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Designing Stable Amorphous Solid Dispersions.: Insights into Polymer Selection Strategies

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Abstract

Poor aqueous solubility remains a limiting step for many recently discovered active pharmaceutical ingredients (API), especially the drugs that are classified under the Biopharmaceutics Classification System (BCS) Class II and IV. These compounds exhibit poor dissolution in gastrointestinal fluids which leads to limited oral bioavailability. One of the strategies that has been studied to combat this challenge is Amorphous solid dispersion (ASD), which acts by improving the drug solubility through molecular dispersion in polymeric carriers. However, the efficacy of ASDs is significantly dependent on the ability of the recruited polymer to maintain the drug in an amorphous state and ensure physical and chemical stability for a long term. Therefore, there is a great interest in rational methods to guide this selection. In this review, the critical criteria involved in polymer screening, including drug-polymer interaction, miscibility along with glass transition temperature (Tg), and hygroscopicity, are discussed. Experimental and analytical techniques ranging from film casting and precipitation inhibition to Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XRPD), Fourier Transform infrared (FTIR), and Nuclear Magnetic Resonance (NMR). Gordon–Taylor (G-T) equation, and Flory-Huggins (F-H) theory, among other methods, are also discussed as part of theoretical approaches. Furthermore, the review examines advanced computational tools such as molecular dynamics simulations (MDs) and machine learning (ML) models, which provide new opportunities for predictive formulation design, in addition to some of their strengths and limitations.

Keywords: Amorphous solid dispersion, Polymer selection, Solubility enhancement, Physical stability, Miscibility prediction.

Introduction

Considering the fact that the majority of the marketed drugs ~(40%) and those in the research and development (R&D) pipeline ~(90%) fall under Classes II and IV of the Biopharmaceutics Classification System (BCS), the formulation of poorly water-soluble compounds is the biggest obstacle in pharmaceutical development [(1)]. Sluggish rates of dissolution and poor water solubility often result in these drugs having restricted oral bioavailability. Amorphous solid dispersion (ASD) has garnered significant attention as a promising formulation strategy to solve this problem [(2-4)]. To increase the drug's solubility, dissolution, and occasionally permeability, solid dispersions (SD) involve dispersing the active pharmaceutical ingredient (API) in a polymeric carrier [(5-7)]. The transformation of a drug into its amorphous state enhances its solubility because the energy that needed to disrupt and disintegrate the crystal lattice of the drug is eliminated, and polymers act to maintain supersaturation throughout the gastrointestinal fluid, preventing recrystallize-tion, improving wettability, and stabilizing the amorphous state [(8)].

Consequently, the stability of ASD outcome, its manufacturability, and in vivo performance depend to a high extent on choosing an appropriate polymer. The preparation methods and types of solid dispersion are extensively discussed and covered in many [(1, 9-11)]. Wide range of polymers have been employed in amorphous solid dispersions, such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), Hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®). However, choosing the optimum polymer that provides maximum formulation stability is extremely challenging and is no longer a trial-and-error process. In this research, the methods and techniques used to predict the best polymer are discussed, and the criteria for selection are also mentioned.

Key elements in selecting the polymer for ASD

Drugs can exist either in a crystalline or amorphous state. In the crystalline form, molecules are arranged in a well- defined lattice with long-

range order, which generally confers higher thermodynamic stability but lower apparent solubility and slower dissolution. In contrast, the amorphous state lacks long-range order, resulting in higher free energy, improved apparent solubility, and faster dissolution; however, it is also more prone to physical instability, such as recrystallization during storage or dissolution[12]. In ASD systems, the polymer not only serves as a carrier but also acts as a solubilizer by improving wettability and maintaining supersaturation, forming stabilizing interactions (e.g., hydrogen bonding, ionic interactions) with the API[13]. Several factors that directly affect the final product solubility and physical stability are taken into account to select the appropriate polymer as mentioned in Figure.1.

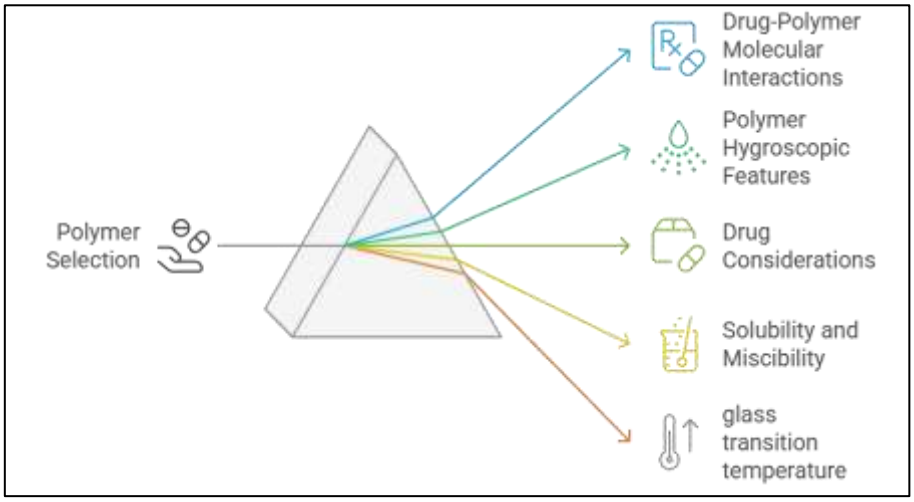

Figure 1. Factors influencing polymer selection.

Drug–polymer interaction

The molecular interactions between the components of ASDs (drug and polymer) strongly influence their stability. Ionic interactions is the most effective in stabilizing supersaturation for example, the weakly basic drug ciprofloxacin was found to interact with the acidic polymer Carbopol, forming an amorphous polymeric salt[14]. Hydrogen bonding (H-bonding) is another widely exploited mechanism of interaction, as observed between tolbutamide and PVPVA[15], exceeds dipole-dipole and van der Waals (non-specific) interactions in strength. The interaction between ibuprofen and polystyrene is reported to be a Van der Waals [16]. Strong interactions enhance miscibility, improve phase homogeneity, while concurrently reducing molecular mobility, all of which contribute to inhibiting drug crystallization in the solid state [17]. A common polymer selection strategy involves choosing a polymer that can specifically interact with the drug, particularly through hydrogen bonding, which helps to maintain a single phase. Additionally, ionic interactions, which are stronger than hydrogen bonds, may provide even greater resistance to crystallization [18].

Glass Transition Temperature (Tg)

The Glass transition temperature refer to the midpoint between "rubbery and glassy" phases of a material. it is practically the midpoint of the temperature range, bounded by the tangents to the two flat regions of the heat flow curve[19, 20]. It is an intrinsic property that reflects the thermal energy required to initiate molecular mobility within the amorphous matrix. A high Tg is associated with reduced molecular motion at the storage condition,and the probability of drug molecules reorganizing into a crystalline lattice, thereby improving physical stability. Conversely, a lower Tg corresponds to an increase in mobility, which facilitates drug diffusion and recrystallization. Since Tg is an intrinsic property of materials, its influence on the material's stability is limited to external conditions, such as temperature and humidity and the presence of plasticizers [21]. Water acts as a plasticizer that disrupts the drug-polymer hydrogen bond (H bonding) and decreases the Tg of the system, thus compromising the stability of the ASD [22]. While using a high Tg polymer or increasing its ratio in the formulation increases the Tg of the system and long-term stability[23]. Polymers widely vary with their Tgs, for example the Tg of Eudragit® L100 is 195°C while for Soluplus® ,it is around 79ºC [24, 25].

Hygroscopicity

A polymer's hygroscopicity is an important factor to consider because when the polymer absorbs water, as mentioned before, it can plasticize or fluidize the ASD, which lowers its Tg, accelerates drug mobility and affects its kinetic and thermodynamic properties that would end up to crystallization. To maintain stability in humid conditions, low-hygroscopicity polymers are required. The Tg and the uniformity of the dispersion can be maintained intact in humid environments due to the significantly reduced water uptake of polymers such as HPMCAS or certain

grades of Eudragit® . It is common practice to test the ASD's stability under accelerated humidity settings and an equilibrium moisture sorption test done (via dynamic vapor sorption analysis) before selecting polymers to guarantee that moisture would not significantly affect stability [26-28].

