A comprehensive overview of the role of intermolecular interactions in amorphous solid dispersions.

Lennert Cools[a b] and Guy Van den Mooter[a*]

[a] *Drug Delivery and Disposition, KU Leuven, Department of Pharmaceutical and Pharmacological Sciences, Campus Gasthuisberg ON2, Herestraat 49 b921, 3000 Leuven, Belgium*

[b] *Applied and Analytical Chemistry, NMR group, Institute for Materials Research (imo-imomec), UHasselt, 3590 Diepenbeek, Belgium*

[*] *Corresponding author:*

Guy Van den Mooter; Drug Delivery and Disposition, KU Leuven, Department of Pharmaceutical and Pharmacological Sciences, Campus Gasthuisberg ON2, Herestraat 49 b921, 3000 Leuven, Belgium
Guy.vandenmooter@kuleuven.be; Tel.: +32 16 330304

35 **Graphical abstract**

36

Abstract

Many recent studies have indicated that drug-polymer intermolecular interactions are an important aspect of amorphous solid dispersions (ASDs) and determine many of the properties of this type of formulations. In this review, a comprehensive overview is given of the latest insights with respect to intermolecular interactions in ASDs. The thermodynamic properties and theoretical considerations of the interactions are discussed, followed by a detailed and critical overview of the various solid-state analysis techniques used to probe interactions at the disposal of the formulation scientist. As the physical stability and the pharmaceutical performance of the ASD are its most crucial properties, the most recent understanding of the influence of drug-polymer interactions on these aspects is addressed as well. It is clear that intermolecular interactions may provide many advantages for ASDs but need to be weighed against the possible disadvantages. Further investigation into the interplay and trade-off between physical stability and dissolution properties is necessary in order to be able to take full advantage of the possible benefits of the interactions.

Keywords: *Amorphous solid dispersions – Intermolecular interactions – Stability – Drug release – Solid-state analysis*

Abbreviations

AAPS	Amorphous-amorphous phase separation
API	Active Pharmaceutical Ingredient
ASD	Amorphous Solid Dispersion
BCS	Biopharmaceutics Classification System
CP/MAS	Cross polarization / Magic angle spinning
DFT	Density functional theory
DVS	Dynamic vapor sorption
FT-IR	Fourier transform infrared spectroscopy
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
HPMCP	Hydroxypropyl methylcellulose phthalate
LLPS	Liquid-Liquid phase separation
LoC	Limit of congruency
mDSC	Modulated differential scanning calorimetry
PAA	Poly(acrylic acid)
PC-SAFT	Perturbed-chain statistical associating fluid theory
PDF	Pair distribution function
PEO	Poly (ethylene oxide)
PEtOx	Poly(Ethyl Oxazoline)
PVP	Poly(vinylpyrrolidone)
PVPVA	Poly(vinylpyrrolidone-co-vinylacetate)
ssNMR	Solid-state nuclear magnetic resonance
T_g	Glass transition temperature
XPS	X-ray photoelectron spectroscopy
XR(P)D	X-ray (powder) diffraction

1. Introduction

In recent years, the formulation of poorly water-soluble drugs as amorphous solid dispersions (ASDs) has gained popularity as a means to enhance their solubility and bioavailability (Bhujbal et al., 2021a). The growing need for such enabling strategies is driven by the fact that an estimated 50-90% of new chemical entities are classified as poorly water-soluble according to the Biopharmaceutics Classification System (BCS)(Benet, 2013; Ricarte et al., 2019). When a drug is formulated as an ASD, it is molecularly dispersed within an inert carrier matrix, which disrupts the crystal lattice of the compound and lowers the energy required for the drug molecules to dissolve. This results in higher apparent solubility and faster dissolution compared to the pure crystalline material (Vaka et al., 2014).

Pure amorphous drugs possess higher free energy compared to their crystalline counterparts, making them thermodynamically unstable (Van den Mooter, 2012), necessitating a carrier to stabilize the drug. The inert carrier is most often of polymeric nature and stabilizes the drug in a variety of ways, reducing the tendency for nucleation and crystal growth. The mobility of drug molecules is restricted in the polymer matrix due to steric hindrance from the polymer chains and the generally higher glass transition temperature (T_g) of the polymer, which increases the T_g of the system. Additionally, dispersing the drug in the polymer matrix reduces the free energy of the drug (Baghel et al., 2016a). Drug-polymer interactions can further stabilize the drug within the matrix, providing an additional energy barrier that must be overcome for drug molecules to aggregate and crystallize (Janssens and Van den Mooter, 2009). These interactions can include hydrogen bonding, halogen bonding, dipole-dipole interactions, and ionic interactions, with their strength depending on the nature of the interaction and the functional groups involved(Huang et al., 2008; Mesallati et al., 2017; Mistry et al., 2015; Xiang and Anderson, 2019).

Research over the years has highlighted that intermolecular interactions influence every aspect of ASDs, from solubility in the polymer matrix to physical stability, maximum drug loading, and drug release. However, a comprehensive overview of how these interactions affect each aspect is still lacking. This review aims to provide a thorough summary of the theory behind intermolecular interactions in ASDs, the various methods to probe them, and their influence on maximum drug loading, physical stability, and drug release.

2. Background and theoretical considerations

2.1. Thermodynamics of interactions

Intermolecular interactions can generally be subdivided in ionic interactions and interactions between permanent or induced dipoles. The latter include van der Waals interactions (London, Keesom and Debye) and hydrogen bonding, which are all attractive interactions, unless the distance between the molecules becomes too small and the electron clouds of the atoms overlap, which causes repulsive forces. Generally, for poorly soluble drugs and ASDs, neutral interactions are most important and govern the properties of these systems. However, it has been reported in several instances that ionic interactions between drug and polymer can also be present (Li et al., 2022; Mesallati et al., 2017). The first part of this review will, however, focus on the neutral interactions as these are most important for ASDs and will facilitate the explanation of the theoretical concepts.

Figure 1

These interactions can be described be plotting the potential energy as a function of the distance between two molecules. When molecules are at a very short distance of each other, they will repel each other and when subsequently brought further apart, the molecules will be attracted to each other. The potential repulsive energy can be described by a/r^m, whereas the attractive potential energy between the two molecules can be characterized by $-b/r^n$ (a and b are the repulsive and attractive coefficients respectively, and m and n are selected positive integers). The sum of the attractive and repulsive energies can be described as the total interaction energy E_{int}. The Lennard-Jones (L-J) model is one of the more simplistic, yet popular models to describe the attractive and repulsive behavior of two molecules (Wang et al., 2020). A typical representation of the behavior according to the L-J model can be found in *Figure 1*, where the total interaction energy can be described by the following equation:

$$V_{LJ}(r) = 4\varepsilon \left(\left[\frac{\sigma}{r}\right]^{12} - \left[\frac{\sigma}{r}\right]^{6} \right) \quad (1)$$

In this equation, r is the distance between two molecules, σ is the distance at which the potential energy V is equal to zero and ε is the depth of the potential well. The minimum of the plot, where $V_{Lj} = -\varepsilon$ and the distance between the molecules is equal to $2^{1/6}\sigma$, is the point where the greatest attractive energy occurs. This distance is also denoted as r_{min}. The interaction force between the two molecules can be described by the following equation:

$$F_{int} = -\frac{\partial V_{LJ}}{\partial r} \quad (2)$$

The interaction force is the negative of the slope of the plot which depicts the potential energy as a function of the distance. A negative slope corresponds to a repulsive force and a positive slope corresponds to an attractive force. Below a distance of $r_{min,}$ the interaction force will be repulsive and at distances larger than r_{min}, the force between the molecules will be attractive. If $r = r_{min}$, there will be no net force acting on the molecules, as the slope is zero. It has to be noted that the depiction in *Figure 1* only displays the potential energy of the two molecules and the kinetic energy is not taken into account. Consequently, the plot represents a situation where the molecules have no kinetic energy and are in constant positions to each other, which happens when there is no heat content (T = 0 K). If the molecules acquire kinetic energy, by adding heat, the total energy will increase according to the quantity of heat that was added. If V_{LJ} remains below zero, the separation distance will remain finite, and the molecules will oscillate between the two separation distances at that energy level due to the alternation of attractive and repulsive forces (Malick, 2014).

It has to be pointed out that the L J-model is straightforward for atoms and simple molecules. However, for more complex organic molecules, where the orientation of the molecules is important, the model is less clear-cut. In this case, the distance between molecules is approximated by the number of molecules in a certain volume unit, which can be described by the density of the material. Nevertheless, it is still a rough approximation for more complex molecules. Therefore, over the years, several alterations of the L J-model have been made in an attempt to improve it, such as for example the Mie potential (Lafitte et al., 2013), the Buckingham potential(Swindells and Sykes, 1938) and the Stockmayer potential (Stockmayer, 1941). The Mie potential is a more generalized case of the LJ potential, where the exponents 12 and 6 are replaced by the more general exponents m and n. The Buckingham potential is a more simplified version of the LJ potential and finally the Stockmayer potential can be defined as an LJ potential where an extra term was added to account for an electric dipole moment. However, the simplicity and often surprising accuracy of the L J-model have contributed to its popularity over the years (Stephan et al., 2020).

2.2. Drug-polymer miscibility and solubility: the influence of interactions

It has been described numerous times that having an ASD homogenously mixed at the molecular level is imperative for its stability (Chan et al., 2015; Meng et al., 2015; Qian et al., 2010; Yuan et al., 2014). When a drug is homogenously distributed in the polymer matrix, the distance between the drug molecules is maximal and the molecules have to travel further in order to aggregate and cause phase separation or crystallization, which requires more energy. Additionally, the polymer chains can provide more steric hinderance and the contact points with the polymer can be optimally used by the drug

molecules (Alonzo et al., 2012). It is important to note that most ASDs nowadays have a drug loading where the drug is above the solubility limit in the polymer, meaning that the drug is in a supersaturated state and there is a thermodynamic driving force for phase separation. However, the system can be kinetically stable if the dynamics are slow enough and if the system is below the miscibility limit (Marsac et al., 2006a). Miscibility can be described as the tendency of the supercooled liquid/glassy form of the drug to mix with the polymer. Solubility on the other hand describes the ability of the polymer to act as a solvent for a crystalline drug (Qian et al., 2010). If the drug loading is below the solubility limit, the ASD is thermodynamically stable, and there is no thermodynamic driving force for phase separation. However, the solubility of most small molecules in the polymer is usually quite low, meaning that in most ASDs, the drug is in de supersaturated state (Newman et al., 2012). Consequently, regarding the miscibility of these low molecular weight molecules in a polymer, the drug is in an unstable form with respect to the crystalline state. The miscibility limit is thus a metastable equilibrium, which in fact can be measured for a specific drug-polymer combination. Eventually over time, a miscible drug-polymer system would reach equilibrium with respect to the crystalline drug, and this equilibrium would be the solubility of the drug in the polymer (Malick, 2014). The solubility and miscibility limit of a drug in a polymer, together with data of the glass transition temperature (T_g) can be incorporated in a state diagram, which describes the phase behavior of the ASD as a function of the composition of the ASD and the temperature (Hu et al., 2022). An example of a state diagram can be found in *Figure 2*.

Figure 2

In order for a drug and polymer combination to form a miscible one-phase ASD system, with respect to thermodynamics, the free energy of mixing (ΔG_{mix}) should be negative. This is represented by equation 3:

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix}. \quad (3)$$

In the equation above, the enthalpy and entropy of mixing are respectively represented by ΔH_{mix} and ΔS_{mix}. These characteristics are dependent on the temperature of the environment and the composition of the mixture. The entropy and enthalpy of mixing can be described in further detail mathematically by the equations (4) and (5) respectively. This allows to understand the phase behavior of ASDs further and explore the factors that influence it. The entropy of mixing can be represented by the following equation(Malick, 2014):

$$\Delta S_{mix} = -R(n_d\ ln\emptyset_d + n_p\ ln\emptyset_p), \quad (4)$$

Where R is the gas constant, n represents the number of moles of either the drug and the polymer and φ describes the volume fraction of either the drug or polymer in the mixture. Since in a mixture the volume fraction φ of the components is smaller than 1, the logarithms, which are used in the equation, will be negative. Consequently, the entropy of mixing will always be positive, contributing to a negative value for $\Delta G_{mix,}$ and will always favor mixing over phase separation. This is to be expected, as mixing increases the disorder of the system, which means that the actual thermodynamic driving force for either phase separation or mixing is determined by the enthalpy of mixing. The enthalpy of mixing can be represented by the following equation:

$$\Delta H_{mix} = H_{dp} - \left(H_{dd} + H_{pp}\right). \quad (5)$$

This equation indicates that the enthalpy of mixing is determined by the difference between the enthalpy of the pure mixture components and the enthalpy of the mixture. Since the entropy of mixing is relatively large in case of the mixing of a polymer and a small molecule (mainly the contribution of the API), it allows for a larger disadvantageous enthalpic contribution while still being able to reach negative free energy of mixing. The enthalpy of mixing will be negative (exothermic mixing) when the interactions between the drug and polymer are stronger and/or more abundant compared to the interactions in the pure ASD components. It is also possible that the cohesive interactions present in the pure components are stronger or similar to those in the ASD, resulting in endothermic or athermal mixing respectively (Baird and Taylor, 2012a; Malick, 2014).

The importance of intermolecular interactions in drug-polymer miscibility can be highlighted by looking at the approaches that predictive methods use to estimate the miscibility of the components. The most well-known and popular method to predict drug-polymer miscibility is through the Flory-Huggins (F-H) lattice theory (Hu et al., 2022). Whereas this theory is based on the free energy in a polymer-solvent system, a small molecule-polymer system can be considered as analogous and thus can be described by the F-H theory (Baird and Taylor, 2012a). The Gibbs free energy of mixing of the system can be calculated based on the position of the molecules in a lattice and on the interactions between the drug and polymer molecules. The free energy of mixing for an ASD can be characterized by the following equation:

$$\frac{\Delta G_{mix}}{RT} = n_d\ ln\varphi_d + n_p\ ln\varphi_p + \chi_{dp}\ n_d\ \varphi_d \quad (6)$$

Where R is the gas constant and T is the absolute temperature. The factor n describes the number of moles of either the drug or polymer and φ describes the volume fraction of the respective component, whereas χ is the F-H interaction parameter. Upon closer inspection, it becomes apparent that the first

two terms of the right-hand side of eq. 6 represent the entropic contribution, as the terms are similar to the terms in eq. 4. Consequently, the third term in the equation represents the enthalpic contribution. As already described, entropy always favors mixing, which means that the enthalpic contribution is the determining factor that decides the thermodynamic favorability of mixing. More specifically, the F-H interaction parameter χ determines whether ΔG_{mix} will become negative for that specific drug-polymer combination. If χ is negative or slightly positive, then the Gibbs free energy of mixing will become negative as well. If χ is positive, then ΔG_{mix} will become positive, and mixing is thermodynamically unfavorable. The F-H interaction parameter is thus an indicator of whether or not the adhesive drug-polymer interactions are stronger or weaker than the cohesive interactions in the pure components (Malick, 2014).

