WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

Coden USA: WJPPCL

2026
Volume: 03
Issue: 08
Page: 04-31

AMORPHOUS SOLID DISPERSIONS IN THE ERA OF MODERN ANTIBIOTIC DEVELOPMENT: PHYSICOCHEMICAL PRINCIPLES, POLYMER SELECTION STRATEGIES AND BIOPHARMACEUTICAL OUTCOMES

Dhembare Sachin Tukaram*, Jori Devram K.

India.

Received: 29 May 2026 **Revised: 16 June 2026** **Accepted: 06 July 2026**

Corresponding Author: Dhembare Sachin Tukaram

Address: India.

DOI: https://doi.org/10.5281/zenodo.21738762,

ABSTRACT

Poor aqueous solubility among clinically essential antibiotics represents a formulation challenge with consequences that extend beyond compromised bioavailability into the pharmacodynamic domain of antimicrobial resistance, where dissolution-imposed sub-therapeutic drug exposure generates selective pressure for resistance emergence. Despite decades of regulatory success applying amorphous solid dispersion technology to antiviral and antineoplastic drug classes, its systematic application to poorly soluble antibiotics remains disproportionately underdeveloped. This review examines the physicochemical principles underlying amorphous solid dispersion performance, including the thermodynamic basis of supersaturation generation, glass transition-mediated solid-state stabilization, and the spring-and-parachute mechanism of gastrointestinal drug release. A science-based polymer selection framework is presented, comparing the properties, drug interaction mechanisms, and processing suitability of vinyl-based, cellulosic, and polymethacrylate carrier families across the physicochemical landscape of antibiotic molecules. Manufacturing considerations specific to thermolabile and high-melting-point antibiotics are addressed, with analysis of hot melt extrusion, spray drying, and KinetiSol approaches and their respective constraints. Translational evidence from itraconazole, griseofulvin, rifampicin, and posaconazole amorphous solid dispersion systems is critically evaluated, including dissolution enhancement, pharmacokinetic outcomes, and in vitro–in vivo correlation data. Physical

stability requirements, ICH-compliant storage protocols, and the regulatory landscape for approved formulations are examined. Emerging directions encompassing machine learning-assisted polymer screening and ternary dispersion architectures are identified as strategic priorities. Applying this formulation framework systematically to poorly soluble antibiotics represents a scientifically compelling and clinically urgent contribution to antimicrobial therapy.

KEYWORDS: amorphous solid dispersion: antimicrobial agents: biopharmaceutics classification system: drug-polymer miscibility: oral bioavailability: supersaturation.

1. INTRODUCTION

The impact of the physicochemical form of a drug on its therapeutic activity has never been more significant as in the present time when almost 90% of drug candidates moving through the development pipeline are of poor aqueous solubility.[1] In the case of compounds for anti-viruses and oncology, the pharmaceutical industry has been remarkably inventive when it comes to formulation 48 amorphous solid dispersion drug products were approved by the United States Food and Drug Administration (FDA) between 2012 and 2023, representing 36 different amorphous drug products, is a testament to the industry's resolve to use solid-state engineering as a commercialization tool.[2] Approximately 33.3% of the approvals are for antivirals, 25% are for antineoplastics and 14.5% are for respiratory agents. One thing that's missing from this landscape, however, is an equivalent response to failure to dissolve well in the body. An antibiotic class for which the failure to dissolve well in the body can lead to both under performance and antimicrobial resistance.[3] Basic pharmacodynamic principles underlie the link between subtherapeutic antibiotic exposure and the promotion of resistance.[4] For antibiotics which have time-dependent or concentration-dependent killing profiles, plasma and tissue levels must be above the minimum inhibitory concentration (MIC) of the targeted pathogen for specific time periods.[5] If formulation limitations prevent the desired concentration of the drug from being achieved, this is not due to an intrinsic pharmacokinetic barrier, but because the drug is dissolved from the solid dosage form is rate-limiting, the selection pressure is exactly what is needed to allow the selection of resistant variants.[6] This pharmacodynamic argument contrasts the clinical significance of low solubility for antibiotics from the other classes of drugs, in which failure to achieve therapeutic plasma concentration may be less likely to result in a long-term biological risk but may still decrease effectiveness.[7]

This challenge is not small in size. The proportion of antibiotic molecules in a clinically important drug repertoire that have high lipophilicity, poor aqueous solubility and, for Class IV, compounded permeability limitations is significant.[8] The dissolution-rate-limited oral absorption profiles of fusidic acid, griseofulvin, rifampicin, azithromycin, tetracyclines and some members of the family of triazole antifungal drugs are all historically managed by co-administering with food, formulation as ester prodrugs or by a single dose increase, which is neither mechanistically pleasing nor practically feasible.[9] The more rigorous solution thermodynamically breaking up the crystalline lattice and dispersing the drug molecule at the molecular level into a polymeric carrier matrix is exactly what amorphous solid dispersion technology does, but this application to the antibiotic space has been done in a fragmentary and not systematic manner.[10] Drug delivery system (DDS) based on amorphous solid dispersion is based on the concept of transforming crystalline active pharmaceutical ingredient (API) into non-crystalline state (amorphous) and maintaining the disordered structure of a drug in a suitable polymeric matrix, which will prevent the drug from recrystallizing, stabilizing the amorphous state until dissolved, and creating a thermodynamic driving force for increasing the apparent solubility.[11] The solubility of amorphous form may be several-fold or even hundreds-fold higher as compared to crystalline form, depending on the molecular structure, crystal lattice energy and the kind of molecular interactions between the drug and the polymer. In these cases, an antibiotic that has a high therapeutic dose requirement (grams for some beta-lactams, hundreds of milligrams for macrolides), such a product achievement requires properly considering the polymer selection, manufacturing platform, and dosage form architecture in relation to the specific physiochemical properties of an antimicrobial molecule.[12,13]

Each of these dimensions is addressed in this review. The main objective is to present a unified and critical review of the physicochemical principles that drive amorphous solid dispersion performance, to share a science-based approach to polymer selection that is tailored to the unique chemical characteristics of antibiotic drug molecules, and to review the knowledge base of the in vitro/in vivo translation for ASD technology applied to the various major classes of poorly soluble antibiotic drug molecules. In addition, the review covers physical stability and regulatory issues as potential practical considerations in commercial viability and concludes with a discussion of the areas of greatest scientific opportunity and advancement in the field, such as computational polymer screening and ternary dispersion systems. These discussions will collectively contribute to a scientific framework for ASD

strategies of poorly soluble antibiotics that will be rationally designed, systematically evaluated, and effectively translated for formulation scientists and pharmaceutical researchers.

2. The Biopharmaceutical Burden of Poorly Soluble Antibiotics

The Biopharmaceutics Classification System (BCS) is one approach that allows the relationship between the physicochemical properties of a drug and its potential for oral absorption to be systematically evaluated.[14] A large percentage of clinically relevant molecules reside in the poorly soluble/permeable categories (BCS Class II or III) within the antibiotic pharmacopeia. Fusidic acid is a prototypical challenge for BCS Class II: it is sparingly soluble in water, has a pKa of about 5.7 and is almost exclusively ionized at physiological pH of 7.4.[15] The intrinsic dissolution behavior of the acid at gastric pH is rate limiting in some formulation situations, despite the fact that the sodium salt is highly water-soluble. The cornerstone of tuberculosis chemotherapy, rifampicin has a more challenging profile (BCS Class II, poor solubility at neutral pH, moderate-high to variable bioavailability 1.5-1.7mg/mL aqueous solubility at neutral pH).[16] It has been known for decades that it does not have a consistent bioavailability due to its instability at acidic gastric conditions, high therapeutic dose and documented polymorphism. An extremely low aqueous soluble antifungal drug that has a long history of use in dermatophytic infections, Griseofulvin is the classic example for which particle size reduction (first micronization and then ultramicronization) was proposed as a formulation approach even before the maturity of the field of solid dispersion science.[17] Azithromycin and some macrolide antibiotics are grouped together as examples of a class of sparsely soluble, biologically active substances, where dissolution from solid oral dosage forms is the major factor controlling bioavailability. The biopharmaceutical summary data of these clinically relevant agents are summarized in Table 1.[18]

Table 1. Physicochemical and biopharmaceutical profile of clinically relevant poorly soluble antibiotics.[19–22]

