

Amorphous Solid Dispersions for Poorly Water-Soluble Drugs: Formulation Strategies, Stabilisation Mechanisms and Recent Advances

Sumit Kumar

Department of Pharmaceutical Sciences,
Central University of Haryana, Jant-Pali, Mahendergarh
drsumitkumar@cuh.ac.in

Abstract

Amorphous solid dispersions (ASDs) remain one of the most versatile and clinically validated formulation strategies for overcoming the poor aqueous solubility that affects a large proportion of new chemical entities and marketed drugs. By dispersing an active pharmaceutical ingredient at the molecular or colloidal level within a polymeric or, increasingly, mesoporous or co-amorphous carrier, ASDs generate a metastable, high-energy drug state capable of producing transient supersaturation and enhanced dissolution relative to the crystalline form. This review synthesises the literature published broadly between 2011 and 2022 on ASD formulation strategies, drug–polymer selection criteria, manufacturing technologies (spray drying, hot-melt extrusion, supercritical-fluid processing and electrospinning), stabilisation mechanisms, and characterisation approaches, with particular attention to recent advances in high-drug-loading systems, co-amorphous formulations, mesoporous-silica-based amorphisation, and artificial-intelligence-assisted formulation and stability prediction. Six comparative tables and four schematic figures consolidate key mechanistic and practical concepts, and the review concludes with a discussion of regulatory, Quality-by-Design and commercial considerations shaping the continued translation of ASD technology.

Keywords: Amorphous Solid Dispersions; Poorly Water-Soluble Drugs; Drug–Polymer Interactions; Spray Drying; Hot-Melt Extrusion;

1. Introduction

Poor aqueous solubility affects an estimated 40–90% of new chemical entities in pharmaceutical development pipelines, placing dissolution rate rather than membrane permeability as the principal barrier to adequate oral bioavailability for a large fraction of Biopharmaceutics Classification System (BCS) Class II and IV compounds [1]. Among the enabling formulation technologies developed to address this challenge, amorphous solid dispersions have emerged as one of the most extensively studied and commercially successful, owing to their capacity to generate substantial, sometimes order-of-magnitude, increases in apparent solubility relative to the crystalline drug [2,3].

An ASD disperses the drug in a non-crystalline, disordered state throughout an inert carrier matrix, typically a hydrophilic polymer, eliminating the lattice energy that must otherwise be overcome for dissolution to proceed. This apparent simplicity belies substantial formulation complexity: the amorphous state is thermodynamically metastable and prone to recrystallisation, drug–polymer miscibility and molecular-level interactions must be carefully engineered, and manufacturing processes must reliably produce a homogeneous single amorphous phase at commercial scale. This review traces the historical development of ASD technology, summarises current formulation components and manufacturing strategies, examines the mechanisms underlying solubility and bioavailability enhancement, reviews characterisation methods and the factors governing ASD stability, and discusses recent advances — including co-amorphous systems, mesoporous-silica amorphisation, high-drug-loading formulations and AI-assisted design — together with the regulatory and commercial considerations that continue to shape clinical translation.

2. Literature Review

2.1 Early Development of Amorphous Solid Dispersions

The solid dispersion concept dates to early observations that dispersing a poorly soluble drug within a water-soluble carrier could markedly improve dissolution relative to the pure drug, with fusion (melt) and solvent methods representing the earliest preparation approaches. Foundational reviews from the early 2010s catalogued the mechanisms by which amorphisation improves solubility, framing the amorphous state as a disordered, higher-free-energy configuration lacking the long-range crystalline lattice that otherwise depresses aqueous solubility [1,2]. Early ASD systems relied predominantly on simple hydrophilic carriers such as polyethylene glycol (PEG) and urea, but these often suffered from poor physical stability and limited drug loading, motivating the shift toward polymeric carriers capable of thermodynamically and kinetically stabilising the amorphous drug [3].

2.2 Advances in ASD Formulation and Polymer Selection

Through the 2010s, systematic investigation of drug–polymer interactions substantially advanced rational polymer selection. Work characterising drug–polymer–water interactions demonstrated that hydrogen bonding and other specific molecular interactions between drug and polymer directly determine dissolution performance and the extent and duration of achievable supersaturation [5], while mechanistic studies of liquid–liquid phase separation showed that drug-rich amorphous nanodroplets, rather than simple molecular dissolution, can act as a supersaturation reservoir that sustains membrane flux [6]. These insights shifted polymer selection from an empirical, trial-and-error exercise toward one grounded in miscibility theory, solubility-parameter matching and specific interaction chemistry.

