INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Research Article

Novel Solid Dispersion Technologies: A Promising Approach for Solubility Enhancement

Pallavi Valvi*, Dr. Sujit Jadhav, Gaurav Takote, Taherim Shaikh

Kalyani Charitable Trust's, R.G Sapkal College of Pharmacy, Sapkal Knowledge Hub, Kalyani Hills, Anjaneri, Trimbakeshwar Road, Nashik, 422213, Maharashtra, India.

ARTICLE INFO

Published: 17 May 2026
Keywords:
solid dispersion, solubility enhancement, poorly water-soluble drugs, BCS classification, polymer carriers.
DOI:
10.5281/zenodo.20261474

ABSTRACT

Solubility represents one of the foremost challenges in contemporary drug development, with more than 40% of newly approved active pharmaceutical ingredients and approximately 70–90% of drug candidates in developmental pipelines classified as poorly water-soluble. Inadequate aqueous solubility directly impairs drug absorption and bioavailability, frequently rendering otherwise pharmacologically potent molecules therapeutically ineffective. Solid dispersions—defined as systems in which one or more active ingredients are dispersed in an inert carrier or matrix in the solid state—have emerged as one of the most versatile and scientifically validated strategies for overcoming this limitation. This review provides a comprehensive, critical appraisal of novel solid dispersion technologies, with emphasis on their physicochemical principles, manufacturing processes, and translational relevance. Technologies examined include hot melt extrusion (HME), spray drying and its advanced variants, electrospinning and electrospraying, supercritical fluid processing, microwave- and ultrasound-assisted techniques, three-dimensional (3D) printing-based platforms, KinetiSol® dispersive mixing, and co-amorphous systems. The review further addresses thermodynamic principles of amorphous solid dispersions (ASDs), polymer carrier selection, drug–polymer miscibility, advanced characterization methodologies, in vitro dissolution performance, in vivo biopharmaceutical outcomes, and the landscape of commercially approved solid dispersion products.

INTRODUCTION

1.1 Solubility as a Critical Parameter in Drug Development

The oral route remains the most preferred mode of drug administration, owing to patient convenience, ease of manufacturing, and the substantial body of regulatory precedent governing oral dosage

***Corresponding Author:** Pallavi Valvi
Address: *Kalyani Charitable Trust's, R.G Sapkal College of Pharmacy, Sapkal Knowledge Hub, Kalyani Hills, Anjaneri, Trimbakeshwar Road, Nashik, 422213, Maharashtra, India.*
Email : Pallavivalvi20181@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

forms.[1,2] Central to the performance of orally administered drugs are two fundamental biopharmaceutical properties: aqueous solubility and intestinal membrane permeability. A drug must dissolve in gastrointestinal (GI) fluid before it can be absorbed across the intestinal epithelium; consequently, inadequate aqueous solubility translates directly into poor dissolution, diminished absorption, low and variable bioavailability, and subtherapeutic plasma concentrations.[3,4]

The biopharmaceutical implications of poor solubility extend beyond reduced efficacy. Erratic absorption profiles driven by solubility limitations contribute to high inter-patient pharmacokinetic variability, food effects, dose-dependent toxicity arising from poorly predictable systemic exposure, and ultimately, increased rates of attrition in clinical drug development.[5,13] Industry analyses consistently estimate that formulation-related failures, a substantial proportion of which are attributable to poor physicochemical properties including solubility, account for approximately 40% of drug attrition during development.[6,14]

1.2 The BCS Classification System and the Poorly Soluble Drug Problem:

The Biopharmaceutics Classification System (BCS), introduced by Amidon et al. in 1995, provides a seminal scientific framework for predicting the in vivo absorption of orally administered drugs on the basis of their solubility and intestinal permeability.[3] Under this system, drugs are categorized into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). BCS Class II and IV drugs present the greatest formulation challenge, as their absorption is rate-limited by dissolution in GI fluids.[7,8]

Epidemiological analyses of approved drug databases and developmental pipelines consistently reveal a striking predominance of poorly water-soluble compounds. According to analyses of the FDA's Orange Book and independent surveys of the Lipinski chemical space, approximately 40% of currently marketed drugs and an estimated 70–90% of drugs in early-stage development exhibit low aqueous solubility.[9,10,16] This disparity reflects, in part, the increasing dominance of high-throughput combinatorial chemistry approaches that systematically favor hydrophobic, high-molecular-weight scaffolds with enhanced target affinity—a phenomenon described as 'molecular obesity.'[17] The net result is an urgent, unmet need for formulation technologies capable of overcoming solubility barriers in a robust, scalable, and regulatorily acceptable manner.[11]

