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Review Article

Exploring an interplay between drug-polymer interactions and amorphous solid dispersion stability: A review

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ABSTRACT

Amorphous solid dispersions (ASDs) represent a promising approach to enhancing the oral bioavailability of poorly water-soluble drugs by forming stable, highly soluble amorphous states. Despite their advantages, significant challenges remain due to the metastable nature of ASDs, which often requires the incorporation of additives to inhibit crystallisation. This article explores the intricate interactions between drugs and polymers within ASDs, focusing on hydrogen bonding, ionic interactions, van der Waals forces, and hydrophobic interactions, and their roles in maintaining drug solubility and stability. It highlights that the drug release mechanism is complex and varies with drug loading, transitioning from polymer-controlled to drug-controlled release. Characterisation techniques such as thermal analysis, spectroscopy, and microscopy provide insights into the interactions and stability of ASDs. Despite advances, challenges remain regarding the complexity of interactions and the long-term stability of ASDs, necessitating further research into optimal polymer selection, drug-polymer ratios, and processing techniques. This study emphasises the need for a deeper understanding of drug-polymer interplay and its implications for the rational design of effective ASD formulations to improve drug delivery systems.

Keywords:
Amorphous solid dispersion; Drug-Polymer interactions; Polymer selection; Physical stability

1. INTRODUCTION

Amorphous solid dispersions have become a topic of interest in recent years due to their potential to improve oral bioavailability by creating highly soluble and stable amorphous forms of drugs. Forty per cent of the new chemical entities currently on the market are poorly water-soluble, and about 90% of drugs in the development pipeline are regarded as poorly soluble. This creates major obstacles to formulation[1]. ASDs are employed as a strategy for improving the oral bioavailability of poorly water-soluble compounds because they possess higher apparent solubility and faster dissolution rates compared to their crystalline equivalents. Nonetheless, this amorphous state is metastable; hence, additives are often necessary to delay crystallisation and take advantage of this high-energy state in pharmaceutical formulations[2,3]. For more than two decades, ASDs have been a topic of research regarding their solid-state stability, and there have been reports of highly stable ASDs with exceptional shelf life, demonstrating the successful management of the risk of crystallisation through appropriate polymer combinations[4,5]. However, the release mechanism of drugs from ASDs is not yet well understood. It has been proposed that drug release from ASDs at low drug loading is controlled by the polymer, since both drugs and polymers are released at the same rate (congruently)[6]. On the other hand, when higher drug loading is reached, which varies for different drug-polymer combinations,

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a sudden fall in drug release rate occurs due to the switch to drug-controlled release, leading to incongruence between the release of drug and polymer. This transition from congruent to incongruent drug-controlled release as a function of drug loading is thought to involve some interplay between the properties of drugs and polymers. Unfortunately, the exact details about this interplay, as well as its related factors, have not yet been explored, thus preventing the rational design of optimum performance-based formulations[7,8].

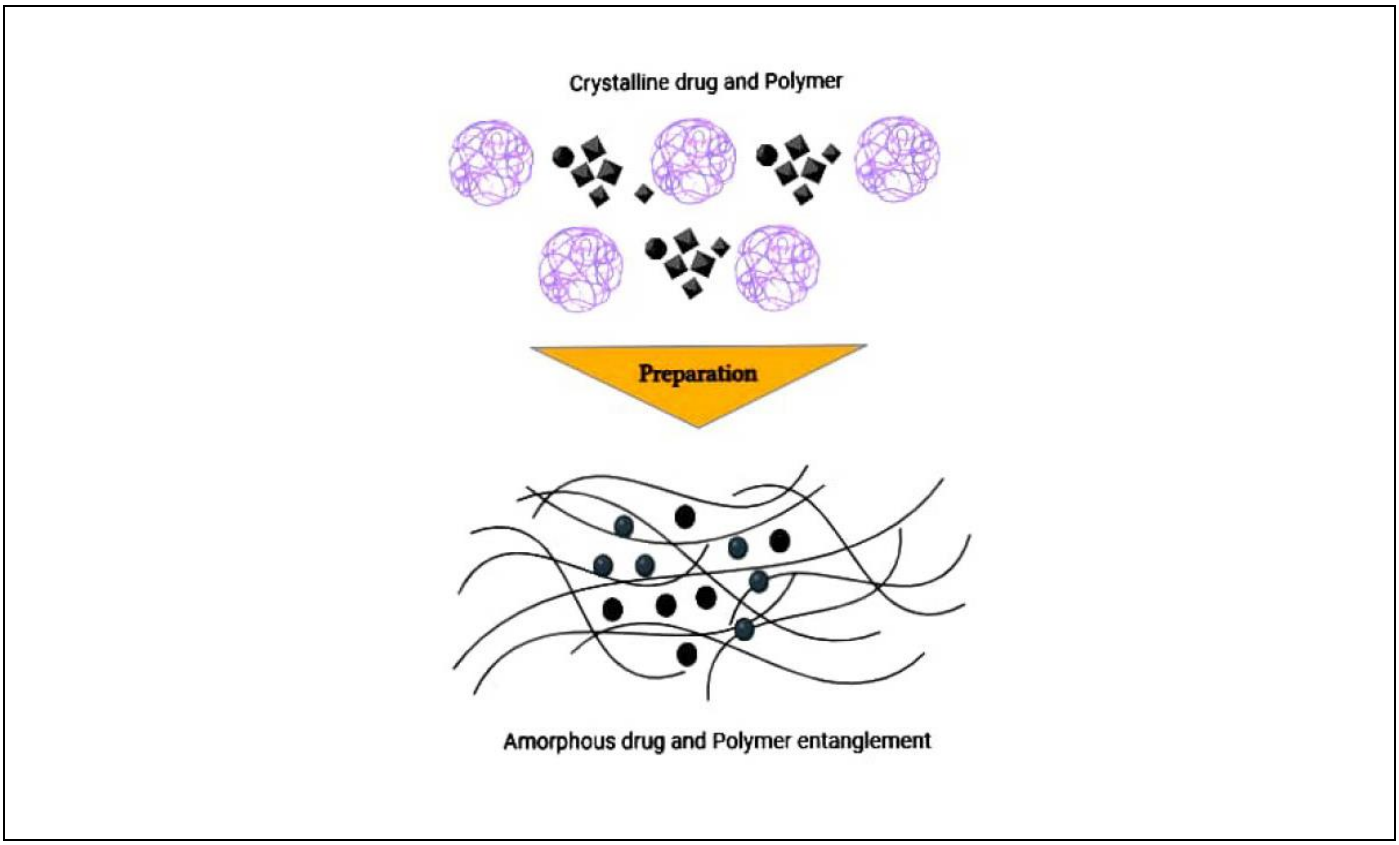

Figure 1. Schematic representation of drug–polymer interactions in amorphous solid dispersions (ASDs), illustrating Amorphous drug and polymer chain entanglement that contribute to physical stability and dissolution enhancement.

2. TYPES OF DRUG-POLYMER INTERACTIONS

2.1 Hydrogen bonding

Hydrogen bonding between drug molecules and polymers plays a central role in reducing the crystallisation tendency of amorphous drugs. Strong hydrogen bonds reduce the enthalpy and free energy of mixing, stabilising the molecular dispersion even at low polymer concentrations[9,10]. Solid-state NMR studies have further confirmed that when these interactions are robust, mixed drug–polymer domains smaller than 5 nm can form, reflecting excellent molecular-level miscibility[11,12]. This nanoscale blending is critical for long-term stability, as it disrupts the formation of drug–drug hydrogen bonds, a key early step in crystallisation, as seen in the case of indomethacin, where carboxylic acid dimers serve as nucleation centres[13]. Moreover, the directional and strong nature of hydrogen bonds between drug and polymer restricts molecular mobility, hindering the movement needed for crystallisation[14]. However, it is important to note that simply having hydrogen-bonding sites on a polymer doesn't guarantee lasting stability. Polymers rich in amide donors don't always produce stable dispersions, highlighting that the presence of bonds isn't the only factor[15]. Two primary explanations exist for such observations. First, polymer solubility within the amorphous drug phase is critical. If the polymer is insufficiently soluble, it may cluster at interfaces rather than distributing uniformly, failing to fully inhibit crystallisation. Instead, it may inadvertently accelerate crystallisation through polymer-induced hetero-nucleation, where drug molecules align and crystallise on polymer surfaces[16,17]. Second, even when hydrogen bonds are present, excessive polymer mobility or low-viscosity regions can promote drug diffusion and nucleation offsetting the stabilising role of hydrogen bonding[18]. Together, these insights show that while hydrogen bonding remains a powerful stabiliser in ASDs, its effectiveness depends on additional factors: uniform molecular-level miscibility, polymer molecular mobility, and suppression of unintended

nucleation pathways. Assessing each of these variables is essential for creating truly stable amorphous formulations.

2.2 Ionic interactions

Ionic interactions occur when ionisable drugs and charged polymers form electrostatic bonds, typically between oppositely charged functional groups. The strength of these interactions is influenced by several factors, including pH, pKa, and the degree of ionisation of both the drug and polymer. When conditions favour ionisation, strong drug–polymer complexes can form, effectively stabilising the amorphous state and enhancing solubility, particularly in environments where the drug's unionised form is poorly soluble[19]. In these systems, the ionised drug is generally much more soluble than its uncharged form. Complexation with a polymer helps maintain that solubility by acting as a solubilising carrier. A good example is indomethacin–cationic Eudragit EPO ASDs: here, the negatively charged carboxylate groups of indomethacin interact with the positively charged amine groups in Eudragit, creating a stable ionic complex. These systems have demonstrated higher glass transition temperatures (Tg), which indicate reduced molecular mobility and better resistance to crystallisation, even under accelerated conditions, compared to non-ionic formulations[20].

This stabilising effect arises because ionic bonds add significant internal energy to the matrix, hindering the drug molecules' ability to reorganise into their crystalline form. In essence, the ionic polymer acts as a cage, locking drug molecules in place. This effect can also extend to tunable release profiles, as the complex may dissolve preferentially under specific pH conditions, leading to targeted drug release. For example, ciprofloxacin ASDs formulated with Eudragit L100-55 exhibited enhanced physical stability and pH-dependent release: ionisation in the gut environment promoted drug release in the intestine while protecting it in the stomach[21]. Solid-state analytical techniques, such as solid-state NMR, can confirm ionic interactions by revealing shifts in chemical signals. These shifts correspond to changes in local electronic environments around ionisable functional groups and provide insight into the ratio of ionised versus unionised species a key factor for optimal complexation[22]. Studies have shown that near-equimolar ratios of drug to polymer often yield the most stable amorphous salts. If there is too little polymer, the drug may not be fully complexed; too much can lead to phase separation or reduced drug loading[23].

It is important to remember that while ionic complexation strengthens physical stability, it requires careful formulation design. The drug–polymer ratio, the pH environment during both manufacturing and storage, and the compatibility of the ionic groups must all be regulated. Poor balance may result in partial ionisation or unstable microenvironments, diminishing both stability and release control.

2.3 Van der Waals Forces

Van der Waals interactions, though individually weak compared to covalent or hydrogen bonds, play a vital supportive role in stabilising ASDs. These forces, comprising London dispersion forces, Keesom (permanent dipole–dipole) interactions, and sometimes even induced-dipole contributions, help to keep drug molecules closely packed within the polymer matrix. In effect, they contribute subtle yet persistent binding energy that helps maintain the amorphous state, ensuring improved solubility and bioavailability over time[24].