2.3 Advances in ASD Manufacturing Technologies

Spray drying and hot-melt extrusion (HME) matured into the two dominant industrial-scale ASD manufacturing platforms over this period. Comprehensive process reviews addressed polymer screening, formulation and process-parameter optimisation, and scale-up considerations for spray-dried dispersions [12], while thermodynamically grounded process-design-space models, using equations of state such as PC-SAFT, enabled prediction of appropriate spray-drying conditions from ternary drug–polymer–solvent phase behaviour [13]. In parallel, supercritical-fluid-based techniques were increasingly explored as a green, solvent-minimised alternative for ASD and related amorphous formulations, avoiding the residual-solvent and thermal-degradation concerns associated with conventional solvent evaporation or high-temperature melt processing [14].

2.4 Stabilisation Mechanisms and Physical Stability

A substantial body of work has focused on elucidating the mechanisms by which polymers and other excipients stabilise the amorphous state against recrystallisation, identifying glass-transition-temperature elevation, reduction of molecular mobility, and specific drug–excipient interactions as the principal stabilisation mechanisms operating, often simultaneously, across polymeric ASDs, co-amorphous systems and amorphous salts [19,24]. Moisture uptake has been repeatedly identified as a critical destabilising factor, since sorbed water plasticises the amorphous matrix and depresses the glass-transition temperature in a manner well described by the Gordon–Taylor relationship, accelerating molecular mobility and recrystallisation kinetics [27].

2.5 Recent Advances in High-Drug-Loading ASDs

Conventional polymeric ASDs are typically limited to modest drug loadings (commonly below 30–40% w/w) before physical stability deteriorates unacceptably. Mesoporous silica carriers have emerged as a particularly effective route to higher drug loading, since nanoscale pore confinement thermodynamically favours a disordered, non-crystalline drug state independent of a stabilising polymer, and can achieve

substantially higher loading capacity than conventional non-porous high-surface-area carriers [16,32]. Ternary systems combining mesoporous silica with a polymeric crystallisation inhibitor have further been shown to improve sustained supersaturation beyond what silica confinement alone can achieve [18].

2.6 Recent Developments in ASD Technology (2020–2026)

The most recent phase of ASD development has been characterised by three converging trends: the maturation of co-amorphous drug–drug and drug–coformer systems as an alternative or complement to polymeric ASDs [20,21,23]; the application of machine-learning models, trained on large formulation datasets, to predict physical stability and accelerate polymer and process selection without lengthy empirical stability studies [26,30]; and continued growth in the number of ASD-based products reaching regulatory approval, reflecting the platform's transition from an academically interesting technology to a mainstream, commercially de-risked formulation option [25].

Table 1. Key milestones in the historical development of ASD technology.

Period	Representative development	Significance
Pre-2010	Early melt and solvent-based solid dispersions using PEG, urea, sugars	Proof of concept for dissolution enhancement via amorphisation
2011–2015	Systematic drug–polymer interaction and miscibility studies; LLPS mechanism elucidated	Shift from empirical to mechanistically grounded polymer selection
2016–2019	Co-amorphous systems formalised; spray-drying/HME process optimisation; electrospinning explored	Broader toolbox of stabilisation and manufacturing strategies
2020–2022	Mesoporous silica high-loading ASDs; supercritical-fluid processing; ML-based stability prediction	Higher drug loading, greener processing, faster development timelines
2022–present	Continued growth in FDA-approved ASD products; AI-assisted formulation platforms	Established, commercially mainstream enabling technology

3. Fundamentals of Amorphous Solid Dispersions

3.1 Definition, Concept and Amorphous versus Crystalline State

An amorphous solid dispersion is a solid-state formulation in which a drug substance is dispersed, ideally at the molecular level, within an inert, typically polymeric, carrier matrix such that the drug lacks the long-range, three-dimensional order characteristic of a crystalline lattice [2]. Whereas a crystalline solid occupies a well-defined thermodynamic energy minimum, the amorphous state represents a higher-energy, kinetically arrested configuration, more closely resembling a frozen liquid than an ordered solid.

3.2 Thermodynamic and Kinetic Aspects

The elevated free energy of the amorphous state confers a correspondingly higher theoretical solubility and faster intrinsic dissolution rate than the crystalline form, but this thermodynamic driving force simultaneously creates a persistent tendency toward recrystallisation. Whether recrystallisation occurs within the shelf life of a product depends on kinetic factors — principally molecular mobility, which is governed by the glass-transition temperature (T_g) of the system relative to storage temperature, and any specific drug–excipient interactions that raise the activation energy for nucleation and crystal growth [19]. Figure 1 illustrates this free-energy relationship schematically.