1.3 Limitations of Conventional Solubility Enhancement Strategies:

A variety of physicochemical and formulation-based strategies have been developed to address the challenge of poor aqueous solubility, including particle size reduction (micronization, nanonization), salt formation, pH adjustment, use of co-solvents and surfactants, cyclodextrin complexation, and lipid-based drug delivery systems.[18] While each of these strategies has demonstrated efficacy in specific contexts, they are collectively associated with important limitations that restrict their general applicability. Micronization and nanonization increase drug surface area and thereby accelerate dissolution rate but do not fundamentally alter the thermodynamic solubility of the drug.[19] Salt formation is applicable only to ionizable molecules and may introduce solid-state stability concerns. Co-solvents and surfactants at concentrations required for solubilization often exceed tolerable thresholds

and may cause GI irritation or systemic toxicity.[20] Cyclodextrin complexation improves aqueous solubility but is constrained by stoichiometric complexation ratios, drug compatibility requirements, and formulation complexity.[21]

1.4 Historical Development and Evolution of Solid Dispersions:

The concept of the solid dispersion as a solubility enhancement strategy was introduced by Sekiguchi and Obi in 1961, who demonstrated that eutectic mixtures of sulfathiazole and urea exhibited markedly faster dissolution rates than the pure drug.[22] This seminal observation established the principle that intimate mixing of a poorly soluble drug with a water-soluble carrier in the solid state could dramatically improve drug release performance. Subsequent work by Chiou and Riegelman (1971) provided a systematic classification of solid dispersions into five types—simple eutectic mixtures, solid solutions, glass solutions, amorphous precipitates in crystalline carriers, and compound or complex formers—a taxonomy that remains foundational to the field.[23]

First-generation systems employed crystalline carriers such as urea, mannitol, and sorbitol.[10] Second-generation systems utilized amorphous polymer carriers, including polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC), which facilitated the preparation of amorphous solid dispersions (ASDs) characterized by higher apparent solubility.[24] Third-generation systems incorporated surfactants or self-emulsifying agents alongside polymeric carriers to further enhance wettability and inhibit recrystallization.[9,25] Contemporary solid dispersion research is increasingly defined by precision engineering of drug–polymer interactions at the molecular level, continuous manufacturing processes, and integration of computational modeling for formulation design.[26]

1.5 Objectives and Scope of This Review:

This review aims to provide a comprehensive and critically evaluative synthesis of the current state of solid dispersion science, with particular emphasis on novel and emerging preparation technologies. Literature was sourced from PubMed, ScienceDirect, Scopus, and Web of Science using search terms including 'solid dispersion,' 'amorphous solid dispersion,' 'hot melt extrusion,' 'spray drying,' 'solubility enhancement,' 'bioavailability,' 'BCS Class II,' and 'polymer carrier.' Priority was given to peer-reviewed publications from 2005 to 2025, with inclusion of seminal older works where appropriate.[4,5,7]

2. FUNDAMENTALS OF SOLID DISPERSIONS:

2.1 Definition and Classification:

A solid dispersion is broadly defined as a molecular-level mixture of one or more active pharmaceutical ingredients within an inert solid matrix, prepared by any of several physicochemical processes.[23] The classification proposed by Chiou and Riegelman (1971) and subsequently refined by Vasconcelos et al. (2007) and Leuner and Dressman (2000) identifies the following principal types: eutectic mixtures, solid solutions, amorphous solid dispersions (ASDs), glass solutions, and co-amorphous systems.[9,10,23] Among these, ASDs represent the thermodynamically highest energy form of the drug and therefore exhibit the greatest apparent solubility advantage over crystalline drug. However, this thermodynamic metastability also renders ASDs susceptible to recrystallization upon exposure to heat, moisture, or mechanical stress.[27,28]