Drug	BCS Class	Approximate Aqueous Solubility	logP (approx.)	Melting Point (°C)	Oral Bioavailability (%)	Primary Formulation Challenge
Fusidic acid (free acid)	II	Sparingly soluble (<0.1 mg/mL at gastric pH)	~5.1	~192	~91 (sodium salt tablet)	Solubility of free acid at low pH; salt-form stability
Rifampicin	II	~1.5–1.7 mg/mL (neutral pH)	~4.0	~183–188 (decomposes)	Variable (40–80%)	Polymorphism; gastric acid degradation; high dose
Griseofulvin	II	~10 µg/mL	~2.2	~218	Incomplete; fat-	Crystal lattice energy;

					dependent	food-dependent absorption
Azithromycin	II	~0.4 mg/mL (pH 7.4)	~4.0	~114	~37	Acid instability; incomplete absorption
Itraconazole	II	<1 µg/mL	~5.7	~166	Highly variable; food-dependent	Extreme lipophilicity; supersaturation collapse
Clindamycin HCl	I	Freely soluble	~2.2	—	~90	Non-applicable (reference)

From the collective data in Table 1, it is clear that the solubility of these antibiotics in aqueous solutions is not just a biopharmaceutical nuisance but a clinically relevant factor. Any dissolution-induced high trough level for a given antibiotic will result in decreased pharmacodynamic target achievement for that antibiotic, if it is a time-dependent antibiotic, meaning one that requires a defined percentage of the dosing interval to have plasma levels above the MIC.[23] A lower C_{max} due to dissolution-limited absorption leads to a lower killing rate to the target organism for concentration-dependent antibiotics, for which a high C_{max} compared to the MIC determines the killing rate. For drugs such as rifampicin, which exhibit a dose-dependent autoinduction effect on CYP3A4, the plasma concentration profile is also concentration dependent, resulting in a decreasing trajectory of plasma exposure during the first few weeks of treatment; when the effects of drug dissolution variability are added to this autoinduction effect, the clinical relevance of the variable exposure profile becomes real.[24] The public health aspect of the problem is emphasized for antitubercular therapy, as sub-MIC exposure of rifampicin during initial treatment has been associated with the acquisition of rpoB mutations that confer resistance a sequence of events linking formulation problems to the development of rifampicin resistant tuberculosis at the patient level. In the context of this, the benefits of the use of amorphous solid dispersion technology for poorly soluble antibiotics is not only scientific, but also epidemiological.[25]

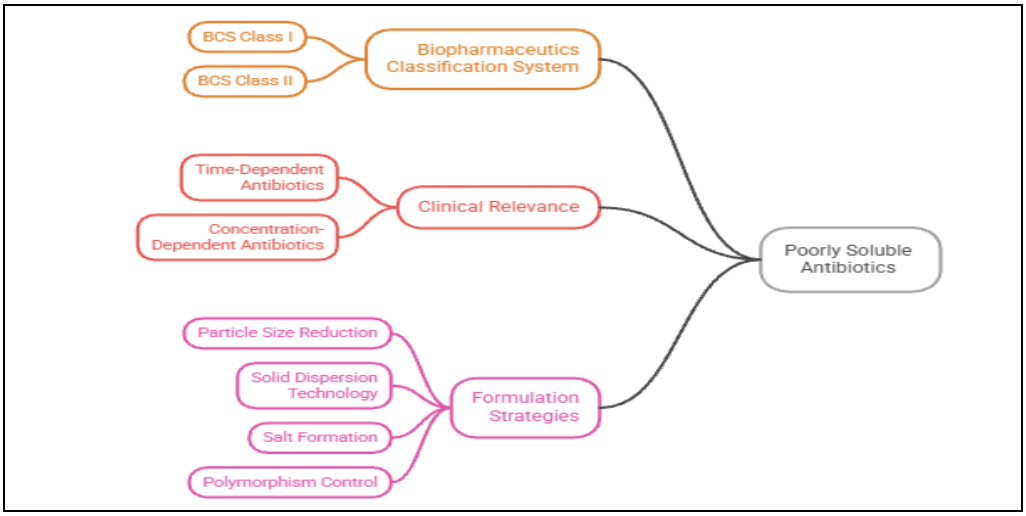

Figure 1: Biopharmaceutical Challenges of Poorly Soluble Antibiotics.

3. Physicochemical Principles Governing Amorphous Solid Dispersions

To appreciate the effectiveness of amorphous solid dispersion as a solubility enhancement strategy, it is important to understand the thermodynamic difference between the crystalline and amorphous states of a pharmaceutical solid.[26] In the case of a crystalline drug molecule, it has a periodic, long-range ordered lattice structure, and the energy needed to free an individual molecule from this lattice is the major thermodynamic barrier to dissolution, known as the crystal lattice energy.[27] In contrast the amorphous form has no long-range order and has higher values of enthalpy, entropy and Gibbs free energy compared to the crystalline state. The result is a completely different dissolution profile amorphous drug does not dissolve by the crystalline solubility ceiling, yet it might create supersaturation solutions with concentrations that surpass the crystalline solubility because of this thermodynamic excessive energy.[28] The amorphous solubility advantages were estimated from the thermal properties of the model compounds from the literature and reported as a fold improvement of amorphous vs crystalline form and ranged from 12 fold to 1652 fold depending on the melting point, heat of fusion, and molecular structure of the compound being studied. This theoretical ceiling for generation of supersaturation is clinically relevant for an antibiotic drug that has a very low aqueous solubility, such as griseofulvin.[29]

The real value of amorphous supersaturation is only if it can be kept for sufficiently long a period to allow gastrointestinal absorption. Unstabilized, an amorphous drug in solution will recrystallize at a rate dependent upon the amount of supersaturation and the molecular mobility in both the solid and solution states.[30] The best phenomenological description of dissolution behavior of a well-formulated ASD is the “spring and parachute” model: the dissolution of the amorphous drug causes a transient increase in concentration above the crystalline solubility the spring followed by the simultaneous dissolution of the polymer, which acts as a parachute to prevent the crystallization of the drug from solution, allowing the concentration to remain above the crystalline solubility for a period long enough to allow the drug to permeate the membrane and be absorbed.[31] Failure of the parachute can occur for polymer-insufficient systems (drug loading is below the polymer's capacity for crystallization inhibition) or systems where the drug loading is above the polymer's ability to inhibit crystallization (polymer insufficient). In either case, the initial solubility gain is lost as the drug precipitates back to its crystalline solubility.[32]

3.1 Thermodynamic Basis of Supersaturation and Solubility Advantage

An advantage of the amorphous state may be obtained from the difference between the Gibbs free energies of the crystalline and amorphous states at the temperature of interest. Practical estimation employs the melting point and heat of fusion of the drug and the assumption that the heat capacities of the crystalline and amorphous forms are more or less the same at temperatures considerably lower than the glass transition.[33] If the drug loading level in the polymer matrix is higher than the equilibrium solubility of the drug in the polymer, the system will experience a supersaturated solid-state condition, with a thermodynamic driving force towards crystallization and phase separation over time. The thermodynamic reality is the major challenge to be overcome when formulating an ASD, the aim being to keep the drug molecules dispersed at the molecular level, that is, to keep the drug dissolved in the polymer matrix; this is achieved by selecting the best possible drug–polymer thermodynamic miscibility that will allow the drug to be dispersed at the molecular level.[34] The Flory–Huggins interaction parameter (χ) is one of the most common parameters used to estimate the miscibility, with negative or small positive values suggesting a favorable mixing, and hence greater thermodynamic stability. The other factor that influences solid-state stability is the glass transition temperature of the dispersion; the higher the system Tg (as estimated using the Gordon–Taylor equation for binary drug–polymer mixtures) the less molecular mobility within the glassy state will allow for recrystallization and therefore restrict the diffusion of drug molecules through polymer matrix below the molecular mobility threshold necessary to nucleate recrystallization.[35]

3.2 Physical Stability: Molecular Mobility, Glass Transition, and Phase Separation

Two complementary mechanisms act to stabilize an amorphous solid dispersion in the solid state. The first is thermodynamic: the interactions between the drug with the polymer, which are generally hydrogen bonding between the drug functionalities and the hydrogen bond donors and/or acceptors of the polymer, decrease the chemical activity of the drug in the dispersion and lower its tendency to crystallize. The second one focuses on kinetic aspects based on the ability to reduce the mobility of the drug molecules by raising the Tg above the storage temperature, thereby limiting the rate of drug molecule diffusion to a level that does not allow for nucleation within a commercially viable shelf-life.[36] The most significant solid-state failure mode for ASD systems is the amorphous–amorphous phase separation (AAPS), which happens when drug-rich and polymer-rich domains are formed within the ASD because of thermodynamic incompatibility under the specific drug loading or at high

moisture or temperature. The presence of drug-rich amorphous domains makes them more prone to crystallization than molecularly dispersed systems, for which the protection of the polymer's surrounding is a key limitation. In more research-oriented investigations, identification of AAPS during storage can be done using the new technique of modulated DSC (which will show a distinct thermal event specific to the drug) as well as by X-ray diffraction and confocal fluorescence microscopy. Thermodynamic and kinetic stabilization by choice of polymer becomes an immediate and critical issue for poorly soluble antibiotics, which often have high melting points associated with a high crystal lattice energy.[37]

