Journal of Drug Delivery Science and Technology 50 (2019) 113–124

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Characterization of amorphous solid dispersions: An update

Xiangyu Ma, Robert O. Williams III*

The University of Texas at Austin, Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, Austin, TX, 78712, USA

ARTICLE INFO

Keywords:
Amorphous solid dispersion
Material characterization
Thermal analysis
Microscopy
Morphology
Spectroscopy

ABSTRACT

Amorphous solid dispersions (ASDs) are a promising formulation approach to improve the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. ASDs have complicated physicochemical properties due to the various formulations and processes used to produce them. These properties influence their physical stability, so it is important to develop comprehensive and effective characterization techniques for ASDs. Our understanding of the properties of ASDs can be improved through the use of a combination of these techniques. Key factors that affect the properties of ASDs include the glass transition temperature (T_g), molecular mobility, miscibility, and crystallinity. These factors must be evaluated to ensure a stable ASD. In this review, we discuss the most relevant analytical characterization techniques and their applications for the evaluation of ASDs.

1. Introduction

High-throughput screening in drug discovery has improved the efficiency of drug discovery and has facilitated the identification of a considerable number of small-molecule drugs that have preferable permeability across biological membranes. However, most of these drugs exhibit low or no solubility in aqueous solution [1,2]. The oral absorption of drugs depends on their solubilization and permeation. Thus, low solubility hinders the oral absorption and bioavailability of drugs, requiring the use of other routes of administration, including intravenous administration, which places a heavy burden on both patients and health care personnel [3]. In contemporary formulation development, the strategy of using *amorphous solid dispersions* (ASDs) to improve the bioavailability of poorly water-soluble drugs has been reported. Compared to the crystalline forms of drugs, ASDs have advantages in terms of supersaturation solubility, dissolution, and improved bioavailability [4,5].

Nevertheless, the lack of physical stability of ASDs reduces the potential for their application in commercial products [6,7]. Chemical potential ultimately governs the solubility of drugs; and in ASD systems, the free energy is increased due to various energy inputs. This leads to the conversion of the crystalline form to the amorphous form [8]. Hence, ASDs are thermodynamically unstable compared to the crystalline form, which has the lowest internal energy [9]. However, polymers, as a matrix-forming excipient for ASDs, can inhibit the recrystallization of amorphous drugs by either exhibiting higher viscosity when it is below the glass transition temperature (T_g) or through drug–polymer interactions [10]. Optimally, ASDs would be kinetically stable for the duration of their anticipated shelf-life, but they eventually revert to their crystalline form, albeit at a slow rate [11]. In addition, when ASDs are exposed to moisture (e.g., during storage under high humidity conditions), the presence of water significantly increases the mobility of the drug and reduces the ability of polymers to inhibit recrystallization.

It was recently reported that between 2007 and 2017, the Food and Drug Administration approved 19 commercial ASD products [12]. Therefore, it is becoming more accepted as a formulation design strategy to address the overabundance of poorly water-soluble drugs now in development (more than about 70%) [13]. However, ASDs are complex dosage forms, and they present challenges in terms of the physicochemical properties that influence their stability and performance. Thus, the development of ASDs requires new and advanced characterization techniques to study their properties.

One challenge that arises when formulating an ASD is that both the drug and the polymer are dispersed and mixed together at the molecular level, making accurate characterization more difficult [14]. Fortunately, newly emerging characterization techniques provide insight into the characterization of ASDs in both quantitative and qualitative ways. Characterizing ASDs optimally should combine different techniques to investigate their physicochemical properties at different stages of development. In this paper, we provide a comprehensive review of ASD characterization techniques. By discussing their theoretical foundations, we provide a basic understanding of how these techniques are applied to the characterization of ASDs. Also, we review the various applications of these characterization techniques for analyzing the key factors that affect the stability of ASDs, including T_g, molecular

* Corresponding author.
E-mail address: bill.williams@austin.utexas.edu (R.O. Williams).

https://doi.org/10.1016/j.jddst.2019.01.017
Received 27 November 2018; Received in revised form 10 January 2019; Accepted 10 January 2019
Available online 12 January 2019
1773-2247/

mobility, drug–polymer miscibility, crystallization tendency, and crystallinity.

2. Properties affecting the stability of amorphous solid dispersions

2.1. Glass transition

Compared to crystalline materials, amorphous solids have both solid-like and liquid-like properties, depending on temperature. The glass transition temperature is the point at which amorphous solids transition from glass to supercooled liquid. During this transition, the amorphous solid will experience a step change in heat capacity, thus the molecular motion changes from vibration to rotation. This process increases the mobility of the molecule and changes the properties of the amorphous solid [15]. Many theories about glass transition have been reported [16,17]. In this review, we focus on glass transition temperature in terms of its use in characterizing ASDs.

2.2. Molecular mobility

Molecular mobility directly relates to the physical stability of ASDs. Amorphous drugs have higher internal energy, leading to a higher solubility and improved dissolution and absorption of the drug. However, this higher internal energy may also increase the mobility of ASDs, causing physical instability. Thus, it is critical to prevent the crystallization of amorphous drugs. This crystallization behavior involves two processes: *nucleation* and *crystal growth*. Both of these processes require the agglomeration of drug molecules, thus molecular mobility is one of the important factors that governs this process [18].

2.3. Miscibility

An ASD drug is, by definition, dissolved in a matrix (e.g., a polymer carrier) at the molecular level. This characteristic is important for the stability of ASDs, and miscibility is an indicator that describes the phase behavior of the drug and the polymer [19]. As an example, consider the attempt to dissolve oil in water. Due to their immiscibility, a single-phase solution can never be achieved. Likewise, if the drug is not miscible with the polymer in a solid dispersion, rapid crystallization can occur and result in phase separation, which creates drug-rich domains and polymer-rich domains [20]. Thus, the miscibility between the drugs and the polymers in ASDs must be characterized and understood. Interactions between drugs and polymers can affect miscibility. Miscibility can be investigated using spectroscopic techniques that measure the specific molecular interactions. It has been reported that if the polymer forms hydrogen bonds with itself, it becomes difficult for the drug to interact with the polymer, thus causing lower miscibility between the drug and the polymer. This influences the stability of ASDs [21,22]. Also, glass transition can be used to study miscibility.

2.4. Crystallinity

Knowledge of the crystallinity of the formulation is important for ASD characterization. First of all, the crystallinity of the drug in an ASD should be zero when it is new, because even a miniscule number of crystals can induce crystallization of the drug during shelf-life storage. Secondly, the crystallinity of ASDs during storage should be evaluated to assess the physical stability of ASDs. Thus, ASDs with zero crystallinity ensure the formulation retains the advantages of ASDs (e.g., increased solubility, improved bioavailability) over time. Since the microstructure of crystals is different from their amorphous state, almost every technique that detects changes in properties based on the molecular structure can be utilized to study crystallinity [23].

2.5. Crystallization

Many factors can influence the crystallization tendency of the drug in an ASD, such as the glass transition temperature, molecular mobility, and drug–polymer miscibility. Polymers can inhibit the crystallization of drugs during shelf-life storage, but the crystallization tendency of the drug itself is most important for the stability of ASDs [24]. The *glass forming ability* (GFA) of a drug is one factor that describes the possibility of the drug transitioning to its amorphous state. GFA is a property of pharmaceutical materials that should be evaluated to provide information for the development of ASDs of poorly water-soluble drugs [24]. GFA is determined using thermal techniques, including *differential scanning calorimetry* (DSC), *modulated DSC* (MDSC), and *hot-stage polarized light microscopy* (HSPLM).

3. Description and applications of characterization techniques for amorphous solid dispersions in the solid state

3.1. Thermal analysis techniques

Thermal techniques are used to characterize ASDs [24]. They are conducted as a function of temperature, which enables the characterization of the thermodynamic properties of ASDs. In this section, the principles and applications of thermal techniques are discussed.

3.1.1. Calorimetric techniques

Calorimetry measures changes in heat [25]. These heat changes correlate with the temperature differences of the samples during specific processes, such as physical transitions or chemical reactions, which can be either endothermic or exothermic processes [26]. Current calorimetric equipment can analyze samples as a function of time or temperature while the temperature profile can be programmed. Based on the principles of measurement, two types of calorimeters exist, the *heat exchanging* calorimeter and the *heat compensation* calorimeter [27]. In the following subsection, the theoretical fundamentals of several universal calorimetric techniques are discussed.

3.1.1.1. Differential scanning calorimetry (DSC). DSC can be classified into two types: *heat flux* DSC and *power compensation* DSC [26]. DSC has a well-defined heat path in which two identical thermocouples are placed symmetrically outside the pan. This enables the quantitative measurement of the heat flow and the calculation of the area under the heat flow curve. Heat flux DSC is more robust and easier to handle compared to power compensation DSC [26]. Yet, by using power compensation DSC, a much higher heating or cooling rate can be achieved [28]. Generally, most current DSCs are designed and developed around the heat flux principle [29].

Kinetic events, such as crystallization, curing, and most forms of degradation, can be described using the Arrhenius equation. To correlate the heat flow signal obtained by DSC with the Arrhenius equation, a constant of proportionality, H', is introduced [26]. Since, during kinetic events, the heat capacity change of the sample also contributes to the total heat flow, a term of the heat capacity contribution is included, and the result is Equation (1):

$$\frac{dQ}{dt} = \beta C_p + H' f(\alpha) A e^{\frac{-E_a}{RT}}, \tag{1}$$

where β is the heating rate, α is the extent of the reaction, $f(\alpha)$ is a function of α, A is a constant, E_a is the activation energy, and R is the gas constant. This correlation is fundamental for the understanding of kinetic processes, and some advanced kinetic functions need more complex analysis and the incorporation of additional parameters to achieve an accurate measurement.

Phase transitions during the heating or cooling cycle are of interest for pharmaceutical science. Most research has usually focused on melting and glass transition. Melting is a first-order phase transition

(Equation (2)) that involves latent heat. For such a process, the system may absorb or eject heat while the temperature remains constant. Integrating the peak area in the heat flow–temperature diagram indicates the heat of fusion, which represents the energy required for melting. Conventional DSC has superior accuracy when measuring the melting process, especially in samples that exhibit a sharp melting transition or crystal defects compared to MDSC, which will be discussed in the next section.

Equations (2) and (3) are as follows:

$$\frac{\delta \Delta G}{\delta T} = -\Delta S \neq 0 \tag{2}$$

and

$$\frac{\delta^2 \Delta G}{\delta T^2} = -\left(\frac{\Delta C_p}{T}\right) \neq 0, \tag{3}$$

where G is the Gibbs free energy and S is entropy.