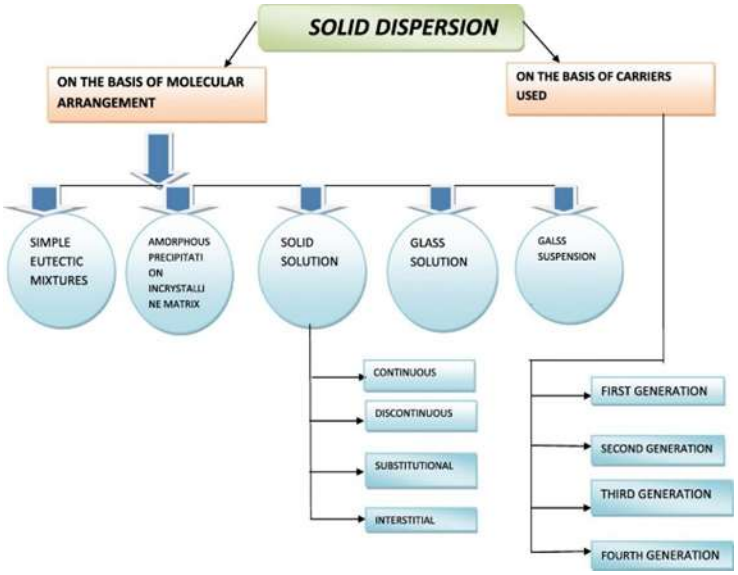

Figure 1: Classification of Solid Dispersions Based on Molecular Arrangement and Carrier Generations

2.2 Physicochemical Basis of Enhanced Solubility:

The solubility advantage conferred by solid dispersions relative to crystalline drug arises from several interrelated physicochemical mechanisms. First and most fundamental is the reduction or elimination of crystalline lattice energy: the highly ordered crystalline lattice of a drug represents a thermodynamic energy barrier to dissolution.[29] In amorphous solid dispersions, this lattice energy is largely absent, resulting in a higher apparent solubility—often termed 'spring' behavior—that can exceed crystalline solubility by one to two orders of magnitude for some drugs.[30] Second, solid dispersions dramatically reduce the effective particle size of the drug, which substantially increases specific surface area available for dissolution according to the Noyes-Whitney equation.[31] Third, dispersal of the drug within a hydrophilic polymer matrix improves wettability, reducing the contact angle between the drug particle surface and the dissolution medium.[5] Fourth, the polymer carrier may function as a precipitation inhibitor, stabilizing the supersaturated drug solution and extending the duration of elevated drug concentration in the GI lumen—so-called 'parachute' behavior. The combination of spring and parachute behaviors is widely recognized as the primary mechanism by which ASDs enhance oral bioavailability.[30,32]

2.3 Role of Polymer Carriers:

The physicochemical properties and molecular structure of the polymeric carrier exert a decisive influence on the performance of a solid dispersion, governing drug–polymer miscibility, physical stability, dissolution behavior, and manufacturability.[33] Polyvinylpyrrolidone (PVP) and its copolymer polyvinylpyrrolidone-vinyl acetate (PVP-VA or copovidone) are among the most extensively used polymers for ASDs prepared by solvent-based methods. PVP forms strong hydrogen bonds with many drug molecules, stabilizing the amorphous phase, but is hygroscopic and plasticized by moisture, which can accelerate crystallization under ambient humidity.[34] Hydroxypropyl methylcellulose acetate succinate (HPMC-AS) has emerged as a preferred carrier for HME-processed ASDs due to its exceptional ability to inhibit drug recrystallization from supersaturated solutions.[35] Soluplus® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) is

specifically engineered for HME processing, exhibiting favorable solubilizing capacity, low Tg, and self-emulsifying properties.[36]

2.4 Thermodynamics of Amorphous Solid Dispersions:

The thermodynamic stability and dissolution behavior of amorphous solid dispersions are governed by the principles of solution thermodynamics, particularly the Flory–Huggins polymer solution theory.[37] The free energy of mixing ($\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix}$) determines whether a drug and polymer are thermodynamically miscible. For an ASD to be physically stable, ΔG_{mix} must be negative at the processing and storage temperatures, and the Flory–Huggins interaction parameter (χ) must be below a critical value depending on the relative molecular volumes of drug and polymer.[38] When χ is large and positive, drug–polymer interactions are enthalpically unfavorable, predisposing the system to phase separation and recrystallization.[39]

The glass transition temperature (Tg) of the drug–polymer mixture is a critical stability parameter. The Gordon–Taylor equation predicts the Tg of a binary amorphous mixture, and storage temperature should ideally be at least 50°C below the Tg of the ASD to minimize molecular mobility and the propensity for recrystallization.[40,41] This thermodynamic framework informs rational polymer selection and drug loading optimization.[37]