4. Polymer Selection Strategies for Antibiotic ASD Systems

The choice of a polymeric carrier is the most critical formulation issue in developing an amorphous solid dispersion. A polymer that is thermodynamically incompatible with the drug will not ensure molecular dispersion even if the manufacturing process is performed well; a polymer that is incompatible with the manufacturing process will either degrade the drug or give a physically heterogeneous product that will act in an unpredictable way during dissolution. The additional layer of nuance applies to the choice of polymer for antibiotics due to the physiochemically diverse nature of the antimicrobial molecules, from triterpenoid acids such as fusidic acid, to macrolactone containing macrolide antibiotics through to the rifamycin class antibiotics.[38]

An optimal polymer for an antibiotic ASD system should meet three requirements at the same time. One is to prevent recrystallization of the API in its solid form during production, storage and shipping. Secondly, it should promote quick disintegration on exposure to gastrointestinal fluid and maintain a supersaturated concentration of the drug for the necessary length of time to allow the drug to be absorbed.[39] Third, it should be compatible with the main production process, causing neither unacceptable impurity profiles nor chemical degradation. The polymeric carriers used in approved ASD products are currently in regulatory use and four families of such polymers are dominant: the vinyl-based polymers (PVP and PVPVA/copovidone), the cellulosic neutral ethers (HPMC), the cellulosic enteric esters (HPMCAS and HPMCP), and the polymethacrylate copolymers (Eudragit grades). Their physicochemical properties that are most relevant to antibiotic ASD performance are compared in a structured form in Table 2.[40]

Table 2. Comparative properties of polymeric carriers commonly used in amorphous solid dispersion formulations with relevance to antibiotic applications.[41,42]

Polymer	Tg (°C)	Water Absorption at 75% RH	pH Solubility Threshold	Drug Interaction Mechanism	Best Manufacturing Route	Suitability for Antibiotic APIs
PVP K30	~164	~23 wt%	pH-independent	H-bonding (strong)	Spray drying	Moderate; high hygroscopicity limits tropics use; not preferred for moisture-sensitive antibiotics
Copovidone (PVPVA 6:4)	~108–111	Lower than PVP	pH-independent	H-bonding + hydrophobic	HME or spray drying	Good; lower hygroscopicity than PVP; FDA-approved in 49% of ASD products
HPMC E5	~160–200*	~10 wt%	pH-independent	H-bonding	Spray drying preferred	Good; slower dissolution compared to PVPVA; suitable for neutral antibiotics
HPMCAS-L	>70 (even at 75% RH)	~6 wt%	Dissolves pH ≥5.5	H-bonding + hydrophobic	Spray drying preferred	Excellent; superior precipitation inhibitor; preferred for lipophilic antibiotics
HPMCAS-M	>70 (even at 75% RH)	~6 wt%	Dissolves pH ≥6.0	H-bonding + hydrophobic	Spray drying preferred	Excellent; suitable for small intestinal release profile
HPMCAS-H	>70 (even at 75% RH)	~6 wt%	Dissolves pH ≥6.8	H-bonding + hydrophobic	Spray drying preferred	Suitable for distal small intestinal release; avoid for rapid-release needs
Soluplus®	~70	Moderate	pH-independent	Amphiphilic self-assembly	HME preferred	Promising for lipophilic antibiotics; low Tg may require drug loading optimization
Eudragit L100	~150–160	Low	Dissolves pH ≥6.0	Ionic (anionic)	Spray drying	Useful for basic antibiotics; potential ion pair formation may retard release

4.1 Vinyl and Cellulosic Polymers: Mechanisms and Comparative Performance

The vinyl based carriers (PVP and copovidone) are well established in solid dispersion research and the major reason for their effectiveness is attributed to the carbonyl oxygen of the pyrrolidone ring, which is a good hydrogen bond acceptor and can interact with the hydroxyl, carboxylic acid, and amine functional groups that are present in the majority of

antibiotic molecules. PVP has a high glass transition temperature (~164°C) and is therefore very well suited for solid state stabilization at ambient conditions but its hygroscopic nature is a big drawback. At 75%RH, PVP is able to absorb around 23% of its weight in water, which significantly plasticizes the polymer, lowers the system Tg, and increases the molecular mobility of the polymer in its solid state; these are all concerns for the storage of antimicrobial drugs in tropical pharmaceutical markets in South Asia, sub-Saharan Africa, and Southeast Asia where the high relative humidity is particularly a concern.[43,44] Copovidone overcomes this limitation by incorporating vinyl acetate units in the polymer backbone to significantly decrease the hygroscopicity, yet still maintain an appropriate Tg of 108-111 °C, which is still protective during normal storage situations, and also increases the polymer's plasticity and melt processability for hot melt extrusion. HPMCAS is the most extensively tested precipitation inhibitor of the polymers available for use in ASD applications. In a series of studies by Curatolo and coworkers, comparing 41 polymeric carriers for nine structurally divergent hydrophobic compounds, HPMCAS was found to be the most effective inhibitor of solution-phase crystallization, as compared to PVP, HPMC and polymethacrylate copolymers in its ability to maintain supersaturation after dissolution.[45] The hydrophobic groups (acetyl and succinoyl) attached to the cellulose backbone may be able to interact favorably in solution with lipophilic drug molecules via non-specific hydrophobic contacts, and the succinoyl groups can also contribute the hydrogen bonding capability to the polar functional groups of the drug molecules. The dual mode of action of hydrophobic interaction and hydrogen bonding is especially well suited for fusidic acid and other triterpenoid or steroidal antibacterials, which have logP values greater than 4.5. HPMCAS is able to retain only about 6% water even at 75%RH relative humidity, significantly less than PVP and even HPMC (~10%) and offers very good moisture protection against crystallization even under harsh storage conditions, with glass transition temperatures above 70°C.[46]

4.2 Rational Screening Criteria and the Role of Drug–Polymer Miscibility Prediction

The selection framework shown in Figure 2 combines four main selection criteria: the ionization state and pKa of the drug, its melting point as an indication of the crystal lattice energy and thermal processing risk, immediate or enteric drug release profile, and the intended manufacturing route.[47] In the case of an antibiotic with a high melting point, like griseofulvin (approx. 218°C), it is necessary to add a plasticizer to the formulation to reduce the processing temperature to the range of 120°C to 180°C, or alternatively to use spray

drying with an appropriate solvent system that dissolves the antibiotic and polymer at low temperature. Spray drying with HPMCAS or HPMC is generally more desirable than melt-based extrusion for heat labile antibiotics that are subject to oxidation, hydrolysis or structural rearrangement at elevated temperatures, such as several β-lactam and macrolide antibiotics. HPMCAS has an enteric property which can be utilized to control the dissolution of drugs with acidic pKa in the stomach and release the drug as a supersaturated solution in the small intestine where the absorption capacity is maximum.[48] On the other hand, HPMCAS could have an inhibitory effect on the dissolution of the polymers and on the release of basic antibiotics due to the anionic nature that can favor the formation of ion pairs, therefore neutral carriers like copovidone or HPMC would be more suitable. Miscibility prediction before committing to laboratory-scale ASD preparation is now standard practice. Values for the Flory–Huggins interaction parameter can be determined from solubility parameters derived from group contribution methods and more recently molecular dynamics simulations have been used to estimate drug–polymer interaction energies at atomistic level. In the case of antibiotic drug molecules, for which published solubility parameter data might be limited, the melting point depression method (which involves watching the drug melting point drop as the amount of polymer in the physical mixture is increased in a hot-stage microscope or DSC) can be a useful preformulation tool that is both time-saving and predictive of miscibility.[49]

5. Manufacturing Strategies and Dosage Form Integration

The development and validation of a technically sound manufacturing process is not the only criterion for successful transition of a polymer–drug combination from a laboratory scale to a commercial product, when the product is required to be in amorphous solid dispersion. The hot melt extrusion and spray drying processes represent 35% and 54% of FDA approved manufacturing routes for ASD respectively, and both processes have constraints of significance to the antibiotic class. Their choice is seldom a neutral one as it depends on the thermal stability of the drug, solubility in most common organic solvent systems, melt viscosity characteristics of the selected polymer, and the scale of production desired. Hot melt extrusion is a process that uses heat and mechanical shear to melt a physical mixture of drug and polymer in a twin-screw extruder and extrudes a continuous product that is a mixture of drug and polymer molecules dispersed within a molten polymer matrix.[50] It is a solventless process that provides environmental benefits and eliminates the possibility of solvent residues. Its principal limitation in antibiotic drug development is thermal degradation: The

processing temperatures used in HME are typically 120°C to 200°C, depending on the melting point of the polymer and the drug. Antibiotics that are susceptible to oxidation, hydrolysis, or thermally induced rearrangement at these temperatures are not suitable for direct HME processing. This evidence is not hypothetical: the benzimidazole class of anti-parasitic drug, albendazole, was found to undergo 97.4% degradation during hot melt extrusion even though parameters were selected based on TGA test. Likewise, fenbendazole, a structurally related compound, was significantly degraded during HME processing at 120°C, producing a degradation product that made processing uneconomical.[50,51]