Component's solubility and miscibility

Solubility and Miscibility as terms are sometimes used interchangeably. However, they refer to distinct physicochemical concepts in the context of ASD. Solubility is thermodynamic equilibrium concentration of a drug molecularly dispersed in a polymer. On the other hand, miscibility refers to the apparent (or kinetic) capacity of several compounds to mix and form a uniform, single-phase system even if thermodynamic equilibrium is not fully attained [29]. Gibbs' phase rule indicates that in systems that are binary, all of the system's components are entirely miscible when the upper critical solution temperature (UCST) is exceeded, whereas below this temperature, the system can produce phases that are rich in polymer and other rich in drug (phase separation). In systems exhibiting a lower critical solution temperature (LCST), temperature increment leads to phase separation [30]. The notion of miscibility is more complex in SD due to the metastability of the amorphous phase. These small organic molecules can exhibit molecular mobility, particularly near or below the Tg, complicating miscibility assessment. Drug loading plays significant role in these concepts because at low drug loading, the API remains within the thermodynamic solubility limit of the polymer, resulting in a stable ASD. However, when the drug content exceeds this solubility threshold, the system shifts into a miscible but metastable state, where the drug is molecularly dispersed yet susceptible to phase separation and recrystallization. In such cases, the formulation reflects miscibility rather than true solubility, and its long-term stability depends on the polymer's capacity to kinetically hinder recrystallization. Figure. 2 illustrates the drug-polymer phase behavior relevant to ASD design. It highlights regions of crystalline solubility (region II), amorphous miscibility (region IV), glassy stability(region 1), and potential phase separation (region VI). The ideal ASD zone lies between the glass transition and miscibility limits, region I, where the drug remains molecularly dispersed and physically stable ([31]).

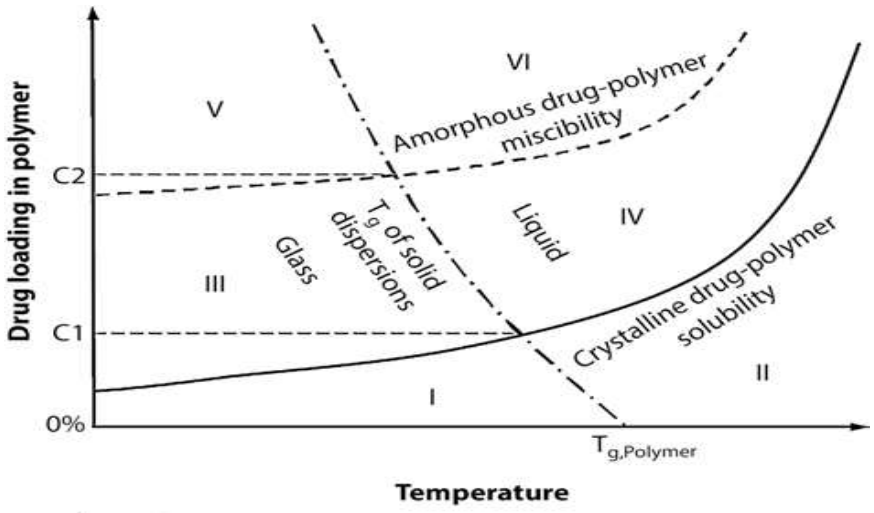

Figure 2. Solubility, miscibility, and crystallization diagram of a solid dispersion system. Reproduced with permission from [31]. Copyright © 2015 Scrivener Publishing LLC.

Considerations for Different API Classes

Poorly soluble drugs exhibit distinct physicochemical properties, making polymer selection highly API dependent. Drug's ionizability (acidic, basic, or non-ionizable as summarized in Figure.3), molecular weight/volume, hydrogen bonding functionality, and lipophilicity all can guide the type of polymer to be used.

Drug ionizability

Weakly Basic Drugs (cationic at low pH): Weak bases (common among BCS II drugs) often dissolve in the acidic stomach but tend to precipitate upon transit to the higher pH intestine [32]. Nevertheless, absorption of some of these compounds occurs predominantly in the small intestine, where surface area and permeability are the highest in addition to the longer residence time[33]. For such, polymers with acidic or enteric functional groups are preferred to harness ionic interactions and pH-dependent solubility. Enteric polymers (anionic carboxylate-bearing polymers) remain unionized and intact in the stomach (limiting drug release there), but dissolve at intestinal pH so release the drug [34,35]. HPMCAS, for example, a polymer that contains carboxylic acid substituents that can form strong ionic bonds with protonated

basic drug molecules [36]. These ionic (salt-like) interactions contribute to stabilizing the amorphous drug and help maintain supersaturation in the intestine. Hypromellose phthalate (HPMCP) and methacrylic acid copolymers (Eudragit® L100, S100) similarly contain carboxyl groups and are often successful with weak bases [37] [38]. The marketed itraconazole ASD "TOLSURA®" illustrates this strategy: it uses an enteric polymer (HPMCP) via spray drying so that the formulation remains insoluble in the stomach and only releases the drug at pH > 5.5 [39] [8]. This prevents premature dissolution/precipitation and yields significantly improved bioavailability over the earlier HPMC-based itraconazole product.

Weakly Acidic Drugs: Weak acids benefit from the opposite approach: polymers with basic or cationic functionality can interact ionically. For instance, Eudragit® E PO (poly (dimethylaminoethyl methacrylate)) is a cationic polymer that is protonated (positively charged) at low pH [8, 40]. It readily forms ionic complexes with acidic drugs (which are deprotonated at higher pH or even can donate a proton to the polymer's amine). Indomethacin, a carboxylic acid drug, was shown to interact strongly with Eudragit E PO in ASDs. These ionic drug-polymer complexes conferred exceptional kinetic stability; in fact, Sarode et al. stated that indomethacin-Eudragit E PO interaction strengthened upon storage conditions (high temperature/humidity), suggesting improved ionic bonding over time, highlighting how ionic ASDs can be extremely robust [8]. However, it is crucial to consider the dissolution behavior of Eudragit EPO, which is soluble in gastric fluid (pH < 5.5) [40]. For an acidic drug like indomethacin, this means the ASD will dissolve in the stomach and release the drug in a largely protonated (neutral) medium, potentially reducing the supersaturation benefit. Thus, formulation scientists might pair acidic drugs with partial enteric polymer or use a combination of polymers to balance immediate release and stabilization. In general, cationic polymers (e.g., polyamines) are less commonly used than anionic ones, but can be very effective for acidic APIs, provided the dissolution profile is managed.

Non-ionizable Drugs: Many drugs are hydrophobic molecules with few ionizable groups (e.g., steroids or highly lipophilic neutral molecules ex: griseofulvin). For these APIs, selection focuses on hydrogen bonding capacity and miscibility. Even non-ionizable drugs often have some hydrogen bond donor/acceptor groups in their structure that a polymer such as PVP, PVP-VA (copovidone), or HPMC can interact with. These H-bonds substitute for the drug–drug intermolecular attractions (which lead to crystallization) with drug–polymer attractions instead [41]. For example, Taylor and Zografi's study showed that indomethacin's carboxyl OH forms H-bonds with PVP's C=O, preventing indomethacin molecules from pairing up as carboxylic acid dimers in the solid state [42]. This "interaction replacement" is a general principle: a polymer should interact more strongly with the drug than the drug interacts with itself. In addition, amphiphilic polymers may be useful for very lipophilic molecules: e.g. Soluplus® has both hydrophilic and lipophilic segments, enhancing wetting and dispersion of insoluble APIs in aqueous media [43]. Amphiphilic polymers can act like molecular surfactants, improving dissolution of highly lipophilic drugs while still stabilizing them amorphously.