For measuring the glass transition point, DSC is the most commonly used technique to directly obtain the glass transition temperature [24]. Glass transition is an essential property of ASDs, which indicates the mobility of the system. It is a second-order phase transition (Equation (3)), which means the heat capacity of the sample has a step change as a function of temperature (i.e., it is a discontinuous process) [30]. Generally, the heat capacity represents the *sensible energy* of a substance (the portion of the internal energy of a system associated with the kinetic energies of the molecules), which consists of vibrational, rotational, and translational energies [31]. When the temperature is below T_g, the heat capacity is dominated by vibrational motion. During the glass transition, rotation controls the phase change. Above T_g, translational motion contributes to the heat capacity change as a function of temperature. Essentially, the glass transition is a change of the heat capacity within a small temperature range, which can be measured by both conventional DSC and MDSC, but MDSC is more sensitive [32].

3.1.1.2. Modulated differential scanning calorimetry (MDSC). DSC exerts a linear temperature program on the sample to obtain the temperature difference between the sample and the reference, while MDSC applies a periodic temperature perturbation on the linear program, which has many advantages for analyzing complex and overlapping thermal events [33]. For example, samples that exhibit strong relaxation show a significant enthalpy recovery peak, which, to some extent, makes it impossible to measure the glass transition using conventional DSC. In Equation (4), the term $C_p \cdot \frac{dT}{dt}$, involves the heat capacity and the heating rate.

First, the heat capacity, as mentioned before, represents molecular motions (i.e., vibrations, rotations, and translations). Therefore, as temperature increases, more energy is stored in the sample as increased motions. When temperature decreases, the same amount of energy is released, and molecular motions return to the exact same state as before the heating occurred.

Second, the heating rate varies in MDSC, which varies the heat capacity of the sample as it responds linearly to the heating rate. Thus, MDSC can separate the event that depends on the heating rate (i.e., the heat capacity change) from the event that is not associated with the heating rate (i.e., kinetically hindered events such as crystallization and decomposition). In the second term on the right side of Equation (4), kinetic events contribute to $f(T,\ t)$, which do not depend on the heating rate. In other words, when the heating rate is zero, the total heat flow represents the kinetic transition (i.e., crystallization, decomposition, and curing).

Based on this theory, the first term is assigned as reversing heat flow, and the second term is non-reversing heat flow (Equation (5)). Essentially, only reversing heat flow and total heat flow are measured, and by subtracting one from the other, the non-reversing heat flow is obtained. Table 1 lists all the thermal events that may occur in either reversing or non-reversing heat flow signals. Modulation can differentiate reversible and irreversible thermal events, but this cannot be interpreted to mean that all signals from reversing heat flow or non-reversing heat flow are reversible or irreversible, respectively.

Table 1
Examples of thermal events in different heat flows in MDSC.

Total Heat Flow	Reversing Heat Flow (thermodynamic components)	Non-reversing Heat Flow (kinetic components)
All thermal events	Heat capacity Glass transition Melting (most)	Enthalpy recovery Evaporation Crystallization Thermoset cure Denaturation Degradation Melting (some)

Equation (4) is as follows:

$$\frac{dQ}{dt} = C_p \cdot \frac{dT}{dt} + f(T,\ t), \tag{4}$$

where $\frac{dQ}{dt}$ is the total heat flow, C_p is the heat capacity of the sample, $\frac{dT}{dt}$ is the heating rate, and $f(T,\ t)$ is a function of temperature and time that consists of the contributions from kinetic events.

Equation (4) is as follows:

$$\dot{Q}_{Total} = \dot{Q}_{Reversing} + \dot{Q}_{\ Non-reversing}. \tag{5}$$

Kinetic and thermodynamic events can be differentiated using MDSC, but this is not the case with melting. Melting involves a latent heat, which means that heat is absorbed or released at a constant temperature. Thus, at the melting temperature of a sample, the amount of energy needed to melt all crystals is fixed. This means that during heating, if heat flow increases (e.g., is doubled), the time for the melting of all crystals is reduced by half [26]. This follows the principle that the heat flow for melting is linearly correlated with the heating rate. Therefore, the heat of fusion is incorporated in the reversing heat flow. There are some exceptions, however. First, crystals are not perfect. In other words, the structure of crystals always includes defects, especially for polymers [34]. The distribution of different crystals with varying imperfections results in a relatively high-energy crystalline structure that melts first with less energy and may transform to a more stable crystalline form. Then, the more stable crystals melt until the melting is complete.

This phenomenon makes it difficult to interpret the melting from reversing heat flow, because it also includes the energy used to melt some of the recrystallized crystals (which often shows a broad endothermic peak in non-reversing heat flow) [26]. In addition, to some extent, heating a sample by transferring heat to it is not complete when the heating rate is high enough so that the sample temperature cannot match the modulated heating rate [35]. This occurs when a large amplitude, a short period, or a higher mass is present. Hence, it also shifts some melting to non-reversing heat flow because it shows kinetic processes [36]. Also, both heat capacity change and the latent heat of fusion are observed during melting. Since these two phenomena respond differently to temperature modulation, the separation of reversing and non-reversing heat flows changes when experimental conditions are varied [37]. Table 2 summarizes some advantages and disadvantages of MDSC and DSC for various thermal events.

3.1.1.3. Applications of DSC and MDSC to characterize ASDs. Glass transition is a thermal event, and several techniques can be used to characterize the glass transition of ASDs. DSC is the most commonly used thermal analysis to investigate the glass transition of ASDs [38]. However, care should be taken when performing DSC on ASDs.

Richardson and Savill reported that DSC cannot directly measure T_g due to kinetic effects. This effect is especially serious for annealed samples. Thus, experimental conditions, such as the heating or cooling

Table 2
Comparison of MDSC and conventional DSC.

	Modulated DSC	Conventional DSC
Advantages	Separation of complex and overlapping thermal events; Deconvolution of heat capacity and kinetically controlled events; Glass transition: increased limit of detection and sensitivity, trustable interpretation, accurate quantification of amorphous phases, available calculation of relaxation time; Study of phase separation; Melting: separation of crystallization from melting; Crystallization: easy interpretation from non-reversing heat flow	Suitable for the measurement of melting; Simple experimental settings; Time-cost efficient
Disadvantages	Carefully experimental designs; Strongly conditions dependent; Melting: difficult interpretation, not accurate measurement in MDSC	Unable to analyze overlapping events; Lower sensitivity for heat capacity measurement; Lower limit of detection of thermodynamic events

rate, can heavily influence the T_g. They also proposed a way to eliminate these effects to acquire an equilibrium T_g value. In this method, they converted the heat flow signal to enthalpy curves, and by extrapolating these curves to the intersection of liquid and glass, the effect of the heating and cooling rate was avoided and a relatively precise T_g was obtained.

Another concern is enthalpy recovery during the glass transition. This event can overlay the T_g and make it difficult to accurately obtain the T_g. This problem can be addressed by MDSC. Geert et al. utilized MDSC to measure the T_g of solid dispersions of itraconazole–HPMC (hydroxypropyl methylcellulose). The enthalpy recovery can be separated by MDSC into non-reversing heat flow, and only the glass transition was presented in the reversing heat flow [39]. Many studies used DSC and MDSC to perform heating and cooling cycles on ASDs to measure the number of glass transition events. If only one glass transition is observed for an ASD, this means the drug and the excipients have good miscibility, which is favorable for the stability of ASDs.

Nayamewa et al. utilized MDSC to study the miscibility of HPMC with various polymers. Their results show that only polyvinylpyrrolidone (PVP) and methylcellulose are miscible with HPMC [40]. Six et al. investigated itraconazole–Eudragit E100 solid dispersions using MDSC. Their results indicate that the limit of miscibility is 13% drug in the polymer, above which excess drug was in a separate amorphous phase. This may cause instability of the ASD [41].

Another study also used DSC to investigate the T_g of the mixtures of two components. The results indicate that only a single T_g is achieved when the drug loading is below 25% [42]. Friesen et al. assessed a set of ASDs containing hypromellose acetate succinate (HPMCAS). They found that compounds having a lower ratio of T_g to T_m tended to crystallize more quickly than those compounds that have a higher ratio of T_g to T_m in ASDs. This result indicated that the inherent crystallization tendency should be considered [43].

Critical cooling rate is also an important parameter to evaluate GFA. It can be obtained using DSC. Several pharmaceutical compounds have been investigated. Results suggest that compounds with very low critical cooling rates have higher GFAs [44]. From a thermodynamic point of view, glass stability relates to the configurational properties of ASDs, including Gibbs-free energy, enthalpy, and entropy. These properties can be measured using MDSC or, more preferably, conventional DSC [24]. Studies show that higher configurational entropy of ASDs could improve the stability of amorphous drugs and inhibit crystallization [45].

Maesac et al. evaluated the thermodynamic and kinetic properties of amorphous drugs using MDSC and HSPLM. Compared to felodipine, a higher crystallization tendency was observed for nifedipine, which possesses a much higher thermodynamic driving force, configurational Gibbs-free energy [46]. Yoshihashi et al. used DSC in the isothermal mode to measure the induction time of crystallization to indicate the capacity of polymers to inhibit crystallization [47].

Various techniques are available for investigating the molecular mobility of ASDs. Several properties of ASDs are good indicators of molecular mobility, such as viscosity, glass transition temperature, and relaxation time [24]. A study investigated the enthalpy relaxation time and spin-lattice relaxation time using DSC and ssNMR to explain the decreased crystallization rate of three drugs at a temperature below their T_g. Researchers observed no crystallization at temperatures 20–30 °C lower than the drug's T_g. In this study, DSC and ssNMR were used to measure the enthalpy relaxation and spin-lattice relaxation time, respectively. In the temperature scale, the enthalpy relaxation time of nifedipine was shorter than phenobarbital and flopropinone. This indicates that nifedipine has a higher molecular mobility. At a temperature below its T_g, nifedipine exhibited a much smaller $T_{1\rho}$ than others. This explained the faster crystallization rate of nifedipine either above or below its T_g [48].

Liu et al. used isothermal microcalorimetry (IMC) to successfully obtain the structural relaxation time. IMC directly measured the heat release during the relaxation processes. By fitting the data to the Kohlrausch–Williams–Watts equation (Equation (6)), the structural enthalpy relaxation time is obtained [49].

$$\varphi(t) = 1 - \frac{\Delta H_{relax}}{\Delta H_{infinite}} = e^{-\frac{t}{\tau_{KWW}}^{\beta}}, \quad (6)$$

where ΔH_{relax} is the enthalpy recovered after isothermal annealing, τ_{KWW} is the average relaxation time, and $\Delta H_{infinite}$ is the total enthalpy available for relaxation at the annealing temperature [50].