A disadvantage of the F-H theory is that it only takes into account nonspecific dispersive interactions and does not account for more specific interactions, such as hydrogen-bonding. This should be taken into consideration when determining χ for a drug-polymer combination that can interact via hydrogen-bonds. For this reason, a modified F-H theory has been suggested to account for systems that can interact via these specific interactions. In the modified F-H theory, an extra free energy term ($\Delta G_H/RT$) can be added, which represents the thermodynamical contribution of the specific interactions. This leads to the following equation:

$$\frac{\Delta G_{mix}}{RT} = n_d \, ln\varphi_d + n_p \, ln\varphi_p + \chi_{dp} \, n_d \, \varphi_d + \frac{\Delta G_H}{RT} \quad (7)$$

Another more recent approach to estimate solubility and miscibility was developed by Gross and Sadowski, and is a thermodynamic equation of state titled perturbed-chain statistical association fluid theory (PC-SAFT) (Gross and Sadowski, 2001). This equation of state approximates molecules by representing them as chains of spherical segments, and it takes into account multiple specific interactions such as hydrogen bonding. The PC-SAFT equation is generally expressed with respect to the residual Helmholtz energy, accounting for dispersive forces, repulsive forces, association and other interactions such as ionic and dipole-dipole interactions.

From the equations above, it can be established that, in terms of thermodynamics, intermolecular interactions play a significant role in the miscibility and solubility of a drug in a polymer matrix. In the following sections, an overview will be provided of the different experimental and theoretical techniques to detect intermolecular interactions, and the influence of these interactions on the physical stability and pharmaceutical performance will be discussed.

3. Methods to probe the microstructure and detect intermolecular interactions

The detection of intermolecular interactions between drug and polymer molecules can be performed both in the solid-state and in solution. Nevertheless, in this review, the discussion of the interaction detection methods focusses on the analysis in the solid-state.

3.1. Spectroscopic methods

3.1.1. Fourier transform infrared spectroscopy

Infrared spectroscopy is a vibrational spectroscopy method, which allows to measure the vibrational motion of molecules (Christy et al., 2001). These vibrational motions are defined as the repetitive motions which go towards and away from the center of gravity. Molecules that can absorb infrared radiation display a change in the dipole moment during the vibrational motion. Infrared radiation can be absorbed by the molecule if the frequency and energy of the radiation match that which is required for the transition in state. This indicates that the molecular vibrations will transition from the ground state to a more excited state. The measurement of IR spectra is based on this principle of the molecular vibrations and is routinely used to characterize compounds, but also to investigate interactions (Larkin, 2017). Traditional IR spectroscopy, where the intensity of each wavelength is checked separately, is used less often nowadays, as it is more time-consuming. Fourier transform infrared spectroscopy (FT-IR) is applied more frequently, where data is collected over a wider range of wavelengths in the form of an interferogram, which is then subsequently Fourier transformed.

FT-IR is also frequently used to investigate intermolecular interactions in ASDs. Usually, intermolecular interactions can be detected by observing shifts in the positions of peaks that correspond to interacting functional groups. Hydrogen bonding can for instance be detected by a shift of a C=O group, which is caused by a decrease of the double bonded character due to the hydrogen bond. For example, Dedroog et al. investigated the interactions between naproxen and poly(vinylpyrrolidone-co-vinylacete) (PVPVA) or fenofibrate and PVPVA in different organic solvents in the liquid-state, but also after drying of the solutions in the solid-state films. Via FT-IR measurements, the researchers could establish that naproxen and PVPVA interacted with several organic solvents and that naproxen and PVPVA also interacted with each other to different extents in different solvents. *Figure 3* displays the FT-IR spectra of mixtures of PVPVA and naproxen in various solvents. The shoulder peak in the VP carbonyl stretching signal around 1636 cm^{-1} indicated the existence of hydrogen bonds between naproxen and PVPVA. It could be observed that stronger interactions were present in acetonitrile and dichloromethane compared to the other alcoholic solvents, as the shoulder peak already was present for the lowest

naproxen concentration of 10 wt% in acetonitrile and dichloromethane. Additionally, hydrogen bonds between drug and polymer could be observed as well in the films after drying of the solutions (Dedroog et al., 2022). Kothari et al. used FT-IR to evaluate the strength of hydrogen bonds between nifedipine and three different polymers, polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose acetate succinate (HPMCAS) and poly(acrylic acid) (PAA). It was observed that the strength of the intermolecular interactions with nifedipine were ranked in the following order: PVP > HPMCAS > PAA. Additionally, dielectric spectroscopy and X-ray powder diffraction (XRPD) were performed to investigate molecular mobility and crystallization kinetics respectively (Kothari et al., 2015a).

Figure 3

Chen et al. used FT-IR to investigate intermolecular interactions between several compounds and different polymers in ASDs before and after exposure to moisture. The compounds used in this study were felodipine, ketoconazole and griseofulvin, and the polymers were PVPVA and HPMCAS. For the ketoconazole ASDs, they could link drug release to the strength of the intermolecular interactions, as the ketoconazole/HPMCAS ASDs showed a faster drug release than the ketoconazole/PVPVA ASDs. The researchers explained that the difference in drug release could partially be attributed to a difference in intermolecular interaction strength, together with the lower crystallization tendency of ketoconazole and the ability of HPMCAS to maintain supersaturation (Y. Chen et al., 2015a). It was observed that the stronger ketoconazole/HPMCAS interactions lead to a higher degree of supersaturation and a stronger resistance of the interactions to disruption by water. FT-IR and attenuated total reflectance (ATR) -FT-IR, are one of the most applied methods to detect intermolecular interactions, due to the ease and speed of the measurements. Interpretation of the spectra can be straightforward, although it is sometimes hard to distinguish peaks shifts for overlapping peaks and interpret the observed changes.

3.1.2.Raman spectroscopy

Raman spectroscopy is another vibrational spectroscopy technique, similar to infrared spectroscopy, though it yields complementary information, as it relies on inelastic scattering of photons. Usually, monochromatic light is used to radiate the sample. The photons will interact with the molecular vibrations of the sample molecules, which results in the energy of the photons being shifted either up or down. These shifts yield information about the vibrational modes of the molecule. Note that only molecules who display a change in their polarizability are Raman active (as opposed to IR, which reflects changes in the dipole moment of molecules) (Larkin, 2017; Vankeirsbilck et al., 2002). Similar to IR, changes in the chemical environment will be reflected in the Raman spectrum through changes in the peak position or peak shape, or by the appearance of new peaks (Palermo et al., 2012). It also

has been described that Raman may be more suited to detect non-specific interactions (e.g. hydrophobic interactions) in drug-polymer systems, which are rich in aromatic groups (Rawlinson et al., 2007). This is due to its working principle, which is based on changes in polarization.

An example of Raman spectrometry being used to investigate intermolecular interactions can be found in the work of Keratichewanun et al. (Keratichewanun et al., 2015) where the researchers used Raman spectrometry and IR spectrometry to investigate the miscibility and intermolecular interactions between components in nifedipine-Soluplus® ASDs, which were produced using different manufacturing techniques. It was found that the drug interacted with Soluplus® via hydrophilic and hydrophobic interactions. The hydrophilic interactions could be identified using IR and the hydrophobic interactions were observable via Raman spectroscopy. Peak shifts could be seen for nifedipine in the spectral region of 790 to 820 cm^{-1}, which is characteristic for aromatic hydrocarbons (Keratichewanun et al., 2015; Rawlinson et al., 2007).

Additionally, Lu and Cuellar et al. (Lu et al., 2016) also investigated the formation of intermolecular interaction between felodipine using various techniques, including FT-IR and Raman spectroscopy. They reported a Raman peak shift that was observed in the region of 1200-1700 cm^{-1}, which was a potential indication of intermolecular interactions. Following theoretical calculations, it became clear that the shifted Raman peaks corresponded to C-H bending, N-H bending and a combination of C-C and N-H bending peaks. Consequently, the shifts in these Raman peaks indicate the formation of hydrogen bonds(Lu et al., 2016).

Admittedly, Raman spectroscopy is for many researchers often not the technique of first choice to investigate intermolecular interactions. Of the vibrational spectroscopic techniques, FT-IR is more popular for this purpose, despite the fact that Raman Spectroscopy can be used for samples dissolved in water, which is not the case for IR. Raman spectroscopy is rather used to investigate phase separation or to detect crystallinity in the ASD(X. Chen et al., 2015; Dohrn et al., 2021; Netchacovitch et al., 2017) . Additionally, Raman mapping is often used as well to examine the phase behavior of ASDs (Krummnow et al., 2023; Luebbert et al., 2018; Meng et al., 2015) or confocal Raman microscopy as well, which is a combination of traditional light microscopy and Raman spectroscopy. This technique provides chemical information of a certain region of interest in the sample. With respect to ASDs, it has for example been used to investigate changes in the phase behavior of the ASDs upon contact with water (Punčochová et al., 2016).

3.1.3.Solid-State nuclear magnetic resonance

Solid-state nuclear magnetic resonance (ssNMR) can be considered as one of the most versatile and accurate techniques in the toolbox of a formulation scientist, especially for the elucidation of the

348 physical structure of ASDs. A detailed description of the working mechanism of ssNMR is beyond the
349 scope of this review but is thoroughly discussed in dedicated literature(Duer, 2004; Levitt, 2015). With
350 respect to the solid-state characterization of ASDs, ssNMR can have multiple applications, ranging from
351 detecting crystallinity and other solid forms of drug candidates, probing molecular miscibility,
352 molecular dynamics, intra- and intermolecular interactions etc. (Kruk et al., 2012) With respect to
353 investigating intra- and intermolecular interactions, ssNMR is often the technique of choice when it
354 comes to exploring the type, strength and extent of different homo- and heteronuclear noncovalent
355 intermolecular interactions. These interactions can range from ionic to dipolar and hydrogen bonding
356 (Vogt et al., 2011)(Vogt et al., 2011).

357 The most straightforward and popular method to detect drug-polymer intermolecular interactions is
358 by observing spectral alterations like peak shifts (upfield or downfield, due to shielding or deshielding)
359 or peak broadening in the one-dimensional spectrum of the ASD compared to the peaks in the spectra
360 of the pure ASD components. These spectral alterations are the result of changes in the local chemical
361 environment of the nuclei, which are inflicted by the interactions. The ^{13}C nucleus is used most often
362 for these types of experiments due to the wider resonance frequency range, which makes it easier to
363 observe and interpret spectral changes, compared to for example the ^{1}H nucleus, which has a narrower
364 isotropic resonance region. Many researchers have investigated the intermolecular interactions in
365 ASDs by comparing peak positions in one dimensional (1D) ^{13}C spectra, which are measured most often
366 via cross-polarization magic angle spinning (CP/MAS) experiments (Mistry et al., 2015; Okada et al.,
367 2020; Pugliese et al., 2021; Song et al., 2015). Other nuclei, which are prominent in a lot of APIs, such
368 as ^{19}F, ^{15}N or ^{17}O are also used in this regard and can provide additional complementary information.
369 An example of this can be found in the work of Song et al. where the researchers performed ^{15}N CPMAS
370 NMR to investigate the protonation state of lapatinib in ASDs with various polymers. In the ^{15}N-spectra
371 of the ASD with hydroxypropyl methylcellulose phthalate (HPMCP), it was observed that there were
372 two nitrogen populations for the amine group, which almost certainly corresponded to ionized and un-
373 ionized lapatinib (*Figure 4*). This indicated that salt formation occurred between lapatinib and HPMCP,
374 whereas no salt formation was observed with the other polymers (Song et al., 2015).

375

376 **Figure 4**

377

378 Besides the standard one-dimensional NMR experiments, multi-dimensional NMR experiments are not
379 only a great tool for structural characterization but can also be applied in the investigation of
380 intermolecular interactions and miscibility of the ASD components. The most commonly used two-

dimensional NMR techniques can roughly be divided in two main categories: correlation experiments and separation experiments (Paudel et al., 2014). In the correlation experiments, the correlations between either homo- or heteronuclear pairs originate from the coupling via dipolar or scalar interactions and are a reflection of the spatial proximity of the nuclei (either through space or through bonds). The most commonly used solid-state 2D NMR techniques are HETCOR, INEPT, MAS-J-HSQC, INADEQUATE, DQ/SQ, etc. The second type of experiments have as a goal to measure specific anisotropic interactions and include techniques that allow the measurement of chemical shift anisotropy, dipolar coupling or quadrupolar coupling. A large variety of different two-dimensional techniques to investigate intermolecular interactions exist and discussing them all would extend beyond the focus of this paper. Readers interested in this topic can be referred to a detailed review on solid-state NMR for ASDs by Paudel et al. (Paudel et al., 2014).

