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Title: Advances in Polymeric Carriers for Solid Dispersion Systems: Mechanistic Insights, Carrier Selection, and Manufacturing Hurdles

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Abstract

Polymeric solid dispersions represent a valuable formulation strategy for enhancing the solubility and bioavailability of poorly soluble drugs, with particular relevance to BCS Class II and IV compounds. This review examines the classification and functional mechanisms of various polymers, including hydrophilic, amphiphilic, pH-sensitive, and surface-active types. Their roles in facilitating amorphisation, maintaining supersaturation, and enabling controlled release are emphasised. Key formulation methods, such as solvent evaporation and hot-melt extrusion, are discussed alongside challenges including thermal stability, polymer miscibility, and scale-up. The review highlights the crucial requirement for preformulation studies, predictive modelling, and analytical tools. A comprehensive understanding of polymer-drug interactions and process parameters is vital to ensure stability, efficacy, and manufacturability. These insights can inform the development of robust, scalable solid dispersion systems.

Keywords: Solid dispersion, Hot Melt Extrusion, Solvent Evaporation, Polymeric carriers.

INTRODUCTION

Polymeric solid dispersions mark a substantial breakthrough in improving the solubility and bioavailability of drugs with poor water solubility, usually classified as BCS Class II and IV, by embedding these molecules within inert carrier matrices (1, 2). This method, initially developed in the early 1960s by Sekiguchi and Obi and later mathematically refined by Chiou and Riegelman, involves dispersing the active pharmaceutical ingredient (API) within a polymer in a solid state via melting, solvent, or combined methodologies(3). The use of polymeric carriers, particularly amorphous polymers, subsequently became the focus of this approach, offering an improved means of enhancing dissolution rates and achieving physical stability (4). In contrast to first-generation solid dispersions featuring crystalline carriers such as urea or sugars with modest dissolution enhancements, second and subsequent generations utilised amorphous polymer matrices like polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), hydroxy propyl methyl cellulose (HPMC), and their analogues(5, 6). These carriers not only efficiently inhibit drug crystallinity during production but also stabilise amorphous drug morphologies by increasing the glass transition temperature (Tg) and forming close molecular associations, thereby inhibiting recrystallisation during storage and dissolution (7). Polymeric solid dispersions enhance performance through several notable mechanisms: reducing particle size to the nanoscale, improving wettability, promoting amorphous morphologies, dispersing molecules uniformly within the carrier, and prolonging supersaturation via the "spring and parachute" effect. The ideal polymer should provide high thermodynamic stability, rapid dissolution, and prolonged supersaturation without compromising manufacturability (8, 9). Over the past three decades, the evolution of solid dispersions has progressed through various generations: from an initial emphasis on crystalline carriers to pure amorphous polymer systems, polymer-surfactant mixtures, and most recently, polymeric surfactants such as poloxamers and Soluplus with combined solubilisation and stabilising activity. These advancements reflect ongoing efforts to optimise formulation approaches, balancing thermal and mechanical processability, drug-polymer compatibility, and regulatory requirements, including residual solvents in spray-drying or preservation of polymer integrity during hot-melt extrusion(10-12).

This review aims to provide a comprehensive overview of polymeric solid dispersions, focusing on the underlying physicochemical principles, carrier selection criteria, processing aspects, and mechanistic drivers that contribute to successful formulation. By synthesising the collective findings of numerous individual studies alongside recent technological advancements, we intend to establish a broad framework for both novice researchers and experienced formulators to design and optimise efficient and producible solid dispersions.

Classification of Polymeric Carriers in Solid Dispersion Technology:

Solid dispersion technology has emerged as a remarkable technique for enhancing drug solubility and bioavailability in the case of poorly water-soluble drugs. The physical state is a critical factor in classifying the polymeric carriers used in solid dispersions, which significantly impacts both the functional efficacy and stability of the resulting formulation(13, 14). Polymeric carriers can exist in either an amorphous (disordered) or crystalline (ordered) physical state. This distinction is not merely structural; it has profound implications for the solubilisation capacity and modes of drug dispersion within the carrier (15).