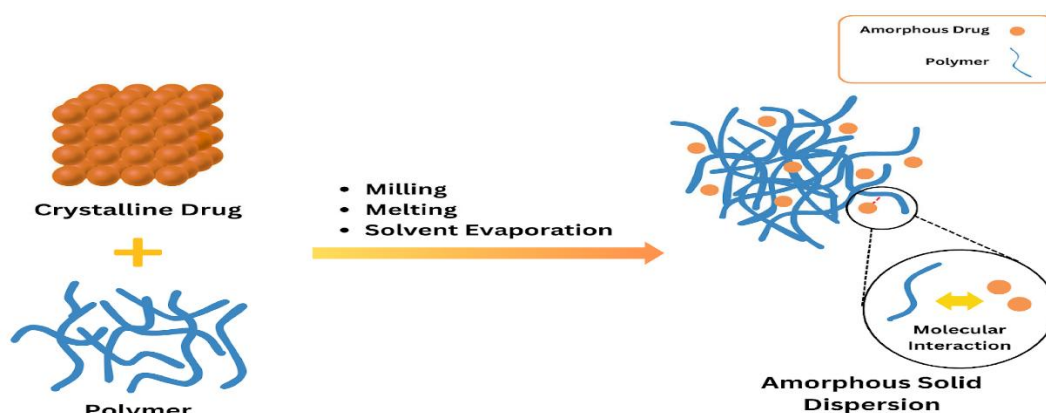


Figure 1. Schematic representation of the relative Gibbs free energy of a drug in the crystalline state, as an amorphous solid dispersion, and transiently in a supersaturated solution. The free-energy difference between states represents the thermodynamic driving force available for enhanced dissolution and membrane flux, but also the driving force for recrystallisation.

3.3 Advantages of Amorphisation and the 'Spring-and-Parachute' Concept

The principal advantage of amorphisation is the generation of a transient supersaturated solution upon dissolution — often described using the 'spring-and-parachute' model, in which the initial rapid dissolution of the amorphous drug ('spring') produces a concentration well above the equilibrium crystalline solubility, and a suitable precipitation-inhibiting polymer or excipient ('parachute') delays recrystallisation for long enough to permit meaningful gastrointestinal absorption [7]. Without an effective parachute, the transient supersaturation collapses rapidly as the drug precipitates, typically as a poorly ordered or crystalline solid, eliminating much of the potential bioavailability benefit.

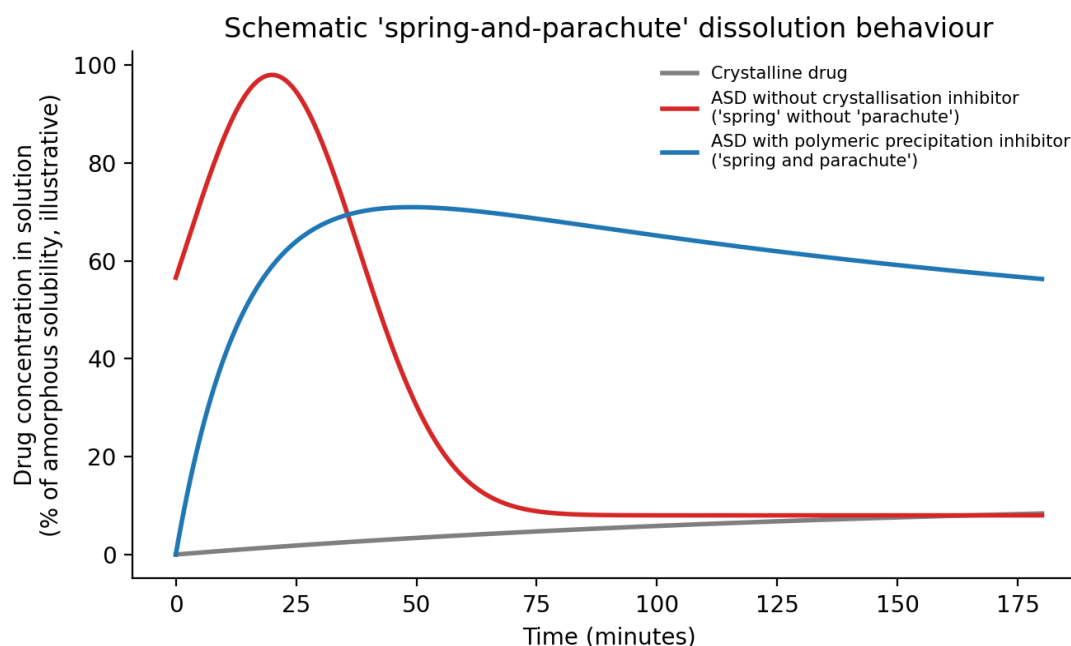


Figure 2. Schematic 'spring-and-parachute' dissolution behaviour, comparing crystalline drug, an amorphous solid dispersion without an effective crystallisation inhibitor, and an amorphous solid dispersion incorporating a polymeric precipitation inhibitor that sustains supersaturation. Curves are illustrative composites of general trends reported in the literature.