An example of applying a two-dimensional NMR technique to investigate intermolecular interactions can be found in a paper by Lu et al. from 2019 where they performed 2D ^{13}C-^{1}H HETCOR NMR to investigate the interactions between posaconazole and HPMCAS (Lu et al., 2019). The experiments revealed a correlation between the triazole group of posaconazole and the hydroxyl group of HPMCAS, which suggested that these functional groups were in close proximity to each other and formed hydrogen bonds. Additionally, another intermolecular contact was detected by utilizing ^{13}C- and ^{15}N-labeled posaconazole and performing 2D ^{13}C-^{1}H HETCOR NMR on the samples. A correlation was observed between the carbonyl of posaconazole and the carboxyl group of HPMCAS, which pointed in the direction of a drug-polymer interaction. Consequently, the combination of multiple NMR techniques allowed the elucidation of two types of interactions between posaconazole and HPMCAS (Lu et al., 2019). Improved miscibility is often a consequence of the presence of intermolecular interactions, and the assessment of the miscibility of ASDs is regularly performed via ssNMR relaxometry measurements. the proton spin-lattice relaxation time (T_{1H}) and the proton spin-lattice relaxation decay time in the rotating frame ($T_{1\rho H}$), which are related to the process of spin diffusion, are associated with the domain size of phase separated domains. The maximum path length over which proton-proton spin diffusion can occur, can be described by $L\sim(6DT_{iH})^{1/2}$, where D denotes the spin diffusion coefficient (~4-6x10^{-16} m^2/s for solids) and T_{iH} represents the relaxation time (either T_{1H} or $T_{1\rho H}$). If the domain size exceeds the maximum path length for spin diffusion, then separate relaxation times will be measured for each of the mixture components. On the other hand, if the domains are smaller than the maximum path length, a similar relaxation time will be measured for each of components (Mehring, 1996; Wang et al., 2002, 2001). ssNMR relaxometry is often combined with other ssNMR spectrometric techniques in the characterization of the physical structure of ASDs.

Herein lies one of the key strengths of solid-state NMR, besides the high accuracy and robustness. The possibility of combining multiple one-dimensional and multi-dimensional NMR techniques and investigating different nuclei, often allows for an in-depth and detailed picture of the intermolecular interactions, miscibility and physical structure of the ASD. This often makes solid-state NMR the technique of choice when it comes to investigating intermolecular interactions. However, it also should be noted that equipment can be relatively expensive and measurement times can be quite long. Additionally, interpretation of the data and performing experiments correctly requires specific expertise.

3.1.4. X- ray photoelectron spectroscopy

X-ray photoelectron spectroscopy (XPS) is a surface-sensitive analysis technique, which allows to probe the elemental composition of the first 10 nm of a solids outer surface (van der Heide, 2011). The technique can detect all elements from Lithium until uranium except for H and He, which are not detectable with XPS. Not only the elemental composition can be detected, but XPS can give an indication of the chemical environment of those respective elements (van der Heide, 2011). This surface analysis technique works by irradiating a sample with monochromatic x-rays in order to excite atoms, which in turn release photoelectrons, often referred to as the 'photoelectric effect'. The kinetic energy of the released photoelectrons is determined and subsequently, the binding energy is calculated, which is a characteristic that is specific for each element, allowing identification of specific elements on the surface (van der Heide, 2011).

With regard to ASDs, XPS is most often used to examine the composition of a particle surface in terms of drug to polymer ratio. An example of this can be found in the work of Borchardt-Setter et al. (Borchardt-Setter et al., 2024) where XPS was used to investigate the surface composition of two ternary ASDs containing posaconazole, PVP K12 and Span 80 or posaconazole, PVPVA and Span 80. It was found that, despite being miscible in the bulk of the formulation, XPS measurements revealed that posaconazole was depleted from the surface.

XPS is less often applied as a tool to investigate intermolecular interactions compared to other spectroscopic techniques such as FT-IR and ssNMR. Nevertheless, it can still be used with this goal in mind, as was proven by for example Trasi et al. (Trasi et al., 2020). In this study, XPS was used to examine the protonation of lumefantrine in ASDs with several different polymers. It was found that the basic compound lumefantrine underwent salt formation with acidic polymers, which was demonstrated by the appearance of an additional N 1s peak around 402 eV, corresponding to the protonated nitrogen of lumefantrine. Varying degrees of salt formation could be detected with respect to the polymer that was used in the formulation of the ASD. The interactions between lumefantrine

448 and the polymers were corroborated by FT-IR measurements, where peak shifts were detected in the
449 carbonyl region of the polymers (Trasi et al., 2020). Other examples exist where researchers observed
450 hydrogen bonding (González Cortes et al., 2023; Maniruzzaman et al., 2015) and π-π stacking (González
451 Cortes et al., 2023) between the components via XPS measurements. Admittedly, XPS is not the first
452 technique of choice when it comes to probing intermolecular interactions, as it only provides
453 information on the surface and not the bulk of the material and some issues have been reported with
454 the reproducibility of the measurements (Pinder et al., 2024). Other techniques, which are applied
455 more often with the aim to investigate intermolecular interactions, allow to acquire more detailed
456 information about the types of interactions in the ASD.

457

458 **3.2. Other methods**

459 3.2.1. (modulated) differential scanning calorimetry

460 With respect to ASDs, (modulated) differential scanning calorimetry (mDSC) is mostly used to
461 investigate drug-polymer miscibility, probe the crystallinity in the formulation or assess the solubility
462 of the drug in the polymer matrix (Dedroog et al., 2020). However, some information on the
463 intermolecular interactions between drug and polymer can still be distilled from mDSC experiments,
464 although this is limited. For a certain binary drug-polymer combination, it is possible to estimate the
465 T_g of the final ASD for different drug-polymer ratios by using the Gordon-Taylor equation (Gordon;
466 Taylor, 1952):

467 $$T_g = \frac{K_1 T_{g1} + K_G W_2 T_{g2}}{W_1 + K_G} \quad (8)$$

468 Where T_g, T_{g1} and T_{g2} are the glass transition temperatures of the final ASD, the amorphous drug and
469 the polymer respectively. W_1 and W_2 are the weight fractions of the drug and polymer respectively. K_G
470 is a constant which can be calculated using the equation below:

471 $$K_G \approx \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (9)$$

472 In this equation ρ_1 and ρ_2 represent the densities of the amorphous drug and the polymer respectively,
473 and T_{g1} and T_{g2} are the glass transition temperatures of the amorphous drug and the polymer, which
474 are the same as in the Gordon-Taylor equation . Besides the Gordon-Taylor equation, other equations
475 are also used to estimate the T_g of the resulting ASD, such as the Fox (Fox, 1952) or Kwei (Kwei, 1984)
476 equation. Nevertheless, the Gordon-Taylor equation is considered to be the most popular equation to
477 estimate the glass transition temperature. The estimation of T_g according to the Gordon-Taylor
478 equation assumes that ideal mixing takes place and that the strength of the drug-polymer interactions

is similar to the homomolecular interactions in the pure separate components. However, sometimes experimental T_g values can deviate significantly from the theoretical ones (Baghel et al., 2016b). Positive or negative deviations can occur due to heteromolecular interactions between drug and polymer being either stronger or weaker than the homomolecular interactions (Baghel et al., 2016b). Therefore, a positive deviation from the T_g values estimated via the Gordon-Taylor equation can indicate that strong intermolecular interactions are present between the drug and polymer in the ASD (See *Figure 5)* for a graphical presentation). A negative deviation, on the other hand, suggests that the homomolecular interactions are stronger than the drug-polymer interactions as a lower Tg indicates that less energy is required to increase the mobility to form the supercooled liquid. Admittedly, deviations from the ideal mixing behavior only provide qualitative information about whether or not some kind of interactions are present, and not which types of interactions it encompasses. Additionally, deviations are not always the direct result of intermolecular interactions, and it is also possible that intermolecular interactions may not lead to deviations from the predicted T_g values (Baird and Taylor, 2012b). Therefore, caution is advised when interpreting interactions via deviations of the predicted T_g values via the Gordon-Taylor equation.

Figure 5

Researchers have used this approach to investigate the possibility of interactions between the APIs sorafenib and regorafenib, and the polymers PVP and PVPVA (Liu et al., 2019). It was found that the experimental T_g values of the ASDs containing sorafenib showed a positive deviation from the predicted values, whereas the regorafenib ASDs displayed a negative deviation or matched the estimated values. This indicated that intermolecular interactions between the polymers and sorafenib where stronger compared to those with regorafenib. These findings where then subsequently corroborated by solution NMR and computational methods (Liu et al., 2019).

3.2.2. Dynamic vapor sorption

Dynamic vapor sorption (DVS) is a gravimetric analysis technique, which is routinely used to investigate how much solvent is sorbed by a solid sample. This is usually done by measuring the changes in mass of the sample as a function of the changing vapor concentration in the environment at a constant temperature. Water is mostly used as a solvent for this technique, although other organic solvents can be used as well (Hunter, 2016). Moisture sorption experiments can give insight into the moisture sorption properties of the material, which is a crucial factor in determining the stability and processing

characteristics of that material. Additionally, water vapor sorption measurements can also be applied to investigate the formation of solvates (Burnett et al., 2007) or hydrates (Vogt et al., 2006).

Although DVS is not a technique that first comes to mind with respect to investigating the interactions in ASDs, it has been applied in this regard by Punčochová et al. (Punčochová et al., 2014) . In this work, the authors tried to relate deviations from the additivity of water sorption isotherms of individual components to intermolecular interactions in the ASDs. When predicting water sorption curves of binary mixtures, additivity of the individual component isotherms is assumed and can be described by the following equation:

$$W_{mixture} = \frac{(W_{API}\, m_{API} + W_{polymer}\, m_{polymer})}{(m_{API} + m_{polymer})} \quad (10)$$

Where W is the mass of the absorbed solvent for each specific dry component and m is the mass of the respective component in the mixture (Kachel et al., 2013). A deviation from this ideal additivity behavior can be interpreted as an indication of intermolecular interactions between drug and polymer and the intensity of the deviation as a sign of the strength of the interactions. The researchers measured the water sorption isotherms for ASDs containing valsartan and either PVP K30, Soluplus or Eudragit. The ASDs with PVP and Soluplus showed a significant negative deviation from the ideal isotherms as according to equation 10. The ASD containing valsartan and Eudragit displayed a positive deviation from the ideal isotherm, and thus had an increased water sorption. The results from the water sorption measurements could be correlated to the observations made in the ATR-FT-IR analysis. It was shown that in the ASDs containing PVP and Soluplus, the C=O peak of valsartan, which usually appears around 1605 cm^{-1}, displayed a shift to lower wavenumbers, indicating interactions between the drug and polymer. For the ASD containing Eudragit, a shift to a higher wavenumber was observed. The differences in interactions between valsartan and the polymers also translated to different dissolution profiles for the ASDs (Punčochová et al., 2014). Similar approaches have been applied by other researchers as well after this study (Baghel et al., 2016c).

Similar to mDSC, the use of DVS to investigate intermolecular interactions only provides an indication that intermolecular interactions might be present in the sample and can supply a measure for the extent of the strength of the interactions. However, it provides no qualitative information about what type of interactions might be present in the sample. Nevertheless, DVS can still be used as a complementary technique to provide additional evidence for the formation of intermolecular interactions.

3.2.3.X-ray atomic pair distribution function

The pair distribution function (PDF) of X-ray scattering patterns can be obtained via Fourier transformation and although it does not probe intermolecular interactions in the true sense of the word, it can reveal information about long-range and short-range structural correlations between molecules(Billinge and Jensen, 2023; Terban and Billinge, 2022). The PDF method gives an indication of the probability of finding an atom at a certain distance of the origin point (Chen et al., 2021). PDF analysis can be used for a very wide variety of applications (Terban and Billinge, 2022) of which the discussion would go beyond the scope of this review. Nevertheless, some of the potential and most popular applications are for example, the determination of the molecular crystal structure (David and Shankland, 2008), phase quantification (Chen et al., 2001), the study of component miscibility (Chieng et al., 2013), measuring impurities (Terban et al., 2015), etc.

Although PDF of X-ray scattering data is not generally used for the investigation of intermolecular interactions in ASDs, Chen et al. (Chen et al., 2023) have applied X-ray PDF in combination with ssNMR and principal component analysis in order to evaluate the molecular structure of amorphous posaconazole and investigate the intermolecular interactions in ASDs with posaconazole and HPMCAS. Next to characterizing the molecular structure of crystalline and amorphous posaconazole, the researchers measured changes in the nearest neighbor peak in the PDF analysis of the X-ray diffraction data of the ASD as a function of the drug loading. Additionally, peak shifts for several carbon peaks of HPMCAS and posaconazole in the ^{13}C ssNMR spectra of the ASDs were observed with respect to the drug loading. The PDF results and peak shifts in the ^{13}C spectra were both incorporated in a PCA analysis. It was found that a similar trend of the first principal component was seen for both the PDF data and the ssNMR data, which indicated that both methods successfully displayed a monotonic change in the drug-polymer interactions as a function of the drug loading (Chen et al., 2023). Previously, another research group was also able to identify ion pair interactions in ASDs containing lapatinib and HPMC-E3 (De Araujo et al., 2017). This was done by extracting the intra- and intermolecular lapatinib and polymer functions from the total structure factors of pure lapatinib and polymer. Subsequently, the contributions of the polymer and the intramolecular lapatinib structure factors were subtracted, leaving the contributions of the drug-drug and drug-polymer interactions (De Araujo et al., 2017).

As a stand-alone technique to investigate intermolecular interactions, the PDF method is not an ideal option, as the interpretation of the diffraction patterns is often challenging. Intra- and intermolecular distances can overlap, which can further complicate interpretation of the peaks (Chen et al., 2021). The PDF method also only detects the proximity of atoms, and it is difficult to distil information about interactions from it. Nevertheless, a combination of X-ray PDF analysis and other complementary

methods (such as ssNMR) can provide a significant advantage in interpreting the molecular structure of ASDs.

3.3. *In silico* predictions of interactions

A large amount of different *in silico* simulation methods and molecular modeling approaches have been developed in recent years, which can be used for a variety of purposes. With respect to ASDs, and simulating drug-polymer intermolecular interactions more specifically, three types of simulations are mainly used: docking studies, molecular dynamics and quantum mechanics (Nambiar et al., 2022). Within these simulation types, there is still a wide array of experiments which are available with different aims in mind. A more in-depth explanation of the different types of molecular modeling approaches which are used to investigate the various properties of amorphous solid dispersions can be found in a review by Nambiar, Singh and Mali et al. (Nambiar et al., 2022).