3.1.2. Thermo-rheological techniques

The rheological properties of polymers are critical for the development and performance of ASDs, which predominantly consist of polymer(s) and a drug [51]. For example, during the preparation of ASDs, their rheological properties (e.g., viscosity) heavily influence processability [52], the degree of mixing [53], and quality control [24]. In rheology, three terms are used to describe the rheological responses of polymers: *elasticity*, *viscosity*, and *viscoelasticity*. Most polymers used for pharmaceutical applications are viscous; specifically, they are non-Newtonian liquids when in the molten state. A non-Newtonian liquid has variable viscosity that corresponds with the shear rate and stress (e.g., shear thinning, shear thickening, plastic effects) [26]. The rheology of polymers is a relevant factor in the formulation of ASDs and can influence the preparation of ASDs by using hot melt extrusion [54].

Now, we will briefly discuss the principles and applications of the two most commonly used methods for measuring these rheological properties: *dynamic mechanical analysis* (DMA) and *thermomechanical analysis* (TMA).

3.1.2.1. Dynamic mechanical analysis (DMA). There are several methods currently used to characterize the rheological properties of polymers, and they are either *oscillatory* or *non-oscillatory*, *destructive* or *non-destructive*, *temperature ramping* or *isothermal* techniques. Dynamic mechanical thermal analysis is a non-sample-destructive technique. It

measures the resultant strain that comes from the applied oscillatory stress, and it builds a function of the strain determined versus frequency or temperature. DMA has different programs that allow the temperature to either ramp or remain constant. Thus, the temperature effects on rheology can also be evaluated [55]. Therefore, DMA is a convenient, accurate, and time-efficient technique for acquiring the viscoelastic properties of polymers.

Some important properties that DMA measures are the *storage modulus* (G'), *loss modulus* (G''), *complex modulus* (G^*), *damping factor* ($\tan\delta$), and *complex viscosity* (η^*) [56]. These will be explained individually. Complex modulus is the ratio of the stress amplitude to the strain amplitude. Since a phase lag exists between strain and stress, the storage modulus is the portion of the strain that is in phase with the stress. Storage modulus represents the energy that is stored in the sample. Loss modulus is the portion of the strain that is 90° out of phase from the stress. Since viscous deformation is not recovered upon the removal of the stress, the energy causing the deformation is transformed to heat due to friction, which referred to as *dissipation*. Thus, loss modulus describes the viscous properties of the sample. Another important parameter is the damping factor. It is the ratio of the loss modulus to the storage modulus, which represents the ability of a sample to transform applied mechanical energy into heat. Generally, amorphous glass and crystals have a damping factor of 0.2–3.0 and 0.01–0.10, respectively [57]. Complex viscosity is especially useful in oscillatory analysis. It is the ratio of the complex modulus to the angular frequency. Due to the Cox–Merz relationship, complex viscosity can be correlated with shear viscosity as a function of the shear rate. This helps characterize those materials that cannot be evaluated under shear conditions [56]. Overall, analyzing the rheological properties of ASDs provides a better understanding of molecular mobility based on viscosity [58], and it provides an extra method to evaluate the glass transitions of ASDs [59].

3.1.2.2. Applications of DMA in the characterization of ASDs. DMA is also a sensitive technique that can measure the glass transition of ASDs. Royall et al. used DMA to successfully detect the amorphous phase in pharmaceutical powdered materials and to determine the glass transition temperature based on the modulus change at T_g [60]. Measuring the glass transition of solid dispersions can provide more information of the physical stability of these systems. For example, some studies used glass transition behavior measured by various techniques to investigate the physical state of the drug and polymers [61], the miscibility of drugs in the matrix [62], and potential specific interactions [63].

Another property of ASDs that can indicate molecular mobility is viscosity, which can be measured by dynamic thermal analysis. Andronis et al. used DMA to study the viscosity of amorphous indomethacin around and above its glass transition temperature. Their results show that the viscosity of indomethacin did not follow Arrhenius kinetics, and they observed significantly higher molecular mobility at T_g. This possibly explains why the crystallization rates were higher at these temperatures [58,64]. DMA can also be used to investigate miscibility. This study found that the miscibility of acetaminophen in poly (ethylene oxide) was dependent on temperature. DMA showed that the miscibility of the drug increased from 14% at 80 °C to 41% at 140 °C. This result was similar to polarized light microscopy, which is discussed below [65].

3.2. Microscopic and morphological techniques

Microscopy is used to characterize ASDs in the solid state [66]. Various applications of microscopy are available in the pharmaceutical field to analyze the physiochemical properties of ASDs, such as glass transition, the miscibility of the drug and polymer, crystallization behavior, crystallinity, morphology, thermal events, and dissolution [67,68]. Generally, microscopic techniques are classified into three types: *optical*, *electron*, and *scanning probe* microscopy. These include polarized light microscopy, X-ray diffraction, scanning electron microscopy, and atomic force microscopy, which are widely used methods that allow rapid, non-destructive measurements [69]. In this section, the theoretical principles of these methods will be briefly discussed.

3.2.1. Polarized light microscopy (PLM)

PLM has great value for investigating the solid-state properties of ASDs by simply examining samples under a microscope. It is the fastest way to examine the successful preparation of the drug in the amorphous state. Various invaluable types of information can be easily obtained with reliability that is comparable to other methods [70,71]. It is an indispensable tool to support other sophisticated methods, such as X-ray diffraction, thermal analysis, solid-state NMR, and vibrational spectroscopy [72].

Crystal systems can be classified into three categories: *isotropic*, *anisotropic uniaxial*, and *anisotropic biaxial* [73]. Each type of crystal system has different optical properties, and each of these optical properties has different principles for characterization using crossed polarizers. For example, neither cubic crystals nor a disordered substance has interference colors or birefringence, while anisotropic materials show such behavior. This difference can be utilized to differentiate crystal systems, although with caution. In general, most crystalline drugs are not isotropic. In other words, they do not have a cubic crystal structure. Thus, PLM can be used to identify crystalline drugs and amorphous drugs (disordered) based on these differences in optical properties [73]. Table 3 lists several optical properties of the three types of crystals.

Table 3
Optical properties of different crystal systems under crossed PLM (Adapted with permission [73]).

Crossed polars	Isotropic	Anisotropic, uniaxial	Anisotropic, biaxial
	Cubic, disordered	Tetragonal, hexagonal	Orthorhombic, monoclinic, triclinic
Interference colors		✓	✓
Anomalous interference colors		✓	✓
Birefringence		✓	✓
Extinction position		✓	✓
Extinction angle			√ (Monoclinic and triclinic Only)
Dispersion of extinction angles			✓
Interference figure		✓	✓
Optic sign		✓	✓
Optic axial angle (measured)			✓
Optic axial angle (calculated)			✓
Dispersion of optic axes			✓
Acute bisectrix			✓
Optical orientation			✓
Sign of elongation		✓	

The most applied criterion to determine crystallinity is birefringence. It is particular to anisotropic systems in which the refractive indices vary inside the crystals, and the difference between the highest and lowest refractive indices generates the birefringence. Hot-stage PLM (HSPLM) is a combination of thermal analysis and microscopic analysis [24]. It incorporates both special features of these two techniques, providing unique insights and comprehensive interpretation of the data. HSPLM can be used to analyze the crystallization behavior of ASDs (stability) and the miscibility of the drug and polymer, and it can visualize the thermal events observed in DSC.

3.2.1.1. Applications of PLM and HSPLM in the characterization of ASDs. PLM is sensitive enough to detect small crystals and nuclei in ASDs compared to XRD. Telang et al. investigated the physical stability of indomethacin ternary ASDs. They find that by adding meglumine into the formulation, indomethacin can form a strong interaction with meglumine through the acid–base mechanism. The stability study shows that the ternary ASDs were stable for up to 7 months, which was indicated by XRD. However, PLM results demonstrate that small crystals were formed at 7 months. Therefore, the authors suggested that PLM may be a more relevant tool to study the physical stability of ASDs because of its high sensitivity compared to XRD [74].

In the study by Cai et al. HSPLM was used to investigate how polymers added to ASDs influence the crystallization of nifedipine. By placing different formulations under different temperatures in a hot stage, the crystal growth can be clearly observed through PLM. Through calculating the diameter of the crystals over a certain period, different crystallization rates were observed for different formulations. Their results demonstrate that only 1% of the polymer can reduce the crystal growth rate by half [75].

Another study by Raina et al. also utilized PLM to study the stability of nifedipine ASDs with different polymer contents when they were exposed to dissolution media. Their results suggest that PLM can detect with high sensitivity the small crystals presented in the ASDs upon exposure to dissolution media. The results also suggest that by adding polymers to form ASDs, crystallization during dissolution was significantly reduced [76].

Also, Andronis et al. used PLM to study the nucleation of amorphous indomethacin, and they quantified the crystallinity as a function of temperature [77]. In addition, HSPLM can help develop the manufacturing process to prepare ASDs. Li et al. reported that HSPLM can be used to investigate the potential interactions between the drug and polymers. By observing the melt depression of different drug–polymer blends, suitable polymers can be selected for hot melt extrusion. Also, a rational drug loading can be chosen based on the occurrence of crystallization through heating and cooling physical blends under HSPLM [78]. Moreover, PLM can be used as a supplemental technique to confirm and explain DSC observations. Liu et al. used PLM to confirm several thermal events, which were observed in DSC experiments. In situ formation of cocrystals or salts between the drugs and excipients were observed under HSPLM, which correspond to the results from DSC [79,80].

3.2.2. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction is a convenient technique for analyzing the crystal structures of organic, inorganic, and polymeric materials. Every crystal has its unique arrangement of atoms and repeating units. When X-rays are applied, these atoms are irradiated and generate a series of distinct peaks, which is used to unambiguously identify the crystalline components. Even if the chemical composition of two materials is identical, XRD can still distinguish these two materials based on their different molecular structures. Since PXRD can rapidly perform measurements on pharmaceutical powders, it has been widely used as a preferable analytical technique in both industry and academia [66].

X-rays are a form of electromagnetic radiation of wavelengths ranging from 10^{-3} Å to several hundred Å. They diffract when they encounter obstacles. Crystals have three-dimensional structures composed of many repeating units of the same motif. Thus, crystals can serve as a diffraction grating for X-rays, which is the basis of PXRD. This dimensional theory was simplified by Bragg in 1914, who demonstrated that this diffraction is analogous to the reflection of X-rays by sets of parallel planes of atoms [81].

