thermal analytical methods. It has been used extensively in material characterization. This method involves monitoring the weight of a sample in a chosen atmosphere (air or nitrogen) as a function of temperature. In ASD characterization, TGA is routinely used to determine the thermal stability and volatile components analysis of the drug and polymer. This information can be used to define the temperature window in hot-melt extrusion to avoid thermal degradation (Liu et al. 2012). TGA has also been used to study the evaporation profile of feed solutions for spray drying. TGA analysis has revealed that the drying kinetics of the binary solvent has a significant impact on the surface chemistry and particle morphology of spray-dried ASDs (Wan et al. 2013; Bohr et al. 2015). TGA is commonly

**Table 4** A brief summary of TGA and DSC (MDSC) in ASD characterization

| Analytical method | Information | Advantages | Disadvantages | Sample destructiveness<br>Measurement time | Reference |
|---|---|---|---|---|---|
| TGA | • Thermal stability<br>• Moisture content<br>• Solvent evaporation rate | • Small sample size<br>• Very little sample preparation<br>• Easy to use | • Difficult to identify chemical composition<br>• Sample destroyed during analysis | (+)<br>Min-hour | Liu et al. (2012), Wan et al. (2013), Bohr et al. (2015) |
| DSC (MDSC) | • Melting point<br>• Glass transition temperature ($T_g$)<br>• Identify crystalline and amorphous state<br>• Detect crystallinity degree<br>• Heat capacity<br>• Drug crystallization tendency<br>• Drug–polymer miscibility<br>• Molecular mobility<br>• Drug–drug and drug–polymer interaction | • Small sample size<br>• Very little sample preparation<br>• Easy to use<br>• Qualitative and quantitative | • Sample destroyed during analysis<br>• No information on the nature of the thermal events<br>• Unable to resolve overlapping thermal events at the same time | (+)<br>Min-hour | Friesen et al. (2008), Kaushal and Bansal (2008), Marsac et al. (2009), Tao et al. (2009), Tobyn et al. (2009), Andrews et al. (2010), Baird et al. (2010), Baird and Taylor (2012), Knopp et al. (2016) |
| Micro-nano-thermal analysis | • Phase separation<br>• Drug distribution uniformity assessment | • Small sample size<br>• Very little sample preparation<br>• Identify phase chemical compositions based on transition temperature | • Time consuming<br>• Potential confusion of glass transition with other softening response | (−)<br>Hour-day | Craig et al. (2002), Zhang et al. (2009), Qi et al. (2011), Dai et al. (2012) |

(+) or (−) Indicates whether the analytical technique is sample destructive or nondestructive, respectively

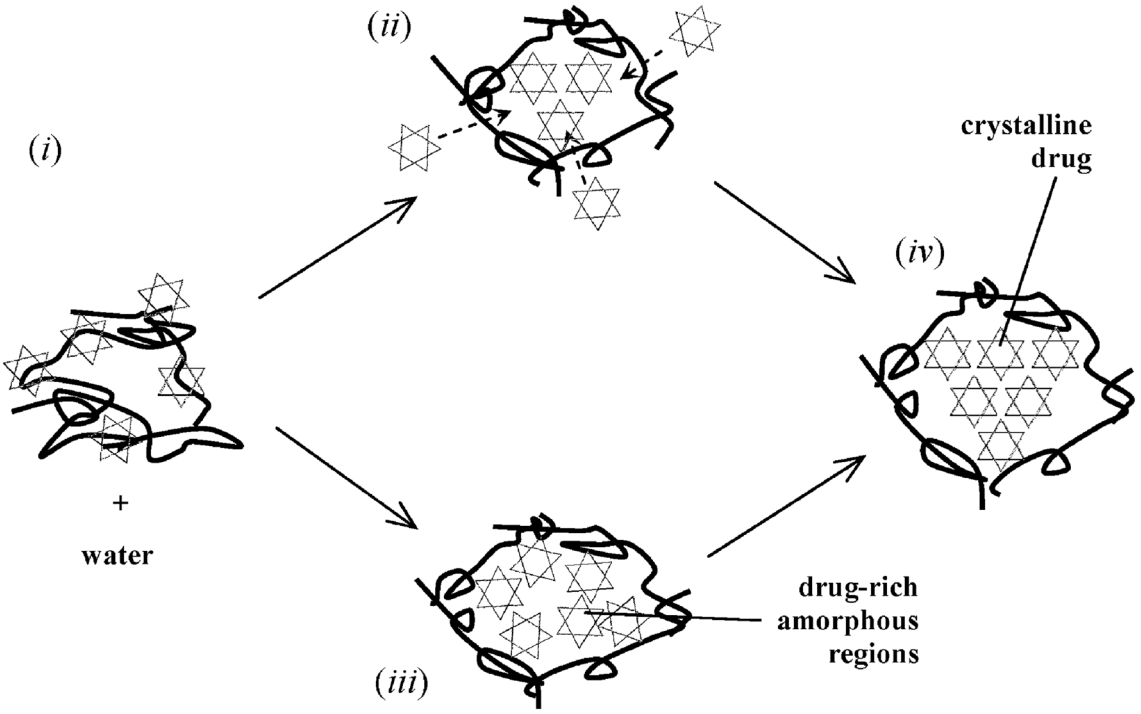


**Fig. 1** Two potential drug recrystallization routes from ASD. Adapted from reference (Rumondor et al. 2009a, b, c, d)

combined with other spectroscopic detection methods, such as IR or gas chromatography, to allow for the chemical identification of volatile materials released from samples.

### Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC) may be the most widely used methods in ASD characterization. In these techniques, the energy input associated with heating materials can be measured to detect thermal transitions such as the melting point, glass transition, polymorphic form transformation, and recrystallization. The theoretical background of DSC and MDSC can be found in (Höhne et al. 1996).

Although DSC is an invaluable analytical tool, DSC has certain limitations when thermal transitions are weak or overlap. MDSC was designed to address these limitations. MDSC can separate overlapping thermal events and has higher sensitivity in measuring heat capacity. MDSC has been used to measure the crystallization tendency of drugs, miscibility between the drug and polymer, glass transition, crystallinity/crystallization (e.g., crystal growth rate, degree of crystallinity), and molecular mobility (e.g., structural relaxation, viscosity) (Baird and Taylor 2012).