3.4 Relationship Between the Amorphous State and Supersaturation

The magnitude and duration of supersaturation achievable from an ASD depend jointly on the intrinsic amorphous solubility advantage of the drug and the effectiveness of the carrier at inhibiting nucleation and crystal growth in solution. Mechanistic studies have shown that drug-rich amorphous nanodroplets formed via liquid–liquid phase separation can act as an in-situ reservoir, continuously replenishing the free drug concentration available for membrane transport as absorption proceeds, effectively prolonging the window of enhanced flux beyond what a simple one-time supersaturation spike would provide [6].

4. Formulation Components of ASDs

An ASD formulation comprises, at minimum, the active pharmaceutical ingredient and a carrier, most commonly a hydrophilic polymer, though surfactants, plasticisers and, increasingly, mesoporous inorganic or small-molecule co-former carriers are also employed. Suitable drug candidates typically possess a moderate-to-high melting point, sufficient thermal stability for melt-based processing (or adequate solubility in a processable solvent for solution-based methods), and some capacity for specific interaction (hydrogen bonding, ionic or π – π interaction) with the chosen carrier.

4.1 Polymeric Carriers

Hydrophilic cellulose derivatives — hydroxypropyl methylcellulose (HPMC) and its acetate succinate ester (HPMC-AS) — are among the most widely used ASD polymers, valued for their strong hydrogen-bond-accepting capacity, pH-dependent solubility (for HPMC-AS) and demonstrated ability to sustain supersaturation across a broad range of drug chemotypes [7]. Povidone (polyvinylpyrrolidone, PVP) and its vinyl-acetate copolymer, copovidone (PVP-VA), offer strong hydrogen-bond-donor/acceptor capacity and have been used extensively in both spray-dried and melt-extruded ASDs [5]. Methacrylate copolymers (Eudragit® grades) provide pH-responsive or sustained-release behaviour alongside amorphisation capacity, while amphiphilic graft copolymers such as Soluplus® combine a hydrophilic backbone with lipophilic side chains, enabling micelle formation that can further assist solubilisation of very lipophilic drugs during dissolution [4].

4.2 Surfactants, Plasticisers and Selection Criteria

Surfactants such as sodium lauryl sulfate, Tween 80 or vitamin E TPGS are frequently incorporated at low concentration to improve wetting, reduce interfacial tension, and provide a complementary nucleation-inhibition mechanism alongside the primary polymer [10]. Plasticisers can be used deliberately to lower processing temperature during hot-melt extrusion of high-T_g polymers, though this must be balanced against the anti-plasticising benefit of a high-T_g carrier for long-term physical stability. Rational drug–polymer selection increasingly draws on solubility-parameter matching, hydrogen-bond donor/acceptor complementarity, and computational miscibility prediction, replacing earlier empirical screening approaches and shortening formulation development timelines.

Table 2. Representative polymeric and inorganic carriers used in ASD formulation.

Polymer class	Representative example(s)	Key properties	Typical processing route
Cellulose derivatives	HPMC, HPMC-AS	Strong H-bond acceptor; pH-dependent solubility (AS grades)	Spray drying, solvent evaporation
Povidone/copovidone	PVP K-series, PVP-VA64	High T _g ; strong crystallisation inhibitor	Spray drying, HME
Methacrylate copolymers	Eudragit® E/L/S	pH-responsive release; H-bonding with basic/acidic drugs	HME, spray drying

Amphiphilic graft copolymers	Soluplus®	Micelle-forming; aids lipophilic drug solubilisation	HME
Polyvinyl alcohol	PVA 4-88, 8-88	Hydrophilic; rapid wetting	Spray drying, casting
Mesoporous inorganic carriers	Silica (e.g., Syloid®, SBA-15, Neusilin®)	Nanoconfinement stabilises amorphous state; high loading capacity	Solvent immersion, supercritical CO ₂ , melt loading

5. Formulation Strategies for Amorphous Solid Dispersions

ASD manufacturing methods are broadly divided into solvent-based and fusion (melt)-based approaches, with several emerging techniques offering distinct processing advantages. Spray drying dissolves drug and polymer in a common solvent and atomises the solution into a heated drying chamber, producing amorphous particles within seconds; the technique is highly scalable and suitable for thermolabile drugs, and thermodynamically grounded process-design-space models have been developed to predict appropriate inlet temperature, feed concentration and solvent selection from ternary phase behaviour [13]. Comprehensive process reviews have further addressed polymer screening, design-of-experiments optimisation and the scale-up challenges specific to spray-dried dispersions [12].