In ASD formulation, it is not just the presence of these forces that matters, but also their cumulative strength a concept often described as "cohesive stabilisation." When polymers and drugs interact via van der Waals forces, they contribute to a continuous, cohesive network within the solid matrix. This cohesion is essential in resisting stressors such as temperature and moisture, which can trigger drug recrystallisation. For example, recent work by Tanaka et al. (2022) showed that the selection of a polymer with appropriate polarizability and dispersion characteristics reinforced the complex through enhanced London forces, significantly delaying crystallisation of a weakly polar antidiabetic drug[25].

Simultaneously, dipole–dipole interactions complement these dispersion forces. Polymers like polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC), which contain permanent dipoles due to carbonyl, methoxy, or hydroxyl groups, can establish Keesom interactions with drugs possessing complementary polar groups. These interactions offer moderate binding energy less than hydrogen bonds but stronger than pure dispersion forces that enhances miscibility and aids in forming a homogenous amorphous dispersion. As described by Williams and Rahman (2023), an ASD of carvedilol and PVP exhibited greater physical stability due to such dipole–dipole interactions, in combination with van der Waals forces, which together raised the activation energy required for crystallisation[26].

Non-polar drugs also benefit from ASDs via dispersion interactions, though the mechanism differs. Since these drugs lack polar functional groups, their stability depends more on weak London forces. However, strategic use of semi-crystalline or highly polarizable polymers like Soluplus or polyacrylic acid

derivative can enhance these dispersion forces by increasing matrix proximity and polarizability. In a study of fenofibrate with Soluplus, van der Waals and hydrophobic interactions were the dominant stabilising mechanisms, maintaining the drug in an amorphous state under ambient conditions for months[27]. Importantly, van der Waals forces act synergistically with other intermolecular interactions. They bolster the overall stabilising network, enabling hydrogen bonds and ionic interactions to act more effectively by maintaining molecular proximity. For instance, in a recent sulfasalazine–PVP-VA ASD, a multi-modal interaction matrix of dispersion, dipole–dipole, and hydrogen bonding collectively prevented crystallisation even after accelerated stress testing demonstrating how each interaction type compensates for another in real-world systems[28]. Van der Waals forces are crucial for the cumulative structural integrity of ASDs. By promoting close molecular packing and enhancing miscibility, they support stronger interactions and contribute significantly to the physical stability of the final product a fact increasingly acknowledged in modern ASD formulation strategies.

2.4 Hydrophobic interactions

Drug-polymer interactions are driven by hydrophobicity and the phase behaviours of amorphous solid dispersions (ASDs). These drug-polymer associations are necessary for stabilising hydrophobic drugs in a polymer matrix, preventing crystal growth, and maintaining drug solubility. The balance between the polar and non-polar properties of the polymer is critical for optimal ASD stability[29]. The interaction of the poorly soluble drug with polymers such as polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose acetate succinate (HPMC-AS) relies primarily on a phase dominated by hydrophobic interactions, which play a crucial role in the stability of the formulation[30].

When the drug is co-dissolved or blended with the polymer in an aqueous medium, both the drug and the polymer's hydrophobic regions can interact through stable associations that help maintain drug solubility. This is particularly critical for drugs that are known to precipitate out of solution. For instance, one study suggests that HPMC-AS can significantly mediate the drug's supersaturation level but exacerbate hydrophobic interactions. This is not the case for PVP, which is dominated by hydrogen bonding interactions that can be much more sensitive to the rate of dissolution and the method of introducing the polymer into the solution[30].

It is necessary to blend hydrophilic and hydrophobic aspects to optimally stabilise the drug-polymer system. An excessively hydrophilic polymer may be ineffective in conferring stability to the drug in the supersaturated state, thus allowing for precipitation and poor bioavailability. On the other hand, an overly hydrophobic polymer may not adequately interact with the drug, resulting in poor solubility and dissolution rates. Therefore, the selection of polymers with tailored hydrophilic-hydrophobic properties is critical[31].

3. DRUG-POLYMER INTERACTION CHARACTERIZATION TECHNIQUES

3.1 Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is widely recognised as a cornerstone technique in the thermal analysis of ASDs. It provides crucial insights into key thermal properties such as the glass transition temperature (Tg), melting point (Tm), and crystallisation behaviour, all of which are directly linked to the miscibility and physical stability of the drug–polymer system. When a single, clearly defined Tg is observed in the thermogram, it generally indicates that the drug has been successfully and uniformly dispersed within the polymer matrix, suggesting good miscibility[32]. On the other hand, the appearance of multiple Tgs or additional melting peaks may signal phase separation or incomplete amorphisation. To estimate the theoretical Tg of such systems, models like the Gordon–Taylor and Fox equations are often employed. If the experimental Tg deviates significantly from the predicted values, this often suggests specific molecular interactions, such as hydrogen bonding or ionic attraction, between the drug and polymer components[33].

One study found that the Tg of a ritonavir–copovidone dispersion was notably higher than expected, which they attributed to strong hydrogen bonding. DSC is also valuable for detecting the onset of recrystallisation. The appearance of an exothermic peak before melting typically signals that the amorphous drug is beginning to recrystallise, indicating potential physical instability. Additionally, the technique helps evaluate drug loading capacity; while higher drug concentrations generally lead to a lower Tg due to plasticisation, this effect can be mitigated if strong drug–polymer interactions are present. In more complex ternary systems involving additional polymers or excipients, DSC can also reveal whether these components are compatible or likely to destabilise the formulation[34].

Modern enhancements such as modulated DSC (MDSC) allow for the separation of overlapping thermal transitions into reversing and non-reversing events, improving Tg resolution in multi-component systems. While DSC cannot directly specify the type of molecular interaction involved and may struggle to detect very small amounts of crystallinity, its rapid

results, ease of use, and reliability make it a valuable tool during early formulation development and screening[35].

3.2 Thermal gravimetric analysis (TGA)

Thermogravimetric analysis (TGA) is a thermal analytical technique widely employed in pharmaceutical development to determine the stability and composition of formulations. In TGA, a sample is gradually heated under a controlled atmosphere (usually nitrogen or air), and its weight change is monitored as a function of temperature. This allows precise measurement of events such as moisture loss, polymer degradation, drug volatilisation, or residue formation insights that are essential for ensuring the quality and shelf life of ASDs[36]. One of the primary applications of TGA in ASD formulation is assessing moisture content. Even small amounts of absorbed water can have significant effects: they can plasticise the matrix, lower Tg, and trigger unwanted crystallisation. For example, a recent study showed that TGA could be used to detect moisture desorption from indomethacin–HPMCAS dispersions, revealing that formulations with critical moisture levels exhibited lower Tg and began recrystallising upon storage[37]. Beyond moisture, TGA helps evaluate the thermal degradation profile of both the drug and the polymer. It identifies the onset temperatures for decomposition, a key factor in selecting processing methods such as hot-melt extrusion or spray drying. A study demonstrated that a copovidone-based ASD of esomeprazole showed thermal stability up to 200°C, indicating suitability for hot-melt processing[38].

TGA also supports composition analysis. By comparing weight loss steps to known thermal behaviours, the relative proportions of polymer, drug, and excipients can be deduced. In a study of ritonavir–copovidone ASDs, TGA under nitrogen was used to profile distinct degradation steps, which aligned with HPLC quantification and confirmed the ASD's integrity[39]. TGA is invaluable for compatibility testing. When formulating ASDs, it is crucial to ensure that no unexpected interactions, such as polymer degradation or drug–excipient incompatibility, occur. In the latest study, TGA profiles of celecoxib–Eudragit were examined, revealing a new weight-loss step at 180°C, suggesting interaction-induced degradation and leading to changes in formulation strategy[40].

3.3 Fourier-transform infrared spectroscopy (FTIR)

Fourier-transform infrared (FTIR) spectroscopy is a widely used, non-destructive technique that plays a crucial role in the development and evaluation of ASDs. Its importance lies in two key areas: first, its ability to distinguish between crystalline and amorphous phases of a substance; and second, its effectiveness in identifying specific interactions between a drug and polymer, such as hydrogen bonding, dipole–dipole interactions, and, in some cases, van der Waals forces. These capabilities make FTIR an essential tool in both early-stage formulation work and routine quality control during product development[41,42]. One of the fundamental applications of FTIR in ASD research is confirming whether a drug has successfully transitioned from a crystalline to an amorphous state. Crystalline compounds typically show sharp, well-defined absorption peaks in the FTIR spectrum due to their orderly molecular structure. In contrast, amorphous forms produce broader, less intense bands because of molecular disorder and varying local environments. For example, the carbonyl (C=O) stretching vibration in crystalline indomethacin usually appears near 1715 cm^{-1}. After processing through methods like spray drying or hot-melt extrusion, this peak may shift to around 1690 cm^{-1} and broaden noticeably. Such changes indicate that the drug has become amorphous and is likely engaging in hydrogen bonding with a polymer like polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC)[43,44]. Similarly, the disappearance or broadening of –OH stretching bands in the 3200–3600 cm^{-1} region is another reliable sign of amorphisation and potential hydrogen bonding. FTIR is especially useful for detecting hydrogen bonds, which are often the dominant stabilising interaction in ASDs. Reductions in the frequency (redshifts) and broadening of peaks corresponding to C=O, O–H, or N–H groups are strong indicators that hydrogen bonding is taking place. For instance, in indomethacin–PVP dispersions, such shifts provide compelling evidence of strong hydrogen bond formation between the drug's acidic group and the polymer's carbonyl functionality[43,45].

The technique can also offer indirect insights into weaker interactions. Dipole–dipole interactions typically cause minor spectral shifts, often observable when comparing ASDs made with polymers of different polarity. For example, slight changes in the vibrational modes of –C–O or –N–H groups may be noted when drugs are formulated with polar polymers like HPMC or Soluplus. Although these shifts are subtle, they can still provide useful information about interaction strength and compatibility[45]. Van der Waals forces, while non-specific and weaker than hydrogen bonds, might still affect the spectrum. These interactions may be suggested by slight broadening or changes in intensity of aliphatic –CH stretching bands (2800–3000 cm^{-1}), particularly in ASDs involving hydrophobic drugs and low-polarity polymers like cellulose derivatives. While FTIR alone may not definitively confirm van der Waals interactions, the technique becomes much more informative when results are interpreted alongside data from DSC or solid-state NMR[46].

3.4 Raman spectroscopy

Raman spectroscopy is a valuable and versatile technique used to study ASDs, especially when analysing drug–polymer interactions and identifying the presence or absence of crystallinity. Unlike infrared (FTIR) spectroscopy, which measures changes in dipole moment, Raman spectroscopy works by detecting inelastic scattering of laser light, making it particularly sensitive to changes in molecular polarizability. This distinction allows Raman to be especially useful in aqueous or hydrated systems, where water interference tends to complicate FTIR measurements[47,48]. In ASDs, Raman spectroscopy helps uncover subtle molecular-level interactions such as hydrogen bonding, π–π stacking, and even van der Waals forces. These interactions typically lead to noticeable changes in spectral features, including slight shifts in peak positions, variations in intensity, or broadening of vibrational bands. For instance, the carbonyl stretching band of carboxylic acid drugs like efavirenz shifts to a lower frequency when hydrogen bonding occurs with polymers such as PVP or HPMC. A study highlighted this effect by using in situ Raman to monitor drug–polymer interactions during hot-melt extrusion, revealing real-time spectral changes that confirmed improved miscibility[49].