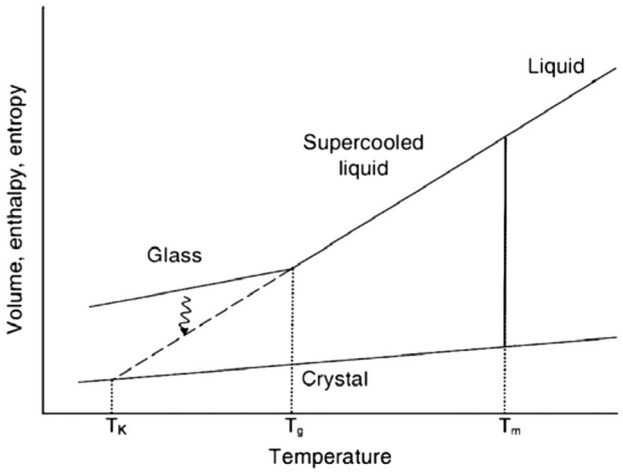


**Fig. 2** Volume, enthalpy, and entropy of the amorphous state in comparison to a crystal, including the supercooled liquid and glass regions. $T_m$ represents the melting temperature, and $T_k$ represents the Kauzmann temperature. Adapted from reference (Baird and Taylor 2012)

#### *Crystallization tendency*

Discerning the crystallization tendency of a drug is important in the development of an ASD. The crystallization tendency of an ASD is determined by the crystallization tendency of the drug (Weuts et al. 2004; Van Eerdenbrugh

and Taylor 2010; Kawakami et al. 2012). DSC can be used to measure the drug crystallization tendency. Taylor's group developed a simple DSC method to assess the crystallization tendency of organic molecules by using a heating–cooling–heating cycle (Baird et al. 2010). Based on the melting and recrystallization behavior during the temperature cycle, the drug crystallization tendency is classified as Class I (strong), Class II (middle) and Class III (weak). Other DSC methods used to measure crystallization tendency include the reduced glass transition temperature rule ($T_{rg}$, 2/3 rule) (Friesen et al. 2008) and the fragility parameter (Kaushal and Bansal 2008). In another case, Feng et al. (2014) utilized an improved kinetic equation to evaluate the recrystallization process of melt-extruded ASD by fitting the DSC data into a mathematical model using a multivariate regression method. The recrystallization rate constant was assessed under accelerated conditions to predict the long-term crystallization tendency of the ASD.

*Miscibility between drug and polymer*

DSC is commonly used as a "rule of thumb" technique to evaluate the miscibility between the drug and polymer. Good miscibility is a prerequisite to form a physically stable ASD. A *miscible* ASD is defined as an ASD that consists of a single chemically homogeneous phase in which all components are mixed at the molecular level (Baird and Taylor 2012). Since ASD is a high-energy drug dispersion system, phase separation could occur due to thermodynamic factors (i.e., enthalpy, entropy of mixing) or environment factors (e.g., temperature, moisture). Figure 1 illustrates two potential routes of ASD recrystallization. Phase separation and crystallization have a negative impact on the performance of an ASD both in vitro and vivo.

Numerous articles have reported that the single $T_g$ method indicates miscibility of the binary or ternary ASD (Rumondor et al. 2009a, b, c, d; Tobyn et al. 2009, Andrews et al. 2010). However, the presence of a single $T_g$ is not an infallible indicator of miscibility for a number of reasons (Qian et al. 2010). First, some drugs and polymers have similar $T_g$ s, and their glass transitions may overlap on DSC thermograms, which makes them difficult to discern. Second, the domain size in phase-separated ASD may fall below the DSC detection limit (Newman et al. 2008). Last, but not the least, some drugs and polymers have broad glass transitions or a small heat capacity change at $T_g$, which makes it difficult to measure the $T_g$.

Besides the single $T_g$ method, many other methods are used to evaluate mixing homogeneity, such as melting point depression (Marsac et al. 2009), evaluation of drug solubility in polymers (i.e., the *solubility parameters method*) (Ghebremeskel et al. 2007; Tao et al. 2009), solution calorimetry (Righetti et al. 2002).

*Glass transition temperature*

For amorphous materials, the glass transition temperature ($T_g$) is a unique temperature range in which the properties of the material shift from the properties of a liquid to those of a solid. Figure 2 shows the relationships between temperature and volume, and enthalpy and entropy. Certain critical properties of ASDs are dependent on their glass transition temperature. These properties include the physical state of the drug and polymer (Gupta et al. 2004), the miscibility between the drug and polymer (Vasanthavada et al. 2004, 2005), and specific interactions (Tong et al. 2002; Weuts et al. 2005). In addition, $T_g$ can be used to guide the selection of the storage conditions for ASDs (Yu 2001). Gordon-Taylor, Fox, and Kwei equations can be used to calculate the theoretical $T_g$ of multicomponent ASDs. The deviation of the experimental $T_g$ from the theoretical $T_g$ can be used to determine the mixing behavior and physical interaction between the drug and polymer (Rumondor et al. 2009a, b, c, d).

*Residual crystallinity*

It is important to monitor the residual crystallinity of ASDs during their processing and storage, because recrystallization of the drug reduces the dissolution rate, which could reduce bioavailability. Comparing the melting enthalpy of the residual crystalline drug in ASDs against the melting enthalpy of the crystalline form of the pure drug can be used to determine the residual crystallinity (Grisedale et al. 2011). Shah et al. (2006) summarize the various thermal methods used to study the crystallization of ASDs.

In summary, DSC is useful for both qualitative and quantitative analysis drug crystallization in ASDs. Although DSC may not detect low levels of crystalline material in ASDs, DSC is commonly combined with other techniques (e.g., XRPD, solid-state NMR) to monitor the crystallization in ASDs.