The two main computational simulations, which are routinely used to investigate interactions between ASD components, are docking studies and molecular dynamics. Molecular docking simulations can be used to generate preliminary binding confirmations and predict the binding affinity between drug and polymer. Generally, if the calculated binding affinity between the two components is negative, then this a good indication that intermolecular interactions will be present in the physical ASD (Barmpalexis et al., 2019). Docking studies have been used in a number of recent investigations to simulate intermolecular interactions in ASDs (Budiman et al., 2022; Rosiak et al., 2024; F. Zhang et al., 2022). An example of this can be found in a study conducted by Rosiak et al. where the researchers investigated ASDs consisting of myricetin and PVP K30 (Rosiak et al., 2024). Molecular docking simulations, which were conducted by use of the Autodock 4.0 sofware, implied that hydrogen bonds were formed between the O-H group of myricetin and the C=O group of PVP K30. The existence of these hydrogen bonds was confirmed by analyzing the samples with FT-IR as well (Rosiak et al., 2024).

Molecular dynamics, on the other hand, provides a tool to simulate the movement of all molecules in a complex system, such as an ASD, as a function of time, based on the physics that dictate the intermolecular interactions (Karplus and McCammon, 2002). This tool requires that the components of the system are parametrized by a force field that appoints the total energy of the system as a sum of potential energy functions (Ma et al., 2020). Different types of force fields exist, which all describe the energy of the system depending on the position of the atoms. Molecular dynamics simulations have been applied in multiple studies investigating the intermolecular interactions in ASDs (Aulifa et al., 2024; Becelaere et al., 2022; Kabedev et al., 2022). Becelaere and Van Den Broeck et al. (Becelaere et al., 2022) used molecular dynamics simulations to investigate drug-polymer interactions between flubendazole and poly(2-ethyl-2-oxazoline) (PEtOx). The researchers constructed customized force

fields for both flubendazole and PEtOx, which were then validated as well. It was observed in the molecular dynamics simulations that hydrogen bonds were present between flubendazole and PEtOx, and that there was a competition for hydrogen bond donor sites, which was dominated by PEtOx. The simulated hydrogen bonds were also confirmed to be present in the experimentally electrospun ASDs by ATR-FT-IR (Becelaere et al., 2022). In this study, a second computational method was used to simulate the interactions that would occur in the ASDs, namely density functional theory (DFT) calculations, which belong to the third and final group of in silico methods.

The final type of computational methods which can be used to study intermolecular interactions is quantum mechanics, of which DFT calculations are an often-applied example, like it was used in the example in the paragraph above. DFT calculations allow for the investigation of non-bonding interactions via the construction of molecular complexes and the associated interaction energy (Mazurek et al., 2020). It is a rapid and powerful technique, which provides a 'static snapshot' of the molecular complexes (Nambiar et al., 2022) and is used as a computational approach in a variety of studies (Sarpal et al., 2019; Wang et al., 2017; S. Zhang et al., 2022). In one such study, Wang et al. used DFT calculations to predict interactions between PVP and resveratrol or griseofulvin (Wang et al., 2017). It was predicted that hydrogen bonds would be formed between PVP and resveratrol, and the distances of the hydrogen bonds were calculated as well. It was verified by FT-IR analysis that in the ASD, hydrogen bonds between PVP and resveratrol could indeed be observed (S. Zhang et al., 2022).

Of course, it has to be mentioned that the *in silico* simulations of intermolecular interactions are, in fact, obviously only predictions and are not a real reflection of the actual interactions that exist in the physical ASDs. Therefore, most studies that apply computational methods to simulate the interactions that could occur between ASD components, also utilize other methods to verify the predictions experimentally. Most often, these predictions are complemented with spectroscopic measurements such as ssNMR or FT-IR. Nevertheless, molecular modeling approaches can hold a significant benefit for researchers investigating intermolecular interactions, as the predictions can give useful insights into the functional groups that are involved in the interactions, help with the interpretation of other results or confirm observations made with other techniques.

4. Influence of intermolecular interactions on the physical stability

It is one thing to be able to detect intermolecular interactions in an ASD system, but the knowledge of interactions only holds real value if it is understood how these molecular interactions affect important end-product properties, such as the physical stability and the pharmaceutical performance. Obviously, the stability and dissolution of ASDs are very complex processes, which depend on a range of different factors besides intermolecular interactions. Nevertheless, drug-polymer interactions still play an

important role in both of these processes and it is crucial to understand every step and aspect of the process to be able to fully comprehend what exactly is occurring and how all steps are connected. Therefore, in this section and the next one, the influence of the drug-polymer interactions on the physical stability and the drug release from ASDs will be discussed.

The physical stability of an ASD can be defined as the ability of the system to maintain its amorphous nature, while remaining a one-phase molecularly mixed dispersion. (Newman et al., 2012)(Bhujbal et al., 2021b)With respect to the physical stability of ASDs, several factors play a key role in determining the stability of the formulation upon storage. The loading of the drug with respect to drug-polymer solubility and miscibility (Chan et al., 2015; Meng et al., 2015; Qian et al., 2010; Yuan et al., 2014), the crystallization tendency of the drug (Van Eerdenbrugh et al., 2010), the T_g of the ASD system with respect to the storage temperature(Yoshioka et al., 1994), the humidity of the environment (Rumondor et al., 2009) and the presence of drug-polymer intermolecular interactions, of which the influence will be discussed below.

Intermolecular interactions can influence the stability of ASDs in a variety of ways. As already discussed in the first section of this review, drug-polymer interactions can have a positive influence on the solubility and miscibility of drug and polymer (Bookwala and Wildfong, 2023). Multiple studies have already indicated that the drugs which interact with the polymer, have an improved solubility in those polymers compared to their solubility in polymers with less potential for intermolecular interactions (Bookwala et al., 2022; Knopp et al., 2015; Tao et al., 2009). Similar to the solubility, the drug-polymer miscibility can also be improved by the existence of intermolecular interactions, as was proven by Marsac et al. who investigated mixing between felodipine and nifedipine with PVP (Marsac et al., 2006b). The researchers could correlate the interaction potential of the two APIs and PVP with the miscibility data of the two systems that were obtained in previous studies.

Besides improving solubility and miscibility of the drug in the polymer, intermolecular interactions can also alter the molecular mobility of the drug molecules in the polymer matrix (Bookwala and Wildfong, 2023; Kapourani et al., 2021). Generally, the higher T_g of the polymer compared to that of the amorphous API increases the T_g of the overall ASD system, leading to an antiplasticizing effect and a decreased molecular mobility of the API in the ASD (Baghel et al., 2016b). The reduced molecular mobility lowers the chance of AAPS and nucleation/crystallization, as the movement of the drug molecules is hampered (Yao et al., 2020). Drug-polymer intermolecular interactions can result in an additional reduction of the molecular mobility of the drug molecules in the ASD system, by decreasing the degrees of freedom of the API (Aso and Yoshioka, 2006) and also reducing the global mobility of the total ASD system (Bhardwaj et al., 2014). This was for instance established in a study by Kothari et

al. where the strength of the intermolecular interactions between nifedipine and three different polymers was correlated with the molecular mobility and the crystallization kinetics (Kothari et al., 2015b). It was found that the strongest drug-polymer interactions could be observed between nifedipine and PVP, which resulted in the largest increase in the relaxation times and the highest reduction of the crystallization kinetics (Kothari et al., 2015b). As a demonstration of this, the dielectric loss of ASDs containing nifedipine and one of three selected polymers (PVP, PAA and HPMCAS) is depicted in *Figure 6.* The dielectric loss peak for the nifedipine-PVP ASD occurred at a much lower frequency compared to the other polymers, indicating a higher reduction of the mobility.

Figure 6

Lastly, drug-polymer interactions can also reduce the risk of nucleation and crystallization of the API in the polymer matrix, beyond the effect of reducing molecular mobility. As already mentioned, if the drug loading of the API in the ASD is above the drug-polymer solubility, then there is a thermodynamic driving force for phase separation and crystallization, as the system is considered a metastable state compared to the crystalline counterpart. The formation of a critical nucleus, the first step in the crystallization process, is associated with an increase in the free energy and the smaller this energy barrier is, the higher the chance of forming that critical nucleus is (Rams-Baron et al., 2018). If drug-polymer interactions are present, then first of all, the free energy of the system is reduced, decreasing the driving force for phase separation (Malick, 2014). Additionally, the energy barrier that needs to be overcome in order for the drug molecules to come together and phase separation to occur is increased, as these intermolecular interactions need to be disrupted for that to happen (Krishna Kumar and Suryanarayanan, 2022). Zhang et al. showed, for example, that the nucleation rates of fluconazole were significantly decreased by HPMCAS and were attributed to strong intermolecular interactions and the larger monomer unit (Zhang et al., 2021). PVP K30, on the other hand, only had a minor inhibitory effect on the nucleation of fluconazole and poly (ethylene oxide) (PEO) even resulted in an increase of the nucleation rates (Zhang et al., 2021). Not only nucleation can be inhibited by the presence of drug-polymer interactions, but the crystal growth after nucleation can also be affected by the interactions. In a study by Kestur and Taylor, a correlation was observed between the crystal growth rate of amorphous felodipine and the strength of the drug-polymer interactions between felodipine and the polymers that were selected (Kestur and Taylor, 2010). The order of crystallization inhibition effectiveness was PVP > PVPVA > HPMCAS > PVAc, and the same order was observed with respect to the strength of the hydrogen bonding interactions between felodipine and the polymers. Consequently, it appeared that polymers which can form stronger interactions with the API inhibit crystallization to a larger extent (Kestur and Taylor, 2010).

A good example of the influence of intermolecular interactions on the stability of ASDs can be found in the comparison study of Wu and Van den Mooter (Wu and Mooter, 2023) where ASDs were manufactured with PVPVA and six different APIs. The APIs could be subdivided according to their crystallization tendency as a slow, moderate or fast crystallizer. In each crystallization category, an API with and without hydrogen bond donor groups was placed and for each API the maximum drug loading was determined in PVPVA and a stability study was performed on the respective ASDs. It was found that, in the same class of crystallization tendency, the APIs which contained hydrogen bond donor groups attained higher possible drug loadings compared to the drugs without donor groups (Wu and Mooter, 2023). Additionally, the ASDs which contained APIs that had hydrogen bond donor groups remained stable for a longer period of time compared to the APIs which did not contain hydrogen bond donor groups.

In conclusion, with respect to the physical stability of ASDs, intermolecular interactions play a very important role. Drug-polymer interactions can improve the solubility of the drug in the polymer and the drug-polymer miscibility, which can lead to higher possible drug loadings as well. Besides this, interactions can reduce the molecular mobility of the drug in the polymer matrix. Lastly, intermolecular interactions can reduce the chance of nucleation and can slow down crystal growth kinetics significantly, which all leads to an improved physical stability. Interestingly, when it comes to spray dried ASDs or ASDs manufactured with other solvent-based techniques, it has been observed that drug-polymer interactions and conformations in solution can be transferred to the solid-state (Defrese et al., 2020). Interactions with the solvent are also of importance, thus the solvent that is used to manufacture the ASDs can impact properties of the ASDs in the solid-state as well (Dedroog et al., 2022).

5. Influence of intermolecular interactions on dissolution and supersaturation

Besides the physical stability upon storage, another important property of ASDs is the release profile of the drug from the formulation. As it is the aim of ASDs to improve the oral bioavailability of poorly soluble drugs compared to the pure crystalline state, it is important that the drug can reach high concentrations and that the supersaturation can be maintained. It is generally assumed that the ideal release profile for an ASD system, if not intended for extended or targeted release, is a fast initial drug release from the formulation followed by the maintenance of supersaturation, which can lead to higher absorption and bioavailability. This type of release profile is commonly referred to as the ‘spring-parachute’ effect, with the ‘spring’ referring to the fast initial drug release and the ‘parachute’

representing the maintenance of the supersaturation (Shi et al., 2021). If the drug were to crystallize in the dissolution medium, then the benefits of the supersaturation are diminished. The dissolution of drug molecules from an ASD formulation is a complex process, which is influenced by a variety of factors such as the drug and its physicochemical properties, the way the formulation is designed and the polymer that is selected, which also relates to the drug-polymer interactions (Baghel et al., 2016d; Taylor and Zhang, 2016).

The initial drug release is highly depending on the polymer that was selected for the formulation and the drug loading of the API in the polymer matrix (Y. Chen et al., 2015b; Indulkar et al., 2019). Depending on the drug-polymer combination, below a certain drug loading, the drug release rate is rapid and polymer-controlled. However, if the drug loading is increased above this critical limit, then the drug release becomes drug-controlled, and the rate and amount of drug release will sharply decrease. The drug loading above which drug release becomes drug-controlled, and the rate and extent of release drop significantly, is generally called 'the limit of congruency' (LoC) (Indulkar et al., 2019; Que et al., 2019; Saboo et al., 2019) . Above the LoC, upon contact with water, the rate of phase separation might be higher than the rate of drug dissolution, resulting in a drug-rich phase with a decreased drug release rate. It has been observed that intermolecular drug-polymer interactions play an important role in the establishment of the LoC. Que, Lou and Zemlyanov et al. have investigated the correlation between the LoC and intermolecular interactions in ASDs of ledipasvir and PVPVA (Que et al., 2019). The researchers found that the relatively low LoC of 5 - 7.5 wt% of the system could be attributed to the fact that drug-polymer interactions were saturated above 10 wt% and drug-drug interactions predominated above the LoC, as was seen in the NMR analysis. This lead to phase separation and surface drug enrichment, hampering the release of the rest of the drug and the polymer, which explained the drop in drug release for drug loadings above 7.5 wt%. (Que et al., 2019). This indicated that intermolecular interactions are in fact important in the establishment of the Loc. Interestingly, the same research group investigated the correlation between the strength of the intermolecular interactions and the LoC, by manufacturing ASDs with PVPVA and APIs with a common chemical scaffold (Que et al., 2021). A negative correlation could be observed between the strength of the intermolecular interactions and the LoC, meaning that APIs which did not interact or did not interact strongly with PVPVA, could reach higher LoC values and showed a higher drug release at larger drug loadings (Que et al., 2021). A follow-up study indicated that the interacting systems displayed a larger amount of polymer in the hydrophobic phase after contact with water, which was suggested to be a determining factor in the increase of the volume of the hydrophobic phase and the formation of an insoluble barrier after phase separation (Deac et al., 2023). However, most of these studies were performed on PVPVA-based systems and studies with other polymers are still limited. Hiew and co-

workers compared PVPVA with enteric polymers in lumefantrine-based ASDs and found that the release behavior of the PVPVA-based ASDs was different compared to the enteric polymers (Hiew et al., 2022). The dissolution rate from the ASDs containing enteric polymers was governed by the release rate of the pure polymer and the drug release decreased with increasing drug loading. It was suggested that this was due to ionic interactions, which diminished hydration of the polymer carboxylate ions, limiting dissolution of the polymer (Hiew et al., 2022).