One of the biggest advantages of Raman over other spectroscopic methods is its potential for real-time, non-invasive monitoring during manufacturing. With the integration of fibre-optic probes, Raman spectroscopy can be applied directly within processing lines, such as during spray drying or extrusion, to track formulation quality as it develops. Wyttenbach and Kuentz (2021) demonstrated how real-time Raman analysis could effectively monitor crystallinity and drug–polymer ratios throughout the ASD production process, minimising the need for time-consuming offline testing[50]. Raman mapping enables the visualization of spatial distribution within a sample, helping identify areas where the drug may not be evenly dispersed or where phase separation has occurred. When combined with chemometric tools like principal component analysis (PCA), this technique can quantify drug uniformity and detect traces of crystallinity that other methods, such as PXRD, might miss. This makes Raman particularly useful for long-term stability studies, where early signs of crystallisation are critical to catch[50].

Raman spectroscopy does come with a few challenges. Fluorescent compounds can interfere with signal detection, especially in coloured formulations, and interpreting the resulting spectra often requires expert knowledge and advanced statistical analysis. Still, given its non-destructive nature, compatibility with aqueous systems, and ability to integrate into real-time manufacturing environments, Raman spectroscopy remains a key analytical tool in modern ASD development, especially within Quality by Design (QbD) frameworks focused on process understanding and control[51].

3.5 Solid-state nuclear magnetic resonance (ssNMR)

Solid-state nuclear magnetic resonance (ssNMR) spectroscopy is a highly advanced analytical technique that offers unparalleled insight into the molecular structure and dynamics of ASDs. Unlike conventional solution NMR, which is limited to liquid samples, ssNMR is specifically designed to work with powdered or solid-state materials, making it ideal for studying systems that lack long-range molecular order, such as ASDs. Where techniques like X-ray crystallography or PXRD may fall short, ssNMR steps in to provide detailed information at the atomic level, especially regarding drug–polymer interactions and physical stability[52,53]. The technique works by detecting the resonance of atomic nuclei, typically ^13C, ^15N, or ^1H, when placed in a magnetic field. When drugs interact with polymers through hydrogen bonding, ionic attraction, or π–π stacking, the chemical environment of these nuclei changes, leading to measurable shifts in the NMR spectrum. In a study by De Vries and colleagues (2020), a change in the ^13C chemical shift of ketoconazole's imidazole group was observed when it was combined with HPMC-AS, providing direct evidence of molecular interaction that contributed to improved amorphous stability[54]. Beyond detecting interactions, ssNMR is also highly effective at distinguishing between amorphous and crystalline states. Crystalline materials produce sharp, narrow peaks in the spectrum due to their uniform molecular environments, while amorphous materials exhibit broader, more diffuse signals that reflect molecular disorder. This makes ssNMR particularly valuable for identifying low levels of recrystallisation that may develop during storage an important concern for long-term stability in ASD formulations[52].

Recent advancements have significantly improved the sensitivity and resolution of ssNMR. Techniques like cross-polarisation magic-angle spinning (CP-MAS) are commonly used to enhance signal quality, especially for nuclei like ^13C, which are present at low natural abundance. Additionally, 2D NMR techniques such as heteronuclear correlation (HETCOR) provide spatial information about how different atoms are arranged relative to one another, allowing researchers to map out drug–polymer interactions in remarkable detail[55]. One of the major advantages of ssNMR is that it allows for direct observation of both the drug and polymer components without the need for labelling, chemical modification, or destructive sample preparation. However, the

technique does have its limitations. It typically requires long measurement times, specialised equipment, and considerable technical expertise. As a result, ssNMR is more commonly used in advanced research settings rather than in routine quality control[55]. Still, recent studies show promising new applications. Shamblin et al. (2022), for example, used ssNMR to monitor molecular mobility in ASDs under accelerated storage conditions. They were able to detect early indicators of instability well before changes were observed with techniques like DSC or PXRD. Such findings highlight ssNMR's potential as a predictive tool for long-term stability, offering a valuable early-warning system in formulation development[56].

3.6 Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) is one of the most fundamental techniques used in the physical characterisation of ASDs, especially when distinguishing between crystalline and amorphous forms. Based on Bragg's law, PXRD works by measuring how X-rays are diffracted by the orderly lattice structures found in crystalline materials. When a material is crystalline, it produces sharp, distinct diffraction peaks at specific 2θ angles due to its regular, repeating atomic arrangement. In contrast, amorphous materials, which lack this long-range order, show up as broad, diffuse halos in the diffractogram[57]. PXRD plays a critical role in confirming whether a drug has been successfully converted into its amorphous form during processing techniques like spray drying or hot-melt extrusion. If the sharp Bragg peaks associated with the crystalline drug disappear and are replaced by a smooth hump, it's a strong indication that amorphisation has occurred. For instance, Saboo and colleagues (2021) demonstrated complete amorphisation of celecoxib when combined with Soluplus, with PXRD confirming the absence of crystalline peaks, supported by complementary DSC data[58].

The technique is also highly valuable in stability studies. Under storage conditions, especially accelerated ones like 40°C/75% relative humidity, PXRD can detect even minor recrystallisation. The reappearance of low-intensity Bragg peaks over time serves as an early warning sign of physical instability. Interestingly, ASDs with stronger drug-polymer interactions or lower drug loading tend to maintain their amorphous state longer, a trend that can be clearly tracked using PXRD over several months[59]. More advanced versions of PXRD, such as variable-temperature PXRD, allow researchers to monitor how crystallisation progresses in real time as temperature changes. This helps define the thermal stability limits of a formulation. In cutting-edge research, synchrotron-based PXRD, offering higher sensitivity and resolution, has even been used to detect trace levels of crystallinity that might go unnoticed with standard equipment[60]. While PXRD excels at identifying whether a drug is crystalline or amorphous, it does have its limitations. It cannot provide details about the type of molecular interactions involved such as hydrogen bonding or ionic interactions so it is often paired with complementary techniques like FTIR or Raman spectroscopy for a more complete understanding. Additionally, sample preparation is important; uneven or improperly packed samples can introduce artefacts like preferred orientation[61].

3.7 Small-angle X-ray scattering (SAXS)

Small-angle X-ray scattering (SAXS) is a highly informative structural analysis technique that plays a vital role in characterising ASDs, especially when it comes to detecting nanoscale features and internal organisation that aren't easily observed using conventional methods. While powder X-ray diffraction (PXRD) is excellent for identifying long-range crystallinity, SAXS excels at capturing subtle structural variations such as micro-phase separation, domain size, and molecular-level dispersion features, particularly relevant in systems where the drug and polymer are poorly miscible or in ternary blends involving multiple excipients[62]. SAXS works by measuring how X-rays scatter at very small angles, typically between 0.1° and 5°, which corresponds to structures between 1 and 100 nanometres in size. This scale is ideal for identifying nano-domains within the ASD matrix, including polymer-rich and drug-rich regions that may signal early phase separation. These features are often invisible to PXRD or optical microscopy. In one notable study, SAXS was applied to evaluate posaconazole–HPMCAS dispersions and was able to detect early-stage nano-aggregation long before crystallinity could be confirmed by PXRD, demonstrating SAXS's superior sensitivity in identifying phase instability[63].

One of the primary applications of SAXS in ASD research is to verify whether the drug is molecularly dispersed within the polymer. A clean, featureless SAXS pattern typically suggests uniform mixing, whereas the appearance of periodic or structured scattering features indicates the presence of phase heterogeneity. This becomes particularly important when working with ternary ASDs or exploring novel polymer combinations, where miscibility may be less predictable. For example, Hulse et al. (2021) used SAXS to map micro-domains in both binary and ternary formulations, providing insight into long-term stability and guiding the selection of excipients that minimise crystallisation risks[64]. Another promising use of SAXS is in situ monitoring during manufacturing processes like spray drying or hot-melt

extrusion. By observing the material in real time, researchers can evaluate how processing parameters such as temperature, shear rate, or solvent removal affect the internal structure and aggregation tendencies of the formulation. Variable-temperature SAXS, in particular, can simulate long-term storage conditions and track how phase separation or clustering evolves over time[65]. While SAXS offers several advantages, including high sensitivity and nanoscale resolution, it does have some practical limitations. High-end SAXS systems often require access to synchrotron radiation sources, which may not be feasible for every research or quality control lab. However, recent advances in benchtop SAXS instrumentation are making the technique more accessible, suggesting it could become a routine part of ASD characterisation in the near future[66].

3.8 Scanning electron microscopy (SEM)

Scanning Electron Microscopy (SEM) is a valuable imaging technique widely used to explore the surface characteristics, particle size, and microstructure of pharmaceutical formulations, including ASDs. Although SEM does not directly reveal molecular-level interactions, it provides detailed visual evidence of drug–polymer miscibility, the uniformity of dispersion, and surface changes that can impact the physical stability and performance of a formulation[66]. The technique works by directing a focused beam of high-energy electrons across the surface of a sample. As the electrons interact with the atoms in the material, they generate signals that are collected and transformed into high-resolution, three-dimensional images. These images allow researchers to distinguish between crystalline and amorphous states based on particle shape and texture. Crystalline drug particles usually appear sharp, faceted, and well-defined, while amorphous particles are more irregular, smoother, and often spherical with a matte surface[67].

One of SEM's key roles in ASD development is verifying whether the drug has been successfully incorporated into the polymer matrix. When crystalline features disappear after processing methods like spray drying or hot-melt extrusion, and particles appear uniformly shaped and amorphous, this visually confirms effective dispersion. For example, it was observed that carvedilol ASDs prepared with HPMCAS displayed consistent, non-crystalline particles, suggesting successful amorphisation[68]. SEM is also instrumental in stability studies. Over time, particularly under accelerated conditions, recrystallisation may occur. This is often visible as the reappearance of crystalline domains on the surface. By comparing SEM images taken before and after storage, researchers can detect early signs of physical degradation. In addition, SEM is frequently paired with energy-dispersive X-ray spectroscopy (EDS), which provides information about elemental composition. This helps track phenomena like drug migration, phase separation, or the enrichment of specific components on the surface[69]. Beyond stability assessments, SEM is useful in evaluating manufacturing processes like granulation, milling, or extrusion. It can detect surface defects, porosity, and coating inconsistencies that might affect dissolution or shelf life. In more complex systems, such as ternary ASDs or formulations containing surfactants, SEM can help visualise micelle structures, wetting behaviour, or interfacial disruptions[70].

3.9 Atomic force microscopy (AFM)

Atomic Force Microscopy (AFM) is a highly advanced imaging technique that provides nanoscale resolution for studying surface morphology, topography, and mechanical properties. In the field of ASDs, AFM is particularly valuable for revealing detailed structural features such as micro-phase separation, assessing drug-polymer miscibility, and evaluating surface characteristics like roughness and adhesion factors that directly influence the stability, dissolution rate, and bioavailability of the final dosage form[71]. AFM works by scanning a very sharp probe tip, mounted on a flexible cantilever, across the surface of a sample. As the tip moves over the surface, it experiences deflections caused by atomic-level forces, and these deflections are recorded to produce high-resolution, three-dimensional images. Unlike Scanning Electron Microscopy (SEM), which primarily provides surface images, AFM also measures interaction forces, elasticity, and adhesion at the nanoscale. This additional layer of mechanical information helps researchers understand localised differences in surface chemistry and formulation behaviour[72].