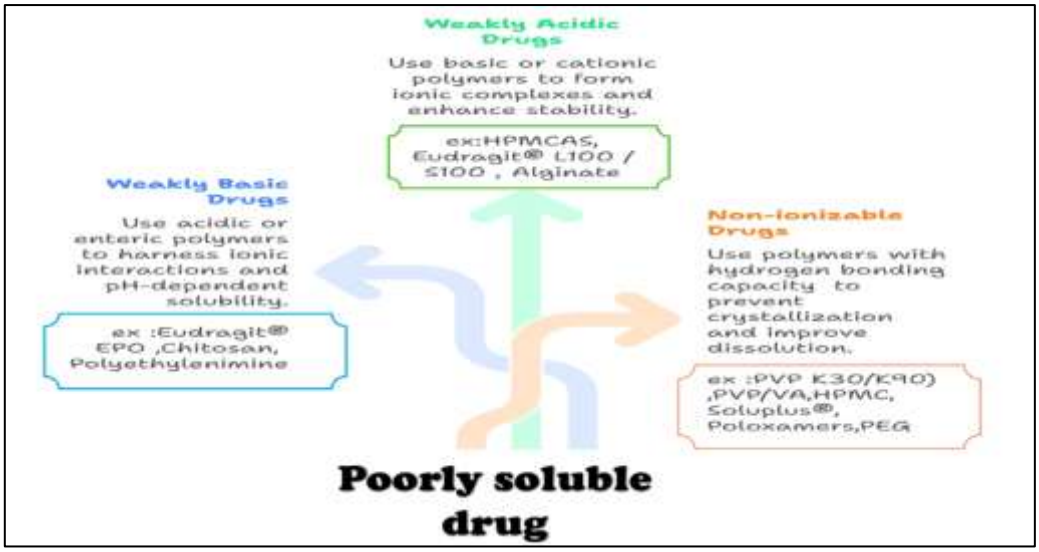

Figure 3. Drug ionizability may dictate polymer choice in ASD.

Molecular Size and Melting Point (MP)

High-molecular-weight drugs or those with very high melting point (an indicator of a strong crystal lattice) may require polymers that impart significant thermodynamic stabilization [44]. A rough heuristic is that drugs with a high melting entropy or rigid structure benefit from polymers with high Tg (to reduce molecular mobility) and multiple

interaction sites; the presence of functional groups that are either donors or acceptors for hydrogen bonds [45]. Sometimes polymer blends are used to combine different complementary advantages: e.g: combining a high-Tg polymer with one that has specific interactions [46]. However, care must be taken as ternary systems (drug plus two polymers) can be even more complex in phase behavior. Ultimately, understanding the API's acid/base nature, functional groups, and lipophilicity guides an initial polymer choice, which is then verified by experimental screening as described below.

Polymer Screening approaches

Several experimental and computational strategies have been developed to assess polymer behavior and compatibility concerning ASD, Figure. 4, which will be discussed briefly:

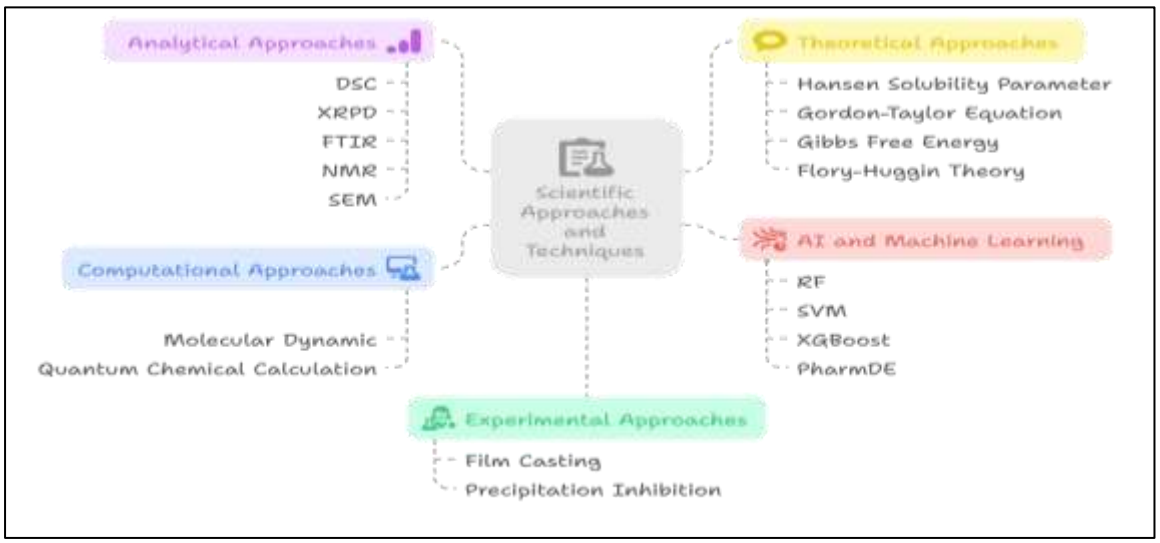

Figure 4. Summary of approaches for polymer selection.

Empirical Screening and High-Throughput (experimental)Approach

It is a practical, experiment-based method of evaluation accomplished through the evaluation of several polymers in small-scale formulations and preliminary modeling with no dependence on previous theories. High-throughput methods have been developed to conserve materials and time, which allow for examining many options **fastly** and efficiently, using very small amounts of materials. This includes thin-film casting, microplate precipitation assays, and solvent evaporation microscale arrays [47]. Film casting in particular has been advocated as a rapid screening tool: drug–polymer films are solution-cast and dried to simulate a spray-dried dispersion, then analyzed for homogeneity and stability [48]. For example, Honick et al. prepared itraconazole films with various HPMCAS polymers and drug loads; the film dissolution performance mirrored that of corresponding spray-dried dispersions, indicating that film casting can reliably predict formulation performance [49]. Similarly, Mosquera-Giraldo and colleagues. demonstrated that film casts of several development compounds may predict both in vitro and in vivo outcomes of spray-dried ASD formulations [50]. Other high-throughput screens include automated turbidity or precipitation inhibition assays, where a concentrated drug solution is diluted into polymer solutions to see which polymers best maintain supersaturation (delay precipitation) and provide the parachute effect, as shown in Figure. 5[51].

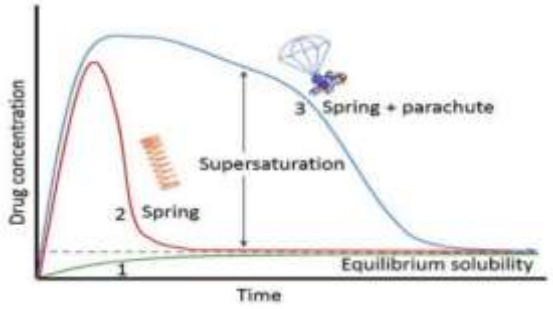

Figure 5. Spring and parachute test; Such tests quickly indicate if a polymer can sustain a drug's supersaturation ("parachute effect") after an initial high concentration ("spring") [51]. where 1: poorly soluble crystalline drug dissolution alone . 2: Amorphous drug dissolution without polymer that tend to spring then rapidly precipitate. 3: The dissolution behavior of ASD where polymer act as a parachute to inhibit the drug precipitation.

Analytical approach

Differential Scanning Calorimetry (DSC)

This is a thermal analysis method that evaluates the thermal behavior of a system, including melting point (MP), crystallinity, and Tg. The fading of drug-specific melting peaks in a DSC thermogram indicates an amorphous state, either molecularly dispersed forming single phase, or partially distributed in a multi-phase matrix within the polymer. In some cases, during DSC run the drug is solubilized by polymers or excipients. Furthermore, alterations in polymer's Tg may occur, signifying drug-polymer molecular interactions. In a solid dispersion, when drug and polymer are completely miscible, that result in single Tg positioned between the Tgs of the individual components, reflecting the formation of a homogeneous amorphous system [52, 53].