*Molecular mobility*

The molecular mobility of a drug and polymer is generally considered a key attribute that determines the physical stability of ASDs. High molecular mobility can lead to faster phase separation, drug nucleation, and crystal growth. A large body of research focuses on the correlation between molecular mobility and physical stability (Korhonen et al. 2008; Mistry et al. 2015). The most common indicators of molecular mobility are *viscosity, structural relaxation time*,

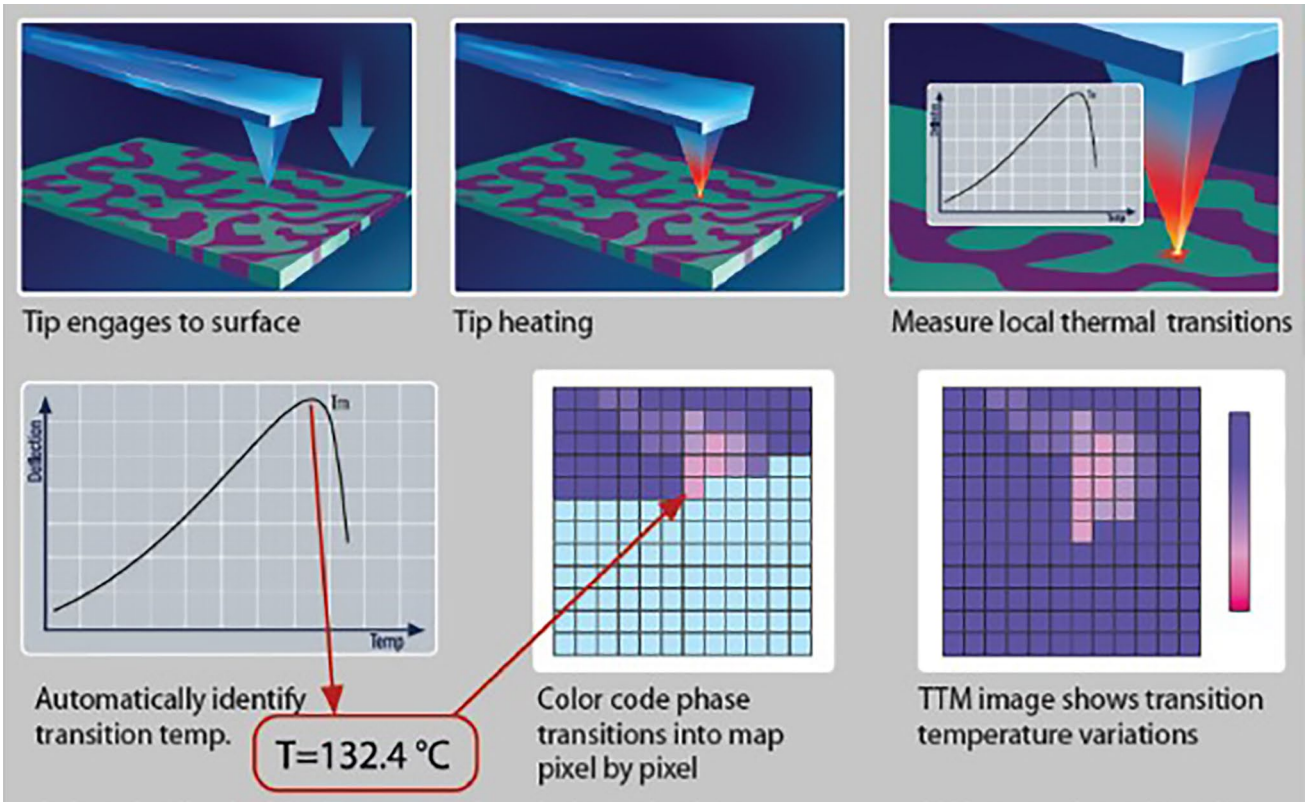


**Fig. 3** The principle of localized nanothermal analysis and thermal transition mapping. Adapted from reference (Kjoller et al. 2010)

and *dielectric relaxation time* (Baird and Taylor 2012). Since all these properties are temperature dependent, DSC is the most commonly used method to measure molecular mobility as a function of temperature. Aso et al. (Aso et al. 2004) used DSC to study the crystallization rate of amorphous drugs and the relationship between changes in the structural relaxation time of amorphous drugs both in the absence povidone and in the presence of povidone. They found that the presence of povidone decreased the molecular mobility of amorphous drugs as the structural relaxation time of the drug increased, and they found that the recrystallization rate of the drug decreased in the presence of povidone.

In summary, DSC and MDSC have a wider range of application in studying ASDs, ranging from testing the properties of the drug and polymer to preformulation screening of ASDs. Furthermore, with the development of new DSC thermal analytical methods and the combination of DSC with other spectroscopic and imaging methods, the application of DSC in ASD characterization continues to expand.

*Micro-nano thermal analysis*

Traditional thermal analysis can provide useful information on the bulk properties of ASDs. However, in some cases, it may be more desirable to analyze the surface properties rather than the bulk properties. The properties of free surfaces are directly responsible for crystal growth on the surfaces of ASDs (Yu 2016). Micro-nano thermal analysis is a particularly important method of thermal analysis to identify the nature of the different phases present at the surface of ASDs (Craig et al. 2002; Dai et al. 2012).

So far, the reported micro-nano thermal analysis methods include localized nanothermal analysis, thermal transition mapping, and thermal analysis by structural characterization. In localized nanothermal analysis, the traditional silicon-based AFM tip is replaced with a specialized micro-fabricated silicon-based probe with a miniature heater. This new probe not only allows researchers to generate topographic images, but also to conduct local thermal analyses at defined points on a surface (Six et al. 2003; Harding et al. 2007).

Zhang et al. (2009) used nanothermal analysis to characterize the heterogeneity of carbamazepine ASD. By combining the topographic and phase images, they found that a 5% drug-loading formulation formed a solid solution. At 50% drug loading, a portion of drug is dispersed as nanocrystals in the polymeric carrier. Figure 3 illustrates the work principle of local thermal analysis and thermal transition mapping. Qi et al. (2013) applied thermal transition mapping to study the phase separation behavior of felodipine ASD. They found that thermal transition mapping was useful to identify