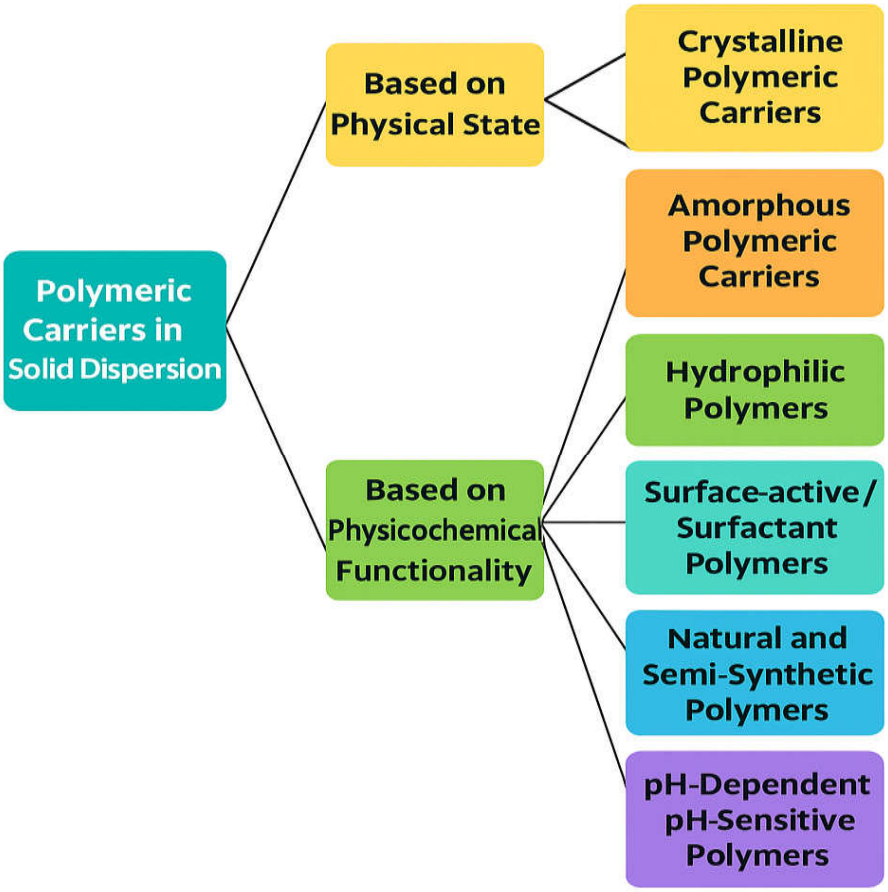

Figure 1: Different types of carriers used in solid dispersion

Classification by Physical State

The physical state of polymeric carriers—either crystalline or amorphous—plays a critical role in drug dispersion, dissolution performance, and long-term stability(16, 17).

1. Crystalline Polymeric Carriers

Crystalline polymers, which are highly molecularly organised, exhibit poor solubility for drugs. Consequently, the quantity of API that can be uniformly dispersed within these matrices is limited. When such a system achieves a single homogeneous phase, it is typically referred to as a solid solution. A useful subcategory within this classification is interstitial solid solutions, particularly

observed when there is a significant difference in molecular size between the drug and the polymeric carrier.

In interstitial solid solutions, it is proposed that the smaller drug molecules are dispersed within the interstitial cavities of the crystalline structure of the carrier material. Polyethylene glycol (PEG) is a notable example of a crystalline polymer utilised in these systems, extensively studied and employed due to its favourable melting point and partial solubilising capacity.

However, the inherent crystallinity of such polymers limits their ability to produce molecular-level dispersions, particularly at high drug loads. Furthermore, the ordered lattice structure is likely to restrict drug molecule mobility and, consequently, the desired enhancement in dissolution rates that solid dispersion systems are intended to provide.

2. Amorphous Polymeric Carriers

In contrast, amorphous polymeric carriers are characterised by the absence of a crystalline arrangement, which generally promotes increased miscibility and drug solubilisation. Amorphous carriers can form single-phase amorphous systems where the drug is dispersed molecularly or exists as a homogeneous amorphous precipitate(18).

Due to the lack of crystalline domains, amorphous polymers facilitate increased drug-polymer interactions, such as hydrogen bonding, and enhance the thermodynamic stability of the dispersion. This tends to result in higher dissolution rates and prolonged supersaturation profiles in gastrointestinal fluids, both of which are beneficial for enhancing oral bioavailability.

Commonly used amorphous carriers include polyvinylpyrrolidone (PVP), copovidone, and hydroxypropylmethylcellulose (HPMC). These carriers have also been reported to prevent drug recrystallisation during storage and upon administration, thereby stabilising the supersaturated state.

Classification by Physicochemical Functionality

Beyond physical state, polymeric carriers can also be classified based on their solubility characteristics, functional roles, and biocompatibility:

1. Hydrophilic Polymers

Hydrophilic polymers are amongst the most widely utilised carriers in solid dispersion technology, owing to their ability to significantly enhance the aqueous solubility and dissolution rates of poorly water-soluble drugs. Their hydrophilic nature enables rapid dissolution or swelling in aqueous

environments, thereby improving drug wettability and dispersibility (19). Upon incorporation into solid dispersions, these polymers act through various significant mechanisms. Notably, they enhance the wettability of drug particles, reducing the interfacial tension between the drug and the dissolution medium. They also disrupt the crystalline nature of drugs, frequently converting them into amorphous forms that exhibit enhanced solubility characteristics, despite being thermodynamically less stable (20). Hydrophilic polymers further enhance the surface area available for dissolution and form solid solutions in which the drug is molecularly distributed within the drug matrix. These interactions result in a substantial enhancement of the dissolution rate and, consequently, improved oral bioavailability.

Amongst the most prevalent hydrophilic polymers are polyvinylpyrrolidone (PVP), copovidone (a vinylpyrrolidone-vinyl acetate copolymer), polyethylene glycol (PEG), hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), and amphiphilic carriers such as Soluplus, which also exhibit hydrophilic properties. PVP and its copolymers are particularly noted for their high solubilising power and hydrogen bonding potential, rendering them effective in stabilising amorphous forms of drugs. However, PVP is hygroscopic and may require protection during packaging to ensure dispersion stability. Although partially crystalline, PEG is commonly employed in melt-processing techniques and exhibits solubilizing and plasticizing activities. HPMC and HPC have high glass transition temperatures and viscosities, which contribute to the inhibition of drug recrystallization and supersaturation in gastrointestinal fluids (21). Soluplus, a graft copolymer, features both hydrophilic and lipophilic domains, thereby enhancing drug-polymer miscibility and drug permeability (22).