As an example, for griseofulvin which is sensitive to prolonged thermal stress, with the melting point depression effect of copovidone, HME can be feasible, but the processing must be done at optimized temperatures and residence times to avoid the chemical degradation of griseofulvin. The thermal stability limitation is overcome by spray drying to carry out the amorphous conversion at temperatures considerably below the melting point of the drug. It entails dissolution of the drug and polymer in a common solvent or cosolvent system followed by atomization of the solution into fine droplets, and rapid evaporation of the solvent as the droplets pass through a hot drying chamber. Particles are amorphous, usually fine, with the drug distributed at the molecular level in the polymer matrix.[52] The challenge lies in finding and removing the solvents: the organic solvents must be removed to concentrations that meet the ICH Q3C guidance for the residual solvents, and Class 2 solvents must be reduced well below the limits of 3000 ppm. Often, additional drying after the primary drying is necessary to meet the requirement for low residual solvent levels and this is an extra processing step and energy expense. A cosolvent approach or a mixed aqueous organic system might be necessary for lipophilic antibiotics that are not very soluble in the common class 3 solvents (ethanol/acetone) as the type of cosolvent system should also take into consideration the antibiotic solubility and the polymer's solubility to prevent phase separation during drying. During evaporation, the atomized droplet gathers into an aggregate that precipitates some of the components, such as the drug or polymer, which results in non-uniform dispersions of lower stability and less effective.[53]

KinetiSol® dispersing has become a viable option for thermolabile and/or organic-solvent-insoluble compounds, working on a principle of heat generation through high-energy frictional blending, which occurs only at the point of mixing and for a short period of time. KinetiSol technology may be considered viable for antibiotics with dual thermal sensitivity

and poor organic solvent solubility for the production of amorphous dispersions with minimal thermal exposure and no solvent burden. The way in which the ASD intermediates dissolve in the gastrointestinal fluid is highly dependent on the fact whether a molecularly homogenous dispersion has been obtained during the manufacturing process or a phase separated system and on the relative dissolution rate of the drug and polymer. Three release scenarios can be envisioned: In the carrier-controlled release, the drug is released through a viscous gel layer formed by the dissolving polymer creating a supersaturation profile that is slower and more controlled; In the dissolution-controlled release, the drug is released at a rate controlled by the dissolution rate of the polymer matrix, which produces a rapid and high supersaturation profile; In the drug-controlled release, the polymer is released at a fast rate and in a relatively small amount, leaving the remaining amorphous drug to dissolve at a rate determined by the dissolution rate of the amorphous drug itself.[54]

The understanding of the predominant mechanism for a specific drug–polymer combination in simulated gastrointestinal conditions is crucial for in vivo predictions. The additional challenges in downstream dosage form development (conversion of the ASD intermediate into tablet or capsule dosage forms for oral administration) make this an even more challenging process. Spray dried dispersions usually have poor flow properties and low bulk density and must be densified by roller compaction before it can be compressed directly into tablet forms. The ability to compress is often improved with HME extrudates if the particle size is the correct size. The excipient composition of the outer phase (diluents, disintegrants and lubricants), should be chosen to ensure sufficient tablet tensile strength which would not impair the wetting and disintegration properties required to start the dissolution-supersaturation sequence in the gastrointestinal fluid.[55]

6. Biopharmaceutical Outcomes and Translational Evidence in Antibiotic ASD Systems

The biopharmaceutical relevance of amorphous solid dispersion technology is finally demonstrated by how much the in vitro dissolution advantage correlates with measurable pharmacokinetic advantages in preclinical models and humans. This translational evidence base extends from well characterized clinical data on antifungals to a much broader range of in vitro and preclinic data on antibacterials, and critical evaluation of this data is required for researchers to make suitable benchmarking choices when developing new formulations. Itraconazole is an example of a drug used in the treatment of fungal infections that has been used as a reference model compound with ASD technology for basic, highly lipophilic and

practically insoluble antimicrobials.[56] Commercial experience with itraconazole has been useful, as the original capsule formulation was amorphous itraconazole adsorbed onto sugar beads which must be taken with a fatty meal and gastric acidity; studies published have shown an interpatient variability of up to 15-fold in plasma levels. The FDA-approved TOLSURA formulation overcomes this variability because it uses an enteric polymer (hypromellose phthalate) that allows itraconazole to be sprayed onto this polymer and dissolve at the pH of the small intestine, where it is most likely to be absorbed, resulting in 35% lower dose entirely due to improved bioavailability – of 65 mg vs 100 mg conventional Sporanox capsule.[57]

Itraconazole formulation as HPMCAS–TPGS ternary ASD in beagle dogs resulted in 1.8-fold greater AUC (0–24 h) than the Sporanox commercial product, and there was more than 40% better extent of absorption than in the binary ASD formed by HPMCAS alone. One important finding from the IVIVC developed for itraconazole spray-dried dispersion tablets was that the HPMCAS grade influenced the release rate in vivo: the L grade which released at pH ≥5.5 showed faster and greater dissolution in vivo than the M grade; and that this difference in the in vivo dissolution was directly reflected in the human pharmacokinetic profiles, indicating that in vitro dissolution conducted under biorelevant conditions can be used as a meaningful predictor of in vivo dissolution properties for itraconazole ASDs.[58] In vivo studies performed in rats have confirmed that HPMCAS based ASD materials, prepared by either spray drying, quick evaporation or lyophilisation, yield higher Cmax and AUC values than do a physical mixture of drug and polymer at the same dose. The ternary spray-dried dispersion of griseofulvin with Soluplus and copovidone in a ratio of 5:1 resulted in a supersaturation of 220% in the first 30 minutes after dissolution, which remained stable for 3 hours during the monitoring. Cellulose ester based amorphous systems have proved their ability to protect the drug from gastric hydrolysis and at the same time to release the drug completely at intestinal pH, this is true for rifampicin which is poorly soluble in water and susceptible to acid-catalyzed degradation at the stomach pH. When developing ASDs for rifampicin, the selection of polymers to prevent release at gastric pH and release the full amount of intact drug at intestinal pH (proof of concept) was essential, even though this is not always as relevant to most non-antibiotic ASD applications. The results of these and other studies are summarized in Table 3.[59]

Table 3: Published in vitro and in vivo performance data from selected antibiotic and antifungal amorphous solid dispersion systems.[60–62]

Drug	Polymer Carrier	Manufacturing Method	In Vitro Enhancement	In Vivo Outcome	Key Observation
Itraconazole	HPMCAS-L	Spray drying (SDD tablets)	N/A (human clinical study)	Bioavailability comparable to oral solution; FDA Level A IVIVC achieved	HPMCAS grade (L vs. M) directly determines human PK profile
Itraconazole	HPMCAS + TPGS (15%)	Spray drying	>40% dissolution increase vs. HPMCAS alone	1.8-fold AUC increase vs. Sporanox® (beagle dogs)	Ternary ASD outperforms binary; surfactant selection critical
Itraconazole (TOLSURA)	HPMC phthalate	Spray drying	pH-triggered dissolution	65 mg bioequivalent to 100 mg conventional capsule (human)	35% dose reduction through ASD
Griseofulvin	HPMCAS	Spray drying, evaporation, lyophilization	Supersaturation above crystalline solubility	Significantly higher Cmax and AUC vs. physical mixture (rat)	AUC equivalent across all three manufacturing processes
Griseofulvin	Soluplus + PVPVA (5:1)	Spray drying (ternary)	220% supersaturation maintained for 3 h	Preclinical data (dissolution-driven)	Synergistic ternary system; micellar + matrix stabilization
Rifampicin	Cellulose ω-carboxyalkanoates	Spray drying	Enteric protection; complete release at intestinal pH	In vitro proof of concept	Chemical stability protection alongside solubility enhancement
Posaconazole	HPMCAS	Spray drying	Rapid dissolution vs. crystalline API	FDA-approved (Noxafil tablets, 2013)	pH-dependent release critical for antifungal exposure

A key note about this evidence base is that not every dissolution enhancement corresponds to an increase in bioavailability. The size of the colloidal species and the permeation advantage given by LLPS depends on the interaction of drug-rich nanoparticles formed on dissolution of ASD with the bile salts and endogenous phospholipids present in the intestinal fluids. However, studies with posaconazole HPMCAS ASD showed that addition of sodium lauryl sulfate as a surfactant to the formulation was counterproductive, leading to in vivo bioavailability of only about 30% of that seen in the formulation that lacked sodium lauryl sulfate, a common approach to enhancing the wettability.[63] This happens mechanistically due to the competitive displacement of HPMCAS from the drug rich colloidal phase by the ionic surfactant, thus interfering with the precipitation inhibition property of HPMCAS. In a drug discovery program creating antibiotic ASDs, this finding is in opposition to the reflex application of solubilizing surfactants as soon as a new molecule is created without biorelevant dissolution evaluation.[64]