3.2.2.1. Applications of XRD in characterization of ASDs. XRD is a commonly used technique for detecting the presence of crystals and evaluating the crystallinity of ASDs. Lyophilized ASDs were examined by using XRD, and a quantitative analysis was achieved [82]. Norman et al. combined XRD and Raman spectroscopy to quantify ternary mixtures in the solid state. Using principal component analysis, quantitative measurements of crystallinity can be achieved using Raman and XRD, with errors of 2.5–4.5% and 5.0–6.9%, respectively [83]. Rumondor et al. used PXRD to measure the crystallinity of different ASDs exposed to various storage conditions to study the effects of polymer types, moisture, and miscibility. It was suggested that over the concentration range of interest, molecular-level mixing was confirmed in nifedipine and felodipine poly(vinyl pyrrolidone) (PVP) ASDs [21]. PVP and HPMCAS were found to effectively inhibit the crystallization of felodipine ASDs [84]. In addition, amorphous–amorphous phase separation was observed when ASDs were exposed to high humidity, which favors the crystallization of ASDs in the stability studies [20].

By combining PXRD with pair distribution functions (PDF) and the pure curve resolution method, the miscibility of ASDs can be analyzed for both completely or partially miscible systems [21]. Another study of Nollenberger et al. demonstrated the feasibility and advantages of using PDF with PXRD. By conducting only PXRD measurements, they could not find differences in formulations with or without EudragitR NE. However, through applying PDF to PXRD, they could observe small changes in local structures of the ASDs, which improved the properties of felodipine ASDs. These results suggest that with the addition of 5% EudragitR NE, felodipine ASDs exhibits a faster dissolution and less crystallinity compared to the ASDs without EudragitR NE [85]. Furthermore, Araujo et al. used high-energy XRD with PDF to successfully differentiate ASDs with concentrated-amorphous domains and molecularly dispersed ASDs. They find that lapatinib interacts with hypromellose phthalate (HPMCP) through ionic mechanisms. This local interaction contributes to the superior stability of lapatinib–HPMCP ASDs, which are molecularly dispersed ASDs [86].

Takeuchi et al. investigated the feasibility of using terahertz time-domain spectroscopy to measure the crystallinity of nifedipine ASDs, and they compared the results with PXRD. Their results suggest that both techniques can measure crystallinity, and the results of both techniques are comparable [87]. Zhu et al. utilized small-angle X-ray scattering to study the crystallization kinetics of ASDs under various temperature and humidity conditions. Their results suggest that naproxen crystallized faster at 25 °C compared to 40 °C, and with the addition of polyethylene glycol, the crystallization rate of the ASDs was slowed down at 40 °C [88].

3.2.3. Scanning electron microscopy (SEM)

Scanning electron microscopy is extensively used in pharmaceutical science for development and quality control [66]. The main purpose of using SEM is to analyze the particle size, morphology, and surface properties of formulations. Also, a quantitative analysis can be achieved for size measurements [89]. SEM can be applied to evaluate the effects of different processes (e.g., hot melt extrusion, spray drying, electrospinning) on the properties of formulations [90]. SEM is different from typical optically based systems. This misunderstanding should be avoided in pharmaceutical development, because all images we obtain from SEM are based on complex electron interactions with the sample.

In SEM, electrons interact with materials, and this interaction generates a complex set of signals based on various mechanisms. These

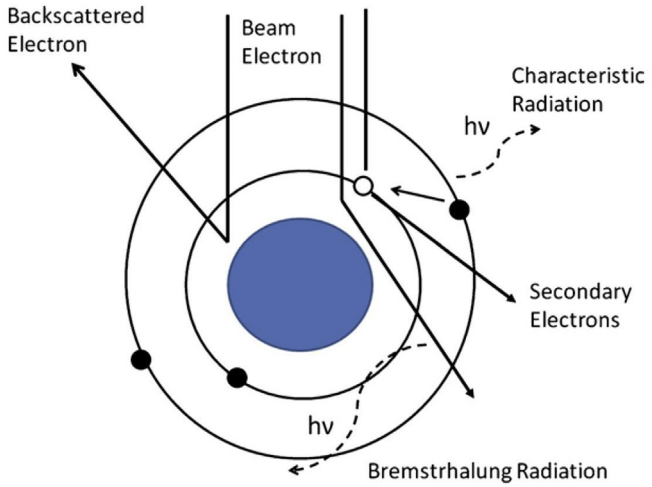

Fig. 1. Elastic and inelastic interactions between electrons and an atom (Adapted with permission [73]).

signals include, but are not limited to, *backscattered electrons* (BSE), *secondary electrons* (SE), *Auger electrons*, and characteristic X-rays (Fig. 1). All these reflective signals can be analyzed using different detectors, which are specifically designed for each of the signals [91]. In physics, electron–specimen interactions can be classified into two groups, *elastic* and *inelastic* collisions. An elastic collision occurs when electrons strike the specimen without losing energy and only change their direction in the process. Inelastic collisions are defined as having no change in direction, but the energy of the electrons will be lost and transferred to the specimen. Fig. 1 depicts these interactions and correlates them with different reflective signals. On the left side of the figure, the backscattered electron is an elastic collision because the negatively charged beam is rejected by the positively charged nucleus, leading to a significant direction change, up to 180°.

The probability of BSE is higher if the specimen has higher atomic number elements. This allows for the analysis of the miscibility between drug and excipients if the drug or excipient consists of more atomic elements [73]. Secondary electrons are generated by a mechanism in which the inner-shell electron is expelled from the atom because of the collision with the incident beam. Then, excited electrons release energy and occupy the empty place left by the inner-shell electrons. This process generates characteristic X-rays. Secondary electrons produce a high-resolution signal for an SEM image, and combining BSE and SE provides a better result for analysis.

Bremsstrahlung radiation derives from the slowing of election beams due to their interactions with nuclei [92]. Assessing every signal from SEM not only provides valuable information about size and morphology but also a molecular-level understanding of materials. Furthermore, until recently, *energy-dispersive X-ray spectrometry* (EDS) attracted attention in pharmaceutical development and has been used in some research. As discussed before, two types of X-rays are generated due to interactions between electrons and specimens. Bremsstrahlung and characteristic radiation are the basis of EDS, and they enable element analysis and mapping of EDS by interpreting these two signals [92]. A combination of SEM and EDS greatly improves the usability of SEM and provides more application possibilities.

3.2.3.1. Applications of SEM in the characterization of ASDs. PLM, SEM, and AFM all have a relatively high sensitivity for detecting tiny crystals [66]. Bruce et al. used SEM to investigate the crystallization onset based on the surface changes of the sample. This method visualizes the crystallinity in bulk ASDs and provides supplementary results to XRD [93]. Also, SEM is useful for studying the morphology and particle size of different formulations. Bohr et al. used SEM to visualize the morphology and particle size of celecoxib particles prepared by different solvents. Their results show that all particles exhibit a spherical shape and their size is within the range of 2–7 μm. Formulations with larger particle size showed slower dissolution rates [90]. Another study by Ye et al. used SEM to study the morphology of efavirenz solid dispersions and the distribution of the drug in the matrices. The particle size was found to be around 20 μm, and the distribution of the drug was uniform [94].

Maniruzzaman et al. used SEM with energy dispersive X-ray spectroscopy (EDS) and X-ray photoelectron spectroscopy (XPS) to determine and characterize drug–polymer interactions in extrudates manufactured by hot melt extrusion. Their results showed that the drugs were homogeneously distributed in the polymer matrices, and their results revealed the strength and nature of the hydrogen-bond interactions between the drugs and polymers [95]. Bruce et al. used SEM to visualize the morphological changes of extruded ASD tablets before and after their dissolution and stability study. The microscopic images of the surface of these tablets indicated that the drug crystallization was a surface phenomenon and was dependent on the drug concentration. In dissolution studies, the surface crystallization did not affect the drug release rate of extruded matrix tablets [93]. In addition, Preimel et al. used SEM to confirm the in situ amorphization of indomethacin compacts upon dissolution. They found that when the compact of indomethacin and EudragitR E dissolved in the dissolution medium, the drug transformed into an amorphous state, which significantly improved the dissolution of this poorly water-soluble drug. Also, this study demonstrates the possibility of using this in situ amorphization process to formulate drugs that have limited solubility [96].

3.2.4. Atomic force microscopy (AFM)

Atomic force microscopy is a tool for observing the shape of a surface in three-dimensional detail down to the nanoscale. Almost all kinds of materials can be analyzed using AFM irrespective of opacity or conductivity [97]. Compared to light microscopy, AFM is a referred to as a “blind” technique that measures the changes of height when a sharp solid force tip touches the sample. By processing these changes, different colors can be assigned according to different heights. Thus, images containing much invaluable information can be interpreted based on the sample [98]. AFM can be operated under various conditions, such as in air, in a liquid, or in a vacuum. It is used for many scientific fields (e.g., hard and soft materials science, nanotechnology, biology, pharmaceuticals science). The highest lateral resolution of AFM can be around 1 nm, which provides extreme detail of the sample [98]. By the aid of Fourier analysis, AFM can identify repeating components (lattices), molecular or atomic crystal structure, and dominant length scales. All these applications can be very helpful to comprehensively understand materials.

Four mechanical properties of the sample can be measured by AFM and are used as tools for the differentiation and analysis of the sample. These are *height* (discussed above), *stiffness*, *adhesion force*, and *friction*. Combining all these gives a comprehensive understanding of the material. For example, an amorphous drug can act as a plasticizer to soften the mixture compared to a crystalline drug (*soften* means less stiff and more viscous). This difference can be used to distinguish amorphous drugs from crystalline drugs and gives details about crystallinity and miscibility [66]. The friction that occurs during sliding contact (see Fig. 2) and the changes in the lateral force signal gives more information about the molecular structure of the sample. Analyzing the heights of the direction loops (as shown in Fig. 2, (a) and (b)) provides the ratio of friction force, which is a quantitative materials contrast [99]. For example, higher friction occurs when the sample is more disordered [100]. This can be utilized as an indicator to evaluate the molecular mobility and miscibility of ASDs.