The selection of a suitable hydrophilic polymer is determined by various factors, including the physicochemical properties of the drug, the desired release profile, and the processing methods to be employed (e.g., spray drying or hot-melt extrusion). Hydrophilic polymers are not only responsible for enhancing drug solubility but also for stabilising the amorphous structure of the drug during storage and post-administration. By forming hydrogen bonds or other interactions with drug molecules, hydrophilic polymers retard molecular mobility and prevent or hinder recrystallisation. Hydrophilic polymers are a crucial component of many successful solid dispersion products and remain the focus of extensive research and development in the pharmaceutical field (23).

2. Amphiphilic Polymers

Amphiphilic polymers represent a distinct and valuable group of excipients in solid dispersion technology, particularly for enhancing the solubility and bioavailability of poorly water-soluble drugs. These polymers are characterised by a molecular structure that incorporates both hydrophilic (water-attracting) and hydrophobic (lipid-attracting) components. This dual affinity enables them to interact strongly with both the hydrophobic drug and the aqueous dissolution medium, resulting in improved drug solubilisation, stabilisation, and delivery to the body in a more bioavailable state(24).

Amphiphilic polymers play multiple key roles in solid dispersions. Firstly, their hydrophobic blocks interact with the poorly soluble drug substance, often via van der Waals forces or hydrophobic bonding, thereby enhancing drug-polymer miscibility. Simultaneously, hydrophilic spacer units facilitate water uptake and dissolution of the drug-polymer matrix upon contact with gastrointestinal fluids. This bimodal capability leads to the formation of molecularly dispersed amorphous systems, which induce significantly increased drug dissolution rates. Secondly, amphiphilic polymers also exhibit surfactant-like properties, reducing surface tension and generating micellar structures or colloidal dispersions that trap the drug, thereby enhancing its apparent solubility.

A significant advantage of amphiphilic polymers is their ability to inhibit drug recrystallisation both during storage and the dissolution process. This property is crucial for maintaining the drug in a supersaturated state following administration, thereby increasing absorption (25). Furthermore, by forming stable complexes or micelles with the drug, these polymers limit the drug's interaction with the aqueous environment in its unbound form, reducing precipitation and promoting a sustained supersaturation profile, a phenomenon often referred to as the "parachute effect".

Various amphiphilic polymers have been synthesised or tailored for application in solid dispersion systems. Soluplus, a graft copolymer of polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol, is one of the most widely utilised amphiphilic carriers. Soluplus has been specifically designed for hot-melt extrusion and spray drying processes (26). It exhibits superior drug solubilising capacity, thermal stability, and high drug-polymer interaction potential. Another notable group is Poloxamers (e.g., Pluronic F68 and F127), which are triblock copolymers

consisting of alternating polyethylene oxide and polypropylene oxide blocks. Poloxamers not only enhance wetting and dissolution but can also form thermoreversible gels and micelles, useful for controlled and targeted drug delivery. Additionally, TPGS (d-alpha tocopheryl polyethylene glycol succinate) is a naturally occurring amphiphilic compound with surfactant activity (27), often used to enhance the oral bioavailability of lipophilic drugs by influencing efflux transporters and facilitating solubilisation (28).

3.pH-Dependent / pH-Sensitive Polymers

pH-sensitive (or pH-dependent) polymers are a specialised class of excipients in solid dispersion formulations for drug delivery, enabling site-specific release in the gastrointestinal (GI) tract. These polymers are specifically formulated to dissolve or swell when exposed to particular pH values, typically corresponding to various parts of the GI tract. The use of these polymers is particularly applicable to drugs that are susceptible to degradation in the acidic environment of the stomach, have a localised action in the intestine, or require delayed or targeted release to achieve maximum therapeutic effect and minimise side effects.(29, 30).

4. Natural and Semi-Synthetic Polymers

Natural and semi-synthetic polymers have emerged as valuable carriers in solid dispersion technology, particularly in response to the growing interest in biocompatible, biodegradable, and sustainable pharmaceutical excipients. These polymers, derived from natural sources or chemically modified to enhance functionality, are well-regarded for their non-toxicity, regulatory acceptability, and functional versatility in drug delivery systems. In solid dispersions, they fulfil roles analogous to those of synthetic polymers, including enhancing drug solubility, stabilising amorphous forms, and modulating drug release kinetics (28, 31).

Examples: Chitosan, Starch derivatives, Guar gum, Carboxymethylcellulose (CMC), Methylcellulose (MC)

5.Surface-active / Surfactant Polymers

Surface-active polymer (surfactant polymers) represent a crucial category of functional excipients employed in the formulation of solid dispersions for poorly water-soluble drugs. These polymers combine structural features of conventional polymers with the amphiphilic characteristics of surfactants, enabling interaction with hydrophobic drug molecules and aqueous dissolution media. Their ability to reduce interfacial tension, form micelles, and stabilise amorphous drug states

enhances drug solubility, dissolution rates, and oral bioavailability in pharmaceutical applications (23, 32, 33).

Surface-active polymers function through a number of synergistic mechanisms. The first of these is their ability to reduce the surface tension between hydrophobic drugs and the aqueous environment, thus improving drug wetting and enabling more rapid and coherent dispersion in gastrointestinal fluids. Several polymers in this category can self-assemble into micelles or colloidal aggregates when they reach their critical micelle concentration (CMC)(34). The micelles can encapsulate drug molecules in their hydrophobic interiors, effectively solubilising the drug in the aqueous phase. Surfactant polymers also enable the establishment of a supersaturated drug concentration following dissolution, preventing precipitation through steric hindrance and thermodynamic stabilisation. This property is particularly important in amorphous solid dispersions, where the risk of recrystallisation threatens the stability and bioavailability of the formulation.