In addition to Tg analysis, melting point depression is used mostly to assess drug–polymer miscibility. Increasing polymer concentrations in miscible systems should cause a notable drop in the drug's MP and/or enthalpy. The observation of distinct Tgs related to both the drug and the polymer , or the persistence of melting peaks despite elevated polymer concentration, strongly indicates immiscibility that results in phase separation, wherein discrete crystalline or amorphous drug domains coexist inside the polymer matrix [42].

In a study, cellulose acetate butyrate (CAB) was used as a carrier; one study tracked the morphological changes of Dasatinib(DST) ASD. Using solvent evaporation technique to produce several ASD formulations ranging in DST:CAB 1:1 to 1:5. In physical mixtures (PMs) and ASDs, the pure drug exhibited a melting endotherm at 280 °C, see Figure. 6, proving its crystalline nature. The increment of polymer content results in gradual disappearance of the drug's melting peak, and amorphization of PM and ASD is indicated by the absence of the peaks. Upon stability testing at 40 °C/75% RH, new thermal events were observed in ASD-1, including peaks at 170 °C and 260 °C, suggesting recrystallization and possible polymorphic transitions, whereas ASD-5 exhibited only a minor broad peak at 240 °C, indicating superior stability [54].

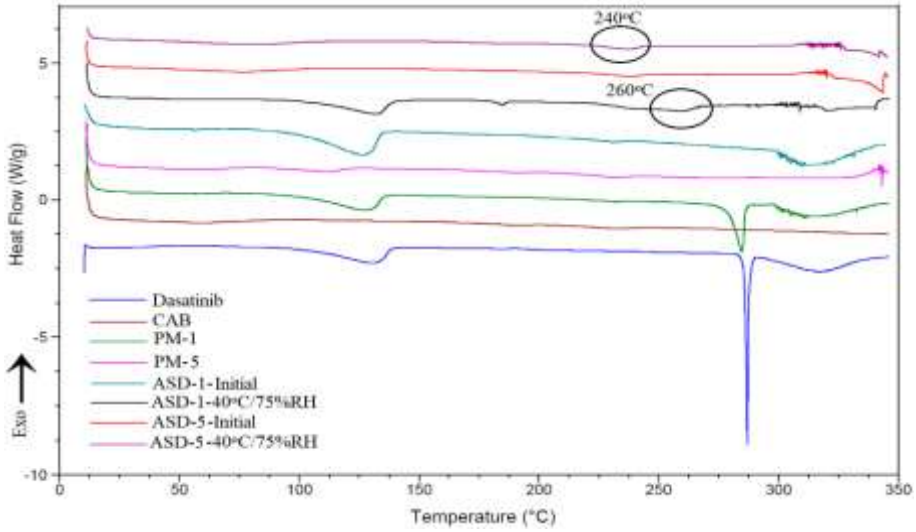

Figure 6. DSC thermogram of PM, and ASD, and evaluating the stability of the ASD [54].

Powder X-ray diffraction (XRPD):

A Fundamental technique used to detect the physical state of a drug in ASD. The presence of sharp Bragg's peaks indicates that the drug in a crystalline state, while the disappearance of these peaks and the formation of a halo and broad pattern indicate transformation to an amorphous form [55]. In a PXRD analysis evaluating ASDs of Apixaban (APX) with Soluplus® as carrier, distinct diffraction peaks at 12.78°, 13.84°, 16.98°, 18.38°, and 22.1° confirmed the crystallinity of pure APX, while a broad halo pattern of Soluplus® is indicative of its amorphous state. Reduced but still distinct APX peaks were displayed by the PM, which is a mix of the polymer and APX signals, as shown in Figure. 7, suggesting minimal interaction with no development of new crystalline phases. Conversely, the patterns of ASDs demonstrated a reduction of the intensity and sharpness of the peaks compared to pure APX and PM, indicating a significant reduction in APX crystallinity and partial amorphization within the dispersions [56].

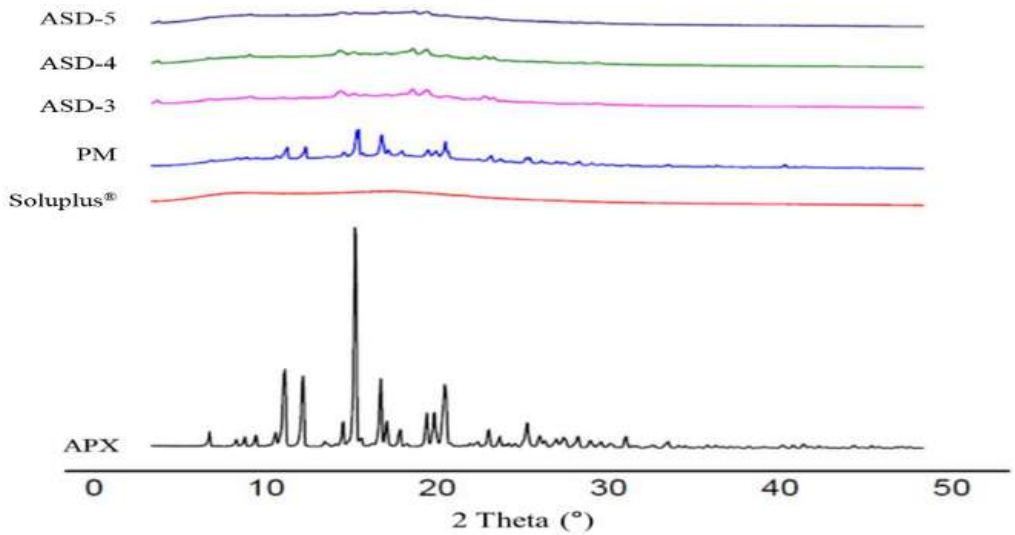

Figure 7. XRPD analysis of Apixaban as pure drug, physical mixture (PM), and in different amorphous solid dispersion formulas [56].

Fourier Transform Infrared (FTIR) and Raman Spectroscopy

FTIR is a vibrational spectroscopic technique that is sensitive to changes in dipole moments and detects drug-polymer molecular-level interactions that assess miscibility within ASD [57]. Hydrogen bonds that form between the drug and polymers that disperse at molecular level cause a shift in the vibrational frequencies. For instance, if carbonyl group of a drug forms a hydrogen bond with a polymer's hydroxyl group, the C=O stretching vibration in the IR spectrum mostly makes a shift to a lower frequency and broadens compared to that of the crystalline drug. Such spectral changes suggest interaction between them [58]. To confirm these interactions, comparative spectral analyses are performed between pure drug, pure polymer, physical mixtures, and the final ASD formulation. Subtle changes in peak location, intensity, or shape -especially in functional group regions- support the presence of molecular-level compatibility. In FT-IR analysis, the interactions between luteolin (LU) and PVP40 in both SDs and physical mixtures were assessed. Figure. 8, shows characteristic peaks at (3230 ,1660 and 1610) cm^{-1} of the crystalline LU. PVP40 also showed its own distinct absorption bands. In the physical mixture (PVP40-LU PM), all characteristic peaks of both components remained, predicting no interaction. In contrast, the spectrum of the solid dispersion (PVP40-LU SD) displayed shifts, reductions, or disappearance of luteolin's peaks, suggesting the formation of H- bonds between the drug and PVP40 in the SD formulation [59].