As already mentioned, the improved drug release from ASDs can lead to high drug concentrations and a supersaturated solution as a consequence. Generally, the maximum theoretical supersaturation, which can be defined as the highest possible drug concentration where the drug is still present in the aqueous medium as free drug molecules is often termed the 'amorphous solubility' (Murdande et al., 2010). When the drug concentration exceeds the amorphous solubility, liquid-liquid phase separation (LLPS) may occur, without the crystallization of the drug. The occurrence of LLPS entails the equilibrium between a drug-rich phase, existing as colloidal nano-droplets, and a water-rich phase where the concentration of the drug is similar to the amorphous solubility (see *Figure7*) (Ilevbare and Taylor, 2013). The appearance of drug-rich nano-droplets and LLPS often happens in ASDs where a congruent polymer-controlled drug release is observed, as this is correlated with a higher rate and extent of drug release (Que et al., 2021). Drug-rich nano-droplets have been observed to act as a kind of 'reservoir' and could lead to higher drug plasma concentrations compared to ASD systems that lead to similar supersaturation degrees but do not form drug-rich aggregates (Saboo et al., 2019). It has been observed by Qian et al. that the LLPS onset point is also related to the intermolecular interaction between drug and polymer. The researchers found that stronger interactions resulted in a higher LLPS onset concentration and higher maximum achievable free drug. However, this effect depended on the type of interactions that were present between the drug and polymer. Hydrogen bonding appeared to be more sensitive to disruption by water and affected the LLPS onset point to a lesser extent (Qian et al., 2024).

Figure 7

The behavior of ASDs upon contact with the dissolution medium can be theoretically described using ternary phase diagrams of the API/polymer/water system. A paper by Krummnow et al. provided an excellent depiction of this, describing the pathways an API/polymer system can follow upon contact with water. Water that is absorbed in the ASD can lead to AAPS in the wet ASD, and simultaneously,

LLPS of the dissolved drug molecules can occur in the dissolution medium, forming drug-rich nanodroplets. Two ternary phase diagrams, depicting these two situations, can be found in *Figure 8.*

Figure 8

When it comes to the second part of the dissolution process, the maintenance of supersaturation after the initial drug release from the ASD formulation, a couple of factors play a determining role. The physicochemical properties of the drug, such as the crystallization tendency (Van Eerdenbrugh et al., 2010), are important, but again also the polymer that was selected and the composition of the formulation are key factors in the whole process. It has been abundantly reported that the polymer is capable of prolonging and maintaining supersaturation and inhibiting crystallization of the drug in solution (Li et al., 2020). The presence of drug-polymer interactions also appears to be crucial for supersaturation and could limit nucleation and crystal growth of the drug molecules in solution (Y. Chen et al., 2015c; Que et al., 2018). Mendes, Andrzejewski and Pinto et al. investigated the supersaturation of sulfamethoxazole from ASDs which contained either Soluplus or Eudragit EPO and correlated the supersaturation results with the drug-polymer interactions (Mendes et al., 2020). It was observed that higher levels of sulfamethoxazole supersaturation could be attained when it was present in an ASD with Eudragit EPO compared to Soluplus. The increased supersaturation could be attributed to hydrogen bond formation between sulfamethoxazole and Eudragit EPO, which reduced nucleation by increasing the activation energy for the drug to nucleate and decreased crystal growth (Mendes et al., 2020). Ugur, Caggiano and Monson et al. indicated that not only the strength of the drug-polymer interactions play a role in supersaturation but also showed that it is a complex interplay between drug-drug, drug-polymer and polymer-polymer interactions, where the interactions with water and the hydrophobicity of the polymer play a role in the drug release as well (Ugur et al., 2024). Furthermore, it was even shown by Li and Taylor that stronger drug-polymer interactions can lead to a larger solubility suppression when the ASD consisted of a poorly soluble polymer, allowing the tailoring of a more sustained release (Li and Taylor, 2018). A study by Ueda et al. discussed the trade-off that needs to be made considering the impact of intermolecular interactions on the supersaturation of the drug (Ueda et al., 2021). The researchers showed that drug-polymer interactions lead to a reduction of the chemical potential, causing a larger amount of polymer distributing in the drug-rich phase when LLPS occurs. This translates into a couple of advantages such as increased inhibition of crystallization (Ueda et al., 2019) and improvement of the size stability of the drug-rich nano-droplets (Ueda and Taylor, 2020). However, increased amounts of polymer in the drug-rich phase also can cause a decrease in the amorphous solubility of the drug, leading to a decline in the amount of free dissolved drug molecules (Ueda et al., 2021).

Compared to the influence of drug-polymer intermolecular interactions on the physical stability of ASDs, which is quite straightforward, the effect of interactions on the dissolution process of the ASD is more complex. As discussed above, intermolecular interactions can influence the various stages of dissolution, going from the initial drug release to supersaturation and can affect these processes in both a negative and positive manner depending on the drug-polymer system. When designing an ASD formulation, both the advantages and disadvantages need to be considered and balanced against each other, while also holding the physical stability of the formulation in mind. It is however certain that, despite all the studies that already have been performed, further research is still necessary in order to elucidate the dissolution process in more detail.

6. Conclusion

This review provides a detailed overview of the role that intermolecular interactions play in the formulation and performance of amorphous solid dispersions. First, the thermodynamics and theoretical considerations of interactions in general were discussed in the first part of the review. An overview was given of all characterization techniques that are applied in research to investigate intermolecular interactions in the solid-state and several examples of applications were provided for each technique. The most useful and popular methods to detect interactions are the spectroscopic techniques, especially FT-IR and ssNMR. We consider ssNMR to be one of the most useful and versatile techniques when it comes to probing intermolecular interactions, due to the large variety of pulse sequences and the range of information that can be distilled from the measurements. Combinations with *in silico* simulation methods can be valuable to deepen the understanding of the type of interactions that are formed and the effect on the physical structure.

Finally, the role of drug-polymer interactions on the physical stability and drug release of ASDs was explored in more detail. Intermolecular interactions show a definite positive effect on the stability of ASDs, and stronger interactions usually lead to more stable dispersions, and can result in higher drug loadings. The effect of drug-polymer interactions on the drug release is less straightforward. Both positive and negative effects on the drug release have been attributed to intermolecular interactions, and many studies are trying to elucidate how they impact the dissolution process. Nevertheless, more work is still needed to acquire a more extensive comprehension of the process.

It is clear that intermolecular interactions play a very important role in various aspects of the formulation and performance of ASDs. However, more systemic studies investigating the interplay and balance between physical stability and dissolution are warranted. A more in-depth understanding of

869 both of these processes needs to be achieved, but especially the combined effect of interactions on
870 both of these aspects should be studied in more detail.

871

Acknowledgements

The authors would like to thank Fonds Wetenschappelijk Onderzoek Vlaanderen (FWO) (grantnumber 1SD5524N) for their support.

Figure Captions

Figure 1: Graphical representation of the Lennard-Jones potential model. Intermolecular potential energy VL J in function of the distance of a pair of molecules.

Figure 2: Graphical representation of a state diagram for an amorphous solid dispersion with different drug loadings in function of the temperature. The crystalline drug-polymer solubility line, the amorphous drug-polymer solubility line and the glass transition divide the diagram in six distinct regions. **I:** thermodynamically stable glass; **II:** Thermodynamically stable liquid; **III:** supersaturated glass; **IV:** supersaturated liquid; **V:** supersaturated and immiscible glass: **VI:** supersaturated and immiscible liquid. (adapted form Qian et al. 2010 with permission)

Figure 3: FT-IR spectra of NAP, PVPVA, and 10, 20, and 30 wt % NAP and PVPVA in MeOH (A), EtOH (B), PrOH (C), ACN (D), and DCM (E). The following color code was applied: NAP in red, PVPVA in black, 10 wt % NAP in blue, 20 wt % NAP in orange and 30 wt % NAP in green. The transmittance is depicted in arbitrary units. (Reprinted with permission from Dedroog et al. 2022. Copyright 2025 American Chemical Society.)

Figure 4: ^{15}N CPMAS NMR spectra of crystalline LB freebase, crystalline LB phthalate, amorphous LB freebase, and LB–HPMCP solid dispersions with drug loadings of 40%, 60%, 80%, in the spectral range of −225 to −400 ppm. (Reprinted with permission from Song, Yang, Cheng et al. 2015. Copyright 2025 American Chemical Society.)

Figure 5: Possible deviations from the ideal behavior of the glass transition temperature in function of the weight fraction of the drug, as predicted by the Gordon-Taylor equation. (Figure adapted from Baghel et al. 2016 with permission.)

Figure 6: Dielectric loss behavior of NIF (blue ●) and NIF solid dispersions with PVP (black ●), HPMCAS (red ▼), and PAA (green ■) at 60 °C with (a) 10% and (b) 20% w/w polymer concentration. The loss curves have been normalized with respect to the maximum loss value. (Reprinted with permission from Kothari et al. 2015. Copyright 2025 American Chemical Society.)

Figure 7: A visual representation of the dissolution of drug molecules from an ASD where the amorphous solubility is exceeded, and liquid-liquid phase separation occurs. Drug-rich nano droplets are formed and act as a sort of reservoir for the drug molecules in solution.

Figure 8: Schematic ternary phase diagram of an API/polymer/water system with schematic pathways of (a) water sorption and amorphous phase separation (according to (**c**)) and (**b**) ASD dissolution in water and liquid–liquid phase separation (according to (**d**)). The black circle depicts the dry ASD, and the blue dash-dotted line represents the path for (a) water sorption and (**b**) ASD dissolution. The gray solid line illustrates the miscibility gap (gray area) with gray dash-dotted tie lines. The red triangle denotes the feed point F for (**a**) amorphous phase separation and for (**b**) liquid–liquid phase separation. Gray diamonds denote the API-poor phase L1 and the API-rich phase L2. (reprinted from Krummnow et al. 2022 with permission)

924

925

926

References

Alonzo, D.E., Raina, S., Zhou, D., Gao, Y., Zhang, G.G.Z., Taylor, L.S., 2012. Characterizing the impact of hydroxypropylmethyl cellulose on the growth and nucleation kinetics of felodipine from supersaturated solutions. Cryst Growth Des 12, 1538–1547. https://doi.org/10.1021/CG201590J/ASSET/IMAGES/MEDIUM/CG-2011-01590J_0011.GIF

Aso, Y., Yoshioka, S., 2006. Molecular mobility of nifedipine-PVP and phenobarbital-PVP solid dispersions as measured by13C-NMR spin-lattice relaxation time. J Pharm Sci 95, 318–325. https://doi.org/10.1002/jps.20545

Aulifa, D.L., Al Shofwan, A.A., Megantara, S., Fakih, T.M., Budiman, A., 2024. Elucidation of Molecular Interactions Between Drug-Polymer in Amorphous Solid Dispersion by a Computational Approach Using Molecular Dynamics Simulations. Advances and Applications in Bioinformatics and Chemistry 17, 1–19. https://doi.org/10.2147/AABC.S441628

Baghel, S., Cathcart, H., O'Reilly, N.J., 2016a. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. J Pharm Sci 105, 2527–2544. https://doi.org/10.1016/J.XPHS.2015.10.008

Baghel, S., Cathcart, H., O'Reilly, N.J., 2016b. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. J Pharm Sci 105, 2527–2544. https://doi.org/10.1016/J.XPHS.2015.10.008/ASSET/B6F13339-7EB1-4B7E-896C-702C2CB1CCF1/MAIN.ASSETS/GR6.JPG

Baghel, S., Cathcart, H., O'Reilly, N.J., 2016c. Theoretical and experimental investigation of drug-polymer interaction and miscibility and its impact on drug supersaturation in aqueous medium. European Journal of Pharmaceutics and Biopharmaceutics 107, 16–31. https://doi.org/10.1016/J.EJPB.2016.06.024

Baghel, S., Cathcart, H., O'Reilly, N.J., 2016d. Theoretical and experimental investigation of drug-polymer interaction and miscibility and its impact on drug supersaturation in aqueous medium. European Journal of Pharmaceutics and Biopharmaceutics 107, 16–31. https://doi.org/10.1016/J.EJPB.2016.06.024

Baird, J.A., Taylor, L.S., 2012a. Evaluation of amorphous solid dispersion properties using thermal analysis techniques. Adv Drug Deliv Rev 64, 396–421. https://doi.org/10.1016/J.ADDR.2011.07.009

Baird, J.A., Taylor, L.S., 2012b. Evaluation of amorphous solid dispersion properties using thermal analysis techniques. Adv Drug Deliv Rev 64, 396–421. https://doi.org/10.1016/J.ADDR.2011.07.009

Barmpalexis, P., Karagianni, A., Katopodis, K., Vardaka, E., Kachrimanis, K., 2019. Molecular modelling and simulation of fusion-based amorphous drug dispersions in polymer/plasticizer blends. European Journal of Pharmaceutical Sciences 130, 260–268. https://doi.org/10.1016/J.EJPS.2019.02.004

Becelaere, J., Van Den Broeck, E., Schoolaert, E., Vanhoorne, V., Van Guyse, J.F.R., Vergaelen, M., Borgmans, S., Creemers, K., Van Speybroeck, V., Vervaet, C., Hoogenboom, R., De Clerck, K.,

2022. Stable amorphous solid dispersion of flubendazole with high loading via electrospinning. Journal of Controlled Release 351, 123–136. https://doi.org/10.1016/J.JCONREL.2022.09.028

Benet, L.Z., 2013. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development. J Pharm Sci 102, 34–42. https://doi.org/10.1002/jps.23359

Bhardwaj, S.P., Arora, K.K., Kwong, E., Templeton, A., Clas, S.D., Suryanarayanan, R., 2014. Mechanism of amorphous itraconazole stabilization in polymer solid dispersions: Role of molecular mobility. Mol Pharm 11, 4228–4237. https://doi.org/10.1021/MP5004515/ASSET/IMAGES/MEDIUM/MP-2014-004515_0013.GIF

Bhujbal, S. V., Mitra, B., Jain, U., Gong, Y., Agrawal, A., Karki, S., Taylor, L.S., Kumar, S., (Tony) Zhou, Q., 2021a. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharm Sin B 11, 2505–2536. https://doi.org/10.1016/J.APSB.2021.05.014

Bhujbal, S. V., Mitra, B., Jain, U., Gong, Y., Agrawal, A., Karki, S., Taylor, L.S., Kumar, S., (Tony) Zhou, Q., 2021b. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharm Sin B 11, 2505–2536. https://doi.org/10.1016/J.APSB.2021.05.014

Billinge, S.J.L.., Jensen, K.M.Ø.., 2023. Atomic pair distribution function analysis : a primer. Oxford University Press.