3.2.4.1. Applications of AFM in the characterization of ASDs. AFM is

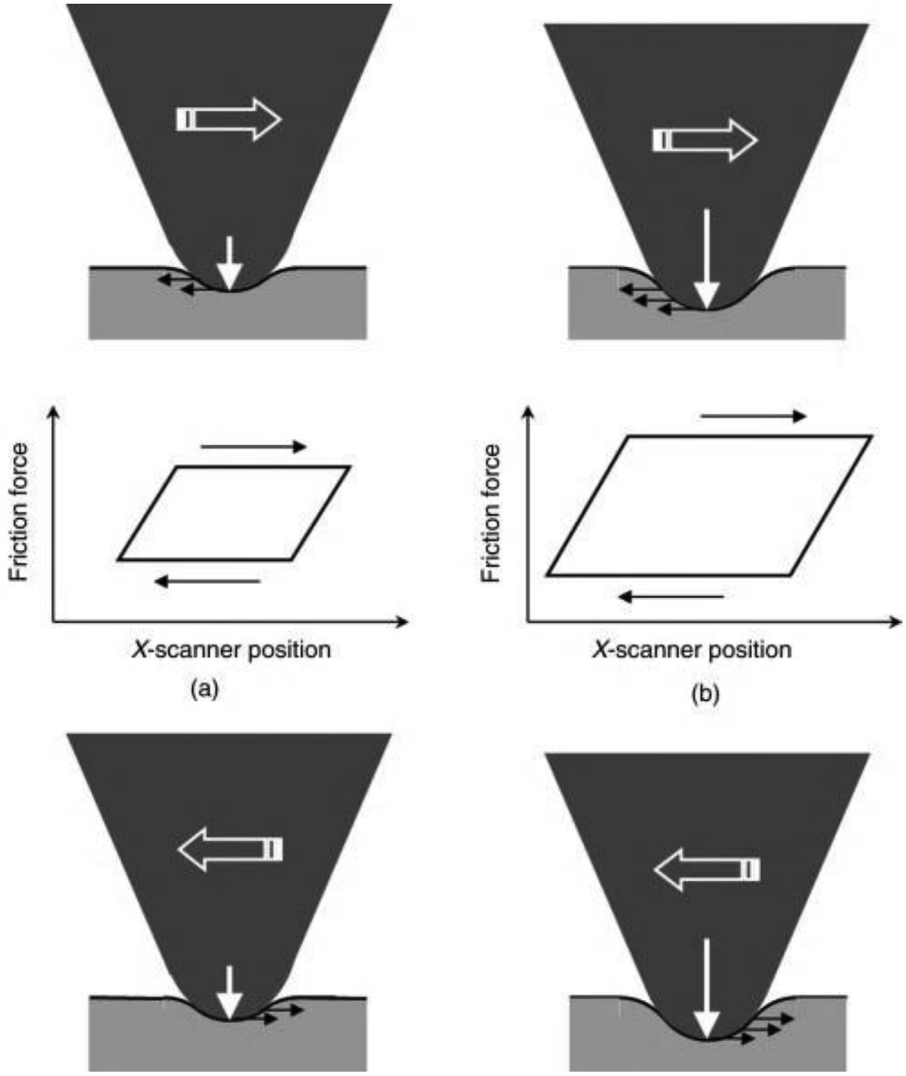

Fig. 2. Tip–sample demonstration of friction in a force-curve cycle (Adapted with permission [127]).

mainly used to characterize the surface topography of ASDs at a nanometer scale. Meeus et al. combined MDSC and AFM to study the phase behavior and drug distribution of ternary ASDs. By using *time-of-flight secondary ion mass spectrometry* (ToF-SIMS) and atomic force microscopy (AFM), differences in the drug distribution of three formulations were revealed. Their results show that a PVP-rich phase was formed under the microspheres. The drug was present as a glass solution. Also, a poly(lactic-co-glycolic acid) (PLGA)-rich phase was deposited on the surface of the microspheres. AFM results discerned the structural and compositional heterogeneity in different drug-loading samples. Also, it was found that the distribution of the drug was dependent on the formulation parameters [101].

Matthias et al. used AFM to investigate the stability of amorphous fractured films, and they successfully quantified the de-mixing by phase separation analysis. Also, AFM was used to successfully identify the homogenously and heterogeneously mixed drug–polymer formulations. Phase separation was observed for homogeneous formulations at molecular scales. This study demonstrates that AFM can achieve a high-resolution analysis of the miscibility of ASDs. However, these experiments may require a few hours to several days to conduct, which limits the wide application of AFM [102].

Another study by Lamm et al. utilized AFM and MDSC to investigate the phase behavior and morphology of ASDs prepared by hot melt extrusion. Their results suggest that formulations with 10% D-α-tocopherol polyethylene glycol 1000 succinate (TPGS 1000) processed at 600 rpm exhibited a single phase, while decreasing the screw speed to 300 rpm resulted in phase separation. This study indicates that a slower screw speed cannot provide sufficient mixing between materials, which leads to phase separation [103].

3.3. Spectroscopic techniques

Spectroscopy is a powerful tool for investigating interactions between drugs and polymers in ASDs. It is primarily dependent on molecular-level and atomic-level changes in molecules present in a complex chemical environment. Using different setups, spectroscopy can provide valuable information on the macro-, micro-, and nanoscale. It is widely used in ASD characterization for product development and quality control. Table 4 lists some useful techniques and their advantages and disadvantages [66]. Each of these techniques will be discussed below.

3.3.1. Solid-state nuclear magnetic resonance (ssNMR)

Nuclear magnetic resonance is used to conduct various characterizations for materials such as gases, liquids, gels, and solids. NMR is used for structural elucidation, chemical identification, quantification of composition, and molecular dynamics [104]. Based on the measuring principle of nuclei spin, NMR can detect very subtle changes in the

Table 4
A summary of spectroscopic techniques used in pharmaceutical science.

Analytical techniques	Information	Advantages	Disadvantages	Time Efficiency
Fourier Transform IR	Interaction between drugs and polymers Molecular motions Polymorph characterization Identification of amorphous and crystalline phases Phase separation	Small sample size Nondestructive Easy to use Simple sample preparation	Effects of moisture	In seconds
Near IR	Molecular structure Structural motions Polymorphs selection	Small sample size Easy to use Simple sample preparation	Weak intensity Lower signal to noise ratio	In seconds
Raman	Interaction between drugs and polymers Phase separation Miscibility by mapping	Small sample size Certain penetration of glass containers Insensitive to water	Higher energy laser may damage samples Sample fluorescence Photodegradation	In seconds
Solid-state NMR	Amorphous identification Relaxation time Molecular mobility Crystallinity Miscibility Interaction between drugs and polymers	Small sample size Simple sample preparation	Expensive	In hours to days

chemical environment of diverse substances, from small molecules to macromolecules. Thus, it can offer valuable information both quantitatively and qualitatively [105]. Compared to XRD (discussed above), NMR can even provide accurate internuclear distances or bond angles of the glasses, and this determination relies on the behavior of nuclei under a magnetic field.

The basis of NMR is thoroughly discussed elsewhere [106]. The signal recorded by NMR is analyzed and interpreted as the fundamental properties of nuclei. Although many atoms are qualified for NMR analysis, proton NMR (^{1}H NMR) and ^{13}C NMR are universal methods for organic materials [107]. Nuclear relaxation times provide invaluable information about the dynamics and mobility of the entire molecule because of their dependence on the modulation of internal interactions in time [108]. There are two types of relaxation times involved for nuclei to return to equilibrium: *decay* and *recovery*, i.e., the characteristic time (T_1) and the characteristic time of decay (T_2). T_1 is also known as the *spin–lattice* relaxation time, and T_2 is known as the *spin–spin* relaxation time. A third relaxation time, $T_{1\rho}$, is important in the solid state; it is known as the spin-lattice relaxation time in the rotating frame. These three relaxation times are very sensitive to internal interactions and molecular motions. The theoretical fundamentals of relaxation times can be found elsewhere; this paper discusses their applications.

3.3.1.1. Applications of ssNMR in the characterization of ASDs. Forster et al. utilized solid-state ^{1}H NMR to compare the mobility of indomethacin and nifedipine as well as their ASDs. They found that the relaxation behavior of nifedipine ASDs significantly changed as a function of temperature, which explained the inferior stability of nifedipine ASDs compared to indomethacin ASDs [109]. However, it is not always true that higher molecular mobility is related to a higher crystallization rate. By measuring the enthalpy relaxation time of various pharmaceutical glasses, Tombari et al. did not found the correlation between the relaxation parameters and the crystallization tendency of the molecules. They conclude that molecular mobility alone is not sufficient to predict nucleation and crystal growth rates of ASDs [110].

As discussed previously, ssNMR was used in a study to investigate the enthalpy relaxation time and spin–lattice relaxation time. Researchers found no observable crystallization at temperatures that were 20–30 °C lower than the T_g of the drug. At a temperature below its T_g, nifedipine exhibited a much smaller $T_{1\rho}$ than the others. This explains the faster crystallization rate of nifedipine either above or below it T_g [48].

Moreover, some researchers studied the effect of moisture on molecular mobility. Aso et al. used ^{13}C NMR to measure the molecular mobility of ASDs in the presence of moisture. They found that the $T_{1\rho}$ of the drug alone decreased with moisture, while in an ASD with polymers, the $T_{1\rho}$ of the drug did not significantly increase. This indicates that the drug in the ASD was stabilized by polymers through molecular interactions [111].

Solid-state NMR also plays an important role in the characterization of miscibility. However, it is not widely accepted by the pharmaceutical field because of its relatively high expense. Some studies of polymer miscibility adequately illustrate that ssNMR is a powerful tool for miscibility characterization. Jian et al. used ssNMR to study the miscibility of two polymers. Their results show that T_1 can indicate a completely homogeneous polymer blend on the scale of 50–80 nm [112]. The miscibility of nifedipine and PVP was studied using ssNMR. Two relaxation times, T_1 and $T_{1\rho}$, were used to evaluate the miscibility of nifedipine ASDs. The domain size of nifedipine was significantly reduced and was similar to that of PVP in ASDs. Thus, Jain et al. demonstrate that a 50:50 ratio of nifedipine and PVP was miscible using either melt quench or hot melt extrusion processes [113]. Solid-state NMR can also perform quantitative analysis on ASDs, but it usually requires hours, or even days, to obtain data. Therefore, other time-effective techniques are usually used to characterize crystallization [66].

3.3.2. Infrared spectroscopy and Raman spectroscopy

Infrared and Raman spectroscopy are vibrational spectroscopies, which measure the vibrational motion of the molecule [114]. The vibrational patterns of molecules are defined as the repetitive movements away from and toward the center of gravity. The energy related to this movement ranges from 4000 to 400 cm^{-1} [115]. When a molecule can absorb infrared radiation, the dipole moment changes during the vibrational motion. This molecule is called *IR active*. For a Raman active molecule, the polarizability changes during the vibrational motion [116]. The infrared radiation is absorbed by the molecule if the frequency and energy of infrared radiation match the frequency and energy required for the transition, which means the vibrational motion of the molecule transits from the ground state to the excited state. IR spectroscopy is based on this property of molecules to investigate molecular structure and interactions [73].