**Table 5** A brief summary of spectroscopy method in ASD characterization

| Analytical method | Information | Advantages | Disadvantages | Sample destructiveness<br>Measurement time | Reference |
|---|---|---|---|---|---|
| Fluorescence spectroscopy | • Drug–polymer miscibility<br>• Phase separation<br>• Drug dissolution behavior in ASD | • High sensitive<br>• Small sample size<br>• Very little sample preparation<br>• Easy to use | • Semi-quantitative | (−)<br>sec | Brittain (2006), Ilevbare and Taylor (2013), Raina et al. (2015), Tian et al. (2016) |
| FTIR | • Drug–drug and drug–polymer interaction<br>• Polymorph screening<br>• Crystalline and amorphous identification<br>• Phase separation<br>• Spatial chemical information with mapping setup | • Fast data acquisition<br>• Small sample size<br>• Easy to use<br>• No sample preparation required for ATR | • Environmental humidity influence<br>• Probes are not yet common | (−)<br>sec | Tobyn et al. (2009), Rumondor and Taylor (2010), Van Eerdenbrugh et al. (2012), Hedoux (2016) |
| NIR | • Identify crystalline polymorphs and solvates<br>• Sensitive to different water states<br>• Spatial chemical information with mapping setup | • Fast data acquisition<br>• Small sample size<br>• Easy to use<br>• No sample preparation required<br>• Use of probes<br>• Ability to penetrate glass containers | • Weak intensity<br>• Significant baseline slope | (−)<br>sec | Almeida et al. (2012), Saerens et al. (2014) |
| Raman | • Drug–drug and drug–polymer interaction<br>• Phase separation<br>• Drug–polymer miscibility<br>• Drug dissolution behavior in ASD | • Fast data acquisition<br>• Small sample size<br>• Easy to use<br>• No sample preparation required<br>• Use of probes<br>• Ability to penetrate glass containers<br>• Insensitive to water | • Local heating of sample<br>• Sample fluorescence<br>• Photodegradation | (±)<br>sec | Andrews et al. (2009), Lust et al. (2015), Paudel et al. (2015), Punčochová et al. (2016) |
| Terahertz spectroscopy | • Identify crystalline and amorphous state<br>• Detect crystallinity degree<br>• Polymorph screening<br>• Crystallization kinetic | • Fast data acquisition<br>• Small sample size | • Spectrum affected by water<br>• Baseline slope<br>• Relatively expensive | (−)<br>sec | Shen (2011), Sibik et al. (2015), Sibik and Zeitler (2016) |
| Dielectric spectroscopy | • Molecular mobility<br>• Drug crystallization tendency | • Fast data acquisition<br>• Small sample size<br>• No sample preparation required | • Complicated mathematical modeling<br>• Not a "fingerprint" technique | (+)<br>Min-hour | Bhardwaj and Suryanarayanan (2012), Rodrigues et al. (2014), Grzybowska et al. (2016) |

(+) or (−) indicates whether the analytical technique is sample destructive or nondestructive, respectively

both the size and chemical composition of the phase separation, which is difficult to achieve by conventional analytical methods. Thermal analysis by structural characterization is another micro-nano thermal analysis method recently developed to study the glass transition kinetics and thermal dissolution behavior of materials. Alhijjaj et al. (2015, 2017) used this method to analyze the influence of drug–excipient miscibility on the heterogeneity and spatial distribution of phase separation in ASDs.

## Spectroscopic methods

Spectroscopic methods are based primarily on molecular and atomic-level changes that occur when the material is exposed to electromagnetic radiation. The changes include electronic transitions, vibrational transitions, and nuclear spin transitions. Based on the energy gap between the ground and excited states, spectroscopy methods can be divided into fluorescence spectroscopy, infrared spectroscopy, near-infrared spectroscopy, Raman spectroscopy, and nuclear magnetic resonance. Terahertz-pulsed spectroscopy is a new technique used to probe low-energy vibrations, such as intramolecular torsional vibrations, and intermolecular vibrations such as translations and liberations (Heinz et al. 2009).

Using different setups, spectroscopy imaging may be performed on the macro-, micro-, and even nano- scales. For ASD characterization, spectroscopy could provide molecular-level information about local structure in amorphous solids, such as drug–polymer interaction, phase separation, and crystallization. Furthermore, spectroscopic tools can be applied in the on-line monitoring of ASDs during manufacturing process. Table 5 summarizes the measurement time, sample status, application, advantages, and disadvantages of each technique.

### Fluorescence spectroscopy

Fluorescence spectroscopy has been used to study the physical properties and dissolution behaviors of ASDs. It detects the fluorescence emitted when a substance is excited by UV–Visible radiation. Fluorescence spectroscopy can be performed in different modes, including (1) emission scans with a constant excitation wavelength, (2) excitation scans with a constant emission wavelength, (3) synchronous scans of both monochromators, and (4) total luminescence scans.

Fluorescence spectroscopy provides new approaches for probing the local behavior of drugs in ASDs (e.g., miscibility, phase separation) and the correlation of these behaviors to ASD performance. Tian et al. (2016) have used fluorescence spectroscopy to evaluate drug–polymer miscibility and to investigate the correlation between miscibility and the physical stability of ASDs. The fluorescence spectroscopy data indicated that drug loading had a significant impact on the drug–polymer miscibility and indicated a strong correlation between poor miscibility and reduced physical stability. They observed a significant difference in intensity and emission maxima between crystalline Form I, a hypromellose-based ASD, and the povidone-based ASD. The difference between the fluorescence spectra of these two solid dispersions was attributed to the differences in the mobility of diflunisal in the glassy solid (Brittain 2006). Fluorescence spectroscopy has also been used to study the dissolution behaviors of ASDs in aqueous environments (Ilevbare and Taylor 2013; Raina et al. 2015). In these studies, the fluorophore was added to the aqueous phase and the emission spectrum was monitored as the drug concentration was increased. Liquid–liquid phase separation was observed in povidone-based ritonavir ASDs.

### Infrared spectroscopy

Infrared spectroscopy (IR) is a form of vibrational spectroscopy that measures the absolute frequencies at which a sample absorbs various forms of radiation. The vibration occurs when there is a change in dipole moment. Based on the spectral range, infrared spectroscopy could be divided into far-IR (FIR: 400–20 $cm^{-1}$), mid-IR (MIR: 4000–400 $cm^{-1}$), and near-IR (NIR: 12,500–4000 $cm^{-1}$). All three IR regions have been employed to study ASDs (Vogt 2015).