A well-defined surface-active polymer is Poloxamer, a series of non-ionic triblock copolymers comprising poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO). Poloxamer 188 (Pluronic F68) and Poloxamer 407 (Pluronic F127) have widespread applications in solid dispersion systems due to their capacity to enhance drug solubility through micellisation and increase the physical stability of amorphous drug forms(35). The polymers have applications in hot-melt extrusion and other thermal processing techniques and are extremely effective when used in combination with hydrophilic carriers to improve the dispersion and dissolution characteristics of lipophilic drugs.

Another important surface-active polymer is D-α-tocopheryl polyethylene glycol succinate (TPGS), a water-soluble analogue of natural vitamin E. TPGS possesses surfactant and bioenhancer properties(36). In addition to enhancing the solubilisation of drugs via formation of micelles, TPGS inhibits efflux transporters such as P-glycoprotein from acting, thus further increasing drug absorption from intestinal membranes. TPGS is particularly beneficial in formulations of BCS Class II and IV drugs, both with low solubility and permeability.

Soluplus, a graft copolymer of polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol, is a surface-active polymer often employed in solid dispersion applications. It is an amphiphilic molecule found to be compatible with a broad range of hydrophobic drugs. It can be used in hot-

melt extrusion and spray drying applications, leading to stable amorphous solid dispersions that improve drug solubility and slow down the onset of recrystallisation.

Other polymer-like surfactant excipients include polyoxyl castor oils (e.g., Cremophor EL and RH 40) and polysorbates (e.g., Tween 20 and Tween 80). They are typically incorporated into major polymeric carriers to improve wetting ability and cause prompt dissolution of the drug. Although they are not polymers per se, their high molecular weight and amphipathic nature allow them to act similarly to solid dispersions.

The benefits of surface-active polymers in solid dispersions are widespread. They facilitate formulation by minimising the requirement for separate surfactants, improving solubility and permeability, and enabling stabilisation of supersaturated conditions. This is crucial for preserving high bioavailability. However, there are particular limitations and disadvantages. The thermosensitivity of some surfactant polymers restricts their application in heat-processing processes. Moreover, the efficiency of micelle formation depends on maintaining levels above the CMC, and excessive amounts can be hazardous in cases of gastrointestinal irritation or affect the behaviour of other formulation ingredients(28).

MECHANISM OF ACTION

pH-dependent polymers function by remaining insoluble under certain pH conditions and becoming soluble or swelling at others. For instance, some polymers are stable and insoluble at low gastric pH but dissolve at the higher pH levels (5.5–7.5) found in the small intestine or colon. When used in solid dispersions, these polymers help in two primary ways:

Protecting the drug from degradation or premature release in the stomach. Facilitating rapid drug release and absorption once the polymer dissolves in the targeted intestinal pH environment.

Additionally, these polymers can enhance drug solubility and dissolution by forming amorphous solid dispersions, especially when combined with hydrophobic drugs. The amorphous state, aided by pH-triggered polymer dissolution, can lead to a supersaturated state that enhances bioavailability.

Examples: Eudragit® L, S (enteric), Eudragit® E (gastric release), HPMC-AS (Hydroxypropylmethylcellulose acetate succinate)

Polymers play a central role in enhancing the solubility of poorly water-soluble drugs in solid dispersion systems, primarily by modifying the drug's physical state, improving its interaction with aqueous environments, and stabilising supersaturated drug solutions. Their functional versatility, physicochemical properties, and ability to form molecular interactions with drug molecules make them indispensable in the formulation of solid dispersions(37). Below is a detailed explanation of how polymers contribute to solubility enhancement:

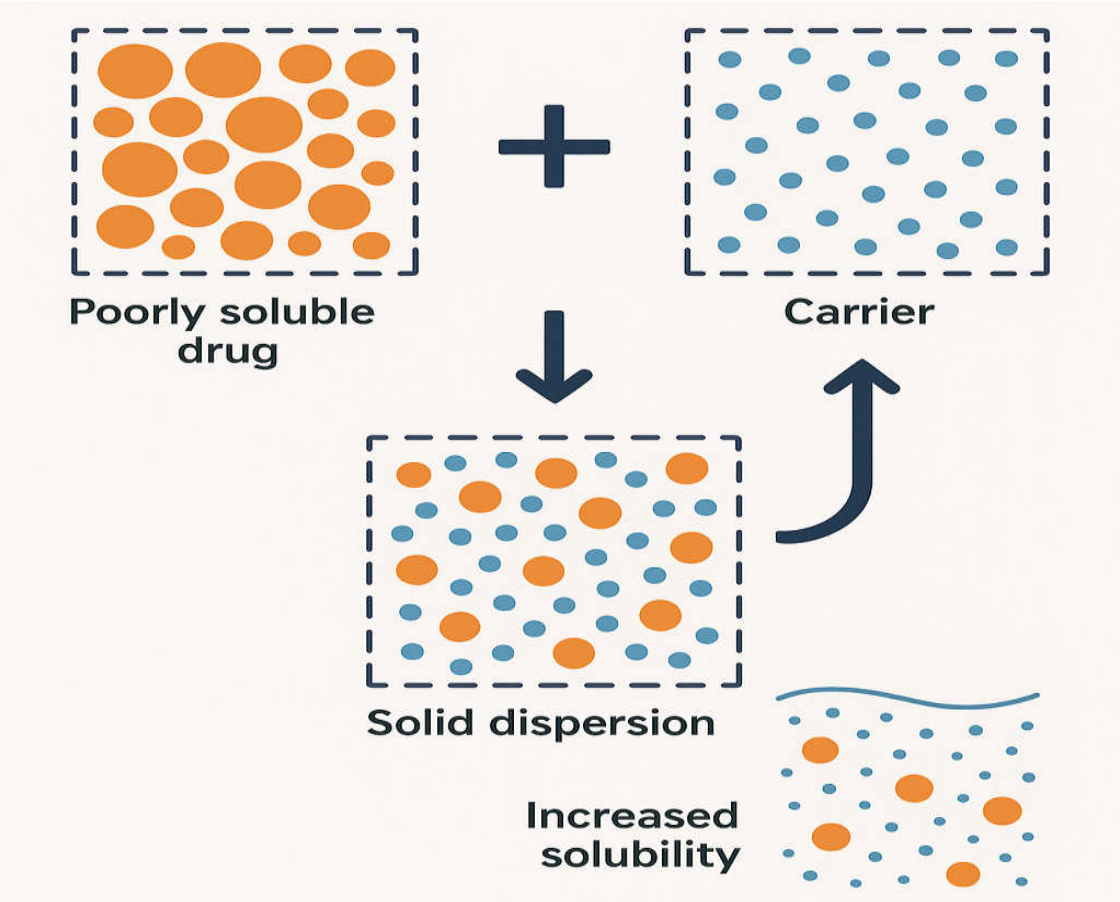

Figure 2: Mechanism of action

1. Conversion of Crystalline Drug to Amorphous Form

One of the most significant contributions of polymers in solid dispersion systems is their ability to convert the drug from its stable crystalline form to an amorphous state, which is thermodynamically less stable but kinetically more soluble. Crystalline drugs have tightly packed molecular arrangements, resulting in high lattice energy that resists dissolution. By contrast, the amorphous form lacks long-range molecular order, allowing for higher molecular mobility and greater apparent solubility.

Polymers facilitate this transition during the preparation of solid dispersions—particularly through hot-melt extrusion, spray drying, or solvent evaporation—by interrupting the crystal lattice and trapping the drug in a disordered state. To stabilise the amorphous drug, polymers such as polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), and copovidone form hydrogen bonds or other molecular interactions with the drug. These interactions inhibit molecular rearrangement, thus preventing recrystallisation during storage and after administration(38).

2. Formation of Molecular Dispersions (Solid Solutions)

Polymers in solid dispersions can serve as matrices within which the drug is dispersed at the molecular level, forming what is known as a solid solution. In this form, the drug molecules are uniformly distributed within the polymer chains without forming any distinct phase or particles. This configuration maximises the drug's surface area exposed to the dissolution medium and significantly enhances dissolution kinetics.

The formation of a true solid solution depends on the thermodynamic compatibility and miscibility of the drug with the polymer. Miscibility is typically evaluated using solubility parameters or techniques such as differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). Polymers like Soluplus® and Eudragit® E are particularly effective in forming stable solid solutions with hydrophobic drugs, thereby improving their solubility and uniformity of release(38).

3. Enhanced Wettability and Dispersibility

Poor water solubility in many drugs is often compounded by poor wettability, meaning that water cannot effectively spread across the drug's surface. Polymers used in solid dispersions—especially hydrophilic and amphiphilic types—can substantially enhance the wetting behaviour of drug

particles by acting as interfacial agents between the hydrophobic drug and the aqueous medium(39, 40).

This improved wettability facilitates faster hydration and uniform dispersion of the drug in gastrointestinal fluids. For example, polymers like PEG, PVP, and HPMC rapidly absorb water, swell, and reduce the interfacial tension, which promotes the dispersion of drug particles and prevents their aggregation. Enhanced wetting translates into faster dissolution rates, which is critical for ensuring timely absorption in the gastrointestinal tract(41).

4. Maintenance of Supersaturation (Parachute Effect)

When amorphous solid dispersions dissolve in aqueous media, they often generate supersaturated drug solutions, where the concentration of the drug exceeds its equilibrium solubility. While this supersaturated state favours improved bioavailability by increasing the concentration gradient across the intestinal membrane, it is inherently unstable and prone to precipitation or recrystallisation(41).

Polymers function as supersaturation stabilisers by inhibiting nucleation and crystal growth. This process, often termed the “parachute effect”, ensures that the drug remains in a metastable supersaturated state long enough to be absorbed. Polymers like HPMC-AS, PVP, and Eudragit® L/S stabilise the solution via hydrogen bonding, viscosity enhancement, and steric hindrance, all of which prevent the self-association of drug molecules that precedes precipitation(38).

5. Micelle Formation and Drug Encapsulation

Amphiphilic or surface-active polymers, such as Poloxamers (Pluronic®), TPGS, and Soluplus®, have the unique ability to self-assemble into micelles in aqueous environments. These micelles consist of a hydrophobic core and a hydrophilic shell, allowing them to encapsulate lipophilic drugs within the core while remaining soluble in water(39).

The formation of micelles enhances the apparent solubility of the drug and maintains it in a solubilised state until it is absorbed. This behaviour is particularly valuable for highly hydrophobic drugs with minimal intrinsic solubility. Additionally, micelle-forming polymers can protect the drug from chemical degradation and promote intestinal permeability, further improving oral bioavailability(41).

6. Drug–Polymer Interactions

Polymers interact with drugs through various non-covalent interactions, including hydrogen bonding, van der Waals forces, ionic interactions, and hydrophobic associations. These interactions not only enhance the physical stability of the solid dispersion but also influence the dissolution and solubility behaviour of the drug.