While the fundamentals of Raman spectroscopy are different from IR, when the beam of a laser is aimed at a molecule, it will collide with the molecule. During this process, inelastic collisions result in a gain or loss of energy of the scattering light from the molecule [117]. When the molecule is at the ground state, the inelastic collision imparts some energy of the incident light to the molecule, which transits to the excited state. This less intensely scattering light is measured by the

detector, and it is called *Stokes scattering*. Stokes scattering is generally used in the pharmaceutical field because most drugs and excipients are at the ground state. Also, symmetric vibrations and nonpolar groups have the most intense Raman scattering spectra, while antisymmetric vibrations and polar groups yield the most intense infrared absorption bands [118].

3.3.2.1. Applications of IR and Raman spectroscopy in the characterization of ASDs. IR and Raman spectroscopy are useful for characterizing molecular interactions between drugs and polymers in ASDs. Tobyn et al. used Fourier transform IR (FTIR) and Raman spectroscopy to identify the molecular interactions between a drug and PVP. This strong intermolecular interaction with PVP led to a higher glass transition temperature and better stability. The poorly water-soluble drug maintained its amorphous state in the ASD during the stability tests [119].

Eerdenbrugh et al. used nanoscale mid-infrared imaging techniques to study phase separation in felodipine ASDs. Localized spectra revealed that a discrete amorphous felodipine-rich phase was formed, and the polymer concentrated in the continuous phase. Also, by choosing certain wave numbers, it was possible to visualize the chemical differences in composition between discrete and continuous phases at sub-micrometer resolution [120].

Rumondor et al. used IR spectroscopy to explore the extent of mixing between drugs and polymers in ASDs before and after stability tests. IR spectroscopy was sensitive in identifying the local changes in molecular chemical environments. Amorphous–amorphous phase separation was observed for the ASDs upon exposure to high humidity. This study demonstrates that the balance between drug–polymer–water is important and affects the moisture-induced amorphous–amorphous phase separation. Less hygroscopic polymers and strong drug–polymer interactions can inhibit phase separation and improve the stability of the ASDs [121].

Feng et al. also used FTIR imaging to explore phase separation in ASDs when exposed to moisture. FTIR imaging indicates that after exposure to humidity, the homogeneity of the molecularly dispersed ASDs was altered, and phase separation was observed [122].

Another application of IR spectroscopy is in-line monitoring for hot melt extrusion. By implementing this advanced characterization technique, the process of hot melt extrusion is easily understood, and the material behavior can be visualized. Also, the in-line monitoring technique can improve the efficiency of designing and adjusting processing parameters to achieve better quality control [123].

By employing multivariate curve resolution (MCR) and principal component analysis (PCA) with Raman spectroscopy, the quantitative analysis of crystallinity can be achieved. Lust et al. used Raman spectra to analyze the crystallinity of piroxicam ASDs during storage. The study indicates that Raman spectra are sensitive and accurate in the detection and measurement of crystallinity [124].Puncochova et al. used FTIR and Raman mapping to study the drug release mechanisms of ASDs during dissolution. Crystallization of the drug occurred upon dissolution. With the addition of increasing SoluplusR content, the onset of crystallization was delayed. Through FTIR and Raman imaging, the concentration profiles and diffusion rates of individual components in the tablet matrix were revealed. Also, Raman imaging provided details about the local composition and about various phase transitions, which occurred on the surface of the tablets in contact with dissolution media [125].

Another study by Tres et al. employed real-time Raman spectroscopy imaging with MCR to investigate the dissolution mechanism of ASD tablets. The paper reports that tablets containing 95% copovidone exhibited the same dissolution profile and no Raman spectral changes during the dissolution process, demonstrating that the ASD was homogeneous without phase separation. However, for tablets with only 50% copovidone, felodipine recrystallized after the polymer dissolved in water. Raman imaging indicated that the rate of recrystallization of felodipine varied at different locations of the tablets [126].

4. Conclusion

Comprehensive characterization of ASDs ensures their rational development. ASDs are complex systems that require complementary techniques to evaluate their properties from different aspects and at the molecular level. Both qualitative and quantitative analysis of ASDs is required to better understand the stability and performance of ASDs. This paper discusses the applications of relevant analytical techniques in detail. We present the principles behind the theories and the instruments to provide a better understanding of these analytical techniques. We also review studies that employ various techniques for characterizing ASDs. We provide insights for characterizing ASDs using advanced analytical techniques to gain a better understanding of ASDs.

Conflicts of the interest

Authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2019.01.017.

References

[1] G.M. Keserü, G.M. Makara, The influence of lead discovery strategies on the properties of drug candidates, Nat. Rev. Drug Discov. 8 (3) (2009) 203.
[2] D.J. Hauss, Oral lipid-based formulations, Adv. Drug Deliv. Rev. 59 (7) (2007) 667–676.
[3] S. Khan, A. ElShaer, A.S. Rahman, P. Hanson, Y. Perrie, A.R. Mohammed, Systems biology approach to study permeability of paracetamol and its solid dispersion, Int. J. Pharm. 417 (1–2) (2011) 272–279.
[4] D.-J. Jang, T. Sim, E. Oh, Formulation and optimization of spray-dried amlodipine solid dispersion for enhanced oral absorption, Drug Dev. Ind. Pharm. 39 (7) (2013) 1133–1141.
[5] D.E. Alonzo, G.G. Zhang, D. Zhou, Y. Gao, L.S. Taylor, Understanding the behavior of amorphous pharmaceutical systems during dissolution, Pharmaceut. Res. 27 (4) (2010) 608–618.
[6] Y. Huang, W.-G. Dai, Fundamental aspects of solid dispersion technology for poorly soluble drugs, Acta Pharm. Sin. B 4 (1) (2014) 18–25.
[7] T. Vasconcelos, B. Sarmento, P. Costa, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, Drug Discov. Today 12 (23–24) (2007) 1068–1075.
[8] S. Huang, C. Mao, R.O. Williams, C.-Y. Yang, Solubility advantage (and disadvantage) of pharmaceutical amorphous solid dispersions, J. Pharmaceut. Sci. 105 (12) (2016) 3549–3561.
[9] C. Ahlneck, G. Zografi, The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 62 (2–3) (1990) 87–95.
[10] X. Feng, X. Ye, J.-B. Park, W. Lu, J. Morott, B. Beissner, et al., Evaluation of the recrystallization kinetics of hot-melt extruded polymeric solid dispersions using an improved Avrami equation, Drug Dev. Ind. Pharm. 41 (9) (2015) 1479–1487.
[11] T. Miyazaki, S. Yoshioka, Y. Aso, T. Kawanishi, Crystallization rate of amorphous nifedipine analogues unrelated to the glass transition temperature, Int. J. Pharm. 336 (1) (2007) 191–195.
[12] S.V. Jermain, C. Brough, R.O. Williams III, Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery–An update, Int. J. Pharm. 535 (1–2) (2018) 379–392.
[13] Y. Kawabata, K. Wada, M. Nakatani, S. Yamada, S. Onoue, Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications, Int. J. Pharm. 420 (1) (2011) 1–10.
[14] F.G. Vogt, Solid-State Characterization of Amorphous Dispersions, Pharmaceutical Sciences Encyclopedia, 2015.
[15] O. Narayanaswamy, A model of structural relaxation in glass, J. Am. Ceram. Soc. 54 (10) (1971) 491–498.
[16] U. Bengtzelius, W. Gotze, A. Sjolander, Dynamics of supercooled liquids and the glass transition, J. Phys. C Solid State Phys. 17 (33) (1984) 5915.
[17] P.G. Debenedetti, F.H. Stillinger, Supercooled liquids and the glass transition, Nature 410 (6825) (2001) 259.
[18] B.C. Hancock, S.L. Shamblin, G. Zografi, Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures, Pharmaceut. Res. 12 (6) (1995) 799–806.
[19] I. Ivanisevic, Physical stability studies of miscible amorphous solid dispersions, J. Pharmaceut. Sci. 99 (9) (2010) 4005–4012.
[20] A.C. Rumondor, P.J. Marsac, L.A. Stanford, L.S. Taylor, Phase behavior of poly (vinylpyrrolidone) containing amorphous solid dispersions in the presence of