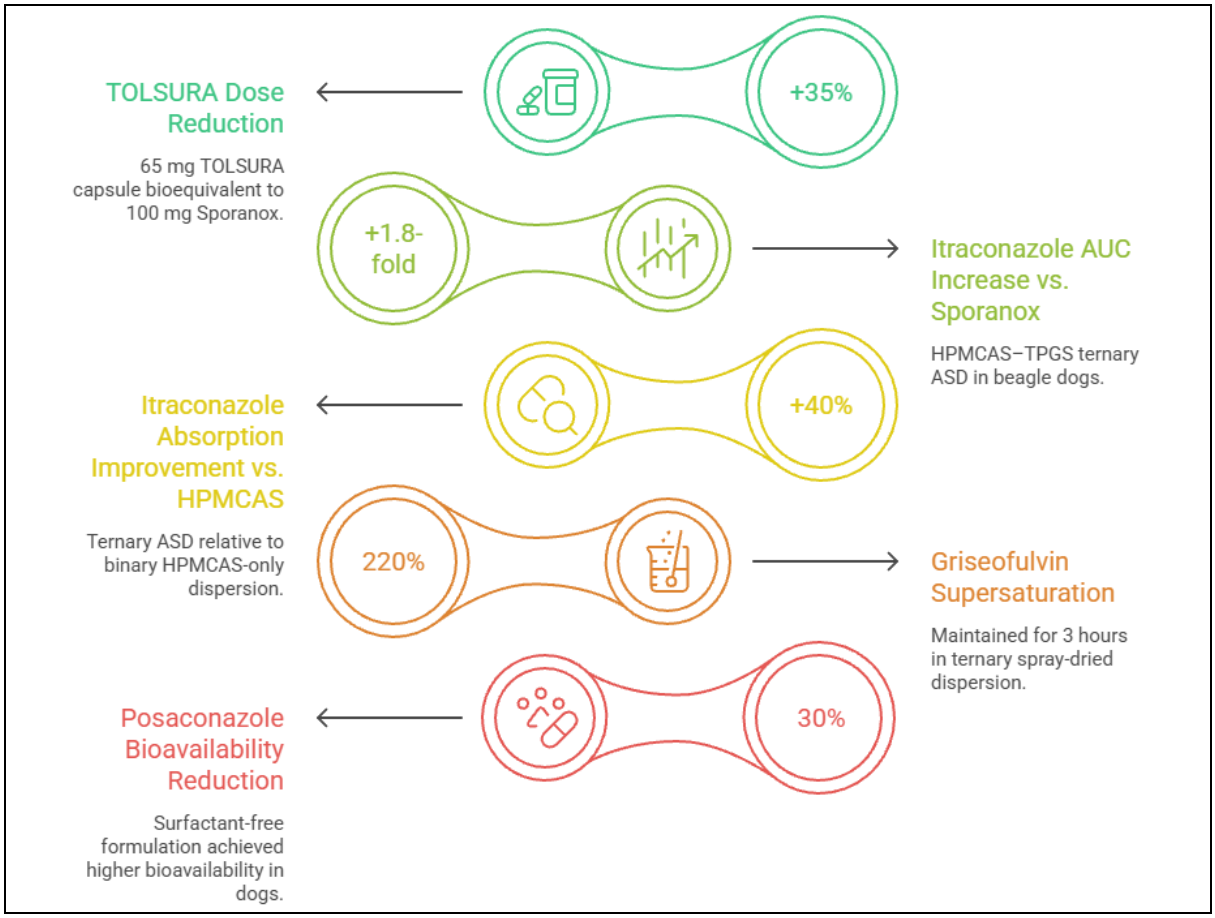

Figure 2: Biopharmaceutical Outcomes and Translational Evidence in Antibiotic ASD Systems.

7. Physical Stability, Storage Considerations, and Regulatory Landscape

For ultimate commercialization, the viability of an amorphous solid dispersion formulation depends on the ability to keep the amorphous drug in a dispersed state, not only during the short period of laboratory characterization, but during the entire process of manufacturing, distribution, storage, and administration in the real world under various environmental conditions. This requirement presents a series of physical stability issues that are more challenging for amorphous products than for their crystalline counterparts, and that are very relevant for antibiotic ASD development in the areas where antimicrobial drugs are needed the most.[65] The most significant environmental factor affecting the stability of ASD is moisture. The water absorbed from the atmosphere can act as a plasticizer in the dispersion, it can hydrogen-bond with the drug molecules as well as the polymer chains, and gradually lower the glass transition temperature, increase molecular mobility from the constrained glassy state up to the rubbery state where the rate of molecular diffusion is adequate to support nucleation. The amount absorbed is largely dependent upon polymer hygroscopicity

and dispersions of PVP are very susceptible to this process with approximately 23% of the polymer weight being absorbed by water at 75%RH, as mentioned earlier. The specific surface area of the extrudates is normally lower than that of the spray dried particles, which have higher surface areas to favor rapid atmospheric moisture equilibration, and hence the rate of moisture uptake.[66]

The surface area effect has direct shelf-life implications on stability; in spray dried ASDs, the surface area is higher, thus increasing the likelihood of moisture making its way into the material, thereby increasing the rate of moisture-induced phase separation and recrystallization. In terms of regulations, the criteria for the stability of ASD are laid out in ICH Q1A (R2), where 40°C and 75%RH is prescribed as accelerated stability conditions for at least 6 months, and 25°C and 60%RH for at least 12 months at submission. One key point is that the long-term storage conditions were 30°C with 65% relative humidity or 40°C with 75% relative humidity; the regions with the highest burden of the bacterial and fungal infections that the poorly soluble antibiotics discussed in this review are used to treat are the climatic zones III and IV, which include South Asia, Southeast Asia, and sub-Saharan Africa. This climatic burden is not a regulatory technicality but rather an antibiotic ASDs that has been designed and tested to be stored in temperate climates and then distributed in a tropical climate without proper packaging and labelling can undergo recrystallisation during the time between manufacture and use by the patient, resulting in a poorly bioavailable drug product.[67] The packaging strategy is thus a critical part of the ASD product design. MOisture barriers that can be shown to prevent moisture entry like aluminum-laminate blister packaging (Alu-Alu), HDPE bottles containing desiccant and sealed aluminum bags for bulk intermediate storage are proven measures. From these options, choices should be made based on previously proven data of how well they permeate the subject polymer at the climatic zone conditions for the combination of polymer and drug. In the regulatory pathway, the dominance of copovidone (representing 49% of FDA-approved ASD products) and HPMCAS (representing 30%) in approved formulations is important for the development of new antibiotic ASD products. These polymer–manufacturing process combinations have well-established regulatory precedents, which minimizes the regulatory risk of safety and compatibility justification, as compared to new or unconventional excipients.[68]

The Center for Drug Evaluation and Research (CDER) at the FDA has indicated that dissolution testing could be used to support biowaiver applications and post-approval change

management as long as the appropriate in vitro–in vivo correlation (IV–IVC) data exist or an appropriate in vitro (IV) surrogate is developed. The Product Quality Research Institute (PQRI) has developed technical guidelines for amorphous solid dispersion stability which have been published, taking into account the ASD-specific considerations in characterisation requirements, recrystallization testing and specification of dissolution. Antibiotic ASDs formulation scientists must be mindful of these as minimum standards, and not necessarily aspirational targets, especially with the pharmacodynamic considerations of maintaining the desired level of drug exposure in the final dosage form for the correct duration in the shelf life.[69]

8. Emerging Directions, Limitations, and Future Perspectives

The pharmacokinetic advantage that has been reported for antifungal ASDs has proven the scientific validity of this technology and the challenge now is to apply the same rigor to antibacterials. There are also several limitations that are specific to the drug class of the antibiotics that have constraints that have not been well-addressed in the literature and present the most promising avenues for future investment. Unlike most antiviral or oncology drugs, the dose challenge of antibiotics is acute. Antifungal drugs such as rifampicin must be taken on a daily basis, and griseofulvin is taken at a dosage of 500-1000mg a day for systemic fungal infections. Tablets of this size present significant patient compliance challenges when made using these dose magnitudes, with the polymer dose needed to achieve molecular-level dispersion, a desirable drug to polymer ratio, of 20%-40% by weight. This is made even more complicated in the pediatric population where dose flexibility, taste masking and swallowability are required for a new antibiotic dosage form, which has not been optimized to suit adult pharmacokinetics. Pediatric acceptability and dose flexibility are facilitated by the incorporation of ASD with the use of ODT platforms, which has been little reported on for antibiotic compounds, and would therefore be a practical research priority. The IVIVC challenge for antibiotic ASDs is different to that for antiviral drugs. The dissolution profiles that are obtained for ASDs, which are characterized by supersaturation, liquid–liquid phase separation, polymer-mediated colloidal stabilization, and precipitation dynamics, do not fit easily into a traditional USP dissolution paradigm that is used for crystalline drug products. Technically, the establishment of an FDA accepted Level A IVIVC for an ASD product is challenging, and only for a limited number of combinations of drug–polymer. One unmet need is the development of biorelevant in vitro dissolution methods which can be validated with in vivo pharmacokinetic–pharmacodynamic endpoints for poorly

soluble antibiotics, where clinical relevance is determined by the concept of MIC-attainment pharmacodynamics.[69]