For instance, strong hydrogen bonding between a drug and PVP or HPMC can lead to enhanced miscibility, reduced drug mobility, and better maintenance of the amorphous form. Such interactions are often confirmed using spectroscopic methods such as FTIR and nuclear magnetic resonance (NMR). The strength and number of these interactions determine the extent of solubility enhancement and the overall stability of the formulation(39).

7. Controlled or Site-Specific Drug Release

In addition to enhancing solubility, polymers can also be tailored to provide controlled, sustained, or targeted release of the drug. pH-sensitive polymers like Eudragit® L and S or HPMC-AS dissolve only at specific pH values, enabling drug release in the small intestine or colon while protecting the drug in the acidic stomach environment(41).Similarly, gel-forming or swellable polymers such as HPMC, HPC, and certain natural polymers (e.g., guar gum, alginate) can modulate drug release by forming a viscous gel matrix upon hydration, which slows down drug diffusion. This functionality is particularly beneficial for drugs with narrow absorption windows or those requiring prolonged systemic exposure(39).

Table 1: Overview of Polymer Types and Their Functional Mechanisms

Polymer Class	Examples	Mechanisms & Role
Hydrophilic	PEG, PVP, HPMC, HPMC-AS, HPC	Amorphous formation, supersaturation maintenance, wetting
Surfactant	Poloxamer (Pluronic), TPGS	Micelle formation, precipitation inhibition
pH-responsive/Coating	Eudragit series	pH-triggered dissolution; controlled release
Insoluble/Controlled-release	Ethylcellulose, polymethacrylates	Diffusion-based release
Hydrophilic	PEG, PVP, HPMC, HPMC-AS, HPC	Amorphous formation, supersaturation maintenance, wetting
Surfactant	Poloxamer (Pluronic), TPGS	Micelle formation, precipitation inhibition
pH-responsive/Coating	Eudragit series	pH-triggered dissolution; controlled release
Insoluble/Controlled-release	Ethylcellulose, polymethacrylates	Diffusion-based release

Manufacturing Issues of Polymers in Solid Dispersion Technology

While solid dispersion technology offers a powerful approach for enhancing the solubility and bioavailability of poorly water-soluble drugs, the successful development of such systems is frequently challenged by various manufacturing issues related to the selection and use of polymers. These challenges stem from the complex physicochemical nature of polymers, their interaction with drugs, and their behaviour during different processing techniques such as hot-melt extrusion, spray drying, solvent evaporation, and freeze drying(3). Ensuring product stability, scalability, and reproducibility requires careful consideration of several critical factors during formulation and processing(42, 43).

One of the foremost challenges is thermal instability. Many polymers used in solid dispersions, particularly hydrophilic and pH-sensitive types, may possess relatively low glass transition temperatures (Tg) or may degrade upon exposure to high temperatures(44). In hot-melt extrusion, which involves elevated temperatures and shear forces, this limitation becomes particularly significant(45). Polymers such as polyvinylpyrrolidone (PVP) and polyethene glycol (PEG) may

undergo degradation or oxidation during processing, resulting in changes to the drug content, polymer functionality, and ultimately, the performance of the final dosage form. Therefore, the selection of a thermally stable polymer or the use of plasticisers and processing aids is often necessary to minimise thermal degradation(46).

Another critical issue is hygroscopicity, particularly in the case of polymers such as PVP and copovidone. These polymers readily absorb moisture from the environment, which can lead to drug recrystallisation, physical instability, and compromised dissolution performance. Hygroscopic polymers can also result in processing complications such as clumping, poor flowability, and difficulty in handling during downstream manufacturing steps like granulation, compression, or encapsulation. Proper packaging, moisture-protective excipients, and environmental control during production are essential to mitigate these risks(42).

Polymer–drug miscibility is another major concern in the manufacturing of solid dispersions. Lack of sufficient miscibility between the drug and the polymer can result in phase separation, heterogeneous dispersion, or crystallisation of the drug either during processing or storage. This not only reduces the solubility benefits of the formulation but may also lead to batch-to-batch variability. Predictive tools such as solubility parameter calculations, Flory–Huggins interaction parameters, and analytical techniques like differential scanning calorimetry (DSC) and X-ray diffraction (XRD) are often employed during formulation development to ensure adequate miscibility and compatibility.

The selection of appropriate solvents in solvent-based methods such as spray drying and solvent evaporation, also poses formulation challenges. Polymers differ in their solubility profiles, and achieving a common solvent system that can dissolve both the drug and the polymer efficiently without causing phase separation during drying is often difficult. Furthermore, residual solvent levels must comply with regulatory guidelines, and improper solvent removal can result in toxicity, chemical instability, or poor product performance(46).

Process scalability and reproducibility are other significant hurdles, especially during the transfer of formulations from laboratory to commercial scale. The viscosity and flow characteristics of polymer–drug mixtures can vary significantly with scale and processing conditions. High-viscosity polymers may hinder the spray drying process or cause pressure build-up in extruders, leading to inconsistent product quality. Uniform distribution of the drug within the polymer matrix at larger volumes requires optimised mixing, feeding, and temperature control systems.

Maintaining these parameters across multiple batches is vital to ensure product consistency and regulatory compliance. Lastly, stability of the final dosage form remains a persistent concern. Even after successful processing, many polymers may not adequately inhibit recrystallisation during storage, especially under stressed conditions such as high humidity and temperature. The amorphous state of the drug–polymer matrix is inherently metastable, and physical ageing of the polymer may reduce its capacity to maintain drug supersaturation over time. Therefore, extensive stability testing, optimised packaging, and, if necessary, incorporation of stabilisers are required to maintain the long-term integrity of the product. This section discusses the polymer-dependent challenges/issues of manufacturing technologies, i.e, solvent evaporation and HME.