moisture, Mol. Pharm. 6 (5) (2009) 1492–1505.
[21] A.C. Rumondor, I. Ivanisevic, S. Bates, D.E. Alonzo, L.S. Taylor, Evaluation of drug-polymer miscibility in amorphous solid dispersion systems, Pharmaceut. Res. 26 (11) (2009) 2523–2534.
[22] J. Dong, Y. Ozaki, K. Nakashima, Infrared, Raman, and near-infrared spectroscopic evidence for the coexistence of various hydrogen-bond forms in poly (acrylic acid), Macromolecules 30 (4) (1997) 1111–1117.
[23] B. Shah, V.K. Kakumanu, A.K. Bansal, Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids, J. Pharmaceut. Sci. 95 (8) (2006) 1641–1665.
[24] J.A. Baird, L.S. Taylor, Evaluation of amorphous solid dispersion properties using thermal analysis techniques, Adv. Drug Deliv. Rev. 64 (5) (2012) 396–421.
[25] G. Hoohne, W. Hemminger, H.-J. Flammersheim, Differential Scanning Calorimetry: an Introduction for Practitioners, Springer-Verlag, 1996.
[26] D. Craig, M. Reading, Thermal Analysis of Pharmaceuticals, CRC Press, Reading, 2007.
[27] S. Gaisford, V. Kett, P. Haines, Principles of Thermal Analysis and Calorimetry, Royal society of chemistry, 2016.
[28] R.L. Danley, New heat flux DSC measurement technique, Thermochim. Acta 395 (1–2) (2002) 201–208.
[29] R.C. MacKenzie, Differential Thermal Analysis, Academic Press, 1970.
[30] S.R. Elliott, Physics of Amorphous Materials, Longman Group, Longman House, Burnt Mill, Harlow, Essex CM 20 2 JE, England, 1983 1983.
[31] Y.A. Cengel, M.A. Boles, Thermodynamics: an engineering approach, Sea 1000 (2002) 8862.
[32] M.M. Knopp, K. Löbmann, D.P. Elder, T. Rades, R. Holm, Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development, Eur. J. Pharm. Sci. 87 (2016) 164–173.
[33] P.K. Gallagher, M.E. Brown, R. Kemp, Handbook of Thermal Analysis and Calorimetry, Elsevier, 1998.
[34] B. Wunderlich, Thermal Analysis of Polymeric Materials, Springer Science & Business Media, 2005.
[35] J. Schawe, Analysis of melting processes using TOPEM®, UserCom 25 (2007) 13–17.
[36] V.L. Hill, D.Q. Craig, L.C. Feely, The effects of experimental parameters and calibration on MTDSC data, Int. J. Pharm. 192 (1) (1999) 21–32.
[37] A. Hensel, J. Dobbertin, J. Schawe, A. Boller, C. Schick, Temperature modulated calorimetry and dielectric spectroscopy in the glass transition region of polymers, J. Therm. Anal. Calorim. 46 (3–4) (1996) 935–954.
[38] C. Booth, C. Price, Comprehensive polymer science, Polymer Characterization 1 (1989).
[39] G. Verreck, K. Six, G. Van den Mooter, L. Baert, J. Peeters, M.E. Brewster, Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion—part I, Int. J. Pharm. 251 (1–2) (2003) 165–174.
[40] N. Nyamweya, S.W. Hoag, Assessment of polymer-polymer interactions in blends of HPMC and film forming polymers by modulated temperature differential scanning calorimetry, Pharmaceut. Res. 17 (5) (2000) 625–631.
[41] K. Six, J. Murphy, I. Weuts, D.Q. Craig, G. Verreck, J. Peeters, et al., Identification of phase separation in solid dispersions of itraconazole and Eudragit® E100 using microthermal analysis, Pharmaceut. Res. 20 (1) (2003) 135–138.
[42] Q. Lu, G. Zografi, Phase behavior of binary and ternary amorphous mixtures containing indomethacin, citric acid, and PVP, Pharmaceut. Res. 15 (8) (1998) 1202–1206.
[43] D.T. Friesen, R. Shanker, M. Crew, D.T. Smithey, W. Curatolo, J. Nightingale, Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview, Mol. Pharm. 5 (6) (2008) 1003–1019.
[44] A.M. Kaushal, A.K. Bansal, Thermodynamic behavior of glassy state of structurally related compounds, Eur. J. Pharm. Biopharm. 69 (3) (2008) 1067–1076.
[45] C. Bhugra, M.J. Pikal, Role of thermodynamic, molecular, and kinetic factors in crystallization from the amorphous state, J. Pharmaceut. Sci. 97 (4) (2008) 1329–1349.
[46] P.J. Marsac, H. Konno, L.S. Taylor, A comparison of the physical stability of amorphous felodipine and nifedipine systems, Pharmaceut. Res. 23 (10) (2006) 2306–2316.
[47] Y. Yoshihashi, H. Iijima, E. Yonemochi, K. Terada, Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry, J. Therm. Anal. Calorim. 85 (3) (2006) 689–692.
[48] Y. Aso, S. Yoshioka, S. Kojima, Relationship between the crystallization rates of amorphous nifedipine, phenobarbital, and flopropione, and their molecular mobility as measured by their enthalpy relaxation and 1H NMR relaxation times, J. Pharmaceut. Sci. 89 (3) (2000) 408–416.
[49] J. Liu, D.R. Rigsbee, C. Stotz, M.J. Pikal, Dynamics of pharmaceutical amorphous solids: the study of enthalpy relaxation by isothermal microcalorimetry, J. Pharmaceut. Sci. 91 (8) (2002) 1853–1862.
[50] C. Mao, S.P. Chamarthy, S.R. Byrn, R. Pinal, A calorimetric method to estimate molecular mobility of amorphous solids at relatively low temperatures, Pharmaceut. Res. 23 (10) (2006) 2269–2276.
[51] J. Aho, J.P. Boetker, S. Baldursdottir, J. Rantanen, Rheology as a tool for evaluation of melt processability of innovative dosage forms, Int. J. Pharm. 494 (2) (2015) 623–642.
[52] R.J. Chokshi, H.K. Sandhu, R.M. Iyer, N.H. Shah, A.W. Malick, H. Zia, Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion processs as a means to manufacture solid dispersion/solution, J. Pharmaceut. Sci. 94 (11) (2005) 2463–2474.
[53] B. Lang, J.W. McGinity, R.O. Williams III, Hot-melt extrusion–basic principles and pharmaceutical applications, Drug Dev. Ind. Pharm. 40 (9) (2014) 1133–1155.
[54] F. Yang, Y. Su, L. Zhu, C.D. Brown, L.A. Rosen, K.J. Rosenberg, Rheological and solid-state NMR assessments of copovidone/clotrimazole model solid dispersions, Int. J. Pharm. 500 (1–2) (2016) 20–31.
[55] D.S. Jones, Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance, Int. J. Pharm. 179 (2) (1999) 167–178.
[56] J. Aho, S. Hvidt, S. Baldursdottir, Rheology in Pharmaceutical Sciences. Analytical Techniques in the Pharmaceutical Sciences, Springer, 2016, pp. 719–750.
[57] S.S. Davis, Viscoeldstic properties of pharmaceutical semisolids III: nondestructive oscillatory testing, J. Pharmaceut. Sci. 60 (9) (1971) 1351–1356.
[58] V. Andronis, G. Zografi, Molecular mobility of supercooled amorphous indomethacin, determined by dynamic mechanical analysis, Pharmaceut. Res. 14 (4) (1997) 410–414.
[59] M.G. Abiad, O.H. Campanella, M.T. Carvajal, Assessment of thermal transitions by dynamic mechanical analysis (DMA) using a novel disposable powder holder, Pharmaceutics 2 (2) (2010) 78–90.
[60] P.G. Royall, C-y Huang, S-wJ. Tang, J. Duncan, G. Van-de-Velde, M.B. Brown, The development of DMA for the detection of amorphous content in pharmaceutical powdered materials, Int. J. Pharm. 301 (1–2) (2005) 181–191.
[61] P. Gupta, V.K. Kakumanu, A.K. Bansal, Stability and solubility of celecoxib-PVP amorphous dispersions: a molecular perspective, Pharmaceut. Res. 21 (10) (2004) 1762–1769.
[62] M. Vasanthavada, W.-Q. Tong, Y. Joshi, M.S. Kislalioglu, Phase behavior of amorphous molecular dispersions I: determination of the degree and mechanism of solid solubility, Pharmaceut. Res. 21 (9) (2004) 1598–1606.
[63] J. Albers, R. Alles, K. Matthée, K. Knop, J.S. Nahrup, P. Kleinebudde, Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion, Eur. J. Pharm. Biopharm. 71 (2) (2009) 387–394.
[64] M. Yoshioka, B.C. Hancock, G. Zografi, Crystallization of indomethacin from the amorphous state below and above its glass transition temperature, J. Pharmaceut. Sci. 83 (12) (1994) 1700–1705.
[65] M. Yang, P. Wang, H. Suwardie, C. Gogos, Determination of acetaminophen's solubility in poly (ethylene oxide) by rheological, thermal and microscopic methods, Int. J. Pharm. 403 (1–2) (2011) 83–89.
[66] X. Liu, X. Feng, R.O. Williams, F. Zhang, Characterization of amorphous solid dispersions, Journal of Pharmaceutical Investigation (2017) 1–23.
[67] R. Hilfiker, Polymorphism: in the Pharmaceutical Industry, John Wiley & Sons, 2006.
[68] Y. Guo, E. Shalaev, S. Smith, Physical stability of pharmaceutical formulations: solid-state characterization of amorphous dispersions, Trac. Trends Anal. Chem. 49 (0) (2013) 137–144.
[69] S. Thakral, M.W. Terban, N.K. Thakral, R. Suryanarayanan, Recent advances in the characterization of amorphous pharmaceuticals by X-ray diffractometry, Adv. Drug Deliv. Rev. 100 (2016) 183–193.
[70] G.R. Desiraju, Counterpoint: what's in a name? Cryst. Growth Des. 4 (6) (2004) 1089–1090.
[71] K.R. Seddon, Pseudo polymorph: a polemic, Cryst. Growth Des. 4 (6) (2004) 1087.
[72] H.G. Brittain, Polymorphism in Pharmaceutical Solids, CRC Press, 2016.
[73] R.A. Carlton, Pharmaceutical Microscopy, Springer, 2011.
[74] C. Telang, S. Mujumdar, M. Mathew, Improved physical stability of amorphous state through acid base interactions, J. Pharmaceut. Sci. 98 (6) (2009) 2149–2159.
[75] T. Cai, L. Zhu, L. Yu, Crystallization of organic glasses: effects of polymer additives on bulk and surface crystal growth in amorphous nifedipine, Pharmaceut. Res. 28 (10) (2011) 2458–2466.
[76] S.A. Raina, D.E. Alonzo, G.G. Zhang, Y. Gao, L.S. Taylor, Impact of polymers on the crystallization and phase transition kinetics of amorphous nifedipine during dissolution in aqueous media, Mol. Pharm. 11 (10) (2014) 3565–3576.
[77] V. Andronis, G. Zografi, Crystal nucleation and growth of indomethacin polymorphs from the amorphous state, J. Non-Cryst. Solids 271 (3) (2000) 236–248.
[78] Y. Li, H. Pang, Z. Guo, L. Lin, Y. Dong, G. Li, et al., Interactions between drugs and polymers influencing hot melt extrusion, J. Pharm. Pharmacol. 66 (2) (2014) 148–166.
[79] X. Liu, M. Lu, Z. Guo, L. Huang, X. Feng, C. Wu, Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion, Pharmaceut. Res. 29 (3) (2012) 806–817.
[80] X. Liu, L. Zhou, F. Zhang, Reactive melt extrusion to improve the dissolution performance and physical stability of naproxen amorphous solid dispersions, Mol. Pharm. 14 (3) (2017) 658–673.
[81] A. Clearfield, J.H. Reibenspies, N. Bhuvanesh, Principles and Applications of Powder Diffraction, John Wiley and Sons, Ltd., 2008.
[82] S.-D. Clas, R. Faizer, R. O'Connor, E. Vadas, Quantification of crystallinity in blends of lyophilized and crystalline MK-0591 using X-ray powder diffraction, Int. J. Pharm. 121 (1) (1995) 73–79.
[83] N. Chieng, S. Rehder, D. Saville, T. Rades, J. Aaltonen, Quantitative solid-state analysis of three solid forms of ranitidine hydrochloride in ternary mixtures using Raman spectroscopy and X-ray powder diffraction, J. Pharmaceut. Biomed. Anal. 49 (1) (2009) 18–25.
[84] A.C. Rumondor, L.A. Stanford, L.S. Taylor, Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions, Pharmaceut. Res. 26 (12) (2009) 2599.
[85] K. Nollenberger, A. Gryczke, C. Meier, J. Dressman, M. Schmidt, S. Brühne, Pair distribution function X-ray analysis explains dissolution characteristics of felodipine melt extrusion products, J. Pharmaceut. Sci. 98 (4) (2009) 1476–1486.
[86] G.L. De Araujo, C.J. Benmore, S.R. Byrn, Local structure of ion pair interaction in lapatinib amorphous dispersions characterized by synchrotron X-ray diffraction and pair distribution function analysis, Sci. Rep. 7 (2017) 46367.