One of AFM's most important applications in ASD research is its ability to detect early signs of nano-phase separation, which often precedes visible crystallisation. It has been demonstrated that AFM phase imaging could identify drug-rich and polymer-rich regions in ASDs, even before such separation became detectable by conventional techniques like PXRD or DSC. This makes AFM especially useful for evaluating high drug-loaded systems, where subtle incompatibilities can lead to long-term instability that isn't immediately obvious at the macro level[73]. In addition to imaging, AFM can operate in force spectroscopy mode, allowing precise measurement of the adhesive force between the tip and the sample surface. These values are closely related to surface energy and wettability two key parameters in understanding dissolution behaviour. A strong adhesive interaction often points to a polymer-dominant surface,

which may promote stability but slow down drug release. On the other hand, drug-rich surfaces tend to have weaker adhesion and may dissolve faster, but they also carry a higher risk of recrystallisation[74].

AFM is also useful for examining the influence of excipients such as surfactants or secondary polymers in ternary formulations. By analysing phase maps and surface structures, researchers can detect regions of incompatibility or crystallised excipients that could negatively impact the performance of the final product. Emerging techniques even combine AFM with localised thermal analysis (AFM-TA), allowing for thermal behaviour to be studied at precise surface locations[75]. Despite its many strengths, AFM does have some limitations. It requires the sample to be flat and dry, which means it is less suited for real-time or hydrated analysis. Additionally, the area that can be scanned is relatively small typically under 100 micrometres squared so it is best used as a complementary method alongside bulk techniques like PXRD or DVS. Still, its ability to offer a window into the nanoscale world makes AFM an invaluable tool in the formulation scientist's toolkit[72].

3.10 Dynamic vapor sorption (DVS)

Dynamic Vapor Sorption (DVS) is a precise and sensitive gravimetric technique commonly used to evaluate how ASDs interact with moisture. It plays a critical role in understanding a formulation's hygroscopic behaviour, water uptake capacity, and vulnerability to moisture-induced phase separation or crystallisation. DVS is particularly useful because moisture can have a profound impact on the physical stability of ASDs, acting as a plasticiser, lowering the Tg, and increasing molecular mobility, all of which can accelerate drug recrystallisation[76]. In a typical DVS experiment, a small sample is placed on an ultra-sensitive microbalance inside a humidity-controlled chamber. The relative humidity (RH) is gradually increased or decreased in a controlled sequence while the instrument continuously records the sample's weight changes over time. The resulting data are plotted as a sorption isotherm, which illustrates how much moisture the material absorbs or desorbs at each RH level. These curves help identify important behaviours, such as the point at which the material begins to deliquesce, the rate at which it takes up or releases water, and any hysteresis between sorption and desorption. Together, these indicators provide a clear picture of the formulation's resilience or sensitivity to moisture under various storage conditions[77].

Moisture's plasticising effect is a particular concern. When water is absorbed, it often lowers the Tg of the amorphous matrix. If the Tg falls below ambient temperature, the increased mobility of molecules can trigger nucleation and eventual crystallisation. In a study on indomethacin-PVP dispersions, significant water uptake above 60% RH was followed by recrystallisation. In contrast, dispersions made with more hydrophobic polymers like HPMCAS exhibited minimal moisture absorption and maintained their amorphous stability[78]. DVS is also highly useful for comparing the moisture-handling capabilities of different polymers. For instance, polymers like PVP or PEG are more hygroscopic and may destabilise moisture-sensitive drugs in high-humidity environments. In contrast, polymers such as HPMCAS or ethyl cellulose offer greater moisture resistance. These insights can inform important formulation choices, including the selection of desiccants, primary packaging materials, and storage recommendations[79]. Another valuable application of DVS is detecting moisture-induced phase separation (MIPS), where absorbed water causes the drug and polymer to separate into distinct regions-a precursor to crystallisation. This behaviour is typically observed as an unusual or sharp increase in mass uptake on the isotherm and can later be confirmed using PXRD or AFM[80].

Despite its strengths, DVS does have some limitations. It generally requires long equilibration times to ensure accurate readings at each RH step, and while it quantifies how much moisture is absorbed, it doesn't directly indicate whether that moisture is chemically bound or simply physically adsorbed. Nonetheless, its ability to sensitively and quantitatively measure water uptake makes DVS an indispensable tool for screening ASDs, especially when moisture stability is a primary concern.

3.11 Inverse gas chromatography (IGC)

Inverse Gas Chromatography (IGC) is an increasingly favoured technique in pharmaceutical formulation, particularly for analysing surface energetics and predicting the miscibility of drugs and polymers in ASDs. Unlike conventional gas chromatography, where a liquid or gas sample is injected into a packed column, IGC reverses the setup: the ASD material itself acts as the stationary phase, and a series of vapour-phase probe molecules are passed over it. By examining how these probes interact with the surface of the sample, researchers can extract important data on surface energy, polarity, and thermodynamic behaviour—critical factors when designing stable, effective ASDs[81]. One of the standout capabilities of IGC is its ability to quantify both dispersive surface energy (associated with van der Waals forces) and specific surface energy (related to polar interactions, such as hydrogen bonding or acid–base chemistry). These measurements can also be used to determine solubility parameters, including the Flory–Huggins

interaction parameter (χ), which is a key indicator of drug–polymer miscibility. Lower χ values (typically below 0.5) suggest strong miscibility and stable systems, while higher values hint at potential phase separation or crystallisation risks. For example, Yousaf et al. (2021) successfully used IGC to predict the compatibility of efavirenz with several polymers, and the findings were later confirmed by complementary techniques such as solid-state NMR and DSC[82].

One of IGC's practical advantages is that it operates under dry conditions and does not require chemical modification of the sample. This is particularly helpful when working with moisture-sensitive compounds or early-stage formulations. Its non-destructive nature and relatively fast turnaround make it an excellent screening tool, especially before committing resources to large-scale processes such as spray drying or hot-melt extrusion[83]. IGC is also valuable for assessing the cohesive–adhesive balance (CAB) in multicomponent systems. A high CAB value between a drug and polymer indicates strong mutual attraction and compatibility, while a low value suggests poor adhesion and a risk of phase separation. In addition, IGC can be used to evaluate the effects of surface treatments, particle ageing, or long-term storage on material stability, making it a versatile tool in both development and quality control[84].

IGC has its limitations. It primarily analyses surface interactions, which may not always represent what's happening within the bulk of the material. Also, setting up uniform, well-packed columns can be challenging, especially with sticky, cohesive, or irregularly shaped powders. Still, IGC continues to grow in popularity as a reliable preformulation technique. It effectively bridges the gap between theoretical miscibility models and real-world experimental data, offering critical insights during the early stages of ASD development and formulation optimisation[85].

4. ASD STABILITY AND DRUG-POLYMER INTERACTIONS

4.1 Physical stability

In ASDs, crystallisation inhibition can be achieved by powerful drug–polymer interactions that limit the mobility of drug molecules, thereby preventing the formation of crystals and maintaining their physical stability. The intensity of these interactions is crucial in delaying crystallisation as well as retaining the drug's amorphous nature within the formulation[86]. Drugs can be stabilised using polymers that have a high Tg, through a process known as anti-plasticisation. This is done by raising the overall Tg of the ASD, thus minimising the movement of drug molecules and inhibiting crystallisation. However, it should be noted that, on its own, Tg may not always provide a reliable prediction about the physical stability of ASDs[87]. To delay crystallisation and maintain drugs in an amorphous state in solid dispersions, these strong drug–polymer interactions cause a reduction in molecular mobility. With drug molecule motion being restricted, the chances of crystallisation decrease, thereby improving its physical stability in ASDs[88].

Recent research continues to shed light on how drug–polymer interactions, polymer selection, and external conditions collectively influence the physical stability of ASDs. A study conducted by Pajzderska et al. explored the long-term stability of felodipine-PVP ASDs using ^1H NMR relaxometry. Their findings showed that the formulation remained physically stable for 250 days when stored under dry conditions (0% relative humidity), underscoring the effectiveness of drug–polymer miscibility in maintaining the amorphous state. However, once the ASD was exposed to 75% RH, water uptake led to a reduction in stability, ultimately resulting in recrystallisation. This demonstrated the destabilising effect of moisture acting as a plasticiser, which increases molecular mobility and facilitates crystal formation-even in systems with strong initial miscibility[89]. A similar trend was observed in ASDs containing α-mangostin formulated with either Eudragit or PVP. When stored at 90% RH and 25°C, the 1:1 α-mangostin–Eudragit formulation began to recrystallise within just seven days. In contrast, PVP-based systems with higher polymer content (1:4 and 1:10 drug-polymer ratios) remained amorphous for the entire duration of the study. These results emphasise how both polymer choice and drug loading play a crucial role in resisting crystallisation, particularly under high-humidity conditions[90]. Another compelling example comes from a comparative study on fenofibrate ASDs prepared by hot-melt extrusion (HME) versus spray drying. Over a one-year storage period, HME-based formulations exhibited superior resistance to recrystallisation, with only minor crystalline content detected via DSC. Meanwhile, spray-dried samples showed earlier signs of physical instability, confirmed by PXRD and SEM. Interestingly, changes in dissolution profiles were noted before any visible signs of crystallinity appeared, indicating that functional performance may begin to decline even before structural changes can be detected[91].

4.2 Chemical stability

Chemical instability in ASDs can lead to the formation of degradation products or impurities, which may compromise the safety, efficacy, and shelf life of the final drug product. Several factors influence chemical stability in these systems, including the nature

and strength of drug–polymer interactions, the local pH environment within the matrix, and exposure to external stressors such as elevated temperature, humidity, light, and oxygen. These elements can accelerate degradation pathways, such as hydrolysis or oxidation, particularly when the drug is in a high-energy amorphous state[92]. One notable example comes from a study that explored the chemical stability of simvastatin ASDs formulated with different polymers. The study found that polyvinylpyrrolidone (PVP) significantly promoted hydrolytic degradation of simvastatin under humid conditions. On the other hand, HPMCAS, a more hydrophobic and acidic polymer, offered better chemical protection, likely due to its reduced moisture uptake and ability to create a localised acidic microenvironment that inhibits hydrolysis[93].

In a similar study, the authors evaluated the chemical stability of olanzapine ASDs. Systems containing PEG-based polymers showed a higher rate of degradation, attributed to both increased hygroscopicity and the presence of residual peroxide impurities within the polymer. Conversely, using Soluplus, a non-PEG-based amphiphilic polymer, resulted in significantly enhanced chemical and physical stability, particularly under accelerated storage conditions[94]. Another relevant case is that of nicotinamide–PVP ASDs, where oxidative degradation was observed to increase over time, especially when the samples were exposed to light and atmospheric oxygen. To mitigate this, antioxidants such as butylated hydroxytoluene (BHT) can be incorporated into the formulation. This approach markedly reduced oxidative degradation, emphasising the role of stabilising excipients in protecting chemically sensitive drugs[95].

Collectively, these studies reinforce the idea that polymer selection affects not just the physical characteristics of ASDs, such as Tg and crystallisation resistance, but also plays a crucial role in governing chemical reactivity. Factors like polymer acidity, moisture affinity, oxidative stability, and residual impurity content must all be taken into account. Additionally, formulation strategies such as the use of antioxidants, inert packaging, or moisture-barrier coatings can further extend the chemical shelf life of these systems. Therefore, assessing chemical stability early in the formulation process, alongside physical characterisation, is essential to ensure the long-term success of ASD-based drug products.