Manufacturing Issues of Polymers in Solid Dispersion Technology: Polymer-Dependent Challenges in Solvent Evaporation and Hot-Melt Extrusion

The manufacture of solid dispersions using polymeric carriers presents a versatile approach to enhance the solubility and bioavailability of poorly water-soluble drugs. Among the various preparation methods, solvent evaporation and hot-melt extrusion (HME) are the most widely applied techniques, both in laboratory development and industrial-scale production. However, the successful implementation of these technologies depends not only on the properties of the active pharmaceutical ingredient (API) but also heavily on the characteristics of the selected polymers. Each method presents specific polymer-dependent challenges that can impact processing efficiency, product quality, and formulation stability(46). A thorough understanding of these challenges is essential to optimise the design, scale-up, and regulatory compliance of solid dispersion-based formulations.

Solvent evaporation involves the dissolution of both the drug and polymer in a mutual solvent or solvent system, followed by controlled removal of the solvent to obtain a solid dispersion. One of the primary challenges associated with this method is the solubility compatibility between the drug and the polymer in the selected solvent(47). Hydrophobic drugs often require non-polar or semi-polar solvents, whereas hydrophilic polymers such as polyvinylpyrrolidone (PVP) or hydroxypropyl methyl cellulose (HPMC) may not dissolve efficiently in such media. This mismatch can lead to phase separation during the drying process, resulting in incomplete drug dispersion, heterogeneous product distribution, or even drug crystallisation(48). To address this, formulation scientists often resort to solvent mixtures, but this introduces further complexity,

including variations in solvent evaporation rates and potential residual solvent retention, which may pose safety and stability concerns(49). The presence of residual solvents is another critical concern in solvent-based processes, especially when using hygroscopic polymers. Polymers like PVP and copovidone have a strong affinity for solvents and moisture, making it difficult to completely remove entrapped solvents even after extended drying. Residual solvents can affect the physical stability of the solid dispersion by promoting recrystallisation of the drug, altering polymer structure, or interfering with downstream processing steps such as granulation and compression(50). Regulatory guidelines such as ICH Q3C mandate strict limits on residual solvent content, and failure to meet these criteria can lead to formulation rejection. Efficient drying technologies, including vacuum drying or lyophilisation, may be required but can significantly increase processing time and cost.

Another important issue in solvent evaporation is the viscosity of the polymer solution. High molecular weight polymers such as PVP K90, HPMC E15, or cellulose derivatives tend to form highly viscous solutions even at moderate concentrations. High viscosity complicates the casting or spraying of the solution, leading to non-uniform drying, poor film formation, and inconsistent drug distribution(51, 52). In addition, high-viscosity solutions can create difficulties in atomisation during spray drying, resulting in clogging, variable particle size distribution, and reduced product yield. These processing limitations necessitate careful control of solution concentration, temperature, and solvent selection to achieve a processable formulation with consistent quality.

In contrast, hot-melt extrusion (HME) involves the application of heat and shear to melt-process the drug and polymer into a uniform dispersion(53). This solvent-free and continuous method offers several advantages, including better scalability, environmental sustainability, and regulatory acceptance. However, HME also presents distinct polymer-dependent challenges. One of the most critical issues is the thermal stability of the polymer. Processing temperatures in HME typically range from 100 to 200°C, and not all polymers can withstand such conditions without undergoing thermal degradation(46, 54). Polymers like polyethylene glycol (PEG) and PVP may degrade at elevated temperatures, leading to discolouration, loss of functional properties, and chemical changes that affect both the drug and the polymer(55, 56).

Closely related to thermal stability is the glass transition temperature (Tg) and melt viscosity of the polymer. Polymers with high Tg, such as HPMC-AS or Eudragit® L/S, may require high processing temperatures to achieve sufficient flow for extrusion, increasing the risk of thermal

stress(57-59). On the other hand, polymers with low Tg may result in extrudates that are too soft, sticky, or prone to deformation, complicating handling and downstream processing(60). The addition of plasticisers such as triethyl citrate or low-molecular-weight PEG can reduce processing temperatures but may compromise the mechanical strength, physical stability, or drug release characteristics of the final product(61).

Another critical factor in HME is drug–polymer miscibility at processing temperatures. A lack of miscibility can lead to phase separation, drug crystallisation, or the formation of multiple amorphous phases, each with different stability profiles(62). Such heterogeneity not only reduces the solubility-enhancing effect of the dispersion but also increases the risk of batch-to-batch variability and long-term instability(63). Tools such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), and modelling approaches like the Flory–Huggins interaction parameter are frequently used to evaluate compatibility prior to extrusion(64, 65).

Shear-related degradation is also a concern during HME, especially for mechanically sensitive polymers. The high shear forces within the extruder barrel can cause polymer chain scission, altering the molecular weight distribution and functional properties of the polymer(66, 67). For example, excessive shear may reduce the Tg of the polymer, decreasing its stabilising capacity for the amorphous drug and affecting the mechanical integrity of the extrudate. Furthermore, polymers with inadequate melt strength or elasticity may result in strand breakage, die blockage, or poor extrudate formation, all of which affect process reliability and product consistency(68).