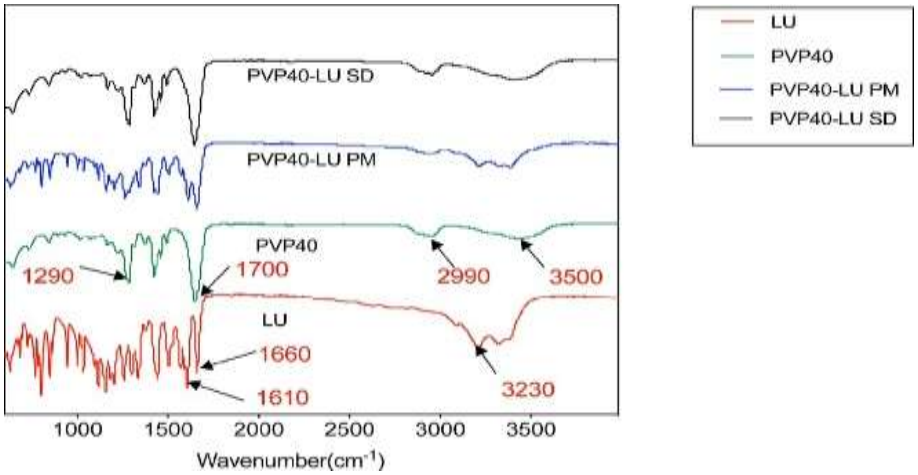

Figure 8. FTIR analysis of luteolin (LU), PVP40, their physical mixture, and solid dispersion [59].

Confocal Raman spectroscopy

It is a vibrational spectroscopic technique that detects changes in molecular polarizability and enabling spatial imaging of the formulation, providing direct visualization of drug distribution within the polymer matrix [58]. It gives an evaluation of the physical state of the drug (crystalline vs. amorphous), the formulation stability, and the

content uniformity. Due to its imaging capability, confocal Raman spectroscopy supports both quality control and process understanding during formulation development of ASD.

In a study using spectroscopic analyses to investigate the molecular interactions between carvedilol (CVL) solid dispersions, Raman spectroscopy confirms drug-polymer interaction. The characteristic crystalline CVL peak at 89.38 cm^{-1}, was retained across formulations. However, the loss or shift of aliphatic and C=C vibration peaks (e.g., 1294 cm^{-1} and 1647 cm^{-1}) and reduced intensity of OH and NH stretching bands (~3073 and 3401 cm^{-1}) indicated partial interaction and encapsulation of CVL within the polymer matrix. HPMC K100M showed greater structural rigidity, while HPMC E15LV resulted in weaker bonding and less rigid dispersion structures, as illustrated in Figure 9 [60].

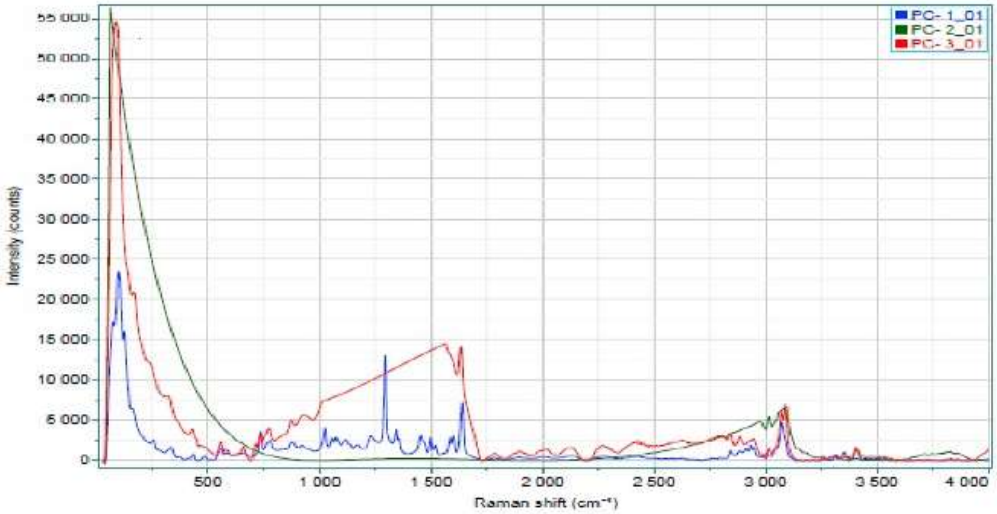

Figure 9. Raman spectroscopy of (a) pure CVL (Blue color),(b) CVL-HPMCK100SDs (Green color)and (C) CVL-HPMCE15LV(Red color) [60].

Nuclear magnetic resonance (NMR)

It is an effective analytical technique investigating the molecular structure, dynamics, and interactions within ASDs. It provides precise information about the chemical environment surrounding the drug and polymer components by detecting subtle variations in shielding caused by intermolecular interactions. High-resolution solid state-NMR (SS-NMR) used to probe drug–polymer miscibility, crystallinity vs. amorphous state, and molecular-level stability in ASDs. In the glassy state, amorphous materials have broad peaks about 3-10 ppm, which is about ten times greater than the crystalline peak linewidths, and these peaks become significantly narrower as the Tg is exceeded [61]. Sharp crystalline peaks disappear, and the presence of broad, isotropic signals in SS-NMR spectra means amorphization successfully occurred and to verify the physical state and molecular dispersion of drugs in ASD systems. It supplements other techniques like DSC and PXRD, where crystalline/amorphous boundaries may be less clearly defined [62, 63]. Pugliese et al. in their study utilized NMR techniques to identify molecular interactions in amorphous acetaminophen/(HPMC-AS) SDs. The results showed that hydrogen bond between the drug and the polymer occurs in the ASD [64].

Scanning Electron Microscopy (SEM)

This technique offers a high-resolution image of surface morphology that can indicate the dispersion level of the drug in the polymer, explain particle morphology (crystalline or irregular shapes), and detect signs of phase separation [65]. Figure. 10 shows SEM images that reveal (a) pure sildenafil citrate (SL) exhibits a high degree of crystallinity, evident from its large, needle-shaped particles. On the other hand, the solid dispersions of SL with different hydrophilic polymers ((b) SL-Poloxamer P188, (c) SL-PVPK30, and (d) SL-Copovidone) did not display any crystalline structures. Instead, these dispersions appeared as aggregates and irregular shapes, meaning a conversion from crystalline to an amorphous state occurs [66].

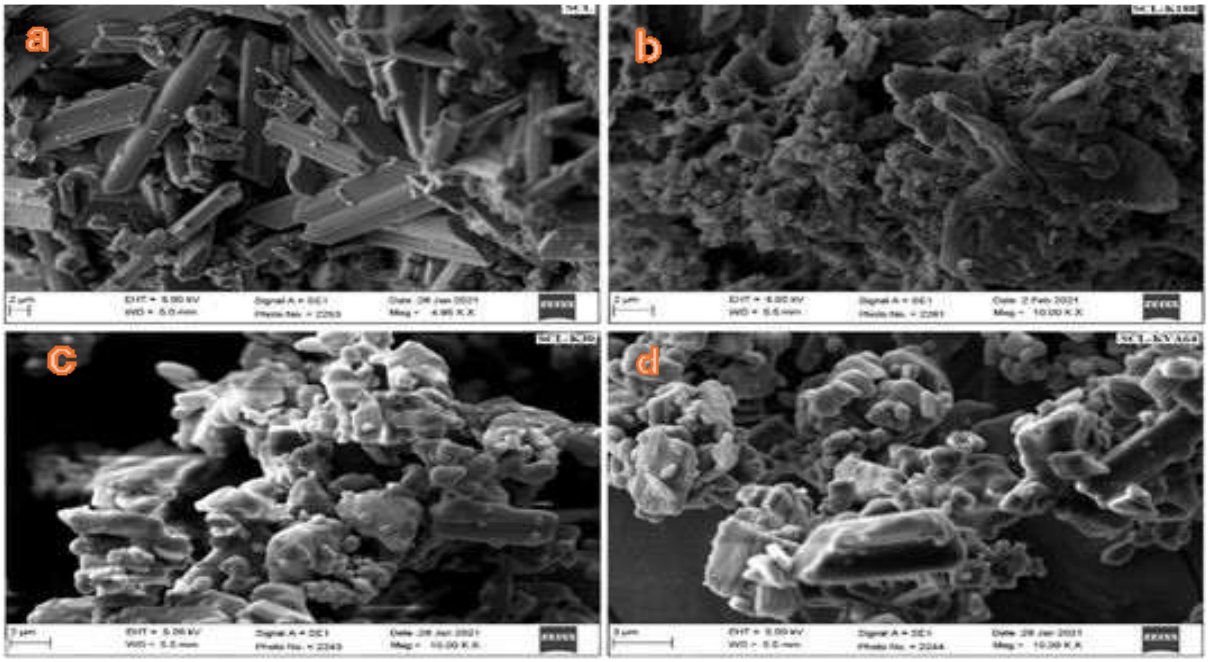

Figure 10. SEM images of (a) pure sildenafil , and (b,c,d) are solid dispersion formulas [66].