4.3 Moisture uptake

Moisture uptake is a critical factor that can significantly influence both the physical and chemical stability of ASDs. These systems are thermodynamically unstable by nature and tend to absorb moisture from the environment, particularly when stored under conditions of high relative humidity (RH). This humidity-driven absorption can lead to plasticisation of the polymer matrix, effectively lowering the Tg. As the Tg drops, molecular mobility increases, making the formulation more susceptible to recrystallisation or even chemical degradation over time. Therefore, understanding and controlling how much moisture an ASD can absorb is essential for predicting its long-term behaviour and ensuring product quality under real-world storage conditions[96].

In indomethacin–PVP ASDs, it was found that at RH levels above 60%, the system absorbed moisture rapidly, causing a measurable reduction in Tg and triggering recrystallisation. In contrast, formulations using HPMCAS, a more hydrophobic polymer, exhibited much lower water uptake and retained their amorphous character even under the same humid conditions[78]. This example clearly highlights how the moisture-barrier properties of hydrophobic polymers can play a protective role in stabilising the drug. In another study,the moisture uptake behaviour of itraconazole ASDs formulated with different polymers are compared. They reported that ASDs containing PVP-VA absorbed significantly more atmospheric moisture than those made with Eudragit L100, resulting in faster degradation under accelerated storage conditions. This observation underscores the importance of polymer hygroscopicity in determining how resistant an ASD will be to moisture-related instability[80]. A further example involved ternary ASDs of carbamazepine formulated with poloxamer 407 and HPMC. These combinations showed improved resistance to humidity compared to binary formulations. The enhanced performance was attributed to a synergistic effect between the two polymers, which formed a denser matrix network that restricted moisture penetration and minimised water uptake, thereby improving physical stability[97].

These studies reveal that moisture sorption is not simply an environmental outcome but a formulation-specific property influenced by factors such as polymer chemistry, drug loading, and matrix structure. Analytical techniques like Dynamic Vapor Sorption (DVS) offer valuable predictive insights into the moisture-handling capabilities of ASDs, making them indispensable tools during formulation development and stability risk assessment.

5. STRATEGIES FOR OPTIMIZING DRUG-POLYMER INTERACTIONS AND STABILITY

5.1 Polymer selection

In developing ASDs, one of the most critical aspects is selecting an appropriate polymer carrier. The physicochemical properties of the drug, the target

release profile, and the manufacturing technique are the primary factors influencing the choice of polymers[98]. A soluble, miscible polymer is desirable to solubilise the drug and prevent crystallisation. By comparing the Hildebrand solubility parameter of the drug with that of various polymers, one can determine how much they are miscible with the drug. The solubility parameters of the polymer should closely match those of the drug to enhance bioavailability and drug release profiles. The better the solubility, the easier it becomes for the polymer matrix to solubilise the drug. A miscible system guarantees that the drug will be evenly incorporated into the polymer, minimising the potential for phase separation and crystallisation of the drug. This is particularly important in ensuring the stability of the ASDs, as crystallisation can render the compound insoluble and, consequently, not bioavailable[99].

Polymers with high thermal stability are able to withstand certain external conditions during processing, such as the application of heat during melting or drying. This is crucial in formulation, as it ensures the polymer and drug retain their properties. Conversely, polymer degradation can lead to unwanted by-products that negatively affect the drug and its release properties. It is also important to note that the thermal transitions, specifically the Tg of the polymer, are critical[100]. For example, if a polymer has a Tg much lower than the processing temperature, it may soften the matrix and ease drug release; however, this raises the likelihood of phase separation. On the other hand, if a polymer's Tg is much higher, it will not permit enough drug release. Therefore, a polymer must be chosen to ensure that all these parameters are met in the correct proportions[101]. A polymer's solubility in a variety of solvents can be altered by its ionisation state. Ionisable polymers, such as those with carboxylic acid or amine groups, may display greater solubility in more polar solvents when in their ionised states. This greatly enhances the possibility of achieving better solubilisation of the drug within the polymer matrix, leading to improved drug release and bioavailability. Hydrophilicity or hydrophobicity of the polymer can also be influenced by alterations in the ionisation state[102]. Typically, polymers with higher molecular weights have increased viscosity, which can affect the processing conditions during the formulation of ASDs. Higher stability of the dispersion can be achieved if the viscosity is high enough to prevent sedimentation or phase separation. However, the dispersion must also remain sufficiently low in viscosity to allow processes like hot-melt extrusion or spray drying. For this reason, a polymer with a specific molecular weight is required to achieve a balance between processability and stability. A higher release rate from the solid dispersion is possible with lower molecular weight polymers because their structure is more open, allowing easier drug diffusion. Conversely, the drug release rate with higher molecular weight polymers is lower due to the thicker matrix[103].

The release profile of the drug is influenced by whether the polymer used is hydrophilic or hydrophobic. Hydrophilic polymers will swell and increase diffusion of the drug, while hydrophobic ones can reduce it. It is therefore possible to tailor the release profile of the drug by selecting polymers that fall between the extremes of hydrophilic and hydrophobic, ensuring that the therapeutic action is maintained[104]. Selected polymers can help achieve and maintain supersaturation by forming a protective matrix that prevents the drug from crystallising. Polymers that form strong interactions with the drug can effectively stabilise the supersaturated state and prevent nucleation and crystal growth. Optimising drug-polymer interactions is crucial for maintaining the stability of the amorphous solid dispersion[104]. Polymers with solubility dependent on pH can be employed to regulate drug release in different parts of the gastrointestinal tract. pH-dependent solubility plays a crucial role in the development of oral drug delivery systems, particularly in designing ASDs with site-specific or delayed drug release. These polymers are engineered to dissolve only at certain pH thresholds, allowing the drug to remain protected in the stomach and to be released in a controlled manner at targeted regions of the gastrointestinal (GI) tract. This approach not only helps protect acid-sensitive drugs from gastric degradation but also minimises drug release in the stomach, reducing gastric irritation and improving absorption in the intestine[105]. Methacrylic acid copolymers, such as Eudragit L100 and Eudragit S100, are classic examples of pH-sensitive polymers. Eudragit L100 begins dissolving at pH ≥6.0, making it suitable for duodenal delivery, while Eudragit S100 dissolves at pH ≥7.0, targeting the distal ileum or colon. These polymers have been widely used in enteric coatings and increasingly in ASDs to prevent premature drug release in the stomach and enable site-specific release further down the GI tract[106]. Another polymer, hydroxypropyl methylcellulose acetate succinate (HPMCAS), has gained attention in ASD formulation due to its pH-dependent solubility (typically dissolving at pH 5.5–6.8) and excellent ability to stabilise amorphous drugs. HPMCAS not only maintains the supersaturated state of the drug in the small intestine, enhancing bioavailability, but also minimises crystallisation due to its hydrophobic backbone and strong drug-polymer interactions. It is commonly used for BCS Class II drugs that are poorly water-soluble and require enhanced solubility and permeability[107,108]. While pH-dependent polymers offer great versatility, formulation scientists must consider factors such as polymer-drug miscibility, drug loading, and GI transit time, which can influence the actual site and extent of release. Moreover,

variability in individual gastric and intestinal pH profiles among patients can lead to inter-subject variability in drug absorption[109].

5.2 Methods of processing

HME and spray drying methods have the ability to promote molecular-level dispersion of poorly water-soluble drugs within a polymer matrix. This is key to enhancing solubility and improving bioavailability. Comparing HME and spray drying also provides meaningful insight into how different processing conditions can affect the long-term physical stability and performance of ASDs. Understanding these differences helps guide the selection of the most suitable method for a given drug–polymer system. Both techniques have a strong track record in the pharmaceutical industry and are supported by a growing body of research, making them logical choices for evaluating formulation strategies in both preclinical and commercial settings[110,111].

5.2.1. Melt extrusion

Polymers possessing appropriate thermoplastic properties, such as a low Tg and melt viscosity, are preferred to facilitate drug solubilisation and mixing. The dissolution of the drug within the polymer matrix is enhanced at elevated temperatures, improving contact between the two components and leading to greater interaction[112]. The amorphous form of the drug is crucially stabilised by stronger intermolecular interactions, such as hydrogen bonding. Externally supplied work is used to soften and mix the material, and this phase locks the drug into the amorphous form. The system is then rapidly cooled, suppressing crystallisation and enhancing the stability of the ASD. There are additional advantages, such as the improved quality of the final product, due to the precise control available during extrusion. During extrusion, the polymer is heated and pulled through a nozzle, which increases viscosity when sheared. This high viscosity provides kinetic stabilisation, making it harder for the drug molecules to move, thus delaying phase separation and crystallisation[113].

5.2.2. Spray drying

Polymers with high solubility in volatile organic solvents are preferred to ensure the formation of a homogeneous ASD. Similarly, another widely used method for preparing ASDs is spray drying. This involves dissolving the drug and polymer in a solvent, which is then dispersed into an atomised hot air stream. The solvent contained in the atomised droplets rapidly evaporates, which is crucial for achieving an amorphous state. The quick evaporation not only increases the surface area but also ensures that the drug does not crystallise during the transformation from liquid to solid[114]. The type of solvent used significantly influences the drug-polymer properties; using one that improves the polymer's dispersibility can enhance dispersion quality. Additionally, using co-solvents or mixed solvent systems can improve drug–polymer solubility and interaction. Regarding ASD dissolution, particle size and shape are important; smaller particles usually enhance the dissolution rate, particularly when spray drying is used, as these factors can be controlled. Most polymers and drugs, including thermolabile compounds, can be used with these techniques to formulate ASDs, making them applicable to most pharmaceutical applications[115].

5.3 Optimization of drug-polymer ratio

The optimisation of the drug–polymer ratio in ASDs is critical for achieving the right balance between enhancing solubility and providing physical stability[116]. A higher drug loading in ASDs can lead to a greater improvement in dissolution when compared with crystalline drugs. Amorphous drugs have higher free energy and molecular mobility, which improves dissolution and results in an apparent enhancement in solubility. However, beyond a certain level, increasing drug loading can compromise the physical stability of ASDs[117]. An increase in drug loading also increases the likelihood of recrystallisation during storage or dissolution. The amorphous drug is kinetically stabilised by the polymer component in the ASD, thus preventing crystallisation. In systems with low drug loading, polymers can significantly inhibit nucleation and subsequent crystal growth, enhancing physical stability. However, at higher drug loading levels, the saturation of drug-polymer interactions may occur, which may not sufficiently stabilise the amorphous state and thus increase the chances of recrystallisation. The release profile of the drug from an ASD can also be altered by the extent of its loading, including supersaturation kinetics and dissolution rates. Controlling release kinetics by optimising this ratio is crucial to achieving the desired delivery profiles[118].