Bookwala, M., Buckner, I.S., Wildfong, P.L.D., 2022. Implications of Coexistent Halogen and Hydrogen Bonds in Amorphous Solid Dispersions on Drug Solubility, Miscibility, and Mobility. Mol Pharm 19, 3959–3972. https://doi.org/10.1021/ACS.MOLPHARMACEUT.2C00434/SUPPL_FILE/MP2C00434_SI_001.PDF

Bookwala, M., Wildfong, P.L.D., 2023. The Implications of Drug-Polymer Interactions on the Physical Stability of Amorphous Solid Dispersions. Pharmaceutical Research 2023 40:12 40, 2963–2981. https://doi.org/10.1007/S11095-023-03547-4

Borchardt-Setter, K.A., Yu, J., Stelzer, T., Yu, L., 2024. Surface Enrichment and Depletion of Components in a Ternary Drug-Surfactant-Polymer Amorphous Solid Dispersion. Mol Pharm 21, 4074–4081. https://doi.org/10.1021/ACS.MOLPHARMACEUT.4C00444/ASSET/IMAGES/LARGE/MP4C00444_0009.JPEG

Budiman, A., Citraloka, Z.G., Muchtaridi, M., Sriwidodo, S., Aulifa, D.L., Rusdin, A., 2022. Inhibition of Crystal Nucleation and Growth in Aqueous Drug Solutions: Impact of Different Polymers on the Supersaturation Profiles of Amorphous Drugs—The Case of Alpha-Mangostin. Pharmaceutics 2022, Vol. 14, Page 2386 14, 2386. https://doi.org/10.3390/PHARMACEUTICS14112386

Burnett, D.J., Thielmann, F., Sokoloski, T.D., 2007. Investigating carbamazepine-acetone solvate formation via Dynamic gravimetric vapor sorption. J Therm Anal Calorim 89, 693–698. https://doi.org/10.1007/S10973-006-7957-8/METRICS

Chan, S.Y., Qi, S., Craig, D.Q.M., 2015. An investigation into the influence of drug–polymer interactions on the miscibility, processability and structure of polyvinylpyrrolidone-based hot melt extrusion formulations. Int J Pharm 496, 95–106. https://doi.org/10.1016/J.IJPHARM.2015.09.063

1008 Chen, X., Bates, S., Morris, K.R., 2001. Quantifying amorphous content of lactose using parallel beam
1009 X-ray powder diffraction and whole pattern fitting. J Pharm Biomed Anal 26, 63–72.
1010 https://doi.org/10.1016/S0731-7085(01)00346-6

1011 Chen, X., Stoneburner, K., Ladika, M., Kuo, T.C., Kalantar, T.H., 2015. High-Throughput Raman
1012 Spectroscopy Screening of Excipients for the Stabilization of Amorphous Drugs. Appl Spectrosc
1013 69, 1271–1280. https://doi.org/10.1366/15-07914

1014 Chen, Y., Liu, C., Chen, Z., Su, C., Hageman, M., Hussain, M., Haskell, R., Stefanski, K., Qian, F., 2015a.
1015 Drug-polymer-water interaction and its implication for the dissolution performance of
1016 amorphous solid dispersions. Mol Pharm 12, 576–589. https://doi.org/10.1021/mp500660m

1017 Chen, Y., Liu, C., Chen, Z., Su, C., Hageman, M., Hussain, M., Haskell, R., Stefanski, K., Qian, F., 2015b.
1018 Drug-polymer-water interaction and its implication for the dissolution performance of
1019 amorphous solid dispersions. Mol Pharm 12, 576–589.
1020 https://doi.org/10.1021/MP500660M/ASSET/IMAGES/MEDIUM/MP-2014-00660M_0009.GIF

1021 Chen, Y., Liu, C., Chen, Z., Su, C., Hageman, M., Hussain, M., Haskell, R., Stefanski, K., Qian, F., 2015c.
1022 Drug-polymer-water interaction and its implication for the dissolution performance of
1023 amorphous solid dispersions. Mol Pharm 12, 576–589.
1024 https://doi.org/10.1021/MP500660M/ASSET/IMAGES/MEDIUM/MP-2014-00660M_0009.GIF

1025 Chen, Z., Huang, C., Yao, X., Benmore, C.J., Yu, L., 2021. Structures of glass-forming liquids by x-ray
1026 scattering: Glycerol, xylitol, and D-sorbitol. J Chem Phys 155, 244508.
1027 https://doi.org/10.1063/5.0073986/14840258/244508_1_ACCEPTED_MANUSCRIPT.PDF

1028 Chen, Z., Nie, H., Benmore, C.J., Smith, P.A., Du, Y., Byrn, S., Templeton, A.C., Su, Y., 2023. Probing
1029 Molecular Packing of Amorphous Pharmaceutical Solids Using X-ray Atomic Pair Distribution
1030 Function and Solid-State NMR. Mol Pharm 20, 5763–5777.
1031 https://doi.org/10.1021/ACS.MOLPHARMACEUT.3C00628/SUPPL_FILE/MP3C00628_SI_001.PDF

1032 Chieng, N., Trnka, H., Boetker, J., Pikal, M., Rantanen, J., Grohganz, H., 2013. Detecting phase
1033 separation of freeze-dried binary amorphous systems using pair-wise distribution function and
1034 multivariate data analysis. Int J Pharm 454, 167–173.
1035 https://doi.org/10.1016/J.IJPHARM.2013.07.030

1036 Christy, A.A.., Ozaki, Y.., Gregoriou, V.G.., 2001. Modern fourier transform infrared spectroscopy 356.

1037 David, W.I.F., Shankland, K., 2008. Structure determination from powder diffraction data. Acta
1038 Crystallogr A 64, 52–64. https://doi.org/10.1107/S0108767307064252

1039 De Araujo, G.L.B., Benmore, C.J., Byrn, S.R., 2017. Local Structure of Ion Pair Interaction in Lapatinib
1040 Amorphous Dispersions characterized by Synchrotron X-Ray diffraction and Pair Distribution
1041 Function Analysis. Scientific Reports 2017 7:1 7, 1–10. https://doi.org/10.1038/srep46367

1042 Deac, A., Qi, Q., Indulkar, A.S., Purohit, H.S., Gao, Y., Zhang, G.G.Z., Taylor, L.S., 2023. Dissolution
1043 Mechanisms of Amorphous Solid Dispersions: Role of Drug Load and Molecular Interactions.
1044 Mol Pharm 20, 722–737.
1045 https://doi.org/10.1021/ACS.MOLPHARMACEUT.2C00892/SUPPL_FILE/MP2C00892_SI_001.PDF

1046 Dedroog, S., Adriaensens, P., Van Den Mooter, G., 2022. Gaining Insight into the Role of the Solvent
1047 during Spray Drying of Amorphous Solid Dispersions by Studying Evaporation Kinetics. Mol

Pharm 19, 1604–1618. https://doi.org/10.1021/ACS.MOLPHARMACEUT.2C00095/SUPPL_FILE/MP2C00095_SI_001.PDF

Dedroog, S., Pas, T., Vergauwen, B., Huygens, C., Van den Mooter, G., 2020. Solid-state analysis of amorphous solid dispersions: Why DSC and XRPD may not be regarded as stand-alone techniques. J Pharm Biomed Anal 178, 112937. https://doi.org/10.1016/J.JPBA.2019.112937

Defrese, M.K., Farmer, M.A., Long, Y., Timmerman, L.R., Bae, Y., Marsac, P.J., 2020. Approaches to Understanding the Solution-State Organization of Spray-Dried Dispersion Feed Solutions and Its Translation to the Solid State. Mol Pharm. https://doi.org/10.1021/acs.molpharmaceut.0c00729

Dohrn, S., Luebbert, C., Lehmkemper, K., Kyerematen, S.O., Degenhardt, M., Sadowski, G., 2021. Solvent influence on the phase behavior and glass transition of Amorphous Solid Dispersions. European Journal of Pharmaceutics and Biopharmaceutics 158, 132–142. https://doi.org/10.1016/j.ejpb.2020.11.002

Duer, M.J., 2004. Introduction to solid-state NMR spectroscopy. Blackwell.

Fox, T., 1952. Influence of diluent and of copolymer composition on the glass temperature of a polymer system. Bull. Am. Phs.

González Cortes, P., Araya-Hermosilla, R., Wrighton-Araneda, K., Cortés-Arriagada, D., Picchioni, F., Yan, F., Rudolf, P., Bose, R.K., Quero, F., 2023. Effect of intermolecular interactions on the glass transition temperature of chemically modified alternating polyketones. Mater Today Chem 34, 101771. https://doi.org/10.1016/J.MTCHEM.2023.101771

Gordon; Taylor, J.S., 1952. Ideal co-polymers and the second order transitions of synthetic rubbers. Journal of Applied Chemistry 2, 493–500.

Gross, J., Sadowski, G., 2001. Perturbed-chain SAFT: An equation of state based on a perturbation theory for chain molecules. Ind Eng Chem Res 40, 1244–1260. https://doi.org/10.1021/ie0003887

Hiew, T.N., Zemlyanov, D.Y., Taylor, L.S., 2022. Balancing Solid-State Stability and Dissolution Performance of Lumefantrine Amorphous Solid Dispersions: The Role of Polymer Choice and Drug-Polymer Interactions. Mol Pharm 19, 392–413. https://doi.org/10.1021/ACS.MOLPHARMACEUT.1C00481/ASSET/IMAGES/LARGE/MP1C00481_0013.JPEG

Hu, Z., Xu, P., Ashour, E.A., Repka, M.A., 2022. Prediction and Construction of Drug-Polymer Binary System Thermodynamic Phase Diagram in Amorphous Solid Dispersions (ASDs). AAPS PharmSciTech 23, 1–12. https://doi.org/10.1208/S12249-022-02319-4/FIGURES/8

Huang, J., Wigent, R.J., Schwartz, J.B., 2008. Drug–polymer interaction and its significance on the physical stability of nifedipine amorphous dispersion in microparticles of an ammonio methacrylate copolymer and ethylcellulose binary blend. J Pharm Sci 97, 251–262. https://doi.org/10.1002/JPS.21072

Hunter, N., 2016. Dynamic Vapour Sorption, in: Principles of Thermal Analysis and Calorimetry. The Royal Society of Chemistry, pp. 47–66. https://doi.org/10.1039/BK9781782620518-00047

Ilevbare, G.A., Taylor, L.S., 2013. Liquid-liquid phase separation in highly supersaturated aqueous solutions of poorly water-soluble drugs: Implications for solubility enhancing formulations.

1089 Cryst Growth Des 13, 1497–1509.
1090 https://doi.org/10.1021/CG301679H/ASSET/IMAGES/MEDIUM/CG-2012-01679H_0011.GIF

1091 Indulkar, A.S., Lou, X., Zhang, G.G.Z., Taylor, L.S., 2019. Insights into the Dissolution Mechanism of
1092 Ritonavir-Copovidone Amorphous Solid Dispersions: Importance of Congruent Release for
1093 Enhanced Performance. Mol Pharm 16, 1327–1339.
1094 https://doi.org/10.1021/ACS.MOLPHARMACEUT.8B01261/ASSET/IMAGES/MEDIUM/MP-2018-
1095 01261V_0010.GIF

1096 Janssens, S., Van den Mooter, G., 2009. Review: physical chemistry of solid dispersions. Journal of
1097 Pharmacy and Pharmacology 61, 1571–1586. https://doi.org/10.1211/jpp/61.12.0001

1098 Kabedev, A., Zhuo, X., Leng, D., Foderà, V., Zhao, M., Larsson, P., Bergström, C.A.S., Löbmann, K.,
1099 2022. Stabilizing Mechanisms of β-Lactoglobulin in Amorphous Solid Dispersions of
1100 Indomethacin. Mol Pharm 19, 3922–3933.
1101 https://doi.org/10.1021/ACS.MOLPHARMACEUT.2C00397/ASSET/IMAGES/LARGE/MP2C00397_
1102 0009.JPEG

1103 Kachel, S., Scharfer, P., Schabel, W., 2013. Sorption isotherms of mixtures of polymers, proteins and
1104 electrolytes—Measurement data and model predictions. Chemical Engineering and Processing:
1105 Process Intensification 68, 45–54. https://doi.org/10.1016/J.CEP.2012.09.006

1106 Kapourani, A., Eleftheriadou, K., Kontogiannopoulos, K.N., Barmpalexis, P., 2021. Evaluation of
1107 rivaroxaban amorphous solid dispersions physical stability via molecular mobility studies and
1108 molecular simulations. European Journal of Pharmaceutical Sciences 157, 105642.
1109 https://doi.org/10.1016/J.EJPS.2020.105642

1110 Karplus, M., McCammon, J.A., 2002. Molecular dynamics simulations of biomolecules. Nat Struct Biol
1111 9, 646–652. https://doi.org/10.1038/NSB0902-646

1112 Keratichewanun, S., Yoshihashi, Y., Sutanthavibul, N., Terada, K., Chatchawalsaisin, J., 2015. An
1113 investigation of nifedipine miscibility in solid dispersions using Raman spectroscopy. Pharm Res
1114 32, 2458–2473. https://doi.org/10.1007/S11095-015-1638-X

1115 Kestur, U.S., Taylor, L.S., 2010. Role of polymer chemistry in influencing crystal growth rates from
1116 amorphous felodipine. CrystEngComm 12, 2390–2397. https://doi.org/10.1039/C001905D