Theoretical approaches

Identifying drug-polymer combinations that form strong interactions using simple and accessible methods would be useful to guide the selection of optimal drug loading, processing conditions, and maximizing the stability of the amorphous solid dispersion. These are:

Hansen solubility parameters (HSP)

A widely used screening tool for polymer selection is Hansen solubility parameter (δ) . This theory based on the idea of " like dissolves like" so , the molecule with the same cohesive energy are more likely to be miscible. It started with Hildebrand solubility parameter (δ) which represent square root of the cohesive energy density (CED) , the energy needed to vaporize molecules per unit volume [67].

$$\delta=\frac{\sqrt{E\ vaporization}}{V}=\sqrt{CED} \qquad (1)$$

where *E* is evaporation energy *V* is the liquid molar volume. A small difference in (δ) of the drug and polymer suggests miscibility. Thus, by calculating δ for a given drug and for various polymers, one can predict which pairings are most compatible. The Hildebrand approach has weak performance for polar system so Hansen [68] refined this approach by separating δ into three parts; a polar (δ_p), a hydrogen bonding (δ_h), and a dispersive component (δ_d) as in equation 2.

$$\delta t=\sqrt{\delta_d^2+\delta_h^2+\delta_\rho^2} \qquad (2)$$

Greenhalgh et al. suggested that a good miscibility prediction occurs when Δδ value is below 7 MPa^0.5, whereas values exceeding 10 MPa^0.5 suggest poor miscibility [68]. In a study investigating the compatibility of bisacodyl with various pharmaceutical polymers using (HSP), the results showed that (Δδ) between the drug and HPMCAS, HPMC, and Soluplus® were less than 7 MPa^0.5. HPMC showed the lowest value, indicating favorable drug-polymer interactions and predicting a stable solid dispersion [69]. Another research analyzed progesterone miscibility with pharmaceutical excipients using this method and found that PVP and SiO_2 showed good miscibility, while larger differences (Δδ) with HPMC, HPMCAS, and MCC indicated poor compatibility. These predictions align with experimental observations during solid dispersion preparation [70]. This screening method is attractive for its simplicity and speed – one can rapidly rank a large polymer library by increasing Δδ to identify likely candidates. Tools like Hansen Solubility Parameters in Practice (HSPiP) software allow automated calculation of HSP from structure.

However, this tool predictive reliability has been questioned. Marsac et al. observed that felodipine and nifedipine exhibited complete miscibility with (PVP) at any ratio, contrary to the solubility parameters prediction [68, 71].

DeBoyace and Wildfong emphasized that this method is semi-empirical and the major limitation that affects its predictivity is that the hydrogen bonding component (δh) does not distinguish between hydrogen bond acceptor and donor [72]. Additionally, Gandhi et al. conducted a high-throughput experimental assessment and compared the results to predictions made using both group contribution and molecular dynamics-based HSP calculations. The study found no consistent correlation between HSP-based miscibility predictions (Δδ) and experimentally observed miscibility limits for several drugs, including flutamide, caffeine, and carbamazepine. Notably, flutamide exhibited high miscibility across all polymers tested despite relatively large Δδ values, while compounds like caffeine showed poor miscibility even when Δδ was within the traditionally accepted miscibility threshold (<7 MPa<1/2).These findings underscore a key limitation of the HSP approach as it does not adequately capture some molecular interactions (e.g., hydrogen bonding, π–π stacking), conformational flexibility, or molecular packing constraints, which are critical for accurate miscibility predictions [73]. Despite these limitations, solubility parameters remain a valuable tool for preliminary screening, helping to rule out incompatible drug-polymer systems and streamline formulation development [74].

Godron-Taylor equation

Several theoretical models have been proposed to estimate the glass transition temperature of drug and polymer mixtures based on their content. Gordon–Taylor (G-T) equation is commonly used among these models [75,76].

$$Tmixg=\frac{w1Tg1+K1w2Tg2+K2w3Tg3w1}{w1+K1w2+K2w3} \quad (3)$$

$$K1=\frac{\rho 1Tg1}{\rho 2Tg2} \quad (4)$$

$$K2=\frac{\rho 1Tg1}{\rho 3Tg3} \quad (5)$$

where $\rho 1$ and $\rho 2$ represent the densities of the respective components and w1 and w2 refer to their weight fraction. And constant K accounts for the thermal expansion behavior [76]. While these models offer a straightforward means to predict Tg, they are based on assumptions of ideal mixing behavior, such as:

Absence of specific drug–polymer interactions, Volume additivity at Tg. Consequently, discrepancies often arise between predicted and experimental Tg values. A negative value suggests poor miscibility or weak interaction, which predicts phase separation. In contrast, a positive deviation between the measured Tg relative to the predicted (Tg mix) assumes good drug–polymer interaction and miscibility.

A solid dispersions of felodipine (FEL) and PVP/VA at ratio of 3:7 w/w , DSC revealed a TG at 88 C, while G-T predict a Tg of 77.0 °C. This positive deviation by 11 °C between the calculated and predicted values indicated a specific intermolecular H bonding between FEL and PVP/VA, indicating enhanced drug–polymer interactions and improved stability of the amorphous form [77]. In a study on hesperidin (Hes) solid dispersions, Tg values of Hes: Soluplus® and Hes: HPMC systems were predicted using G–T model based on their individual Tgs ≈(107°C, 79 °C, and 134 °C, respectively). Experimental Tg values for the 1:5 drug:polymer systems were found to match closely with the G–T predictions, supporting complete miscibility. However, the 1:2 Hes: Soluplus® system showed a higher value of the experimental Tg compared with the G–T predicted value (Tg mix), suggesting some degree of non-ideality in mixing. This reflects specific drug–polymer interactions (e.g., hydrogen bonding), which enhance miscibility and stabilize the amorphous form [78].

Flory- Huggin theory

The Flory–Huggins (F–H) theory is a lattice model widely applied to thermodynamically assess drug–polymer miscibility in amorphous solid dispersions [79]. It provides a framework to calculate Gibbs free energy of mixing (ΔG_{mix}) and predict phase behavior using F-H parameter, χ, by the following equation :

$$\Delta Gmix = RT(\frac{\phi_1}{r_1} ln\phi_1 + \frac{\phi_2}{r_2} ln\phi_2 + x\phi_1\phi_2) \quad (6)$$

Where $\phi 1$ $\phi 2$ are volume fractions of drug and polymer, r_1 is the degree of polymerization of the drug molecule ($r_1 = 1$), while r_2 is the degree of polymerization of the polymer, and since polymers are made of many repeating units, $r_2 \gg 1$),), χ is Flory–Huggins interaction parameter, R is gas constant and T for temperature. A negative ΔG_{mix} indicates spontaneous mixing and thermodynamic miscibility, while a positive value suggests phase separation is likely. This theory enables constructing a phase diagrams, where drug–polymer mixtures are mapped across composition and temperature. These diagrams, as in Figure. 11, identify:

The maximal stable drug loading in each polymer during storage or processing temperature.