5.4 Using co-polymers and ternary systems

Ternary ASDs are gaining attention as an effective strategy to address some of the challenges associated with conventional binary systems. By incorporating two excipients typically a combination of polymers or a polymer and a surfactant ternary systems can offer enhanced physical stability, improved solubility, and the potential for more tailored drug release profiles. However, these benefits come with

increased formulation complexity, as developers must consider not only how the drug interacts with each polymer but also how the two polymers interact with one another[119]. A notable example of a ternary system designed to enhance physical stability is the formulation of nifedipine with HPMC-AS and Soluplus. In this combination, HPMC-AS helped raise the glass transition temperature and reduce moisture uptake, while Soluplus contributed to improved miscibility with the drug. Together, they formed a more stable amorphous matrix than either polymer alone, significantly reducing the likelihood of recrystallisation during storage under stress conditions[120]. Ternary systems have also shown great promise in achieving customised drug release profiles. For instance, a study on curcumin demonstrated that blending Eudragit RSPO, PVP K30, and a small amount of poloxamer 407 allowed researchers to fine-tune the release rate simply by adjusting the component ratios. The hydrophilic nature and plasticising effect of poloxamer altered the matrix porosity and polymer relaxation, enabling a range of release behaviours from immediate to sustained. This adaptability is particularly valuable for optimising treatment across different therapeutic contexts[121].

Despite their advantages, ternary ASDs do present some challenges. With more components in the mix, there is a higher risk of incompatibility or phase separation, especially if the polymers are not well-matched. Predicting how each component will interact requires a combination of theoretical modelling and extensive experimental testing. Additionally, manufacturing can become more complicated, particularly during processes like hot-melt extrusion or spray drying, where differences in polymer viscosity, solubility, or thermal behaviour can affect the uniformity and quality of the final product[122].

6. CONCLUSION

ASDs are being investigated to enhance the effectiveness of orally administered medicines, particularly for drugs with poor water solubility. Compared to crystalline forms, solid dispersions have consistently demonstrated an ability to enhance both drug solubility and stability. Specific interactions between drugs and polymers are essential for the retention of the amorphous state, including ionic forces, hydrogen bonds, van der Waals interactions, and hydrophobic effects. However, challenges remain in understanding the complexity of these interactions, choosing the appropriate polymers, and predicting the long-term stability of ASDs. Molecular strategies aimed at reducing macromolecular barriers to drugs in ASDs have explored adjustments such as polymer selection, variation in drug–polymer ratios, and the use of co-polymers, among others. Further research is required to overcome these challenges and fully unlock the potential of ASDs in pharmaceutical formulations.

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REFERENCES

1. Patel H, Parikh R. Pharmaceutical amorphous solid dispersion: A review of formulation technologies for poorly water-soluble drugs. Int J Pharm. 2021;604:120770. doi:10.1016/j.ijpharm.2021.120770.
2. Bhujbal S V., Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharm Sin B. 2021;11:2505–36. doi:10.1016/j.apsb.2021.06.013.
3. Sihorkar V, Dürig T. The role of polymers and excipients in developing amorphous solid dispersions: An industrial perspective. In: Drug Delivery Aspects. Elsevier; 2020. p. 79–113. doi:10.1016/B978-0-12-821222-6.00005-1.
4. Theil F, Milsmann J, Kyerematen SO, Anantharaman S, Rosenberg J, van Lishaut H. Extraordinary long-term stability in kinetically stabilized amorphous solid dispersions of fenofibrate. Mol Pharm. 2017;14:4636–47. doi:10.1021/acs.molpharmaceut.7b00634.
5. Theil F, Anantharaman S, Kyerematen SO, van Lishaut H, Dreis-Kühne SH, Rosenberg J, et al. Frozen in time: Kinetically stabilized amorphous solid dispersions of nifedipine stable after a quarter century of storage. Mol Pharm. 2017;14:183–92. doi:10.1021/acs.molpharmaceut.6b00985.
6. Chen Y, Wang S, Wang S, Liu C, Su C, Hageman M, et al. Initial drug dissolution from amorphous solid dispersions controlled by polymer dissolution and drug–polymer interaction. Pharm Res. 2016;33:2445–58. doi:10.1007/s11095-016-1974-4.
7. Saboo S, Mugheirbi NA, Zemlyanov DY, Kestur US, Taylor LS. Congruent release of drug and polymer: A “sweet spot” in the dissolution of amorphous solid

dispersions. J Control Release. 2019;298:68–82. doi:10.1016/j.jconrel.2019.02.014.
8. Indulkar AS, Lou X, Zhang GGZ, Taylor LS. Insights into the dissolution mechanism of ritonavir–copovidone amorphous solid dispersions: Importance of congruent release for enhanced performance. Mol Pharm. 2019;16:1327–39. doi:10.1021/acs.molpharmaceut.8b00886.
9. Mustapa Bookwala M, Buckner IS, Wildfong PLD. Implications of coexistent halogen and hydrogen bonds in ASDs: Solubility, miscibility, mobility. Mol Pharm. 2022;19(11):3959–72. doi:10.1021/acs.molpharmaceut.2c00434.
10. Pugliese A, Tobyn M, Hawarden LE, Abraham A, Blanc F. New development in understanding drug–polymer interactions in ASDs. Mol Pharm. 2022;19(11):3685–99. doi:10.1021/acs.molpharmaceut.2c00479.
11. Zhang J, Guo M, Luo M, Cai T. Advances in the development of amorphous solid dispersions: The role of polymeric carriers. Asian J Pharm Sci. 2023;18(4):100834.
12. Wang Y, Wang Y, Cheng J, Chen H, Xu J, Liu Z, et al. Recent Advances in the Application of Characterization Techniques for Studying Physical Stability of Amorphous Pharmaceutical Solids. Crystals (Basel). 2021;11(12):1440.
13. Benmore CJ, Yarger JL, Davidowski SK, Shrader CD, Smith PA, Byrn SR. Hydrogen Bonding in Amorphous Indomethacin. Pharmaceutics. 2024;16(8):1002.
14. Wang Y, Ma R, Wang B, Liu X, Zhao X, Liu L, et al. Influence of Number and Strength of Hydrogen Bonds on Fracture Property and Microscopic Mechanisms of Associative Hydrogen-Bonded Polymers via Molecular Dynamics Simulation. Langmuir. 2024;40(52):27501–10.
15. Bookwala M, Wildfong PLD. The Implications of Drug-Polymer Interactions on the Physical Stability of Amorphous Solid Dispersions. Pharm Res. 2023;40(12):2963–81.
16. López Burgos G, Hernández Espinell JR, Graciani-Massa T, Yao X, Borchardt-Setter KA, Yu L, et al. Role of Heteronucleants in Melt Crystallization of Crystalline Solid Dispersions. Cryst Growth Des. 2023;23(1):49–58.
17. Lemanowicz M, Mielańczyk A, Walica T, Kotek M, Gierczycki A. Application of Polymers as a Tool in Crystallization—A Review. Polymers (Basel). 2021;13(16):2695.
18. Ni Q, Ye W, Du M, Shan G, Song Y, Zheng Q. Effect of Hydrogen Bonding on Dynamic Rheological Behavior of PVA Aqueous Solution. Gels. 2022;8(8):518.
19. Liu J, Singh J. Mechanisms of ionic polymer interactions in amorphous formulations. Mol Pharm. 2022;19(8):2638–50. doi:10.1021/acs.molpharmaceut.2c00314.
20. Novakovic D, Peltonen L, Isomäki A, Fraser-Miller SJ, Nielsen LH, Laaksonen T, et al. Surface Stabilization and Dissolution Rate Improvement of Amorphous Compacts with Thin Polymer Coatings: Can We Have It All? Mol Pharm. 2020;17(4):1248–60.
21. Bakhtiari SE, Zhu Z, Magdysyuk O V., Brocchini S, Williams GR. Amorphous solid dispersions of lidocaine and lidocaine HCl produced by ball milling with well-defined RAFT-synthesised methacrylic acid polymers. Int J Pharm. 2023;644:123291.
22. Sanchez A, Wyss J, Smith A. Solid-state NMR evidence for drug–polymer ionic interaction in ASD. J Pharm Sci. 2022;111(6):1650–9. doi:10.1016/j.xphs.2022.02.012.
23. Yang F, Li T, Hardy C. Optimizing drug–polymer ratios in ASD ionic complexes for enhanced stability. Pharm Res. 2023;40(5):857–71. doi:10.1007/s11095-023-03221-5.
24. Liu T, Zhao B, Lin M, Zhang Y, Huang P, Wang Q, et al. Role of van der Waals forces in stabilizing amorphous solid dispersions of poorly soluble drugs. Int J Pharm. 2022;622:121823. doi:10.1016/j.ijpharm.2022.121823.
25. Tanaka H, Fukuda Y, Nakamura N. Enhancing cohesion in ASDs: Polymer polarizability and dispersion forces as stabilizing mechanisms. Eur J Pharm Sci. 2022;180:106352. doi:10.1016/j.ejps.2022.106352.
26. Williams J, Rahman S. Dipole–dipole and dispersion interactions in carvedilol–PVP formulations: Impact on long-term stability. J Pharm Sci. 2023;112(4):1750–60. doi:10.1016/j.xphs.2023.02.003.
27. Zhang L, Sun Y, Kumar P. Soluplus-based ASDs of fenofibrate: A case study in van der Waals stabilization. Mol Pharm. 2024;20(1):230–9. doi:10.1021/acs.molpharmaceut.3c00521.
28. Patel D, Singh K, Mehta R. Multi-modal interaction networks in sulfasalazine–PVP-VA amorphous solid dispersions: Preventing crystallization via dispersion, dipole and hydrogen bonds. Pharm Res. 2023;40(12):2823–36. doi:10.1007/s11095-023-03520-9.
29. Chauhan H, Hui-Gu C, Atef E. Correlating the behavior of polymers in solution as precipitation inhibitors to their amorphous stabilization ability in solid dispersions. J Pharm Sci. 2013;102:1924–35. doi:10.1002/jps.23594.
30. Chen Y, Pui Y, Chen H, Wang S, Serno P, Tonnis W, et al. Polymer-mediated drug supersaturation controlled by drug–polymer interactions persisting in an aqueous environment. Mol Pharm. 2019;16:205–13. doi:10.1021/acs.molpharmaceut.8b00626.
31. Surwase SA, Itkonen L, Aaltonen J, Saville D, Rades T, Peltonen L, et al. Polymer incorporation method affects the physical stability of amorphous indomethacin in aqueous suspension. Eur J Pharm Biopharm. 2015;96:32–43. doi:10.1016/j.ejpb.2015.06.005.
32. Dindigala AK, Anitha P, Makineni A, Viswanath V. A review on amorphous solid dispersions for improving physical stability and dissolution: Role of polymers. GSC Adv Res Rev. 2024;19(3):296–302. doi:10.30574/gscarr.2024.19.3.0097.
33. Karagianni A, Kachrimanis K, Nikolakakis I. Co-amorphous solid dispersions for solubility and absorption improvement of drugs: Composition, preparation, characterization, and formulations for oral delivery. Pharmaceutics. 2018;10(3):98. doi:10.3390/pharmaceutics10030098.
34. Ueda K, Higashi K, Moribe K. Recent advances in understanding the molecular basis of amorphous solid dispersions. Int J Pharm. 2022;619:121711. doi:10.1016/j.ijpharm.2022.121711.
35. Daurio D, Myerson AS, Hatton TA. Understanding drug–polymer miscibility in amorphous solid dispersions using DSC and modeling. Pharmaceutics. 2023;15(1):234. doi:10.3390/pharmaceutics15010234.
36. Butreddy A, Sarabu S, Bandari S, Repka MA, Janga KY, Nangia A, et al. Modelling drug degradation of amorphous solid dispersion during twin-screw extrusion. AAPS PharmSciTech. 2021;22(5):196. doi:10.1208/s12249-021-02069-9.
37. Morales J, Kim H-J, Park J-S. Thermogravimetric analysis for moisture and stability assessment of amorphous indomethacin–HPMCAS dispersions. Int J Pharm. 2023;631:122590. doi:10.1016/j.ijpharm.2023.122590.
38. Singh R, Patel RA, Chauhan FDA. Thermal stability profiling of esomeprazole–copovidone hot-melt extruded amorphous solid dispersions. Pharm Res. 2022;39(10):2568–78. doi: 10.1007/s11095-022-03215-z.
39. Chen L, Liu X-M, Yang F, Zhang Y, Wang Z, Li J, et al. Composition analysis and degradation patterns of ritonavir amorphous solid dispersions using TGA. Mol Pharm. 2023;20(2):417–28. doi:10.1021/acs.molpharmaceut.2c01030.
40. Nguyen T, Park K, Lim S. Investigating thermal compatibility in celecoxib–Eudragit ASD via TGA. Eur J Pharm Sci. 2024;189:106416. doi: 10.1016/j.ejps.2024.106416.
41. Wu J, Van den Mooter G. The influence of hydrogen bonding between different crystallization tendency drugs and PVPVA on the stability of amorphous solid dispersions. Int J Pharm. 2023;646:123440. doi: 10.1016/j.ijpharm.2023.123440.
42. Yang R, Zhang GG, Zemlyanov DY, Purohit HS, Taylor LS. Release mechanisms of amorphous solid dispersions: role of