The use of two-phase dissolution models and dynamic pH shift methods which mimic the pH change from stomach to small intestine is promising as more discriminating tools than the single-compartment sink dissolution and could be systematically tested in antibiotic ASD systems. Computational improvements now include a new generation of machine learning and artificial intelligence platforms that are starting to make a difference in polymer screening and eliminating the combinatorial problem. With the aid of ML models, a series of 1272 binary and ternary ASDs were generated and tested; the best model (random forest) obtained test-set prediction accuracies of about 82.5% for long-term physical stability prediction. The molecular dynamics simulations have been used to predict the solubility parameters of Hansen, drug–polymer hydrogen bond lifetimes, and dissolution behavior at the atomistic level of resolution. For all molecules, especially those with limited published preformulation data, these computational methods provide a route to hypothesis-driven experimental screening that limits API usage in early development, which is of particular importance for expensive synthetic drugs and those that are only available in limited amounts. The ternary (two polymers or a polymer with a carefully selected co-former) ASD systems have a combined advantage of stabilization and maintenance of supersaturation which is not possible in binary systems at equivalent drug loading.[70]

This amphiphilic self-assembling polymer and the conventional matrix-forming polymer are simultaneously able to provide different stabilization mechanisms in the solid state and in solution. This structural concept has shown promise in pre-clinical trials and should be systematically expanded to the entire class of antibiotic drugs. Notably, lipid–ASD hybrid approaches, involving co-processing of an ASD intermediate with a lipid excipient to take advantage of the lymphatic transport pathways, are a frontier that had been explored with some oncology compounds but is under explored with antibiotics.[70]

9. CONCLUSION

The evidence presented in this review points toward a conclusion that ASD technology is at the same time an extremely scientific advanced formulation approach for pharmaceutical scientists and a technology that is least applied in the context of poorly soluble antibiotics. The thermodynamics of amorphous solubility advantage, the mechanisms of maintaining supersaturation in the presence of polymers, and engineering approaches to commercial-scale

production are well known. Regulatory tracks for approved polymer–process combinations are set up. The biopharmaceutical justification for the use of these approaches with Class II and Class IV antibiotics is clear and, as the pharmacodynamic argument in this review points out, not just a matter of product performance, but a matter of the whole scientific discussion on antimicrobial resistance. What the field has yet to do is take the systematic, evidence-based formulation development that has produced the TOLSURA, Noxafil and posaconazole tablets into the antibacterial pharmacopeia – and into the suboptimally bioavailable crystalline formulations that have reached the patient and continue to reach the patient. The selection of polymers, pathways of polymer workup, and stability issues outlined in this review are directly transferable to this challenge but must be driven by the dedication of committed preclinical and clinical research programs. Machine learning-assisted formulation design, coupled with biorelevant dissolution methodology and pharmacokinetic–pharmacodynamic target attainment analysis, as a single development paradigm is the most direct approach to bridging the science of amorphous formulation with its application in the safe delivery of antimicrobial drugs to patients in the world, where the need is greatest: reliable, affordable, and consistent.

10. REFERENCES

1. Danilovski A, Meštrović E. The Evolution of Pharmaceutical Solids: From Early Polymorphism to Cutting-Edge Drug Development. Croatica Chemica Acta., 2024; 97: 243–59. https://doi.org/10.5562/cca4154.
2. Tripathi D, B.h MP, Sahoo J, Kumari J. Navigating the Solution to Drug Formulation Problems at Research and Development Stages by Amorphous Solid Dispersion Technology. Recent Advances in Drug Delivery and Formulation, 2024; 18: 79–99. https://doi.org/10.2174/0126673878271641231201065151.
3. Budiman A, Hafidz NPM, Azzahra RSS, Amaliah S, Sitinjak FY, Rusdin A, et al. Advancing the Physicochemical Properties and Therapeutic Potential of Plant Extracts Through Amorphous Solid Dispersion Systems. Polymers, 2024; 16: 3489. https://doi.org/10.3390/polym16243489.
4. Tripathi D, B.h MP, Sahoo J, Kumari J. Navigating the Solution to Drug Formulation Problems at Research and Development Stages by Amorphous Solid Dispersion Technology. Recent Advances in Drug Delivery and Formulation, 2024; 18: 79–99. https://doi.org/10.2174/0126673878271641231201065151.

5. Rezende SC de, Santamaria-Echart A, Dias MM, Barreiro MF. Solid Dispersions as a Tool for Innovation in the Food Industry: A Path From Pharma to Food. Journal of Food Science, 2026; 91: e70917. https://doi.org/10.1111/1750-3841.70917.
6. Taylor LS, Zografi G. From Unwanted Annoyances to Oral Delivery Saviors: The Rollercoaster Journey of Amorphous Drugs. Mol Pharmaceutics, 2025; 22: 5125–38. https://doi.org/10.1021/acs.molpharmaceut.5c00013.
7. Kapoor DU, Singh S, Sharma P, Prajapati BG. Amorphization of Low Soluble Drug with Amino Acids to Improve Its Therapeutic Efficacy: a State-of-Art-Review. AAPS PharmSciTech., 2023; 24: 253. https://doi.org/10.1208/s12249-023-02709-2.
8. Naeem A, Yu C, Wang X, Peng M, Liu Y, Liu Y. Hydroxyethyl Cellulose-Based Hydrogels as Controlled Release Carriers for Amorphous Solid Dispersion of Bioactive Components of Radix Paeonia Alba. Molecules, 2023; 28: 7320. https://doi.org/10.3390/molecules28217320.
9. Jia Y, Gengji J, Gong T, Zhang Z, Deng L. An Amorphous Solid Dispersion of Baicalin and its Oral Therapeutic Effect on Ulcerative Colitis. Pharm Res., 2024; 41: 2377–89. https://doi.org/10.1007/s11095-024-03804-0.
10. Ishtiaq M, Manzoor H, Khan IU, Asghar S, Irfan M, Albekairi NA, et al. Curcumin-loaded soluplus® based ternary solid dispersions with enhanced solubility, dissolution and antibacterial, antioxidant, anti-inflammatory activities. Heliyon, 2024; 10. https://doi.org/10.1016/j.heliyon.2024.e34636.
11. Amaliah S, Aulifa DL, Gazzali AM, Budiman A. Ternary Solid Dispersions as an Alternative Approach to Enhance Pharmacological Activity. Drug Design, Development and Therapy, 2025; 19: 5663–84. https://doi.org/10.2147/DDDT.S533359.
12. Wdowiak K, Tajber L, Miklaszewski A, Cielecka-Piontek J. Sweeteners Show a Plasticizing Effect on PVP K30—A Solution for the Hot-Melt Extrusion of Fixed-Dose Amorphous Curcumin-Hesperetin Solid Dispersions. Pharmaceutics, 2024; 16: 659. https://doi.org/10.3390/pharmaceutics16050659.
13. K.s. NS, Yarlagadda DL, Dengale SJ. 13 - Polymeric carriers for amorphous solid dispersion. In: Parambath A, editor. Polymers for Oral Drug Delivery Technologies, Elsevier Science Ltd., 2025; 541–71. https://doi.org/10.1016/B978-0-443-13774-7.00013-X.
14. Meesters K, Alemayehu T, Benou S, Buonsenso D, Decloedt EH, Pillay-Fuentes Lorente V, et al. Pharmacokinetics of Antimicrobials in Children with Emphasis on Challenges

Faced by Low and Middle Income Countries, a Clinical Review. Antibiotics, 2023; 12: 17. https://doi.org/10.3390/antibiotics12010017.