1117 Knopp, M.M., Olesen, N.E., Holm, P., Langguth, P., Holm, R., Rades, T., 2015. Influence of Polymer
1118 Molecular Weight on Drug-Polymer Solubility: A Comparison between Experimentally
1119 Determined Solubility in PVP and Prediction Derived from Solubility in Monomer. J Pharm Sci
1120 104, 2905–2912. https://doi.org/10.1002/jps.24410

1121 Kothari, K., Ragoonanan, V., Suryanarayanan, R., 2015a. The role of drug-polymer hydrogen bonding
1122 interactions on the molecular mobility and physical stability of nifedipine solid dispersions. Mol
1123 Pharm 12, 162–170. https://doi.org/10.1021/MP5005146/SUPPL_FILE/MP5005146_SI_001.PDF

1124 Kothari, K., Ragoonanan, V., Suryanarayanan, R., 2015b. The role of drug-polymer hydrogen bonding
1125 interactions on the molecular mobility and physical stability of nifedipine solid dispersions. Mol
1126 Pharm 12, 162–170. https://doi.org/10.1021/MP5005146/SUPPL_FILE/MP5005146_SI_001.PDF

1127 Krishna Kumar, N.S., Suryanarayanan, R., 2022. Crystallization Propensity of Amorphous
1128 Pharmaceuticals: Kinetics and Thermodynamics. Mol Pharm 19, 472–483.
1129 https://doi.org/10.1021/ACS.MOLPHARMACEUT.1C00839/SUPPL_FILE/MP1C00839_SI_001.PDF

Kruk, D., Privalov, A., Medycki, W., Uniszkiewicz, C., Masierak, W., Jakubas, R., 2012. NMR Studies of Solid-State Dynamics. Annu Rep NMR Spectrosc 76, 67–138. https://doi.org/10.1016/B978-0-12-397019-0.00003-0

Krummnow, A., Danzer, A., Voges, K., Kyeremateng, S.O., Degenhardt, M., Sadowski, G., 2023. Kinetics of Water-Induced Amorphous Phase Separation in Amorphous Solid Dispersions via Raman Mapping. Pharmaceutics 15. https://doi.org/10.3390/PHARMACEUTICS15051395

Kwei, T.K., 1984. The effect of hydrogen bonding on the glass transition temperatures of polymer mixtures. Journal of polymer science. Polymer letters edition 22, 307–313. https://doi.org/10.1002/POL.1984.130220603

Lafitte, T., Apostolakou, A., Avendaño, C., Galindo, A., Adjiman, C.S., Müller, E.A., Jackson, G., 2013. Accurate statistical associating fluid theory for chain molecules formed from Mie segments. Journal of Chemical Physics 139, 154504. https://doi.org/10.1063/1.4819786/193734

Larkin, P.J., 2017. Infrared and Raman Spectroscopy: Principles and Spectral Interpretation. Infrared and Raman Spectroscopy: Principles and Spectral Interpretation 1–276. https://doi.org/10.1016/C2015-0-00806-1

Levitt, M.H., 2015. Spin Dynamics: Basics of Nuclear Magnetic Resonance. Chapter 1. Matter, Wiley. John Wiley & Sons, Ltd.

Li, H., Zhang, M., Xiong, L., Feng, W., Williams, R.O., 2020. Bioavailability Improvement of Carbamazepine via Oral Administration of Modified-Release Amorphous Solid Dispersions in Rats. Pharmaceutics 2020, Vol. 12, Page 1023 12, 1023. https://doi.org/10.3390/PHARMACEUTICS12111023

Li, J., Duggirala, N.K., Kumar, N.S.K., Su, Y., Suryanarayanan, R., 2022. Design of Ternary Amorphous Solid Dispersions for Enhanced Dissolution of Drug Combinations. Mol Pharm 19, 2950–2961. https://doi.org/10.1021/ACS.MOLPHARMACEUT.2C00307/SUPPL_FILE/MP2C00307_SI_001.PDF

Li, N., Taylor, L.S., 2018. Tailoring supersaturation from amorphous solid dispersions. Journal of Controlled Release 279, 114–125. https://doi.org/10.1016/J.JCONREL.2018.04.014

Liu, C., Xu, C.Q., Yu, J., Pui, Y., Chen, H., Wang, S., Zhu, A.D., Li, J., Qian, F., 2019. Impact of a Single Hydrogen Substitution by Fluorine on the Molecular Interaction and Miscibility between Sorafenib and Polymers. Mol Pharm 16, 318–326. https://doi.org/10.1021/ACS.MOLPHARMACEUT.8B00970/ASSET/IMAGES/LARGE/MP-2018-00970A_0006.JPEG

Lu, J., Cuellar, K., Hammer, N.I., Jo, S., Gryczke, A., Kolter, K., Langley, N., Repka, M.A., 2016. Solid-state Characterization of Felodipine-Soluplus® Amorphous Solid Dispersions. Drug Dev Ind Pharm 42, 485. https://doi.org/10.3109/03639045.2015.1104347

Lu, X., Huang, C., Lowinger, M.B., Yang, F., Xu, W., Brown, C.D., Hesk, D., Koynov, A., Schenck, L., Su, Y., 2019. Molecular Interactions in Posaconazole Amorphous Solid Dispersions from Two-Dimensional Solid-State NMR Spectroscopy. Mol Pharm 16, 2579–2589. https://doi.org/10.1021/acs.molpharmaceut.9b00174

Luebbert, C., Klanke, C., Sadowski, G., 2018. Investigating phase separation in amorphous solid dispersions via Raman mapping. Int J Pharm 535, 245–252. https://doi.org/10.1016/J.IJPHARM.2017.11.014

Ma, S.M., Zhao, L., Wang, Y.L., Zhu, Y.L., Lu, Z.Y., 2020. The coarse-grained models of poly(ethylene oxide) and poly(propylene oxide) homopolymers and poloxamers in big multipole water (BMW) and MARTINI frameworks. Physical Chemistry Chemical Physics 22, 15976–15985. https://doi.org/10.1039/D0CP01006E

Malick, N.S.H.S.D.S.C.; H.C.A.W., 2014. Amorphous Solid Dispersion.

Maniruzzaman, M., Snowden, M.J., Bradely, M.S., Douroumis, D., 2015. Studies of intermolecular interactions in solid dispersions using advanced surface chemical analysis. RSC Adv 5, 74212–74219. https://doi.org/10.1039/C5RA13176F

Marsac, P.J., Shamblin, S.L., Taylor, L.S., 2006a. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. Pharm Res 23, 2417–2426. https://doi.org/10.1007/S11095-006-9063-9

Marsac, P.J., Shamblin, S.L., Taylor, L.S., 2006b. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. Pharm Res 23, 2417–2426. https://doi.org/10.1007/S11095-006-9063-9/TABLES/2

Mazurek, A.H., Szeleszczuk, Ł., Pisklak, D.M., 2020. Periodic DFT Calculations—Review of Applications in the Pharmaceutical Sciences. Pharmaceutics 2020, Vol. 12, Page 415 12, 415. https://doi.org/10.3390/PHARMACEUTICS12050415

Mehring, M., 1996. K. Schmidt-Rohr and H. W. Spiess: “Multidimensional Solid-State NMR and Polymers”, Academic Press, London 1994, ISBN 0-12-626630-1, S. 478, Preis: 65 £. Berichte der Bunsengesellschaft für physikalische Chemie 100, 1091–1091. https://doi.org/10.1002/BBPC.19961000669

Mendes, C., Andrzejewski, R.G., Pinto, J.M.O., de Novais, L.M.R., Barison, A., Silva, M.A.S., Parize, A.L., 2020. Impact of Drug-Polymer Interaction in Amorphous Solid Dispersion Aiming for the Supersaturation of Poorly Soluble Drug in Biorelevant Medium. AAPS PharmSciTech 21, 1–10. https://doi.org/10.1208/S12249-020-01737-6/FIGURES/7

Meng, F., Dave, V., Chauhan, H., 2015. Qualitative and quantitative methods to determine miscibility in amorphous drug–polymer systems. European Journal of Pharmaceutical Sciences 77, 106–111. https://doi.org/10.1016/J.EJPS.2015.05.018

Mesallati, H., Umerska, A., Paluch, K.J., Tajber, L., 2017. Amorphous Polymeric Drug Salts as Ionic Solid Dispersion Forms of Ciprofloxacin. Mol Pharm 14, 2209–2223. https://doi.org/10.1021/ACS.MOLPHARMACEUT.7B00039/SUPPL_FILE/MP7B00039_SI_001.PDF

Mistry, P., Mohapatra, S., Gopinath, T., Vogt, F.G., Suryanarayanan, R., 2015. Role of the Strength of Drug-Polymer Interactions on the Molecular Mobility and Crystallization Inhibition in Ketoconazole Solid Dispersions. Mol Pharm 12, 3339–3350. https://doi.org/10.1021/acs.molpharmaceut.5b00333

Murdande, S.B., Pikal, M.J., Shanker, R.M., Bogner, R.H., 2010. Solubility advantage of amorphous pharmaceuticals: I. a thermodynamic analysis. J Pharm Sci 99, 1254–1264. https://doi.org/10.1002/jps.21903

Nambiar, A.G., Singh, M., Mali, A.R., Serrano, D.R., Kumar, R., Healy, A.M., Agrawal, A.K., Kumar, D., 2022. Continuous Manufacturing and Molecular Modeling of Pharmaceutical Amorphous Solid

1211 Dispersions. AAPS PharmSciTech 2022 23:7 23, 1–26. https://doi.org/10.1208/S12249-022-
1212 02408-4

1213 Netchacovitch, L., Dumont, E., Cailletaud, J., Thiry, J., De Bleye, C., Sacré, P.Y., Boiret, M., Evrard, B.,
1214 Hubert, P., Ziemons, E., 2017. Development of an analytical method for crystalline content
1215 determination in amorphous solid dispersions produced by hot-melt extrusion using
1216 transmission Raman spectroscopy: A feasibility study. Int J Pharm 530, 249–255.
1217 https://doi.org/10.1016/J.IJPHARM.2017.07.052

1218 Newman, A., Knipp, G., Zografi, G., 2012. Assessing the performance of amorphous solid dispersions.
1219 J Pharm Sci 101, 1355–1377. https://doi.org/10.1002/jps.23031

1220 Okada, H., Ueda, K., Yasuda, Y., Higashi, K., Inoue, M., Ito, M., Noguchi, S., Kawakami, K., Moribe, K.,
1221 2020. Correlation between drug dissolution and resistance to water-induced phase separation
1222 in solid dispersion formulations revealed by solid-state NMR spectroscopy. Int J Pharm 577.
1223 https://doi.org/10.1016/J.IJPHARM.2020.119086

1224 Palermo, R.N., Anderson, C.A., Drennen, J.K., 2012. Review: Use of thermal, diffraction, and
1225 vibrational analytical methods to determine mechanisms of solid dispersion stability. J Pharm
1226 Innov 7, 2–12. https://doi.org/10.1007/S12247-012-9121-2/TABLES/1

1227 Paudel, A., Geppi, M., Van Den Mooter, G., 2014. Structural and dynamic properties of amorphous
1228 solid dispersions: The role of solid-state nuclear magnetic resonance spectroscopy and
1229 relaxometry. J Pharm Sci 103, 2635–2662. https://doi.org/10.1002/jps.23966

1230 Pinder, J.W., Major, G.H., Baer, D.R., Terry, J., Whitten, J.E., Čechal, J., Crossman, J.D., Lizarbe, A.J.,
1231 Jafari, S., Easton, C.D., Baltrusaitis, J., van Spronsen, M.A., Linford, M.R., 2024. Avoiding
1232 common errors in X-ray photoelectron spectroscopy data collection and analysis, and properly
1233 reporting instrument parameters. Applied Surface Science Advances 19, 100534.
1234 https://doi.org/10.1016/J.APSADV.2023.100534

1235 Pugliese, A., Toresco, M., Mcnamara, D., Iuga, D., Abraham, A., Tobyn, M., Hawarden, L.E., Blanc, F.,
1236 2021. Drug-Polymer Interactions in Acetaminophen/Hydroxypropylmethylcellulose Acetyl
1237 Succinate Amorphous Solid Dispersions Revealed by Multidimensional Multinuclear Solid-State
1238 NMR Spectroscopy. Mol Pharm 18, 3519–3531.
1239 https://doi.org/10.1021/ACS.MOLPHARMACEUT.1C00427/SUPPL_FILE/MP1C00427_SI_001.PDF

1240 Punčochová, K., Heng, J.Y.Y., Beránek, J., Štěpánek, F., 2014. Investigation of drug–polymer
1241 interaction in solid dispersions by vapour sorption methods. Int J Pharm 469, 159–167.
1242 https://doi.org/10.1016/J.IJPHARM.2014.04.048

1243 Punčochová, K., Vukosavljevic, B., Hanuš, J., Beránek, J., Windbergs, M., Štěpánek, F., 2016. Non-
1244 invasive insight into the release mechanisms of a poorly soluble drug from amorphous solid
1245 dispersions by confocal Raman microscopy. European Journal of Pharmaceutics and
1246 Biopharmaceutics 101, 119–125. https://doi.org/10.1016/J.EJPB.2016.02.001

1247 Qian, F., Huang, J., Hussain, M.A., 2010. Drug–Polymer Solubility and Miscibility: Stability
1248 Consideration and Practical Challenges in Amorphous Solid Dispersion Development. J Pharm
1249 Sci 99, 2941–2947. https://doi.org/10.1002/jps.22074

1250 Qian, K., Stella, L., Liu, F., Jones, D.S., Andrews, G.P., Tian, Y., 2024. Kinetic and Thermodynamic
1251 Interplay of Polymer-Mediated Liquid-Liquid Phase Separation for Poorly Water-Soluble Drugs.
1252 Mol Pharm 21, 2878–2893.

https://doi.org/10.1021/ACS.MOLPHARMACEUT.4C00033/ASSET/IMAGES/LARGE/MP4C00033_0013.JPEG