Scalability and reproducibility of polymer processing parameters represent additional challenges. Polymers may exhibit different behaviour at laboratory and production scales due to variations in thermal conductivity, screw design, and residence time within the extruder. Formulations that perform well at small scale may fail to reproduce the same quality at commercial scale unless process parameters are carefully optimised and validated. Such discrepancies are particularly relevant for polymers with narrow processing windows or for those highly sensitive to changes in temperature and shear. Both solvent evaporation and hot-melt extrusion are influenced significantly by the choice and characteristics of the polymer(43, 69). While solvent evaporation is hindered by issues related to solubility compatibility, residual solvents, and solution viscosity, HME is constrained by thermal stability, melt rheology, miscibility, and mechanical robustness of the polymer. A deep understanding of polymer science, process engineering, and drug–polymer interactions is essential to overcome these challenges. Comprehensive preformulation studies,

supported by analytical tools and predictive modelling, are critical to designing robust manufacturing processes that ensure the physical stability, bioavailability, and regulatory compliance of solid dispersion formulations(70).

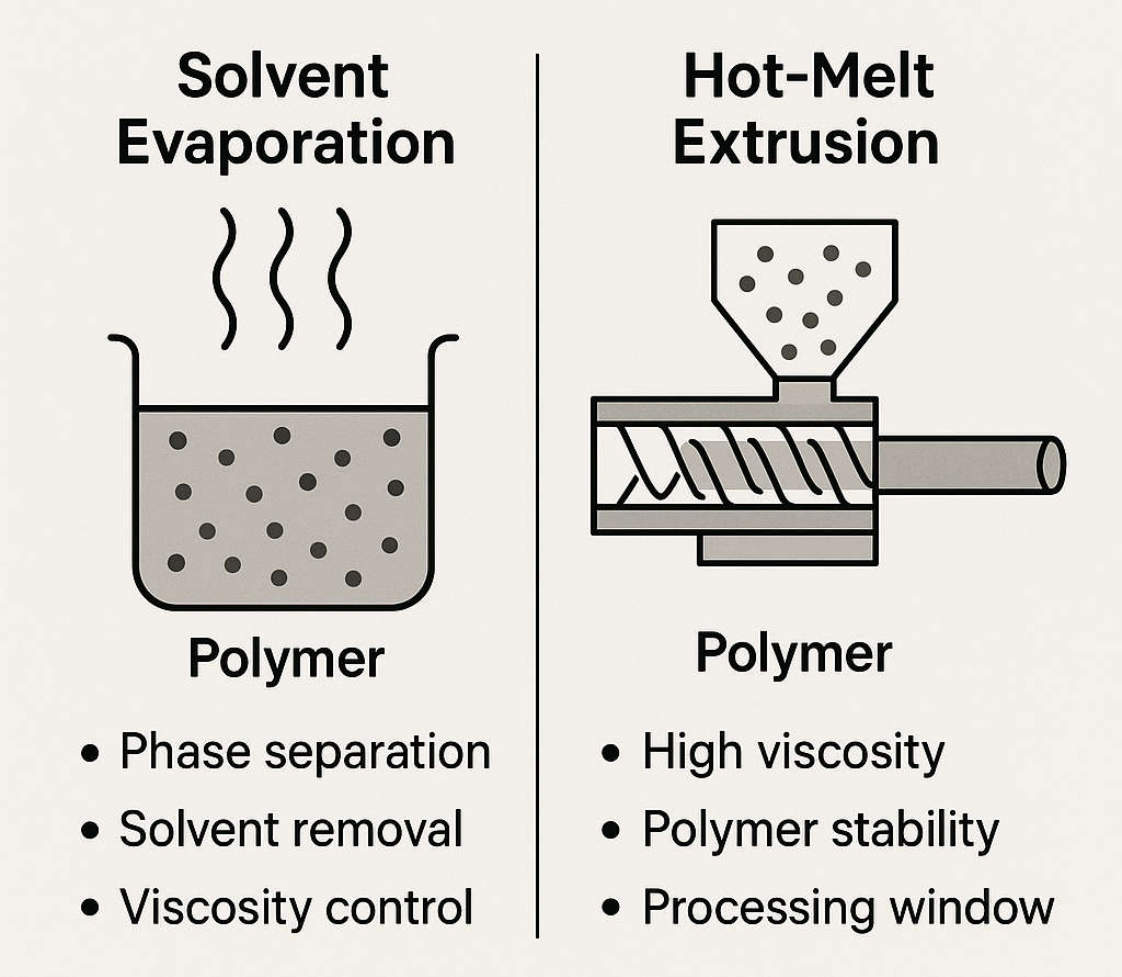

Figure 3: Manufacturing challenges in the Solvent evaporation and Hot melt extrusion process.

CONCLUSION

This paper highlights the crucial role of polymers in solid dispersion products, demonstrating their impact on drug solubility, stability, and overall formulation efficacy. It explores the functions of various polymer classes through mechanisms such as amorphisation, supersaturation maintenance, and controlled release. The review also addresses key manufacturing challenges, including thermal degradation, miscibility, and scale-up issues associated with solvent evaporation and hot-melt extrusion. These challenges underscore the importance of careful polymer selection, thorough preformulation studies, and predictive modelling. By integrating polymer science and process engineering, it is now possible to develop more robust and scalable drug delivery systems that meet both therapeutic and regulatory requirements.

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CONFLICT OF INTEREST

Mithun Bandivadekar, Sakshi Nigade, Vedanti Godbole confirm that there is no conflict of interest related to the review.

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