Hot-melt extrusion (HME) is a solvent-free, continuous process in which drug and polymer are melt-blended under shear and elevated temperature and extruded into a solidified strand, subsequently milled into granules or powder; HME-produced posaconazole–Soluplus dispersions, for example, achieved markedly higher in vivo exposure than the marketed suspension formulation [4]. Solvent evaporation and freeze-drying remain valuable at laboratory scale, particularly for thermolabile or high-melting-point drugs unsuitable for HME, while co-precipitation offers a further solution-based route for simultaneous drug–polymer amorphisation.

Supercritical-fluid-based techniques, most commonly employing supercritical carbon dioxide, offer a green, low-residual-solvent alternative capable of achieving amorphisation at reduced processing temperature, since dissolved CO₂ depresses the melting point and viscosity of the drug–carrier mixture, facilitating penetration into mesoporous carriers or fine particle formation via rapid expansion [14,15]. Electrospinning generates high-surface-area amorphous nanofibres through electrostatic extrusion of a drug–polymer solution, offering tunable fibre morphology and rapid dissolution, and has been reviewed extensively as a versatile platform bridging conventional ASDs and advanced nanostructured dosage forms [9]. Emerging continuous manufacturing approaches, integrating HME or spray drying with in-line process analytical technology and downstream tableting, are increasingly displacing traditional batch processing to improve reproducibility, reduce cost, and align with regulatory expectations for real-time quality assurance.

Table 3. Comparison of principal ASD manufacturing techniques.

Technique	Solvent requirement	Typical scale suitability	Key advantage	Key limitation
Spray drying	Organic solvent or solvent blend	Lab to commercial	Fast, scalable, suits thermolabile drugs	Residual solvent; equipment cost
Hot-melt extrusion	Solvent-free	Lab to commercial; continuous	No solvent; continuous processing	High temperature; unsuitable for thermolabile drugs

Solvent evaporation	Organic solvent	Laboratory	Simple; low equipment cost	Poor scalability; slow solvent removal
Freeze-drying	Aqueous/organic	Laboratory to pilot	Suited to thermolabile/biologic-adjacent drugs	Slow; energy-intensive; costly at scale
Supercritical-fluid processing	Minimal/none (SC-CO ₂)	Pilot to commercial (growing)	Green; low residual solvent; lower temperature	High capital cost; specialised equipment
Electrospinning	Organic/aqueous solvent	Laboratory to pilot	High surface area; rapid dissolution	Low throughput; fibre uniformity challenges

6. Mechanisms of Solubility and Bioavailability Enhancement

ASDs enhance oral bioavailability through a combination of interrelated mechanisms. The absence of a crystalline lattice increases apparent (kinetic) solubility, since less energy is required to transfer drug molecules into solution; this is compounded by improved wettability of the hydrophilic polymer matrix relative to the often poorly wetted crystalline drug, and by the markedly increased effective surface area of the finely divided, molecularly dispersed drug, together enhancing the intrinsic dissolution rate [1,2].

The generation of transient supersaturation elevates the free drug concentration at the absorptive intestinal membrane well above the equilibrium crystalline solubility, directly increasing the concentration gradient that drives passive membrane flux under the Fickian diffusion principles underlying intestinal absorption. Provided precipitation is sufficiently delayed by the polymeric or co-former stabiliser, this elevated intestinal drug concentration is sustained long enough to meaningfully increase the fraction of dose absorbed, translating directly into improved oral bioavailability relative to the crystalline drug or an unformulated suspension [6,7]. Congruent, matched release of drug and polymer from the dissolving ASD matrix has additionally been identified as an important predictor of consistent in vivo performance, since incongruent release can lead to drug-rich residual particles with reduced dissolution potential [7].

Table 4. Key characterisation techniques for amorphous solid dispersions.