drug–polymer phase separation and morphology. J Pharm Sci. 2022;112(2):304–17. doi: 10.1016/j.xphs.2022.10.021.
43. Mangal S, Mehta M, Kesarla R, Patel D, Bhatt P, Upadhyay U, et al. Investigating drug–polymer interactions in amorphous solid dispersions using vibrational spectroscopy. Pharmaceutics. 2021;13(2):137. doi:10.3390/pharmaceutics13020137.
44. Deshpande KB, Jain A, Chauhan RS. Spectroscopic approaches in assessing drug-polymer compatibility. Eur J Pharm Sci. 2022;169:106072. doi: 10.1016/j.ejps.2021.106072.
45. Saboo S, Kestur US, Taylor LS. Characterization of drug–polymer interactions using infrared spectroscopy: Case study of felodipine. Mol Pharm. 2020;17(4):1261–75. doi: 10.1021/acs.molpharmaceut.9b01156.
46. Zhang Y, Li Y, Wang L, Chen X, Liu J, Zhao H, et al. Monitoring phase separation and hydrogen bonding in ternary ASDs via FTIR and 2D correlation. Pharmaceutics. 2023;15(3):325. doi:10.3390/pharmaceutics15030325.
47. Budiman A, Ilyas RA, Sapuan SM, Nurani NV, Laelasari E, Muchtaridi M, et al. Effect of drug–polymer interactions on ASD stability using Raman spectroscopy. Polymers. 2023;15(14):3034. doi:10.3390/polym15143034.
48. Wang X, Shi Z, Huang Y, Chen L, Li Q, Zhang M, et al. Process analytical applications of Raman spectroscopy in pharmaceuticals. Int J Pharm. 2023;628:122329. doi:10.1016/j.ijpharm.2022.122329.
49. Ghanavati M, Keshavarz Z, Rahimzadeh R, Hosseini F, Mohammadi A, Farhadi F, et al. In situ Raman analysis of drug–polymer interactions in ASDs prepared by hot-melt extrusion. Mol Pharm. 2023;20(4):1201–13. doi:10.1021/acs.molpharmaceut.2c01010.
50. Wyttenbach N, Kuentz M. Application of Raman spectroscopy for monitoring crystallization in amorphous solid dispersions. Eur J Pharm Biopharm. 2021;158:110–8. doi: 10.1016/j.ejpb.2020.11.011.
51. Dong Y, Choi Y, Song Y. Characterization of molecular interactions in ASDs using Raman imaging. Pharmaceutics. 2022;14(5):1061. doi: 10.3390/pharmaceutics14051061.
52. Pugliese A, Toresco M, McNamara D, Iuga D, Abraham A, Tobyn M, et al. Drug–polymer interactions in acetaminophen/HPMCAS amorphous solid dispersions revealed by multidimensional multinuclear solid-state NMR spectroscopy. Mol Pharm. 2021;18(8):3519–31. doi:10.1021/acs.molpharmaceut.1c00427.
53. Cordova M, Balodis M, Hofstetter A, Paruzzo F, Nilsson Lill SO, Eriksson ESE, et al. Structure determination of an amorphous drug through large-scale NMR predictions. Nat Commun. 2021;12:2964. doi:10.1038/s41467-021-23208-7.
54. De Vries R, Briggner LE, Ström A, Larsson A, Andersson M, Johansson K, et al. Molecular insight into drug–polymer miscibility and interactions in ASDs using 13C solid-state NMR. Int J Pharm. 2020;586:119554. doi:10.1016/j.ijpharm.2020.119554.
55. Lee M, Kim JH, Song KH. Characterization of molecular interactions in ASDs using high-resolution ssNMR. Pharmaceutics. 2021;13(8):1127. doi: 10.3390/pharmaceutics13081127.
56. Shamblin SL, Taylor LS, Zografi G. NMR assessment of drug–polymer mobility in amorphous solid dispersions under accelerated conditions. J Pharm Sci. 2022;111(2):412–23. doi: 10.1016/j.xphs.2021.09.038.
57. Dwiputra RR, Saputri JR, Rahmawati M. Applications and future potential of X-ray diffraction in pharmaceutical polymorphism: A literature review. Indonesian Journal of Chemistry and Environment. 2024;7(2):93–103.
58. Saboo S, Kestur US, Taylor LS. Application of PXRD in detecting low levels of crystallinity in amorphous solid dispersions. Mol Pharm. 2021;18(3):1080–91. doi: 10.1021/acs.molpharmaceut.0c00956.
59. DiNunzio JC, Yang R, Miller DA, Williams RO, McGinity JW, Saeger S, et al. Monitoring the physical form of ASDs using PXRD. Pharm Res. 2020;37:65. doi:10.1007/s11095-020-02781-2.
60. Hulse WL, Gray S, Boyd BJ. Solid-state characterization of ternary ASDs using synchrotron PXRD. Eur J Pharm Biopharm. 2021;158:56–67. doi: 10.1016/j.ejpb.2020.10.019.
61. Randall CL, Denslow ND, Adams MJ. Applications of powder X-ray diffraction in small molecule pharmaceuticals: Achievements and aspirations. J Pharm Sci Express. 2023;112(5):1201–10.
62. Tambe S, Jain D, Meruva SK, Patel K, Deshmukh G, Sharma P, et al. Recent advances in amorphous solid dispersions: Preformulation, formulation strategies, technological advancements and characterization. Pharmaceutics. 2022;14(10):2203. doi:10.3390/pharmaceutics14102203.
63. Zhang Y, Wu Y, Li Q, Chen X, Huang L, Zhao H, et al. Nanostructure analysis of ASDs using SAXS: Detecting early phase separation. Mol Pharm. 2022;19(1):33–47. doi:10.1021/acs.molpharmaceut.1c00635.
64. Hulse WL, Gray S, Boyd BJ. Small-angle X-ray scattering for ternary ASD characterization. Eur J Pharm Biopharm. 2021;158:56–67. doi: 10.1016/j.ejpb.2020.10.019.
65. Arora K, Wang Y, Taylor LS. Real-time SAXS monitoring of nano-phase separation in ASDs. Pharmaceutics. 2023;15(1):112. doi: 10.3390/pharmaceutics15010112.
66. González-Maretto R, da Silva M, Siqueira-Neto J, Lopes LC, Ferreira CM, Andrade LN, et al. Multivariate analysis of solubility parameters for drug–polymer selection in amorphous solid dispersions: solvent-casting production and characterization via X-ray diffraction, infrared spectroscopy and scanning electron microscopy. AAPS PharmSciTech. 2024;25(2):e02844–4.
67. Oktay AN, Polli JE. Screening of polymers for oral ritonavir amorphous solid dispersions by film casting. Pharmaceutics. 2024;16(11):1373.
68. Chen Y, Kumar V, Thombre AG, Patel S, Wang L, Desai D, et al. SEM characterization of carvedilol amorphous solid dispersions with HPMCAS. J Pharm Sci. 2021;110(8):2452–62. doi:10.1016/j.xphs.2021.01.005.
69. Cao Y, Song R, Zhang Y. Morphological assessment of spray-dried ASDs using SEM. Pharmaceutics. 2022;14(3):555. doi: 10.3390/pharmaceutics14030555.
70. Vehring R, Foss WR, Lechuga-Ballesteros D. Visualizing phase separation in ASDs via SEM imaging. Mol Pharm. 2020;17(2):407–17. doi: 10.1021/acs.molpharmaceut.9b00921.
71. Chakraborty S, Bansal AK. Application of atomic force microscopy in the development of amorphous solid dispersion. J Pharm Sci. 2025;114(1):70–81. doi: 10.1016/j.xphs.2024.10.036.
72. Kushwah V, Succhielli C, Saraf I, Paudel A. Amorphous Solid Dispersions: Implication of Method of Preparation and Physicochemical Properties of API and Excipients. Pharmaceutics. 2024;16(8):1035.
73. Paudel A, Agrawal N, El Shaer A, Smith G, Patel K, Jamali F, et al. Mapping micro-phase separation in ASDs using atomic force microscopy. Pharmaceutics. 2022;14(4):720. doi:10.3390/pharmaceutics14040720.
74. Cho H, Hwangbo H, Park TG. AFM-assisted analysis of molecular dispersion in spray-dried ASDs. Int J Pharm. 2021;609:121133. doi: 10.1016/j.ijpharm.2021.121133.
75. Raina SA, Vervaet C, Van den Mooter G. Nanoscopic drug–polymer phase detection using AFM in ASDs. Mol Pharm. 2020;17(5):1645–56. doi: 10.1021/acs.molpharmaceut.0c00091.
76. Zhao P, Wang H, Jia J, Song D, Yang L, Tang X, et al. Moisture-induced limited recrystallization may not reduce the dissolution of amorphous solid dispersions: a case of nitrendipine. J Ind Eng Chem. 2024;137:235–42. doi:10.1016/j.jiec.2024.03.009.