2.5 Physical Stability Considerations:

Physical stability specifically, resistance to recrystallization during manufacturing, storage, and dissolution is the foremost challenge in ASD development.[27] Key stability-governing factors include the Tg of the ASD relative to storage temperature, the strength of drug–polymer hydrogen bonding and other molecular interactions, drug loading, moisture content (water acts as a plasticizer, dramatically depressing Tg), and the intrinsic crystallization tendency of the drug molecule.[28,42] Effective stability strategies encompass selection of high-Tg polymers, inclusion of moisture-barrier packaging, optimization of drug loading, and use of precipitation inhibitors in the formulation matrix.[33,43]

3. NOVEL SOLID DISPERSION TECHNOLOGIES:

3.1 Hot Melt Extrusion (HME):

Hot melt extrusion (HME) is a solvent-free continuous manufacturing technology that has emerged as arguably the most industrially significant method for the production of amorphous solid dispersions.[44] Originally developed for the plastics and food industries, HME was adapted for pharmaceutical applications in the 1980s and has since achieved widespread adoption in both clinical development and commercial manufacturing.[45] The technology involves feeding a blend of drug and thermoplastic carrier into a heated barrel containing one or two intermeshing rotating screws, which simultaneously convey, mix, melt, and disperse the blend components at controlled temperatures and shear rates. The resulting molten dispersion is extruded through a die and collected as strands, pellets, or directly shaped forms.[46]

The primary physicochemical process during HME is the disruption of drug crystallinity by thermal energy and mechanical shear, followed by molecular dispersion of the drug within the molten polymer matrix and rapid solidification, yielding an amorphous solid dispersion.[47] Key process parameters governing product quality include

barrel temperature profile, screw design and configuration, screw speed and throughput rate, feed rate and composition, and die geometry. Twin-screw extruders are strongly preferred over single-screw designs for pharmaceutical ASD manufacturing due to their superior mixing capability and flexibility.[44,48]

Process analytical technology (PAT) tools, including near-infrared (NIR) spectroscopy and Raman spectroscopy, have been integrated into HME lines to provide real-time monitoring of drug–polymer mixing, amorphous conversion, and melt temperature—enabling Quality by Design (QbD) compliant continuous manufacturing.[49] Commercially approved products prepared by HME include Kaletra® (lopinavir/ritonavir in PVP-VA), Onmel® (itraconazole in HPMC), Noxafil® (posaconazole in HPMC-AS), and Kalydeco® (ivacaftor in HPMC-AS), demonstrating the commercial viability and regulatory acceptability of the platform.[50,51]

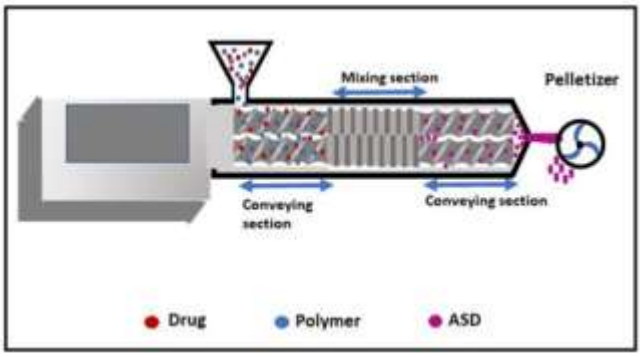

Figure 2: Schematic representation of hot melt extrusion process for preparation of amorphous solid dispersions.

3.2 Spray Drying and Advanced Spray Drying Technologies:

Spray drying is a solvent-based continuous process in which a solution or suspension of drug and polymer in a volatile solvent is atomized into fine droplets within a heated drying chamber, yielding dried particles upon rapid solvent evaporation.[52] The high surface-to-volume ratio of the spray droplets, combined with the thermal energy of the drying gas, facilitates nearly instantaneous solvent evaporation and quench-solidification of the drug-polymer matrix in the amorphous state. Spray drying is particularly well-suited to drugs and polymers that are thermolabile or incompatible with the thermal processing conditions of HME.[53]

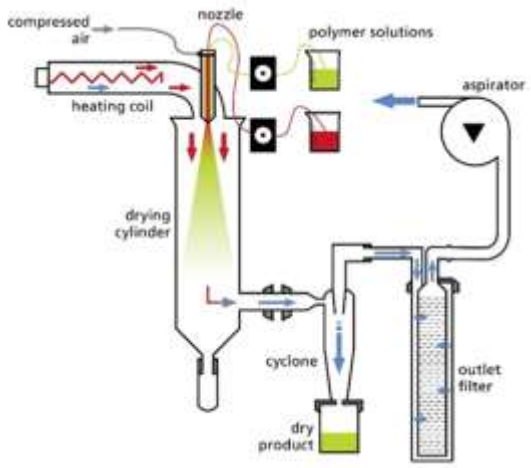

Figure 3: Schematic illustration of spray drying process used for preparation of amorphous solid dispersions.