Technique	Primary information obtained	Key strength
DSC	Glass-transition temperature; absence of melting endotherm; miscibility (single vs multiple T _g)	Rapid, quantitative thermal fingerprint
PXRD	Crystallinity; amorphous halo vs Bragg reflections	Direct, sensitive measure of residual/recrystallised drug
FTIR	Hydrogen bonding and specific drug-polymer interaction	Fast; minimal sample preparation
Raman spectroscopy	Molecular interaction; compatible with in-line PAT monitoring	Non-destructive; suited to real-time process control
Solid-state NMR	Molecular-level miscibility and nanoscale phase separation	Highest resolution of local molecular environment

TGA / particle-size & morphology analysis	Residual solvent/moisture; particle size and surface morphology	Critical quality attributes for stability and processability
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8. Characterisation and Evaluation of ASDs

Rigorous solid-state characterisation is essential to confirm complete amorphisation, assess drug–polymer miscibility, and predict physical stability. Differential scanning calorimetry (DSC) detects the absence of a crystalline melting endotherm and identifies the glass-transition temperature of the dispersion, a key determinant of molecular mobility and storage stability. Powder X-ray diffraction (PXRD) distinguishes the diffuse halo pattern of an amorphous material from the sharp Bragg reflections of residual or recrystallised drug, providing a direct, quantitative measure of crystallinity.

Fourier-transform infrared (FTIR) spectroscopy and Raman spectroscopy detect shifts in characteristic vibrational bands arising from hydrogen bonding or other specific drug–polymer interactions, complementing thermal and diffraction data; Raman spectroscopy additionally offers the advantage of minimal sample preparation and compatibility with in-line process monitoring. Solid-state nuclear magnetic resonance (ssNMR) provides molecular-level resolution of drug–polymer proximity and miscibility beyond what bulk thermal or diffraction methods can resolve, and is particularly valuable for detecting nanoscale phase separation not evident by DSC or PXRD. Thermogravimetric analysis (TGA) quantifies residual solvent and moisture content, both of which strongly influence physical stability, while particle-size and morphology analysis, by laser diffraction, and scanning or transmission electron microscopy, confirms the physical form and homogeneity of the final drug product intermediate.

Table 5. Factors affecting ASD performance and physical stability.

Factor	Direction of typical effect	Practical implication
Drug loading	Higher loading → reduced physical stability (polymeric ASD)	Optimise loading against stability data; consider silica/co-amorphous for high loading
Polymer molecular weight/concentration	Higher → improved crystallisation inhibition; increased viscosity	Balance dissolution rate against stability
Drug–polymer miscibility	Poor miscibility → phase separation, reduced stability	Screen via solubility parameters/single-Tg confirmation
Residual solvent	Higher → plasticisation, accelerated recrystallisation	Confirm via TGA; optimise drying conditions
Moisture/relative humidity	Higher → Tg depression (Gordon–Taylor), faster recrystallisation	Moisture-protective packaging; desiccant
Storage temperature relative to Tg	Closer to/above Tg → increased molecular mobility, faster recrystallisation	Store well below moisture-adjusted Tg

9. Factors Affecting ASD Performance and Stability

ASD performance and long-term physical stability are governed by an interacting set of drug-, formulation- and process-related variables. Drug physicochemical properties — melting point, intrinsic

T_g, lipophilicity and hydrogen-bonding capacity — determine both the feasibility of amorphisation and the drug's inherent recrystallisation tendency. Drug loading is inversely related to physical stability in most polymeric systems: higher loading reduces the proportion of stabilising polymer available per unit mass of drug, increasing local molecular mobility and nucleation probability, which is precisely why mesoporous silica and co-amorphous approaches have attracted interest as high-loading alternatives [16,20].

Polymer molecular weight and concentration influence both the glass-transition temperature of the dispersion and solution viscosity during dissolution, with higher molecular weight and concentration generally improving crystallisation inhibition at the cost of increased processing viscosity. Drug–polymer miscibility, often assessed via a single, composition-dependent glass-transition temperature consistent with the Gordon–Taylor relationship, is a prerequisite for a genuinely homogeneous, single-phase ASD; poor miscibility instead yields a phase-separated system with diminished physical stability and less predictable dissolution behaviour [19,27].

Processing temperature must be sufficient to achieve complete drug dissolution or melting (for HME) without inducing thermal degradation, while residual solvent remaining after spray drying or solvent evaporation can plasticise the matrix and accelerate recrystallisation if not adequately removed. Moisture and humidity represent perhaps the single most consistently reported destabilising factor: sorbed water plasticises the amorphous matrix, depressing the glass-transition temperature in accordance with the Gordon–Taylor equation, and thereby increasing molecular mobility and recrystallisation rate at a given storage temperature [27]. Storage temperature relative to the (moisture-adjusted) T_g, and appropriate moisture-protective packaging, are therefore critical to maintaining the intended shelf life of a commercial ASD product.