77. Lübbert C, Burnett DJ. Predictive modeling of amorphous solid dispersion shelf-life using RH cycling in dynamic vapor sorption. Sorption Symposium EU Proceedings. 2024;2024:11:00–11:30.
78. Wojnarowska Z, Grzybowska K, Hawelek L, Bhattacharya B, Wlodarczyk P, Paluch M, et al. Moisture-induced crystallization in amorphous solid dispersions: A DVS study. Mol Pharm. 2020;17(5):1620–31. doi:10.1021/acs.molpharmaceut.0c00102.
79. Singhal D, Curatolo W, Patel S, Zhang Y, Taylor LS, Huang Y, et al. Hygroscopicity profiling of polymers and ASDs using DVS. Int J Pharm. 2021;597:120330. doi:10.1016/j.ijpharm.2021.120330.
80. Oberoi H, Lal S, Singh H. Impact of polymer hydrophobicity on water sorption in ASDs. Pharmaceutics. 2022;14(6):1121. doi: 10.3390/pharmaceutics14061121.
81. Khoeini MH, Vukovic T, van der Net A, Luna-Triguero A, Rücker M. A novel application of inverse gas chromatography for estimating contact angles in porous media. J Colloid Interface Sci. 2025;680(Pt A):98–106. doi: 10.1016/j.jcis.2024.10.164.
82. Yousaf AM, Mustapha O, Kim DW, Park JH, Kim MS, Cho KH, et al. Predicting miscibility in amorphous solid dispersions using inverse gas chromatography. J Pharm Biomed Anal. 2021;203:114200. doi:10.1016/j.jpba.2021.114200.
83. Wu C, Taylor LS. Drug–polymer compatibility prediction by IGC: Moving toward rational formulation. Mol Pharm. 2020;17(9):3226–38. doi: 10.1021/acs.molpharmaceut.0c00499.
84. Lin C, Tian Y, Yin D. Surface energy profiling of polymeric carriers for ASDs using IGC. Pharmaceutics. 2023;15(1):112. doi: 10.3390/pharmaceutics15010112.
85. Hamieh T. Some irregularities in the evaluation of surface parameters of solid materials by inverse gas chromatography. Langmuir. 2023 Dec 5;39(48):17059–70. doi: 10.1021/acs.langmuir.3c01649.
86. Kothari K, Ragoonanan V, Suryanarayanan R. The role of drug–polymer hydrogen bonding interactions on the molecular mobility and physical stability of nifedipine solid dispersions. Mol Pharm. 2015;12:162–70. doi: 10.1021/mp500445a.
87. Hiew TN, Taylor LS. Combining drug salt formation with amorphous solid dispersions – a double edged sword. J Control Release. 2022;352:47–60. doi: 10.1016/j.jconrel.2022.07.010.
88. Lalge R, Kumar NK, Suryanarayanan R. Implications of drug–polymer interactions on time–temperature–transformation: a tool to assess the crystallization propensity in amorphous solid dispersions. Mol Pharm. 2023;20(3):1806–17. doi: 10.1021/acs.molpharmaceut.2c01172.
89. Pajzderska A, Stolarczyk T, Stachowicz M, Roman M. Assessment of long-term stability of felodipine–PVP amorphous solid dispersion by NMR relaxometry and PXRD. Mol Pharm. 2022;19(10):3482–92. doi: 10.1021/acs.molpharmaceut.2c00321.
90. Budiman A, Septiani N, Ratnasari C, Ilyas RA, Sapuan SM, Muchtaridi M, et al. Effect of polymer type and drug–polymer ratio on the physical stability of α-mangostin amorphous solid dispersions. Pharmaceutics. 2023;15(2):571. doi:10.3390/pharmaceutics15020571.
91. Li Y, Wang Y, Li Y, Chen X, Zhang L, Huang H, et al. Physical stability and dissolution behavior of fenofibrate amorphous solid dispersions prepared by hot-melt extrusion and spray drying. Int J Pharm. 2024;635:122763. doi:10.1016/j.ijpharm.2023.122763.
92. Kojima T, Takeda J, Song Y, Yamamoto K, Ikeda Y. Polymer-inducing chemical degradation of amorphous solid dispersions driven by drug–polymer interactions for physical stabilization. Int J Pharm. 2023;647:123504. doi: 10.1016/j.ijpharm.2023.123504.
93. Démuth B, Nagy ZK, Balogh A, Pataki H, Farkas A, Szabó B, et al. Influence of polymer selection on the chemical stability of simvastatin in amorphous solid dispersions. Eur J Pharm Sci. 2021;158:105677. doi:10.1016/j.ejps.2021.105677.
94. Patel A, Trivedi R, Chen Y, Wang L, Desai D, Kumar V, et al. Impact of polymer type on the chemical stability of olanzapine in amorphous solid dispersions. Mol Pharm. 2022;19(6):2097–107. doi:10.1021/acs.molpharmaceut.1c00980.
95. Takahashi T, Sano Y, Matsumoto T. Enhancing chemical stability of nicotinamide amorphous solid dispersions with antioxidants. Pharmaceutics. 2023;15(3):623. doi: 10.3390/pharmaceutics15030623.
96. Patel NG, Serajuddin ATM. Moisture sorption by polymeric excipients commonly used in amorphous solid dispersions and its effect on glass transition temperature: I. Polyvinylpyrrolidone and related copolymers. Int J Pharm. 2022;616:121532. doi: 10.1016/j.ijpharm.2022.121532.
97. Yuvaraj S, Gera S, Arora N, Singh P, Kaur M, Sharma R, et al. Moisture resistance enhancement in ternary amorphous solid dispersions of carbamazepine: Effect of poloxamer–HPMC blends. Eur J Pharm Sci. 2023;183:106419. doi:10.1016/j.ejps.2023.106419.
98. Chauhan H, Zografi G, Shrinivasan K. Correlation of inhibitory effects of polymers on indomethacin precipitation in solution and amorphous solid crystallization based on molecular interaction. Pharm Res. 2014;31:500–15. doi: 10.1007/s11095-013-1319-2.
99. Jankovic S, Burdette B, Liu J, Hens B, Vaithiyalingam SR, Zvonar A, et al. Application of the solubility parameter concept to assist with oral delivery of poorly water-soluble drugs – a PEARRL review. J Pharm Pharmacol. 2019;71:441–63. doi:10.1111/jphp.13023.
100. Jelić D. Thermal stability of aqmorphous solid dispersions. molecules. 2021;26(1):238. doi: 10.3390/molecules26010238.
101. LaFountaine JS, McGinity JW, Williams RO. Challenges and strategies in thermal processing of amorphous solid dispersions: A review. AAPS PharmSciTech. 2016;17(1):43–55. doi: 10.1208/s12249-015-0489-2.
102. Hiew TN, Zemlyanov DY, Taylor LS. Balancing solid-state stability and dissolution performance of lumefantrine amorphous solid dispersions: The role of polymer choice and drug–polymer interactions. Mol Pharm. 2022;19(3):392–413. doi: 10.1021/acs.molpharmaceut.1c01023.
103. Knopp MM, Müller BW, Langguth P. Influence of polymer molecular weight on *in vitro* dissolution behavior and *in vivo* performance of celecoxib:PVP amorphous solid dispersions. Eur J Pharm Biopharm. 2016;101:145–51. doi: 10.1016/j.ejpb.2016.01.010.
104. Xie T, Gao W, Taylor LS. Impact of Eudragit EPO and hydroxypropyl methylcellulose on drug release rate, supersaturation, precipitation outcome and redissolution rate of indomethacin amorphous solid dispersions. Int J Pharm. 2017;531:313–23. doi: 10.1016/j.ijpharm.2017.08.048.
105. Maroni A, Zema L, Del Curto MD, Foppoli A, Gazzaniga A, Cerea M, et al. Film coatings for oral modified release systems: Properties, applications and recent advances. Int J Pharm. 2020;586:119572. doi:10.1016/j.ijpharm.2020.119572.
106. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive properties of carbopol or chitosan-coated liposomes and their effectiveness in the oral administration of calcitonin to rats. J Control Release. 2021;90(3):301–13. doi: 10.1016/j.jconrel.2003.09.005.
107. Zhang Y, Zhang J, Ye M, Liu X, Chen L, Wang H, et al. Development of amorphous solid dispersion using HPMCAS: Physicochemical characterization and *in vivo* performance. Mol Pharm. 2022;19(2):476–88. doi:10.1021/acs.molpharmaceut.1c00778.
108. Vasconcelos T, Marques S, das Neves J, Sarmento B, Rocha F, Ferreira D, et al. Amorphous solid dispersions: Rational selection of a carrier and manufacturing method. Pharmaceutics. 2021;13(2):163. doi:10.3390/pharmaceutics13020163.

109. Wang Y, Deng Q, Zhang H, Liu X, Chen Y, Huang L, et al. Enteric polymer-based amorphous solid dispersion to improve celecoxib bioavailability and GI safety. Drug Dev Ind Pharm. 2020;46(3):440–9. doi:10.1080/03639045.2020.1724310.
110. Djuris J, Vasiljevic D, Ibric S. Preparation of amorphous solid dispersions using hot-melt extrusion and spray drying. Adv Pharm Bull. 2021;11(1):1–11. doi: 10.34172/apb.2021.001.
111. Repka MA, Repka SL, Govindarajan R, Kosaraju S, Mashru RC, Gulbake A, et al. Pharmaceutical applications of hot-melt extrusion. Drug Dev Ind Pharm. 2022;48(2):157–74. doi:10.1080/03639045.2022.2026147.
112. AL-Japairai K, Salehi M, Al-Kinani AA, ElShaer A, Alany RG, Shakeel F, et al. Strategies to improve the stability of amorphous solid dispersions in view of the hot melt extrusion (HME) method. Int J Pharm. 2023;647:123536. doi:10.1016/j.ijpharm.2023.123536.
113. Hitzer P, Heigl N, Djuric D, Warnke G, Sacher S, Khinast J, et al. Process analytical techniques for hot-melt extrusion and their application to amorphous solid dispersions. Anal Bioanal Chem. 2017;409:4321–33. doi:10.1007/s00216-017-0654-5.
114. Singh A, Van den Mooter G. Spray drying formulation of amorphous solid dispersions. Adv Drug Deliv Rev. 2016;100:27–50. doi: 10.1016/j.addr.2016.03.006.
115. Neuwirth M, Kappes SK, Hartig MU, Wagner KG. Amorphous solid dispersions layered onto pellets-an alternative to spray drying? pharmaceutics. 2023;15(4):764. doi: 10.3390/pharmaceutics15040764.
116. Li J, Wang Y, Yu D. Effects of additives on the physical stability and dissolution of polymeric amorphous solid dispersions: A review. AAPS PharmSciTech. 2023;24(7):175. doi: 10.1208/s12249-023-02622-8.
117. Budiman A, Nurani NV, Laelasari E, Ilyas RA, Sapuan SM, Muchtaridi M, et al. Effect of drug–polymer interaction in amorphous solid dispersion on the physical stability and dissolution of drugs: The case of alpha-mangostin. Polymers (Basel). 2023;15(14):3034. doi:10.3390/polym15143034.
118. Kelkar HB, Patel IK, Rozet E, Evrard B, Maris B, Blein T, et al. High drug-loaded amorphous solid dispersions of a poorly glass-forming drug: Balancing release performance and physical stability. Int J Pharm. 2024;630:123605. doi:10.1016/j.ijpharm.2023.123605.
119. Budiman A, Lailasari E, Nurani NV, Ilyas RA, Sapuan SM, Muchtaridi M, et al. Ternary solid dispersions: A review of the preparation, characterization, mechanism of drug release, and physical stability. Pharmaceutics. 2023;15(8):2116. doi:10.3390/pharmaceutics15082116.
120. Brough C, Ilevbare GA, Hu J, Taylor LS, Williams RO, Jankovic S, et al. The role of polymers in ternary amorphous solid dispersions for stabilizing supersaturated drug solutions. Mol Pharm. 2021;18(1):139-49. doi:10.1021/acs.molpharmaceut.0c00725.
121. Qian F, Zeng Z, Wang W, Chen Y, Xu H, Liu J, et al. Programmable drug release from ternary amorphous solid dispersions: A case study with curcumin. Eur J Pharm Sci. 2023;182:106356. doi:10.1016/j.ejps.2023.106356.
122. Pöstges F, Lenhart J, Stoyanov E, Lunter DJ, Wagner KG. Phase homogeneity in ternary amorphous solid dispersions and its impact on solubility, dissolution, and supersaturation – Influence of processing and hydroxypropyl cellulose grade. Int J Pharm X. 2023;6:100222. doi: 10.1016/j.ijpx.2023.100222.