The binodal region is characterized as the metastable area: it may stay mixed until a fluctuation (like a crystal nucleus) triggers separation.

In the spinodal region, the system is unstable: it separates spontaneously without any external trigger [80].

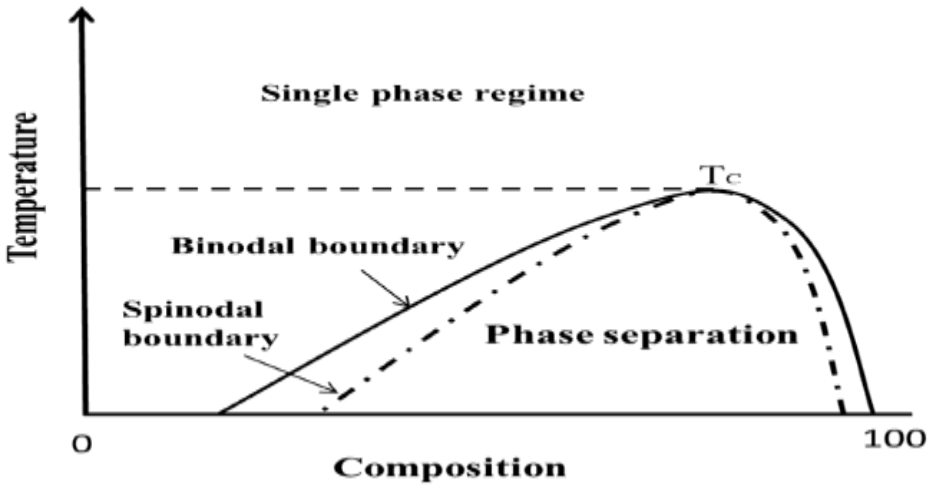

Figure 11. Phase diagram [80].

There are several methods used to experimentally or computationally estimate χ, which may be summarized by:

DSC-based melting point depression: χ is derived by fitting drug melting point shifts at various polymer ratios.

Solubility parameter correlation.

Molecular modeling: simulations (e.g., COSMO-RS, MD) to compute χ over temperature and composition.

***Calorimetry and NMR*:** provide additional insight into drug–polymer interaction energies.

A low or negative χ indicates favorable drug–polymer interactions (exothermic mixing), promoting miscibility, whereas a high positive χ signifies unfavorable interactions, promoting phase separation [81].

A study done by Tian et al., a thermodynamic phase diagram has been constructed to predict the maximal drug loading for felodipine (FEL) with Soluplus® and HPMCAS-HF grade using the F-H theory and calculating ΔGmix. The results showed that in FEL–Soluplus® system, ΔGmix remained negative across a wide range of concentrations and temperatures, indicating good miscibility and a broad one-phase region in the phase diagram, while for FEL–HPMCAS-HF system, ΔGmix became positive at higher drug loadings, suggesting a narrower miscibility window and potential phase separation risk during storage [82]. In practice, Flory–Huggins remains popular due to its conceptual simplicity and minimal data needs, often just a DSC-measured miscibility point or known δ values can get one started [80].

Molecular modeling and simulation

Molecular Dynamics Simulations for drug–Polymer Interactions

Molecular dynamics (MD) simulation has become a valuable technique to probe interactions and miscibility of the drug and polymer at an atomic level [83]. It enables the study of the physical movement of atoms and molecules over time by numerically solving Newton's equation of motion. MD thus offers a molecularly detailed "virtual experiment" of mixing: one can observe whether drug molecules remain dispersed among polymer chains or if they aggregate, what kinds of intermolecular interactions form, and how the mixture's structure and dynamics behave [84]. As shown in Figuer.12, the process involves sequential steps starting with system definition (drug, polymer, and solvents) and assigning interaction potential through appropriate force fields to describe energetic interactions among atoms and molecules. The system is constrained by specified thermodynamic conditions (density, pressure, and temperature), followed by initialization of atomic coordination and velocities. Once equilibrated, the simulation is executed to generate molecular trajectories that describe the time-dependent behavior of the system [85]. As a concrete case, Aulifa et al. used MD to study Ritonavir ASD with poloxamer. Their simulations mimicked the solvent evaporation and melt-quench processes of ASD preparation.

During the solvent-evaporation simulation, π–alkyl interactions formed between ritonavir's aromatic rings and the polymer's hydrophobic chains, whereas in the melt-quench simulation, hydrogen bonds formed between ritonavir and poloxamer. Such details indicated the molecular mechanism of miscibility: the polymer can engage the drug via different interaction modes depending on processing, helping to stabilize it. The study suggested that MD provides insight into the nature of drug polymer interaction, which is difficult to observe through experimental techniques [86].

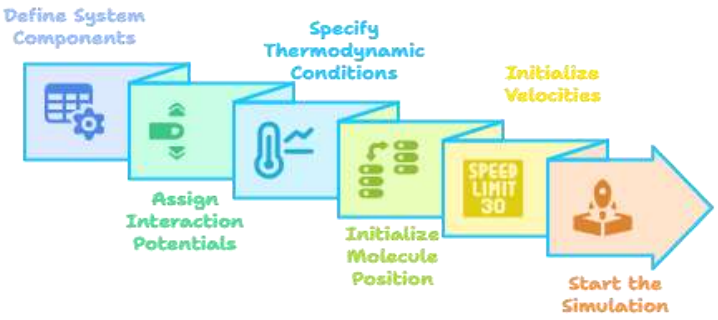

Figure 12.Workflow of MD simulation.

In a recent comprehensive MD study, Aulich et al. (2025) examined combinations of four drug molecules and three polymers, tracking their interactions and computing properties like excess enthalpy of mixing and Tg via simulation. They found that the trends from simulation aligned with experimental observations of solubility, for example, PVP was identified as the most potent hydrogen-bond acceptor forming the strongest interactions and yielding the most stable dispersions), and ranked the drugs by their hydrogen bond donating ability consistent with known miscibility (ibuprofen, a carboxylic acid, was predicted to interact strongly and be stabilized, whereas carbamazepine, with limited H-bonding, showed weaker interaction with the polymers) [87]. An MD simulation study explored the behavior of α-mangostin (AM) in ASD with poloxamer and pullulan. The results indicated that poloxamer, particularly at a ratio of 1:5 drug-to-polymer, yielded the most stable system through strong hydrogen bonding, compact molecular packing, and enhanced dispersion stability [88].

Table 1. The challenges of the MD simulation method.

Challenges	Impact
High computational cost	Limits system size and simulation time.
Limited time scale	Many misses phase separation or crystallization.
Force field limitations	Some interactions are poorly modeled.
Over–interpretation risk	Misleading miscibility if the run-time is too short
Requires expertise	Thermodynamic cycles, biasing methods, and validation essentials.

Quantum Chemical Calculations (Interaction Energies via DFT)

Unlike (MD), which uses force fields, quantum chemical calculations, particularly Density Functional Theory (DFT) models, directly calculate how electrons distributed around atoms and molecules allowing precise evaluation of drug – polymer interaction at molecular level, identifying non-covalent forces like H bonds, Ionic interactions, π–π stacking, and Dipole–dipole forces [89]. Because DFT is computationally expensive, small h representative models are used, such as Short polymer oligomers (dimers or trimers) or Key drug fragments (90) Figure. 13 explains some applications of this method [91-93].