10. Recent Advances in ASD Technology

High-drug-loading ASDs address a long-standing limitation of conventional polymeric dispersions, in which stability constraints have historically limited drug loading to well below 50% w/w. Mesoporous silica carriers achieve substantially higher loading by confining the drug within nanoscale pores, where geometric restriction thermodynamically disfavors the formation of a critical crystalline nucleus, stabilising the amorphous state largely independent of a polymeric anti-nucleant [15,16]. Co-amorphous drug systems represent a complementary high-loading strategy, in which two low-molecular-weight components — either two drugs or a drug and a small-molecule coformer such as an amino acid or carboxylic acid — form a single homogeneous amorphous phase stabilised by intermolecular interactions rather than a bulk polymer matrix, offering both solubility enhancement and, in many cases, superior physical stability relative to conventional polymeric ASDs at equivalent drug loading [20,21,22]. Quantitative literature analyses of published co-amorphous systems have begun to systematise co-former selection rationale, physical stability outcomes and dissolution performance across the growing body of reported systems [23].

Novel functional polymers, polymer combinations (blending a high-T_g crystallisation inhibitor with a rapidly wetting, hydrophilic polymer), and lipid-containing ASDs that combine amorphisation with a self-emulsifying lipid component are all active areas of formulation innovation, aiming to combine the complementary strengths of multiple solubility-enhancement mechanisms within a single dosage form. Nanostructured amorphous systems and 3D-printing approaches, including fused-deposition modelling of polymer filaments pre-loaded with amorphous drug, are being explored for flexible, potentially patient-specific dose manufacturing, with polymer selection for printability, drug-release profile and drug–polymer miscibility identified as key formulation variables [31].

AI/ML-assisted formulation optimisation is increasingly applied specifically to ASD development: machine-learning models trained on large historical stability datasets, using molecular descriptors of drug

and polymer alongside formulation composition, have achieved good predictive accuracy for physical stability classification, substantially reducing reliance on lengthy empirical stability testing during early formulation screening [26]. Complementary advanced predictive stability modelling approaches combine moisture-sorption isotherms with the Gordon–Taylor relationship to forecast shelf-life as a function of storage temperature and humidity from a small number of accelerated stability measurements [27], and broader reviews of machine learning and AI applications in pharmaceutical formulation more generally point to continued growth in computationally guided ASD design [28,29,30].

12. Regulatory and Commercial Considerations

Quality by Design (QbD) has become close to a regulatory expectation for ASD product development, requiring systematic identification of critical material attributes (drug and polymer particle size, polymer grade and molecular weight, residual solvent specification) and critical process parameters (spray-drying inlet/outlet temperature, atomisation conditions, extrusion temperature and screw speed) and their quantitative linkage, through design-of-experiments methodology, to critical quality attributes such as residual crystallinity, particle size distribution, encapsulation homogeneity and dissolution performance [12,13]. Process analytical technology (PAT) — in-line Raman or near-infrared spectroscopy during spray drying or extrusion, for example — enables real-time monitoring of residual crystallinity and moisture content, supporting continuous manufacturing and reducing reliance on time-consuming offline testing. Stability requirements under International Council for Harmonisation (ICH) guidelines demand demonstration of adequate physical and chemical stability across the intended shelf life and storage conditions, with accelerated and long-term testing supplemented, increasingly, by predictive modelling to rationalise study design and de-risk formulation selection earlier in development [27].

Scale-up and commercialisation require robust technology transfer from laboratory to commercial manufacturing scale while maintaining consistent critical quality attributes, a challenge that has been substantially eased by the maturation of both spray-drying and hot-melt-extrusion equipment and by growing regulatory familiarity with the platform. More than twenty-five ASD-based drug products have received regulatory approval to date, spanning antifungal, antiviral, oncology and other therapeutic areas, with copovidone and HPMC-AS the most frequently used polymers and spray drying and hot-melt extrusion the dominant manufacturing routes; notable examples include the SUBA™ spray-dried itraconazole product marketed as Tolsura®, illustrating how ASD technology can enable 'super-bioavailability' formulations of long-established but poorly soluble active ingredients [25]. Table 6 summarises representative marketed ASD products.