15. Allaw F, Vu Thi Lan H, Nagao M, Ndegwa L, Levy Hara G, Kanj SS, et al. Antibiotic shortages: An overview by the alliance for the prudent use of antibiotics (APUA). International Journal of Antimicrobial Agents, 2025; 65: 107456. https://doi.org/10.1016/j.ijantimicag.2025.107456.
16. Miri AH, Kamankesh M, Llopis-Lorente A, Liu C, Wacker MG, Haririan I, et al. The Potential Use of Antibiotics Against Helicobacter pylori Infection: Biopharmaceutical Implications. Front Pharmacol., 2022; 13: 917184. https://doi.org/10.3389/fphar.2022.917184.
17. Baral PK, Dummer J, Pletzer D, Das SC. Inhaled Antibiotic and Biologic Formulations Targeting Pseudomonas aeruginosa. Pharmaceutics., 2026; 18: 162. https://doi.org/10.3390/pharmaceutics18020162.
18. Panthi VK, Fairfull-Smith KE, Islam N. Ciprofloxacin-Loaded Inhalable Formulations against Lower Respiratory Tract Infections: Challenges, Recent Advances, and Future Perspectives. Pharmaceutics., 2024; 16: 648. https://doi.org/10.3390/pharmaceutics16050648.
19. Hasan M, Stratford RE. Biopharmaceutical Drug Products: An Overview of Physicochemical Properties and Their Modification. The ADME Encyclopedia, Springer, Cham., 2022; 164–78. https://doi.org/10.1007/978-3-030-84860-6_19.
20. Biernat M, Sylla A, Stępień KA, Giebułtowicz J, Ciołek L, Szterner P, et al. Multi-Antibiotic Porous Systems for Tailored Drug Delivery in Dentistry: Formulation Strategy, Physicochemical Properties, and Release. Pharmaceutics., 2026; 18: 409. https://doi.org/10.3390/pharmaceutics18040409.
21. Boczar D, Bocian W, Sitkowski J, Pioruńska K, Michalska K. Development of a Cyclodextrin-Based Drug Delivery System to Improve the Physicochemical Properties of Ceftobiprole as a Model Antibiotic. IJMS., 2025; 26: 5953. https://doi.org/10.3390/ijms26135953.
22. Subbaiah MAM, Rautio J, Meanwell NA. Prodrugs as empowering tools in drug discovery and development: recent strategic applications of drug delivery solutions to mitigate challenges associated with lead compounds and drug candidates. Chem Soc Rev., 2024; 53: 2099–210. https://doi.org/10.1039/d2cs00957a.
23. Krzyżek P, Opalińska A, Migdał P, Tusiewicz K, Szpot P, Zawadzki M, et al. Antibiotic stress affects the secretion and physicochemical features of extracellular vesicles

produced by Helicobacter pylori. J Antimicrob Chemother., 2025; 80: 2032–43. https://doi.org/10.1093/jac/dkaf172.

24. Liang D, Li F, Duan J, Sun W, Yu X. Two Novel Hydrate Salts of Norfloxacin with Phenolic Acids and Their Physicochemical Properties. Antibiotics, 2024; 13: 888. https://doi.org/10.3390/antibiotics13090888.
25. Bhat AR, Padder RA, Husain M, Patel R. Development of Cholinium-Based API Ionic Liquids with Enhanced Drug Solubility: Biological Evaluation and Interfacial Properties. Mol Pharmaceutics., 2024; 21: 535–49. https://doi.org/10.1021/acs.molpharmaceut.3c00673.
26. Budiman A, Ivana H, Huang KA, Huang SA, Nadhira MS, Rusdin A, et al. Biocompatible Natural Polymer-Based Amorphous Solid Dispersion System Improving Drug Physicochemical Properties, Stability, and Efficacy. Polymers., 2025; 17: 2059. https://doi.org/10.3390/polym17152059.
27. Aher AA, Shaikh KS, Chaudhari PD. Stability of co-Amorphous Solid Dispersions: Physical and Chemical Aspects. J Struct Chem., 2023; 64: 686–738. https://doi.org/10.1134/S0022476623040157.
28. Wang W, Lin Y, Wang S, Zhang Z. Solid dispersions: a review on instability, improvement methods, and future development directions. Drug Development and Industrial Pharmacy, 2026; 0: 1–15. https://doi.org/10.1080/03639045.2026.2680189.
29. Kumar P, Pradeep P, Indermun S, Govender M, Choonara YE, Pillay V. Physicochemical Basic Principles for Solid Dosage Forms. Handbook of Space Pharmaceuticals, Springer, Cham., 2022; 49–67. https://doi.org/10.1007/978-3-030-05526-4_13.
30. Deac A, Luebbert C, Qi Q, Courtney RM, Indulkar AS, Gao Y, et al. Dissolution Mechanisms of Amorphous Solid Dispersions: Application of Ternary Phase Diagrams To Explain Release Behavior. Mol Pharmaceutics, 2024; 21: 1900–18. https://doi.org/10.1021/acs.molpharmaceut.3c01179.
31. Raje V, Patel K, Serajuddin ATM. Development of amorphous solid dispersion of delamanid, an extremely water-insoluble drug, by hot melt extrusion applying acid-base supersolubilization (ABS) principle. International Journal of Pharmaceutics, 2026; 694: 126739. https://doi.org/10.1016/j.ijpharm.2026.126739.
32. Budiman A, Handini AL, Muslimah MN, Nurani NV, Laelasari E, Kurniawansyah IS, et al. Amorphous Solid Dispersion as Drug Delivery Vehicles in Cancer. Polymers., 2023; 15: 3380. https://doi.org/10.3390/polym15163380.

33. Gan Y, Baak JPA, Chen T, Ye H, Liao W, Lv H, et al. Supersaturation and Precipitation Applicated in Drug Delivery Systems: Development Strategies and Evaluation Approaches. Molecules., 2023; 28: 2212. https://doi.org/10.3390/molecules28052212.
34. Wohlrab J, Eichner A. Supersaturation as a Galenic Concept for Improving the Cutaneous Bioavailability of Drugs in Topical Therapy. Dermatol Ther (Heidelb), 2023; 13: 391–8. https://doi.org/10.1007/s13555-022-00873-0.
35. El Sayed M, Alhalaweh A, Kovac L, Bergström CAS. Excipient effects on supersaturation, particle size dynamics, and thermodynamic activity of multidrug amorphous formulations. International Journal of Pharmaceutics, 2024; 666: 124738. https://doi.org/10.1016/j.ijpharm.2024.124738.
36. Kawakami K. Roles of Supersaturation and Liquid–Liquid Phase Separation for Enhanced Oral Absorption of Poorly Soluble Drugs from Amorphous Solid Dispersions. Pharmaceutics, 2025; 17: 262. https://doi.org/10.3390/pharmaceutics17020262.
37. Fujita M, Tsuchida T, Kataoka H, Tsunoda C, Moritake K, Goto S. *Spring* and *parachute* approach for piroxicam dissolution; its phenomenological model on the thermodynamics of irreversible processes. International Journal of Pharmaceutics, 2024; 667: 124886. https://doi.org/10.1016/j.ijpharm.2024.124886.
38. Voronin AP, Ramazanova AG, Churakov AV, Vologzhanina AV, Kulikova ES, Perlovich GL. Virtual Screening, Polymorphism, and Formation Thermodynamics Study of Riluzole Multicomponent Crystals with Dihydroxybenzoic Acids. Crystal Growth & Design, 2024; 24: 9773–89. https://doi.org/10.1021/acs.cgd.4c01278.
39. Newman LM, Kavanagh ON, Machado TC. DSPindex guides dose selection to extend drug supersaturation lifetime during cocrystal dissolution. International Journal of Pharmaceutics, 2025; 671: 125298. https://doi.org/10.1016/j.ijpharm.2025.125298.
40. Surov AO, Voronin AP, Drozd KV, Volkova TV, Vasilev N, Batov D, et al. Extending the Range of Nitrofurantoin Solid Forms: Effect of Molecular and Crystal Structure on Formation Thermodynamics and Physicochemical Properties. Crystal Growth & Design, 2022; 22: 2569–86. https://doi.org/10.1021/acs.cgd.2c00044.
41. Pardhi VP, Pathak A, Jain K. Solid dispersions of bedaquiline fumarate to improve its pharmaceutical attributes: A comparative study between PEG and PVP. Journal of Drug Delivery Science and Technology., 2024; 94: 105461. https://doi.org/10.1016/j.jddst.2024.105461.
42. Cao J, Zhang S, Hao Y, Fan K, Wang L, Zhao X, et al. Amorphous solid dispersion preparation via coprecipitation improves the dissolution, oral bioavailability, and

intestinal health enhancement properties of magnolol. Poultry Science., 2023; 102: 102676. https://doi.org/10.1016/j.psj.2023.102676.