IR spectroscopy can be used to measure drug–polymer interactions in ASDs by observing changes in peak shape or position. The changes in wavelength, bandwidth, and band intensity can also provide molecular-level information on the solid-state form of both the drug and polymer (Hedoux 2016). Therefore, FTIR can be used to identify molecular interactions and to evaluate the physical stability of ASDs. In addition, FTIR is a useful tool for measuring the distribution of the drug in the polymer matrix as well as phase separation.

FTIR imaging has been used to study the moisture-induced phase separation in melt-extruded ASDs (Rumondor and Taylor 2010; Feng et al. 2016). FTIR spectroscopy has also been used successfully in combination with other analytical techniques (e.g., XRPD, DSC, AFM) (Tobyn et al. 2009; Van Eerdenbrugh et al. 2012). In-line NIR has been applied to monitor phase transformations during ASD production, such as hot-melt extrusion and spray drying (Almeida et al. 2012; Saerens et al. 2014). Furthermore, the development of FTIR imaging technology has made possible the real-time monitoring of drug release from ASDs (Kazarian and Ewing 2013; Pudlas et al. 2015).

**Table 6** A brief summary of SSNMR in ASD characterization

| Analytical method | Information | Advantages | Disadvantages | Sample destructiveness<br>Measurement time | Reference |
|---|---|---|---|---|---|
| SSNMR | • Amorphous identification<br>• Detect crystallinity degree<br>• Recrystallization kinetic<br>• Drug–polymer miscibility<br>• Drug–drug and drug–polymer interaction<br>• Molecular mobility<br>• Microstructure of ASD | • Small sample size<br>• Very little sample preparation<br>• Qualitative and quantitative | • Risk of recrystallization during the analysis process<br>• Relative expensive | (−)<br>Hour-day | Aso et al. (2000, 2009), Ito et al. (2010), Pham et al. (2010), Dahlberg et al. (2011), Paudel et al. (2014a, b), Song et al. (2015) |

(+) or (−) indicates whether the analytical technique is sample destructive or nondestructive, respectively

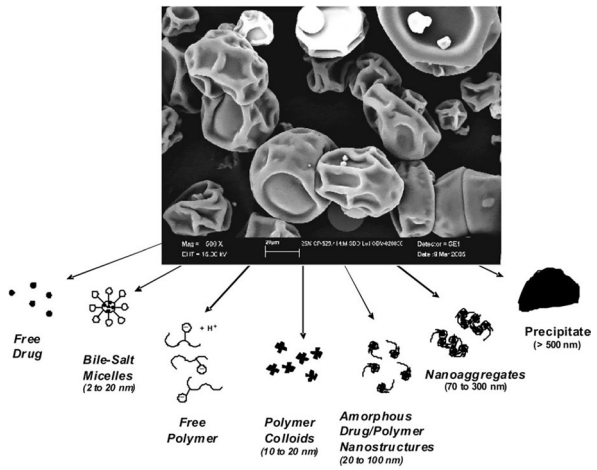


**Fig. 4** Species generated when ASDs are added to aqueous solution simulating duodenal and intestinal contents. Adapted from reference (Friesen et al. 2008)

Compared to other techniques, the advantage of FTIR is that samples in different physical states can be analyzed in a fast and noninvasive manner and with high chemical specificity. Given recent advancements in hardware and software, FTIR will continue to play a key role in ASD characterization, coupled with other advanced characterization methods.

## Raman spectroscopy

Raman spectroscopy is a complement to IR spectroscopy. Raman spectroscopy depends on changes in the polarizability of a molecule while IR spectroscopy depends on changes in the dipole moment. Raman spectroscopy measures the relative frequencies at which a sample *scatters* radiation. This is unlike IR spectroscopy, which measures the *absolute* frequencies at which a sample *absorbs* radiation.

Because light of shorter wavelengths is used, it is more common to combine Raman with microscopic analysis, as in *confocal Raman microscopy* (Paudel et al. 2015; Punčochová et al. 2016). In addition, Raman spectroscopy has been extensively used to characterize ASDs in the investigation of drug–polymer interactions, miscibility, and phase distribution (Andrews et al. 2009; Lust et al. 2015). Furthermore, chemical mapping with Raman spectroscopy has been employed to investigate in situ, real-time dissolution mechanisms of ASDs (Tres et al. 2014).

## Solid-state nuclear magnetic resonance

Solid state nuclear magnetic resonance (SSNMR) has been proven to be a powerful tool for gathering molecular-level information on the dynamics and phase compositions of

ASDs based on dipolar correlation, spin diffusion, and relaxation measurements (Paudel et al. 2014a, b). Table 6 summarizes the measurement time, sample status, application, advantages, and disadvantages of each technique. SSNMR is a stand-alone, nondestructive technique for the analysis of crystallization tendency (Aso et al. 2000), molecular mobility (Aso et al. 2009), miscibility, drug–polymer interactions (Pham et al. 2010), degree of crystallinity, and crystallization kinetics of ASDs (Ito et al. 2010).

SSNMR has even been used to monitor the dissolution behavior of ASDs. A strong correlation has been found between the crystallization rate of amorphous drugs and their molecular mobility as measured by their enthalpy relaxation and $H^1$ NMR relaxation times. The observation of spin diffusion effects with the 2D cross-polarization heteronuclear correlation experiment was used to probe the association between the amorphous drug and polymer.

Proton-relaxation measurement using variable temperature SSNMR (VT-SSNMR) is a valuable new thermal analysis method for predicting the physical stability of amorphous pharmaceuticals. $^{13}C$ and $^{15}N$ SSNMR are often used to examine hydrogen bonding between donors and acceptors. In addition, the application of standalone $T_1$ relaxation, or $T_1$ relaxation in combination with $T_1\rho$ measurements, has been used to determine whether an ASD has multiple domains or is homogeneous (Pham et al. 2010).

Song et al. (2015) used SSNMR to investigate drug–excipient interaction in lapatinib ASDs. $^{15}N$ SSNMR, $^1HT_1$, and $^1HT_{1\rho}$ provided direct spectroscopic evidence for the ionic interaction between lapatinib and HPMCP. This interaction was the key driver in stabilizing lapatinib ASDs. Dahlberg et al. (2011) employed NMR imaging technology to study the flutamide release profile of compacts of flutamide/HPMC ASDs in $D_2O$ at the beginning and after 6 h. The NMR data vividly demonstrated that the drug dissolution process from HPMC-based ASDs resulted from the following chain of events: water ingression of the tablet, hydration, mobilization, and the upward growth of the polymer gel layer.