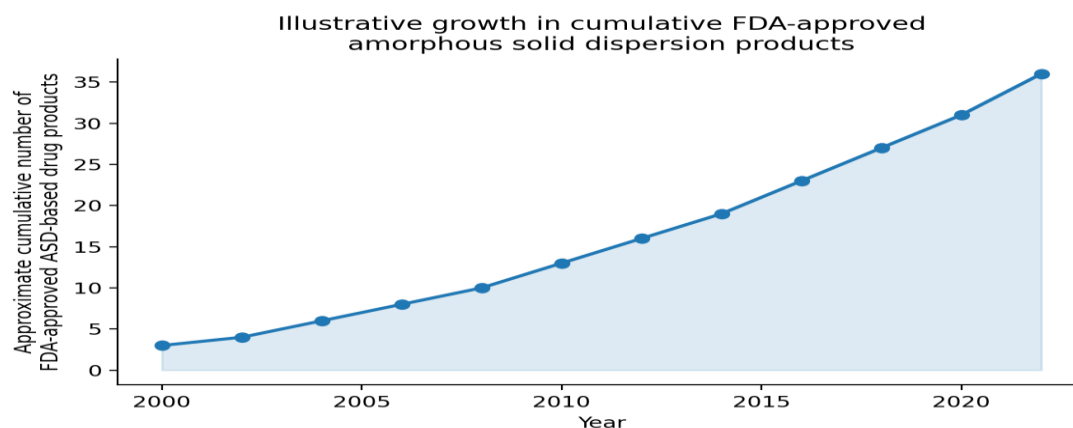


Figure 3. Illustrative cumulative growth in the number of amorphous-solid-dispersion-based drug products approved by regulatory authorities over time. Values are schematic and intended to convey the general reported growth trend rather than an exact, source-verified annual count.

Table 6. Representative marketed amorphous solid dispersion product types.

Representative product type	Polymer/carrier commonly used	Manufacturing technique	Therapeutic area (illustrative)
Spray-dried dispersion (SDD) tablet/capsule	HPMC-AS, copovidone	Spray drying	Antiviral, antifungal, oncology
Melt-extruded solid dispersion	Copovidone, Soluplus®, Eudragit®	Hot-melt extrusion	Antifungal, antiretroviral, cardiovascular
Enteric-polymer ASD ('super-bioavailability' formulation)	HPMC phthalate / HPMC-AS	Spray drying (e.g., SUBA™ process)	Antifungal (e.g., itraconazole)
Amorphous dispersion in capsule (powder-filled)	Povidone, copovidone	Spray drying, solvent evaporation	Oncology, antiviral

13. Future Perspectives

Continued progress in rational polymer selection, informed by computational miscibility prediction and growing mechanistic understanding of drug–polymer interaction, is expected to further reduce empirical screening burden during early formulation development. Solution-state stabilisation strategies that extend the spring-and-parachute concept — including engineered nanodroplet reservoirs and multi-component precipitation inhibitors — offer a route to more consistently sustained supersaturation across diverse drug chemotypes.

High-drug-loading formulations, whether achieved through mesoporous silica confinement, co-amorphous systems, or novel multifunctional polymers combining crystallisation inhibition with permeation-enhancing or self-emulsifying character, will likely continue to expand the range of challenging, high-dose poorly soluble drugs amenable to ASD technology. Continuous manufacturing, increasingly integrated with real-time process analytical technology, is positioned to become the industry standard for both spray-drying and hot-melt-extrusion-based ASD production, improving reproducibility and reducing development timelines.

AI-assisted ASD development, spanning polymer selection, process-parameter optimisation and physical-stability prediction, is likely to mature from an emerging research tool into a routine component of formulation workflows, complementing rather than replacing mechanistic physicochemical understanding [26,28,29,30]. Personalised dosage forms, enabled by 3D-printing and flexible continuous manufacturing, and improved prediction of in vivo performance through biorelevant dissolution testing and physiologically based pharmacokinetic modelling, represent longer-term but increasingly tangible opportunities for the continued evolution of ASD technology.

14. Conclusion

Amorphous solid dispersions have matured, over the 2011–2022 period reviewed here, from a mechanistically incompletely understood formulation curiosity into a well-characterised, commercially mainstream enabling technology for poorly water-soluble drugs. Advances in drug–polymer interaction science, manufacturing technology, high-drug-loading strategies including mesoporous silica and co-amorphous systems, and, increasingly, AI-assisted formulation and stability prediction, have collectively expanded both the range of drugs amenable to amorphisation and the confidence with which physically stable, commercially manufacturable ASD products can be developed. Continued attention to the stabilisation mechanisms, characterisation rigor, and regulatory and Quality-by-Design frameworks discussed throughout this review will remain essential to sustaining this trajectory as the technology is applied to an increasingly challenging pipeline of poorly soluble drug candidates.

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