[87] I. Takeuchi, K. Shimakura, H. Kuroda, T. Nakajima, S. Goto, K. Makino, Estimation of crystallinity of nifedipine–polyvinylpyrrolidone solid dispersion by usage of terahertz time-domain spectroscopy and of X-ray powder diffractometer, J. Pharmaceut. Sci. 104 (12) (2015) 4307–4313.
[88] Q. Zhu, S.J. Toth, G.J. Simpson, H.-Y. Hsu, L.S. Taylor, M.T. Harris, Crystallization and dissolution behavior of naproxen/polyethylene glycol solid dispersions, J. Phys. Chem. B 117 (5) (2013) 1494–1500.
[89] K.J. Frank, U. Westedt, K.M. Rosenblatt, P. Holig, J. Rosenberg, M. Magerlein, et al., The amorphous solid dispersion of the poorly soluble ABT-102 forms nano/microparticulate structures in aqueous medium: impact on solubility, Int. J. Nanomed. 7 (2012) 5757–5768.
[90] A. Bohr, M. Yang, S. Baldursdóttir, J. Kristensen, M. Dyas, E. Stride, et al., Particle formation and characteristics of Celecoxib-loaded poly (lactic-co-glycolic acid) microparticles prepared in different solvents using electrospraying, Polymer 53 (15) (2012) 3220–3229.
[91] L. Reimer, Scanning Electron Microscopy: Physics of Image Formation and Microanalysis, Springer, 2013.
[92] J.I. Goldstein, D.E. Newbury, J.R. Michael, N.W. Ritchie, J.H.J. Scott, D.C. Joy, Scanning Electron Microscopy and X-Ray Microanalysis, Springer, 2017.
[93] C. Bruce, K.A. Fegely, A.R. Rajabi-Siahboomi, J.W. McGinity, Crystal growth formation in melt extrudates, Int. J. Pharm. 341 (1–2) (2007) 162–172.
[94] X. Ye, H. Patil, X. Feng, R.V. Tiwari, J. Lu, A. Gryczke, et al., Conjugation of hot-melt extrusion with high-pressure homogenization: a novel method of continuously preparing nanocrystal solid dispersions, AAPS PharmSciTech 17 (1) (2016) 78–88.
[95] M. Maniruzzaman, M.J. Snowden, M.S. Bradely, D. Douroumis, Studies of intermolecular interactions in solid dispersions using advanced surface chemical analysis, RSC Adv. 5 (91) (2015) 74212–74219.
[96] P.A. Priemel, R. Laitinen, H. Grohganz, T. Rades, C.J. Strachan, In situ amorphisation of indomethacin with Eudragit® E during dissolution, Eur. J. Pharm. Biopharm. 85 (3) (2013) 1259–1265.
[97] G. Binnig, C.F. Quate, C. Gerber, Atomic force microscope, Phys. Rev. Lett. 56 (9) (1986) 930.
[98] D. Sarid, Scanning Force Microscopy: with Applications to Electric, Magnetic, and Atomic Forces, Oxford University Press on Demand, 1994.
[99] V. Kalihari, D.J. Ellison, G. Haugstad, C.D. Frisbie, Observation of unusual homoepitaxy in ultrathin pentacene films and correlation with surface electrostatic potential, Adv. Mater. 21 (30) (2009) 3092–3098.
[100] K. Puntambekar, J. Dong, G. Haugstad, C.D. Frisbie, Structural and electrostatic complexity at a pentacene/insulator interface, Adv. Funct. Mater. 16 (7) (2006) 879–884.
[101] J. Meeus, D.J. Scurr, X. Chen, K. Amssoms, M.C. Davies, C.J. Roberts, et al., Combination of (M) DSC and surface analysis to study the phase behaviour and drug distribution of ternary solid dispersions, Pharmaceut. Res. 32 (4) (2015) 1407–1416.
[102] M.E. Lauer, O. Grassmann, M. Siam, J. Tardio, L. Jacob, S. Page, et al., Atomic force microscopy-based screening of drug-excipient miscibility and stability of solid dispersions, Pharmaceut. Res. 28 (3) (2011) 572–584.
[103] M.S. Lamm, J. DiNunzio, N.N. Khawaja, L.S. Crocker, A. Pecora, Assessing mixing quality of a copovidone-TPGS hot melt extrusion process with atomic force microscopy and differential scanning calorimetry, AAPS PharmSciTech 17 (1) (2016) 89–98.
[104] D. Courtier-Murias, H. Farooq, H. Masoom, A. Botana, R. Soong, J.G. Longstaffe, et al., Comprehensive multiphase NMR spectroscopy: basic experimental approaches to differentiate phases in heterogeneous samples, J. Magn. Reson. 217 (2012) 61–76.
[105] A. Paudel, M. Geppi, G. Van den Mooter, Structural and dynamic properties of amorphous solid dispersions: the role of solid-state nuclear magnetic resonance spectroscopy and relaxometry, J. Pharmaceut. Sci. 103 (9) (2014) 2635–2662.
[106] F.G. Vogt, J.S. Clawson, M. Strohmeier, A.J. Edwards, T.N. Pham, S.A. Watson, Solid-state NMR analysis of organic cocrystals and complexes, Cryst. Growth Des. 9 (2) (2009) 921–937.
[107] V.I. Bakhmutov, NMR Spectroscopy in Liquids and Solids, CRC Press, 2015.
[108] M. Geppi, G. Mollica, S. Borsacchi, C.A. Veracini, Solid-state NMR studies of pharmaceutical systems, Appl. Spectrosc. Rev. 43 (3) (2008) 202–302.
[109] A. Forster, D. Apperley, J. Hempenstall, R. Lancaster, T. Rades, Investigation of the physical stability of amorphous drug and drug/polymer melts using variable temperature solid state NMR, Die Pharmazie-An International Journal of Pharmaceutical Sciences 58 (10) (2003) 761–762.
[110] E. Tombari, C. Ferrari, G. Johari, R.M. Shanker, Calorimetric relaxation in pharmaceutical molecular glasses and its utility in understanding their stability against crystallization, J. Phys. Chem. B 112 (35) (2008) 10806–10814.
[111] Y. Aso, S. Yoshioka, J. Zhang, G. Zografi, Effect of water on the molecular mobility of sucrose and poly (vinylpyrrolidone) in a colyophilized formulation as measured by 13C-NMR relaxation time, Chem. Pharmaceut. Bull. 50 (6) (2002) 822–826.
[112] J. Wang, M.K. Cheung, Y. Mi, Miscibility and morphology in crystalline/amorphous blends of poly (caprolactone)/poly (4-vinylphenol) as studied by DSC, FTIR, and 13C solid state NMR, Polymer 43 (4) (2002) 1357–1364.
[113] X. Yuan, D. Sperger, E.J. Munson, Investigating miscibility and molecular mobility of nifedipine-PVP amorphous solid dispersions using solid-state NMR spectroscopy, Mol. Pharm. 11 (1) (2013) 329–337.
[114] A.A. Christy, Y. Ozaki, V.G. Gregoriou, Modern Fourier Transform Infrared Spectroscopy, Elsevier, 2001.
[115] E. Smith, G. Dent, Modern Raman Spectroscopy: a Practical Approach, John Wiley & Sons, 2013.
[116] J.R. Ferraro, Introductory Raman Spectroscopy, Academic press, 2003.
[117] S. Ekins, Pharmaceutical Applications of Raman Spectroscopy, John Wiley & Sons, 2008.
[118] O. Faix, Fourier Transform Infrared Spectroscopy. Methods in Lignin Chemistry, Springer, 1992, pp. 83–109.
[119] M. Tobyn, J. Brown, A.B. Dennis, M. Fakes, Q. Gao, J. Gamble, et al., Amorphous drug–PVP dispersions: application of theoretical, thermal and spectroscopic analytical techniques to the study of a molecule with intermolecular bonds in both the crystalline and pure amorphous state, J. Pharmaceut. Sci. 98 (9) (2009) 3456–3468.
[120] B. Van Eerdenbrugh, M. Lo, K. Kjoller, C. Marcott, L.S. Taylor, Nanoscale mid-infrared imaging of phase separation in a drug–polymer blend, J. Pharmaceut. Sci. 101 (6) (2012) 2066–2073.
[121] A.C. Rumondor, L.S. Taylor, Effect of polymer hygroscopicity on the phase behavior of amorphous solid dispersions in the presence of moisture, Mol. Pharm. 7 (2) (2010) 477–490.
[122] X. Feng, A. Vo, H. Patil, R.V. Tiwari, A.S. Alshetaili, M.B. Pimparade, et al., The effects of polymer carrier, hot melt extrusion process and downstream processing parameters on the moisture sorption properties of amorphous solid dispersions, J. Pharm. Pharmacol. 68 (5) (2016) 692–704.
[123] L. Saerens, C. Vervaet, J.P. Remon, T. De Beer, Process monitoring and visualization solutions for hot-melt extrusion: a review, J. Pharm. Pharmacol. 66 (2) (2014) 180–203.
[124] A. Lust, C.J. Strachan, P. Veski, J. Aaltonen, J. Heinämäki, J. Yliruusi, et al., Amorphous solid dispersions of piroxicam and Soluplus®: qualitative and quantitative analysis of piroxicam recrystallization during storage, Int. J. Pharm. 486 (1–2) (2015) 306–314.
[125] K. Punčochová, A.V. Ewing, M. Gajdošová, T. Pekárek, J. Beránek, S.G. Kazarian, et al., The combined use of imaging approaches to assess drug release from multicomponent solid dispersions, Pharmaceut. Res. 34 (5) (2017) 990–1001.
[126] F. Tres, K. Treacher, J. Booth, L.P. Hughes, S.A. Wren, J.W. Aylott, et al., Real time Raman imaging to understand dissolution performance of amorphous solid dispersions, J. Contr. Release 188 (2014) 53–60.
[127] G. Haugstad, Atomic Force Microscopy: Understanding Basic Modes and Advanced Applications, John Wiley & Sons, 2012.