## Methods for characterizing ASD behavior in aqueous media

The ultimate success of an ASD in improving the bioavailability of a poorly water-soluble drug is determined by its performance in the gastrointestinal tract after oral administration. The ability to monitor the extent and rate of drug solubilization is particularly important, since the drug release is the rate-limiting step in the absorption of these drugs. Inconsistent drug release from an ASD might lead to changes in bioavailability and concerns about safety or efficacy. Therefore, dissolution analysis is a critical characterization step in formulation screening, manufacturing process selection, and the monitoring of the physicochemical stabilities of ASDs during storage. The standardized dissolution test description and apparatus can be found in USP general chapter <711> (Fotaki et al. 2014).

The typical dissolution profiles of ASDs that show rapid initial buildup of drug supersaturation and then retardation of precipitation have been qualitatively characterized as a "spring and parachute." It is challenging to explore the ASD dissolution mechanisms because several dissolution processes occur simultaneously. Figure 4 shows that the main contributors to the final dissolution performance of ASDs are (a) the recrystallization of the drug in the ASD or after precipitation from a supersaturated solution, (b) the formation of nanoparticles and microparticles during the dissolution, and (c) the dissolution of polymeric carriers (Friesen et al. 2008).

Conventional dissolution methods only measure the drug concentration in dissolution media; they fail to offer any chemically or spatially resolved information about potential changes in the solid forms during the dissolution process. Given the limitations of conventional methods, innovative approaches have been developed in an attempt to provide a more holistic picture of drug release from ASDs. These approaches include UV imaging (Østergaard et al. 2014; Sun and Østergaard 2016), mid-IR (Van Eerdenbrugh et al. 2012; Kazarian and Ewing 2013), NIR (Wartewig and Neubert 2005), Raman spectroscopy (Alonzo et al. 2010; Tres et al. 2014; Punčochová et al. 2016), magnetic resonance imaging (Langham et al. 2012; Tres et al. 2015), $^1H$-NMR (Coombes et al. 2014), particle analysis (e.g., asymmetrical flow field–flow fractionation, cryogenic TEM) (Kanzer et al. 2010; Harmon et al. 2016).

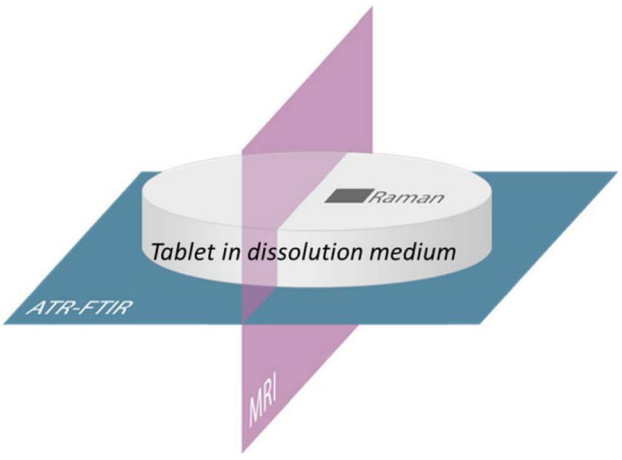


**Fig. 5** Scheme of image position relative to the tablet, provided by each imaging method. Adapted from reference (Punčochová et al. 2016)

UV imaging provides not only the drug dissolution rate in real-time, but also information on how the polymer influences drug recrystallization in the dissolution medium (Colombo et al. 2015). Tres et al. (2015) combined integrated magnetic resonance imaging, a UV–Vis flow cell system, and $^{1}$H-NMR to obtain a clear picture of drug release while simultaneously measuring the dissolution profiles and the rates of both drug and polymer release from ASDs. MRI and $^{1}$H-NMR data showed that a compact containing 5% of the drug eroded linearly. A model drug and KollidonVA64 were released at approximately the same rate from the molecular dispersion. At high drug loading (e.g., 30%), the data indicated a slower water ingress into the compact, which corresponded to a slower dissolution rate of both drug and polymer (Tres et al. 2015).

IR and Raman spectroscopy can provide chemically specific information. Raman spectroscopy is not as sensitive to water as IR spectroscopy. Therefore, Raman spectroscopy is more suited to characterizing dissolution behavior in aqueous environments. Tres et al. (2015) utilized Raman spectroscopic imaging along with multivariate curve resolution (MCR) analysis to study real-time, in situ dissolution mechanisms that underpin ASDs, and these were collected directly from the dosage form itself. Their study found that amorphous felodipine crystallized at different rates in different regions of the compact surface, indicating that crystallization followed an initial stage of heterogeneous nucleation (Tres et al. 2014).

Langham and Booth et al. (2012) used MRI to study the dissolution mechanism of spray-dried felodipine ASDs, and they found that drug loading has a profound impact on the physical behavior of the compact surface, which directly influenced drug dissolution performance.

Each of these techniques has been applied to study the dissolution behavior of ASDs. A better understanding of drug release can be achieved when these techniques are used in rational combination.

## Characterization tools used in conjunction

Most research studies combine different characterization techniques to build the most comprehensive profile of an ASD. Since each technique has specific limitations, the best practice is to combine two or more methods to provide sample information that cannot be achieved using a single method. In addition, simultaneous multi-method measurements on the same sample complement each other and either reveal important properties of ASD or increase confidence in the data interpretation of these complex systems (Paudel et al. 2014a, b). Reported conjunction tools include DSC–FTIR (Wu et al. 2011; Lin and Wang 2012), DSC–Raman (Huang and Dali 2013), DSC–PXRD (Pili et al. 2010), IR–AFM (Dazzi et al. 2012; Van Eerdenbrugh et al. 2012), and MRI–FTIR–Raman imaging.

Another example is the combined DSC–FTIR technique, a quick and easy analytical method used for collecting real-time thermodynamic and spectroscopic data from ASDs as they undergo thermal modifications (Lin and Wang 2012). FTIR provides real-time qualitative information that complements the heat flow changes measured by DSC. Lin et al. (1995) used DSC–FTIR to investigate heat-induced drug–polymer interactions.