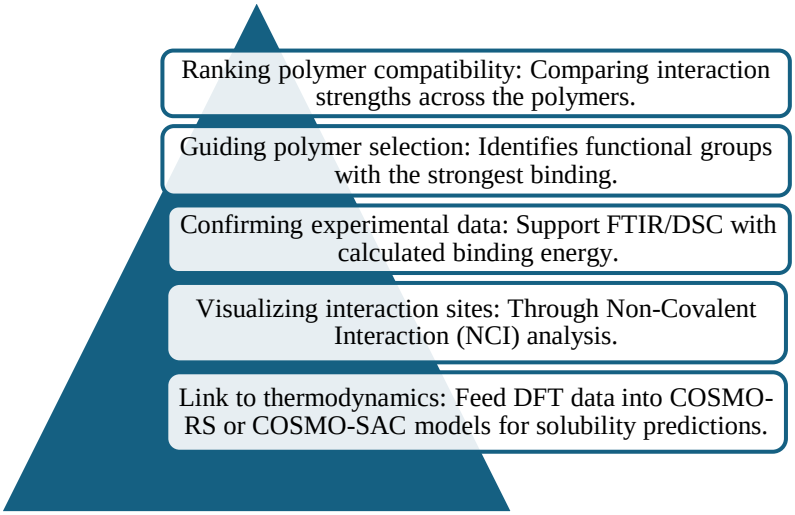

Figure 13. Application of DFT simulation.

In a study, Zhao and Wang employed (DFT) to investigate hydrogen bond between (PVP) and resveratrol (Res). They found that the hydrogen bond distance between PVP and Res was 2.76 Å, while for the Res-Res system it was 2.88 Å, where Å (angstroms) refers to a distance, where 1 Å = 10^{-10} m. These results indicate a strong PVP-Res interaction, suggesting that this polymer can effectively inhibit the crystallization of amorphous resveratrol [94].

Table 2. Challenges of Quantum chemical methods (DFT).

Challenges	Impact
Scale constraints	Limited to small systems; full drug–polymer models are too large.
Approximation errors	May ignore real–life factors like temperature and entropy.
Lack of bulk mixing data	Only provides interaction energy, not the full energy of mixing.

Artificial intelligence and machine learning

During a 1956 conference, Marvin Minsky and John McCarthy introduced the principle of artificial intelligence (AI) that involves the employment of computers to emulate human intelligence [95]. Since then, AI has attracted people's attention and succeeded in becoming the core engine and driver of a new wave of industrial change and continually creating new technologies. Now a days, It is used in many sectors, such as economics, sales, and health in addition to the pharmaceutical industry, such as solid dispersion. Figure. 14 shows the steps of the AI-driven formulation workflow.

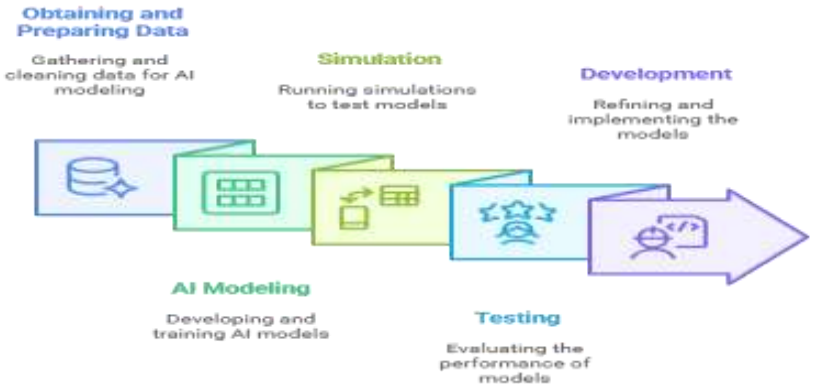

Figure 14. Typical AI workflow.

AI and its subfield, machine learning (ML), algorithms can provide data-driven predictions and construct a quantitative predictive model by utilizing a large amount of accumulated experimental data. Formulation optimization and development, cost reduction, and product consistency can be obtained by a well-designed AI system [96].

ML can map a high-dimensional non-linear correlation based on a big database and study the impact of a minor variance of inputs on the targeted outcomes [97, 98]. According to ASD, it predicts TG, miscibility level, dissolution profile, and physical stability at storage conditions; therefore, it helps in formulation optimization. There are diverse ML algorithms, including Random Forest (RF), Support

Vector Machine (SVM), XGBoost, LightGBM, K-Nearest Neighbors (KNN), and Artificial Neural Networks (ANN) that have been applied to different tasks during formulation development [99]. In a recent study using ECFP-LightGBM and ECFP-XGBoost models, ML techniques, notable accuracies for predicting amorphization (92.8%) and chemical stability (96.0%) [100]. Additionally, Run Han and colleagues utilize ML to estimate a 3-month and 6-month physical stability prediction of ASD [100]. PharmDE, an integrated ML-based platform developed by wang and colleagues. It is a powerful tool in polymer selection and screening for ASD because it can predict the drug–exipient compatibility and the potential chemical degradation at the preformulation evaluation step [101, 102].

Conclusion

Considering a polymer as an optimal one for ASDs needs a comprehensive understanding of the interaction between the drug and polymer, physicochemical properties, and stabilization mechanisms. By leveraging analytical, computational, and miniaturized screening tools, researchers can identify optimal polymers that can improve the stability and performance of the final compound. The integration of theoretical modeling, experimental validation, and in vivo testing can ensure the development of robust formulations with improved bioavailability and shelf-life stability.

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Conflicts of Interest

There is no conflict of interest regarding this investigation.

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Ethics Statements

There is no animal study in this review.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Sarah Salim Oleiwi and, Ghaidaa S. Hameed; data collection: Sarah Salim Oleiwi; draft manuscript preparation: Sarah Salim Oleiwi and, Ghaidaa S. Hameed. All authors reviewed the results and approved the final version of the manuscript.

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تصميم مشتتات صلبة غير متبلورة مستقرة: رؤى في استراتيجيات اختيار البوليمرات

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الخلاصة

لا تزال ضعف الذوبانية في الماء عائقًا رئيسيًا أمام العديد من المواد الفعالة الدوائية المكتشفة حديثًا، لا سيما تلك المصنفة ضمن الفئتين الثانية والرابعة من تصنيف الخصائص البيولوجية والكيميائية .(BCS) إذ تُظهر هذه المركبات ضعفًا في التوافر الحيوي الفموي بسبب انحلالها المحدود في سوائل الجهاز الهضمي. وقد ظهرت المشتتات الصلبة غير المتبلورة (ASDs) كإستراتيجية فعالة لمعالجة هذا التحدي من خلال تحسين ذوبانية الدواء عن طريق تشتيته جزيئيًا ضمن حاملات بوليمرية. ومع ذلك، فإن نجاح هذه المشتتات يعتمد إلى حد كبير على قدرة البوليمر المختار في الحفاظ على الدواء في حالته غير المتبلورة وضمان ثباته الفيزيائي والكيميائي على المدى الطويل. ومن هنا برز اهتمام كبير بتطوير طرق عقلانية لاختيار البوليمر المناسب. في هذا الاستعراض، يتم مناقشة المعايير الأساسية المعتمدة في اختيار البوليمرات، بما في ذلك تفاعلات الدواء مع البوليمر، وقابلية الامتزاج، ودرجة حرارة الانتقال الزجاجي، وامتصاص الرطوبة. كما يتم تناول التقنيات التجريبية والتحليلية مثل تقنيات تشكيل الأفلام، واختبار تثبيط التبلور، والقياسات الحرارية(DSC) ، والحيود بالأشعة السينية(XRPD) ، والأطياف تحت الحمراء(FTIR) ، والرنين المغناطيسي النووي (NMR).بالإضافة إلى ذلك، يستعرض البحث الأساليب النظرية مثل معلمات الذوبانية لهانسن، ومعادلة غوردون–تايلور، ونظرية فلوري–هاجينز. كما يتطرق إلى أدوات الحوسبة المتقدمة مثل محاكاة الديناميكيات الجزيئية ونماذج التعلم الآلي، والتي تتيح آفاقًا جديدة لتصميم التركيبات بشكل تنبؤي، إلى جانب بيان نقاط قوتها وبعض التحديات المرتبطة بها.

الكلمات المفتاحية : التشتت الصلب غير المتبلور،اختيار البوليمرات ، تعزيز الذوبانية، الاستقرار الفيزيائي ،التنبؤ بقابلية الامتزاج