Que, C., Deac, A., Zemlyanov, D.Y., Qi, Q.Q., Indulkar, A.S., Gao, Y., Zhang, G.G.Z., Taylor, L.S., 2021. Impact of Drug-Polymer Intermolecular Interactions on Dissolution Performance of Copovidone-Based Amorphous Solid Dispersions. Mol Pharm 18, 3496–3508. https://doi.org/10.1021/ACS.MOLPHARMACEUT.1C00419/ASSET/IMAGES/LARGE/MP1C00419_0007.JPEG

Que, C., Gao, Y., Raina, S.A., Zhang, G.G.Z., Taylor, L.S., 2018. Paclitaxel Crystal Seeds with Different Intrinsic Properties and Their Impact on Dissolution of Paclitaxel-HPMCAS Amorphous Solid Dispersions. Cryst Growth Des 18, 1548–1559. https://doi.org/10.1021/ACS.CGD.7B01521/SUPPL_FILE/CG7B01521_SI_002.PDF

Que, C., Lou, X., Zemlyanov, D.Y., Mo, H., Indulkar, A.S., Gao, Y., Zhang, G.G.Z., Taylor, L.S., 2019. Insights into the Dissolution Behavior of Ledipasvir-Copovidone Amorphous Solid Dispersions: Role of Drug Loading and Intermolecular Interactions. Mol Pharm 16, 5054–5067. https://doi.org/10.1021/ACS.MOLPHARMACEUT.9B01025/ASSET/IMAGES/LARGE/MP9B01025_0016.JPEG

Rams-Baron, M., Jachowicz, R., Boldyreva, E., Zhou, D., Jamroz, W., Paluch, M., 2018. Amorphous drugs: Benefits and challenges, Amorphous Drugs: Benefits and Challenges. Springer International Publishing. https://doi.org/10.1007/978-3-319-72002-9/COVER

Rawlinson, C.F., Williams, A.C., Timmins, P., Grimsey, I., 2007. Polymer-mediated disruption of drug crystallinity. Int J Pharm 336, 42–48. https://doi.org/10.1016/J.IJPHARM.2006.11.029

Ricarte, R.G., Van Zee, N.J., Li, Z., Johnson, L.M., Lodge, T.P., Hillmyer, M.A., 2019. Recent Advances in Understanding the Micro- and Nanoscale Phenomena of Amorphous Solid Dispersions. Mol Pharm 16, 4089–4103. https://doi.org/10.1021/ACS.MOLPHARMACEUT.9B00601/ASSET/IMAGES/LARGE/MP9B00601_0009.JPEG

Rosiak, N., Tykarska, E., Cielecka-Piontek, J., 2024. Myricetin Amorphous Solid Dispersions—Antineurodegenerative Potential. Molecules 29, 1287. https://doi.org/10.3390/MOLECULES29061287/S1

Rumondor, A.C.F., Stanford, L.A., Taylor, L.S., 2009. Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions. Pharm Res 26, 2599–2606. https://doi.org/10.1007/S11095-009-9974-3/FIGURES/8

Saboo, S., Mugheirbi, N.A., Zemlyanov, D.Y., Kestur, U.S., Taylor, L.S., 2019. Congruent release of drug and polymer: A “sweet spot” in the dissolution of amorphous solid dispersions. Journal of Controlled Release 298, 68–82. https://doi.org/10.1016/J.JCONREL.2019.01.039

Sarpal, K., Delaney, S., Zhang, G.G.Z., Munson, E.J., 2019. Phase Behavior of Amorphous Solid Dispersions of Felodipine: Homogeneity and Drug-Polymer Interactions. Mol Pharm 16, 4836–4851. https://doi.org/10.1021/ACS.MOLPHARMACEUT.9B00731/SUPPL_FILE/MP9B00731_SI_001.PDF

Shi, Q., Li, F., Yeh, S., Moinuddin, S.M., Xin, J., Xu, J., Chen, H., Ling, B., 2021. Recent Advances in Enhancement of Dissolution and Supersaturation of Poorly Water-Soluble Drug in Amorphous

Pharmaceutical Solids: A Review. AAPS PharmSciTech 2021 23:1 23, 1–19. https://doi.org/10.1208/S12249-021-02137-0

Song, Y., Yang, X., Chen, X., Nie, H., Byrn, S., Lubach, J.W., 2015. Investigation of Drug–Excipient Interactions in Lapatinib Amorphous Solid Dispersions Using Solid-State NMR Spectroscopy. Mol Pharm 12, 857–866. https://doi.org/10.1021/MP500692A

Stephan, S., Staubach, J., Hasse, H., 2020. Review and comparison of equations of state for the Lennard-Jones fluid. Fluid Phase Equilib 523, 112772. https://doi.org/10.1016/J.FLUID.2020.112772

Stockmayer, W.H., 1941. Second Virial Coefficients of Polar Gases. J Chem Phys 9, 398–402. https://doi.org/10.1063/1.1750922

Swindells, N., Sykes, C., 1938. The classical equation of state of gaseous helium, neon and argon. Proc R Soc Lond A Math Phys Sci 168, 264–283. https://doi.org/10.1098/RSPA.1938.0173

Tao, J., Sun, Y., Zhang, G.G.Z., Yu, L., 2009. Solubility of small-molecule crystals in polymers: D-Mannitol in PVP, indomethacin in PVP/VA, and nifedipine in PVP/VA. Pharm Res 26, 855–864. https://doi.org/10.1007/S11095-008-9784-Z/FIGURES/12

Taylor, L.S., Zhang, G.G.Z., 2016. Physical chemistry of supersaturated solutions and implications for oral absorption. Adv Drug Deliv Rev 101, 122–142. https://doi.org/10.1016/J.ADDR.2016.03.006

Terban, M.W., Billinge, S.J.L., 2022. Structural Analysis of Molecular Materials Using the Pair Distribution Function. Chem Rev 122, 1208–1272. https://doi.org/10.1021/ACS.CHEMREV.1C00237/ASSET/IMAGES/LARGE/CR1C00237_0032.JPEG

Terban, M.W., Johnson, M., Di Michiel, M., Billinge, S.J.L., 2015. Detection and characterization of nanoparticles in suspension at low concentrations using the X-ray total scattering pair distribution function technique. Nanoscale 7, 5480–5487. https://doi.org/10.1039/C4NR06486K

Trasi, N.S., Bhujbal, S. V., Zemlyanov, D.Y., Zhou, Q. (Tony), Taylor, L.S., 2020. Physical stability and release properties of lumefantrine amorphous solid dispersion granules prepared by a simple solvent evaporation approach. Int J Pharm X 2, 100052. https://doi.org/10.1016/J.IJPX.2020.100052

Ueda, K., Moseson, D.E., Pathak, V., Taylor, L.S., 2021. Effect of Polymer Species on Maximum Aqueous Phase Supersaturation Revealed by Quantitative Nuclear Magnetic Resonance Spectroscopy. Mol Pharm 18, 1344–1355. https://doi.org/10.1021/ACS.MOLPHARMACEUT.0C01174/ASSET/IMAGES/LARGE/MP0C01174_0011.JPEG

Ueda, K., Taylor, L.S., 2020. Polymer Type Impacts Amorphous Solubility and Drug-Rich Phase Colloidal Stability: A Mechanistic Study Using Nuclear Magnetic Resonance Spectroscopy. Mol Pharm 17, 1352–1362. https://doi.org/10.1021/ACS.MOLPHARMACEUT.0C00061/ASSET/IMAGES/MEDIUM/MP0C00061_M001.GIF

Ueda, K., Yamamoto, N., Higashi, K., Moribe, K., 2019. Molecular Mobility Suppression of Ibuprofen-Rich Amorphous Nanodroplets by HPMC Revealed by NMR Relaxometry and Its Significance with Respect to Crystallization Inhibition. Mol Pharm 16, 4968–4977.

https://doi.org/10.1021/ACS.MOLPHARMACEUT.9B00840/ASSET/IMAGES/LARGE/MP9B00840_0010.JPEG

Ugur, B.E., Caggiano, N.J., Monson, S., Bechtold, A.G., Seo, Y., Prud'homme, R.K., Priestley, R.D., Webb, M.A., 2024. Molecular Interactions Underlying Dissolution Trends in Cannabidiol-Polymer Amorphous Solid Dispersions. Macromolecules 57, 8287–8297. https://doi.org/10.1021/acs.macromol.4c01579

Vaka, S.R.K., Bommana, M.M., Desai, D., Djordjevic, J., Phuapradit, W., Shah, N., 2014. Excipients for Amorphous Solid Dispersions, in: Shah, N., Sandhu, H., Choi, D.S., Chokshi, H., Malick, A.W. (Eds.), Amorphous Solid Dispersions: Theory and Practice. Springer New York, New York, NY, pp. 123–161. https://doi.org/10.1007/978-1-4939-1598-9_4

Van Den Mooter, G., 2012. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discov Today Technol 9, e79–e85. https://doi.org/10.1016/J.DDTEC.2011.10.002

van der Heide, P., 2011. Introduction, in: X-Ray Photoelectron Spectroscopy. John Wiley & Sons, Ltd, pp. 1–12. https://doi.org/10.1002/9781118162897.CH1

Van Eerdenbrugh, B., Baird, J.A., Taylor, L.S., 2010. Crystallization Tendency of Active Pharmaceutical Ingredients Following Rapid Solvent Evaporation—Classification and Comparison with Crystallization Tendency from Under cooled Melts. J Pharm Sci 99, 3826–3838. https://doi.org/10.1002/jps.22214

Vankeirsbilck, T., Vercauteren, A., Baeyens, W., Van der Weken, G., Verpoort, F., Vergote, G., Remon, J.P., 2002. Applications of Raman spectroscopy in pharmaceutical analysis. TrAC Trends in Analytical Chemistry 21, 869–877. https://doi.org/10.1016/S0165-9936(02)01208-6

Vogt, F.G., Brum, J., Katrincic, L.M., Flach, A., Socha, J.M., Goodman, R.M., Haltiwanger, R.C., 2006. Physical, crystallographic, and spectroscopic characterization of a crystalline pharmaceutical hydrate: Understanding the role of water. Cryst Growth Des 6, 2333–2354. https://doi.org/10.1021/CG060324K

Vogt, F.G., Clawson, J.S., Strohmeier, M., Pham, T.N., Watson, S.A., Edwards, A.J., 2011. New Approaches to the Characterization of Drug Candidates by Solid-State NMR. Pharmaceutical Sciences Encyclopedia 1–77. https://doi.org/10.1002/9780470571224.PSE418

Wang, B., Wang, D., Zhao, S., Huang, X., Zhang, J., Lv, Y., Liu, X., Lv, G., Ma, X., 2017. Evaluate the ability of PVP to inhibit crystallization of amorphous solid dispersions by density functional theory and experimental verify. European Journal of Pharmaceutical Sciences 96, 45–52. https://doi.org/10.1016/J.EJPS.2016.08.046

Wang, J., Cheung, M.K., Mi, Y., 2002. Miscibility and morphology in crystalline/amorphous blends of poly (caprolactone)/poly(4-vinylphenol) as studied by DSC, FTIR, and 13C solid state NMR. Polymer (Guildf) 43, 1357–1364. https://doi.org/10.1016/S0032-3861(01)00673-5

Wang, J., Cheung, M.K., Mi, Y., 2001. Miscibility in blends of poly (4-vinylpyridine)/poly (4-vinylphenol) as studied by 13C solid-state NMR. Polymer (Guildf) 42, 3087–3093. https://doi.org/10.1016/S0032-3861(00)00643-1

Wang, X., Ramírez-Hinestrosa, S., Dobnikar, J., Frenkel, D., 2020. The Lennard-Jones potential: When (not) to use it. Physical Chemistry Chemical Physics 22, 10624–10633. https://doi.org/10.1039/C9CP05445F

Wu, J., Mooter, G. Van den, 2023. The influence of hydrogen bonding between different crystallization tendency drugs and PVPVA on the stability of amorphous solid dispersions. Int J Pharm 646, 123440. https://doi.org/10.1016/J.IJPHARM.2023.123440

Xiang, T.-X., Anderson, B.D., 2019. Effects of Molecular Interactions on Miscibility and Mobility of Ibuprofen in Amorphous Solid Dispersions With Various Polymers. J Pharm Sci 108, 178–186. https://doi.org/10.1016/j.xphs.2018.10.052

Yao, X., Huang, C., Benson, E.G., Shi, C., Zhang, G.G.Z., Yu, L., 2020. Effect of Polymers on Crystallization in Glass-Forming Molecular Liquids: Equal Suppression of Nucleation and Growth and Master Curve for Prediction. Cryst Growth Des 20, 237–244. https://doi.org/10.1021/ACS.CGD.9B01095/ASSET/IMAGES/LARGE/CG9B01095_0011.JPEG

Yoshioka, M., Hancock, B.C., Zografi, G., 1994. Crystallization of Indomethacin from the Amorphous State below and above Its Glass Transition Temperature. J Pharm Sci 83, 1700–1705. https://doi.org/10.1002/JPS.2600831211

Yuan, X., Sperger, D., Munson, E.J., 2014. Investigating miscibility and molecular mobility of nifedipine-PVP amorphous solid dispersions using solid-state NMR spectroscopy. Mol Pharm 11, 329–337. https://doi.org/10.1021/mp400498n

Zhang, F., Mao, J., Tian, G., Jiang, H., Jin, Q., 2022. Preparation and Characterization of Furosemide Solid Dispersion with Enhanced Solubility and Bioavailability. AAPS PharmSciTech 23, 1–11. https://doi.org/10.1208/S12249-022-02208-W/TABLES/3

Zhang, J., Liu, Z., Wu, H., Cai, T., 2021. Effect of polymeric excipients on nucleation and crystal growth kinetics of amorphous fluconazole. Biomater Sci 9, 4308–4316. https://doi.org/10.1039/D1BM00104C

Zhang, S., Zhang, X., Meng, J., Lu, L., Du, S., Xu, H., Wu, S., 2022. Study on the Effect of Polymer Excipients on the Dispersibility, Interaction, Solubility, and Scavenging Reactive Oxygen Species of Myricetin Solid Dispersion: Experiment and Molecular Simulation. ACS Omega 7, 1514–1526. https://doi.org/10.1021/ACSOMEGA.1C06329/ASSET/IMAGES/LARGE/AO1C06329_0017.JPEG