The combined AFM–IR method is another promising technique for the evaluation of polymer–polymer and polymer–drug miscibility. AFM can achieve nanoscale resolution, but it fails to identify the chemical composition of different phases. IR can provide specific information about chemical composition, but it is typically limited in spatial resolution. Li et al. (Li and Taylor 2016) successfully used AFM–IR to characterize drug–polymer miscibility, and they found that AFM–IR is a unique analytical tool for the study of the microstructure of ASDs. The information collected from their AFM–IR analysis contributed to a mechanistic understanding of ASD phase behaviors.

Punčochová et al. (2016) employed three chemical imaging methods (MRI, ATR–FTIR spectroscopic imaging, and confocal Raman mapping) to understand the behavior of drug release from ASDs in a mixed polymer matrix. Each imaging method contributed a different aspect of the dissolution process, as shown in Fig. 5. A combination of these methods provides a powerful approach that can reveal the mechanisms and phenomena that control drug release from ASDs. They can also paint a global picture of different water penetration and polymer dissolution rates, which none of these techniques could conclusively determine alone.

## Emerging new techniques

### Terahertz spectroscopy

Terahertz spectroscopy (TPS) is a nondestructive technique that uses spectral information in the far-IR region of the electromagnetic spectrum to probe the long-range crystalline lattice vibrations, low-energy torsion, and hydrogen-bonding vibrations of pharmaceutical materials (Shen 2011). Over the past several years, TPS has received considerable attention in the field of pharmaceutics research. TPS and imaging technology provide novel approaches to characterize ASDs.

Since TPS relates to the *intermolecular* vibrations inside the lattice structure rather than intramolecular vibrations, TPS of amorphous materials shows no distinct spectral bands. Any recrystallization in an ASD may be monitored and qualified using TPS (Sibik et al. 2015). Using in situ

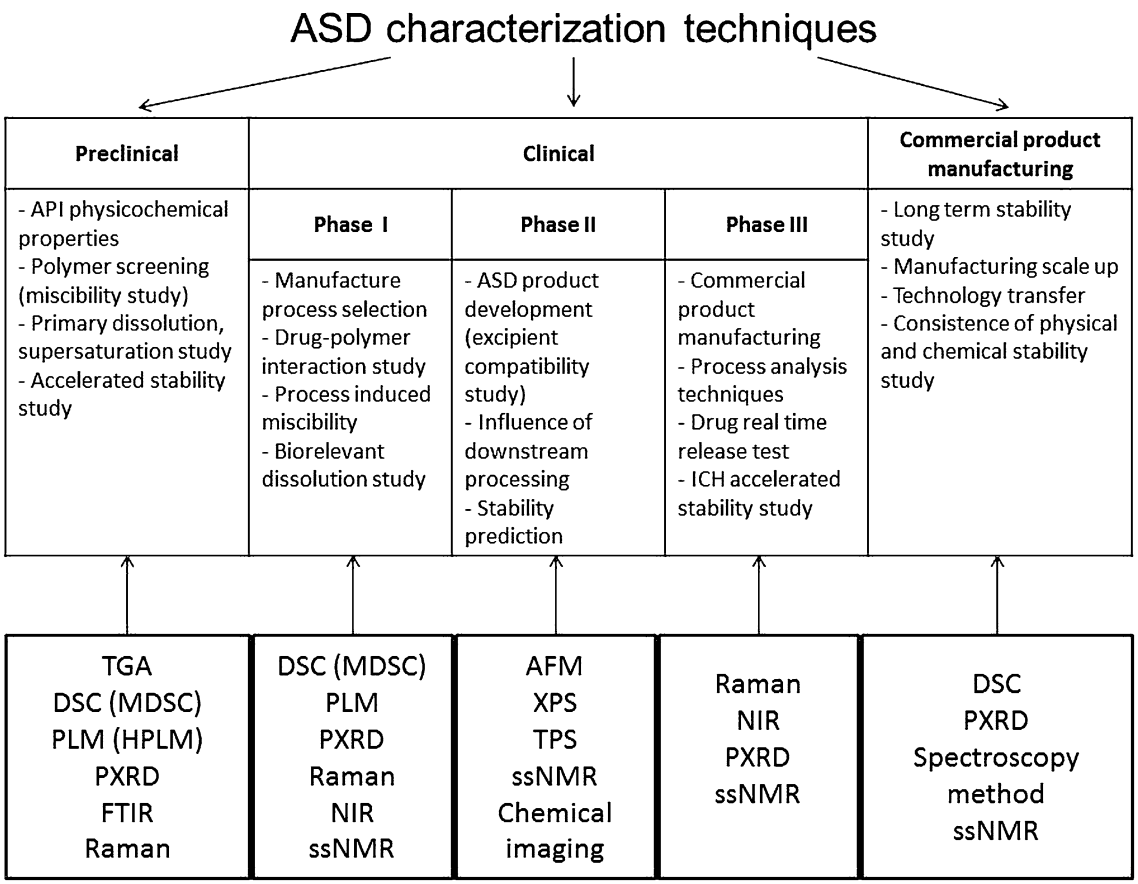


**Fig. 6** An overview of the application of various characterization methods at different stages of ASD-based product development. Modified from reference (Paudel et al. 2014a, b)

temperature-dependent TPS, the distinctive spectral changes that occur with increasing temperature provide essential information about relaxation and crystallization processes (Zeitler et al. 2007). In addition, TPS can be used to determine the onset and strength of molecular mobility, which underpins the crystallization of amorphous drugs (Sibik and Zeitler 2016).

### Dielectric spectroscopy

In dielectric spectroscopy, dipoles that have sufficient mobility respond to an external electric field. This response allows for the detection of molecular motions that have a relaxation time of $10^{-3}$–$10^{9}$ s over a wide temperature range (− 170 to 300 °C) (Bhardwaj and Suryanarayanan 2012). Dielectric spectroscopy is widely used to study complex systems in materials science, and it is attracting increasing attention as a powerful tool for the characterization of pharmaceutics materials (Grzybowska et al. 2016).