43. Hou Y, Dong R-Y. Comparative analyses of thermal transport in cellulose at crystalline, paracrystalline and amorphous states. Carbohydrate Polymers, 2025; 367: 124063. https://doi.org/10.1016/j.carbpol.2025.124063.
44. He H, Qi R, Zhao Q, Deng C, Zhao Z-Y, Wang Y-Z. Influence of crystalline vs. amorphous hollow microspheres on the Ceramization process and mechanism in EVA composites. Polymer Degradation and Stability., 2025; 240: 111449. https://doi.org/10.1016/j.polymdegradstab.2025.111449.
45. Jørgensen JR, Mohr W, Rischer M, Sauer A, Mistry S, Müllertz A, et al. Stability and intrinsic dissolution of vacuum compression molded amorphous solid dispersions of efavirenz. International Journal of Pharmaceutics., 2023; 632: 122564. https://doi.org/10.1016/j.ijpharm.2022.122564.
46. Osei-Yeboah F, Sun CC. Effect of drug loading and relative humidity on the mechanical properties and tableting performance of Celecoxib–PVP/VA 64 amorphous solid dispersions. International Journal of Pharmaceutics., 2023; 644: 123337. https://doi.org/10.1016/j.ijpharm.2023.123337.
47. Pavliš J, Mathers A, Fulem M, Klajmon M. Can Pure Predictions of Activity Coefficients from PC-SAFT Assist Drug–Polymer Compatibility Screening? Mol Pharmaceutics., 2023; 20: 3960–74. https://doi.org/10.1021/acs.molpharmaceut.3c00124.
48. Al Nuss R, Al Tahan MA, El-Zein H. Assessing the Impact of Mesoporous, Co-Amorphous, and Polymer-Based Systems on Cefdinir's Dissolution and Stability Via Predictive Modeling. Br J Biomed Sci., 2026; 83: 15242. https://doi.org/10.3389/bjbs.2026.15242.
49. Su J, Song Y, Wu H, Li Y, Shen P, Ji Y. An interpretable machine learning approach for quantitative structure-permeation prediction of polymeric microneedles. Chemical Engineering Science., 2026; 331: 123979. https://doi.org/10.1016/j.ces.2026.123979.
50. Li Y, Wei Q, Su J, Zhang H, Fan Z, Ding Z, et al. Encapsulation of astaxanthin in OSA-starch based amorphous solid dispersions with HPMCAS-HF/Soluplus® as effective recrystallization inhibitor. International Journal of Biological Macromolecules., 2024; 279: 135421. https://doi.org/10.1016/j.ijbiomac.2024.135421.
51. Yun T, Lee S, Yun S, Cho D, Bang K, Kim K. Investigation of Stabilized Amorphous Solid Dispersions to Improve Oral Olaparib Absorption. Pharmaceutics., 2024; 16: 958. https://doi.org/10.3390/pharmaceutics16070958.

52. Almeida H, Teixeira N, Sarmento B, Vasconcelos T. Freeze-drying cycle optimization of an amorphous solid dispersion of resveratrol. European Journal of Pharmaceutical Sciences, 2024; 200: 106855. https://doi.org/10.1016/j.ejps.2024.106855.
53. Jørgensen JR, Mohr W, Rischer M, Sauer A, Mistry S, Rades T, et al. *In vitro-in vivo* relationship for amorphous solid dispersions using a double membrane dissolution-permeation setup. European Journal of Pharmaceutics and Biopharmaceutics., 2023; 188: 26–32. https://doi.org/10.1016/j.ejpb.2023.04.026.
54. Vidiyala N, Sunkishala P, Parupathi P, Mandati P, Mantena SK, Kasu RRR, et al. High Drug Loading of Amorphous Solid Dispersion by Hot Melt Extrusion: The Role of Magnesium Aluminometasilicate (Neusilin® US2). Sci Pharm., 2025; 93: 30. https://doi.org/10.3390/scipharm93030030.
55. Cousineau ML, Deac A, Purohit HS, Zhang GGZ, Gao Y, Taylor LS. Hydrogen Bonding as a Failure Mechanism for Release of Ibuprofen-Copovidone Amorphous Solid Dispersions. Mol Pharmaceutics., 2026; 23: 2119–30. https://doi.org/10.1021/acs.molpharmaceut.5c01901.
56. Thom RP, Warren TL, Khan S, Muhle RA, Wang PP, Brennand K, et al. A Blueprint for Translational Precision Medicine in Autism Spectrum Disorder and Related Neurogenetic Syndromes. Journal of Child and Adolescent Psychopharmacology, 2025; 35: 178–93. https://doi.org/10.1089/cap.2025.0023.
57. Yu H, Zhang Y, Yang D, Luo H, Zhou Y. Advances in capsule-based fecal microbiota transplantation: clinical applications and innovations. J Transl Med., 2025; 23: 1370. https://doi.org/10.1186/s12967-025-07407-0.
58. Banerjee S, Banerjee D, Ram V, Kulhari H, Pooja D, Singh A, et al. Cannabidivarin: current evidence on pharmacological activity, biopharmaceutical limitations and clinical prospects. Phytochem Rev., 2026. https://doi.org/10.1007/s11101-026-10252-8.
59. Zhang J, Jiang Q, Xu Z, Yang Q, Hao G, Liu M, et al. Recent Progress on Crystal Nucleation of Amorphous Solid Dispersion. Crystal Growth & Design., 2024; 24: 8655–66. https://doi.org/10.1021/acs.cgd.4c01114.
60. Coutinho AL, Adhikari A, Krug S, Kane M, Hollenbeck RG, Hoag SW, et al. In Vitro-In Vivo Correlation Of Amorphous Solid Dispersion Enabled Itraconazole Tablets. Pharm Res., 2025; 42: 485–502. https://doi.org/10.1007/s11095-025-03837-z.
61. Mahfud MAS, Syahirah NA, Akram M, Mahfufah U, Saputra MD, Elim D, et al. Solid Dispersion Incorporated into Dissolving Microneedles for Improved Antifungal Activity

of Amphotericin B: In Vivo Study in a Fungal Keratitis Model. Mol Pharmaceutics., 2023; 20: 6246–61. https://doi.org/10.1021/acs.molpharmaceut.3c00647.

62. Patel K, Kevlani V, Shah S. A novel Posaconazole oral formulation using spray dried solid dispersion technology: in-vitro and in-vivo study. Drug Deliv and Transl Res., 2024; 14: 1253–76. https://doi.org/10.1007/s13346-023-01461-1.
63. Riccio BVF, Nascimento ALCS do, Meneguin AB, Rodero CF, Santos KP, Sábio RM, et al. Solid Dispersions Incorporated into PVP Films for the Controlled Release of Trans-Resveratrol: Development, Physicochemical and In Vitro Characterizations and In Vivo Cutaneous Anti-Inflammatory Evaluation. Pharmaceutics, 2022; 14: 1149. https://doi.org/10.3390/pharmaceutics14061149.
64. Sánchez-Aguinagalde O, Sanchez-Rexach E, Polo Y, Larrañaga A, Lejardi A, Meaurio E, et al. Physicochemical Characterization and In Vitro Activity of Poly(ε-Caprolactone)/Mycophenolic Acid Amorphous Solid Dispersions. Polymers., 2024; 16: 1088. https://doi.org/10.3390/polym16081088.
65. Maruthapandi M, Luong JHT. Chitosan–Curcumin Bioactive Platforms: Mechanistic Synergy, Antimicrobial Performance, and Design Principles for Next-Generation Wound Therapies. Polymers, 2026; 18: 1329. https://doi.org/10.3390/polym18111329.
66. Kapourani A, Chachlioutaki K, Andriotis EG, Fatouros DG, Barmpalexis P. Evaluating PAA/PVA thermal crosslinking process during the preparation of in-situ high-drug loading amorphous solid dispersions. Journal of Drug Delivery Science and Technology., 2023; 79: 104030. https://doi.org/10.1016/j.jddst.2022.104030.
67. de Aguiar MMGB, Polo G, Ariede MB, Martinez RM, Alves FRS, Boni FI, et al. Solid dispersions enhanced nystatin solubility without significant improvement in permeability: Potential application in localized therapies. Journal of Drug Delivery Science and Technology, 2026; 118: 108072. https://doi.org/10.1016/j.jddst.2026.108072.
68. Shen J, Hu A, Yang Y, Nie T, Huang S, Cheng Z, et al. Ternary solid dispersions of lacidipine: Enhancing dissolution and supersaturation maintenance through strategic formulation optimization. International Journal of Pharmaceutics., 2024; 654: 123989. https://doi.org/10.1016/j.ijpharm.2024.123989.
69. Zhang J, Zhang L, Liu M, Zeng Z. Impact of Surfactants as Formulation Additives and Media Components on the Performance of Amorphous Solid Dispersions. Crystal Growth & Design, 2025; 25: 5561–83. https://doi.org/10.1021/acs.cgd.5c00417.

70. Sigfridsson K, Zhang X, Llinas A. Case study: cremophor EL-based liquid formulations as simple substitutes for amorphous solid dispersions in early preclinical in vivo studies. J Pharm Pharmacol., 2025; 77: 645–57. https://doi.org/10.1093/jpp/rgae099.