Dielectric spectroscopy has been used to directly measure the time scale of intramolecular and molecular motion, since both the cooperative and noncooperative motion of drug molecules can be obtained from this analysis. Various models can be used to analyze the dielectric data that capture the functional dependence of the dielectric response on the frequency, time, or temperature of ASDs. Fitting the data to these models, or applying the appropriate curve resolution to deconvolute various overlapping motions, provides an insight into the temperature and frequency dependence of each mode of motion. The time scale of physical instability can then be measured after identifying a link between specific modes of molecular motion and the crystallization tendency (Kothari et al. 2015; Mistry et al. 2015).

### X-ray micro-computed tomography

X-ray micro-computed tomography is a 3D image reconstruction technique that uses X-rays for medical imaging and materials science analyses. Compared to X-ray diffraction methods in which X-rays are reflected by an ordered array of atoms, X-ray micro-computed tomography generates 3D X-ray images based on the electron density differences observed between different phases contained within a

sample. X-ray micro-computed tomography has been used in ASD characterization to visualize and quantify the structure of spray drying particles, such as wall thickness and internal structures (Wong et al. 2014; Gamble et al. 2016).

It is difficult to use X-ray micro-computed tomography to distinguish samples that have similar attenuation coefficients, such as amorphous and crystalline materials. This limitation can be overcome by applying synchrotron radiation to improve the phase contrast (Álvarez-Murga et al. 2012). Qi et al. (Alhijjaj et al. 2017) have used X-ray micro-computed tomography as a quantitative method to characterize the drug phase separation in patches prepared by hot-melt extrusion and injection molding.

## Characterization methods in different stages of product development

The final quality of ASD-based products (including in vitro stability, in vitro dissolution, and in vivo performance) can be governed by the various physiochemical properties of ASD intermediates and ASD final products. These properties include molecular mobility, miscibility, glass transition temperature, hygroscopicity, and crystallinity. It is critical to characterize the primary quality attributes of ASDs at different stages in the product life cycle to ensure final product quality and meet project timelines. Figure 6 provides a brief overview of the various characterization techniques used at different stages of ASD-based product development.

### Preclinical studies

The major limitation of ASD products are their thermodynamic instability and their tendency to recrystallize during storage (Janssens and Van den Mooter 2009; Kawakami 2016). A desirable ASD product should maintain its amorphous state from the time of manufacture until drug administration. A proper formulation composition and optimal manufacturing process are important to develop a stable amorphous product with enhanced bioavailability. Before using ASD techniques to formulate a poorly water-soluble drug, it is important to understand whether the compound has the desired physiochemical properties (e.g., crystallization tendency, melting point, hygroscopicity, thermal stability) at preclinical stage. It has been proven that a compound must have a low crystallization tendency in order to be formulated as an ASD.

The physiochemical properties of the drug are the primary criteria for selecting the manufacturing process both at the laboratorial scale and the industry scale (Vasconcelos et al. 2016). Techniques such as PLM (HSPLM), TGA, DSC (MDSC), or PXRD are the most commonly used methods to probe the physicochemical properties of a drug. Polymer screening is another important aspect for ASD development, since good miscibility between the drug and the polymer is generally believed to be the prerequisite for physically stable ASDs. Techniques that have been explored for miscibility evaluation include DSC (MDSC), FTIR, PXRD, SSNMR, AFM, SEM, TEM, and Raman mapping. Last, other equally important aspects of a preformulation study for the development of an ASD include the drug loading, the selection of other formulation ingredients, primary drug dissolution, supersaturation studies, and stability studies.

### Clinical phase study

A clinical study generally consists of phase I, phase II, and phase III studies. Each phase has a different purpose and emphasis, so each phase requires different characterization methods to ensure the product meets the clinical study requirements.

In a phase I study, the formulation and process should be selected based on the preformulation study. Comprehensive studies on the kinetic miscibility between the candidate drugs and the selected polymers require various thermal and spectroscopic analyses. DSC (or MDSC), FTIR, NIR, and Raman spectroscopy are the core methods used to characterize the drug–excipient interaction and miscibility. SSNMR and PXRD (PDF) measurement can be used to determine the intensity of properties such as molecular interaction and crystallinity. Furthermore, the in vitro drug release from ASDs in biorelevant dissolution media is commonly used in the rational screening of formulations for human clinical trials. Finally, process analytical technology (PAT), which includes FTIR, NIR, and Raman spectroscopy, could also be used to monitor the manufacturing process to ensure product quality.

In a phase II study, the intermediate ASDs are always formulated into solid oral dosage forms such as tablets or capsules. The compatibility between the intermediate ASDs and other excipients, such as filler, binders, and lubricants, should be thoroughly investigated using DSC and Raman spectroscopy. In addition, the effects of downstream processing, such as roller compaction, on the physical stability of ASDs should not be ignored.

In a phase III study, reliable PAT methods should be used continuously to monitor the manufacturing process in real time. Since poor physical stability is the inherent shortcoming of ASDs, solid-state analytical methods of higher sensitivity (e.g., solid-state NMR or Raman spectroscopy) should be used to analyze the critical quality attributes of the intermediate and final ASD products.

## Commercial product manufacturing

Managing the commercial production of ASD-based products is more challenging than traditional products that contain crystalline drugs. Reports have shown that nearly 100 solid oral dosages of small molecular drug products were recalled by the FDA, and these reports indicate that failure in the dissolution rate specification was the prominent cause for recall. Since the dissolution performance of an ASD product is closely related to the physical state of the drug (Recall 2011–2013), the commercial manufacturing process should focus on the long-term stability of the product. In addition, qualitative and quantitative analyses of product quality attributes are required to support the technology transfer and manufacturing scale-up.

## Conclusion

Effective characterization methods play a critical role in the development of ASDs, although the complexities of ASDs present unique characterization challenges. Various techniques have been applied to analyze the critical quality attributes of ASDs. These techniques help us to better understand their thermodynamics and molecular-level processes, such as glass transition, molecular mobility, and the molecular interactions between the drug and polymer. This type of information is essential to the rational selection of formulation compositions and manufacturing processes of ASDs.

Over the past decade, significant progress has been made in the characterization of ASDs. This paper has summarized the basic methods that are widely applied in the characterization of ASDs in both the solid state and solution state. With more sensitive and accessible analytical tools, pharmaceutical scientists are gaining a better understanding of ASDs, which will lead to greater success in the delivery of poorly water-soluble drugs.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of human and animal right** This article does not contain any studies with human and animal subjects performed by any of the authors.

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