Critical process parameters in spray drying include inlet and outlet gas temperatures, feed solution concentration and solvent composition, feed rate, atomization pressure and nozzle type, and drying gas flow rate.[54] Advanced variants of spray drying include spray freeze drying (lyophilization-spray hybrid), nano spray drying using vibrating mesh atomizers, and spray congealing.[55] Nano spray drying, employing piezoelectric mesh atomizers to generate droplets as small as 1–3 µm, enables production of sub-micron particles with uniquely defined morphology and enhanced dissolution rates.[56] Marketed products prepared by spray drying include Zelboraf® (vemurafenib in HPMC-AS), Incivek® (telaprevir in HPMC-AS), and Intelence® (etravirine in HPMC).[57,58]

3.3 Electrospinning and Electrospraying:

Electrospinning and electrospraying are electrostatic processing technologies that exploit high-voltage electric fields to generate nano-to-microscale fibers or particles from polymer solutions containing dissolved drug.[59] In electrospinning, a viscous polymer solution is fed through a charged metallic needle; the electrostatic repulsion between surface charges stretches the solution into a Taylor cone and then a fine jet that undergoes bending instabilities, solvent evaporation, and solidification during flight to the grounded collector, yielding continuous nanofibers with diameters typically in the range of 100–1000 nm.[60]

Electrospun nanofibers present several advantages for solid dispersion applications: their extremely high surface area and nanoscale diameter dramatically accelerate drug dissolution; the rapid solvent evaporation during fiber formation prevents drug recrystallization.[61] Drug–polymer combinations investigated in electrospun solid dispersions include ibuprofen-PVP, indomethacin-PVP, and felodipine-HPMC.[62] Despite promising laboratory results, the primary limitation of electrospinning for pharmaceutical manufacturing remains the challenge of scale-up, with current industrial implementations relying on multineedle or needleless configurations.[63]

3.4 Supercritical Fluid Technology:

Supercritical fluid (SCF) technologies exploit the unique physicochemical properties of fluids above their critical temperature and pressure—particularly carbon dioxide (CO_2, critical temperature 31.1°C, critical pressure 73.8 bar)—to produce solid dispersions under mild conditions without residual organic solvents.[64] The most widely investigated SCF processes include Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS) process, and Particles from Gas-Saturated Solutions (PGSS).[65] SCF technologies offer the key advantages of solvent-free or minimal-solvent processing, low residual solvent levels compliant with ICH Q3C guidelines, mild processing temperatures compatible with thermolabile drugs, and precise particle size control.[66]

3.5 Solvent Evaporation and Co-precipitation Methods:

Conventional solvent evaporation methods—including rotary evaporation, freeze drying (lyophilization), and thin-film evaporation—represent established laboratory-scale approaches to solid dispersion preparation.[10] In these methods, drug and polymer are co-dissolved in a common volatile solvent, which is subsequently removed by evaporation, yielding solid dispersions that are amorphous to the extent that

solvent removal is sufficiently rapid to prevent drug recrystallization.[67] Freeze drying is particularly valuable for labile macromolecules and biological drugs, as its low-temperature processing avoids thermal degradation.[68]

3.6 Microwave- and Ultrasound-Assisted Techniques:

Microwave-assisted and ultrasound-assisted processing represent emerging energy-assisted approaches that offer significant reductions in processing time and energy consumption compared with conventional thermal methods.[69] Microwave irradiation heats materials through dielectric polarization and ionic conduction, generating rapid, volumetric heating that can melt drug–polymer blends in seconds to minutes while minimizing exposure to elevated temperatures.[70] Microwave-assisted fusion has been demonstrated for the preparation of solid dispersions of ibuprofen, griseofulvin, and other BCS Class II drugs with carriers including PEG, PVP, and HPMC, yielding products comparable in dissolution performance to conventionally prepared dispersions.[71]

Ultrasound-assisted preparation employs high-intensity ultrasonic irradiation to generate cavitation phenomena in drug–polymer solutions or suspensions, accelerating dissolution of crystalline components, enhancing mixing, and facilitating nucleation control during co-precipitation or solvent evaporation.[72] Both microwave and ultrasound techniques are currently at early stages of pharmaceutical development, with limited scale-up data and no approved commercial products, but they represent scientifically compelling platforms for accelerated, energy-efficient solid dispersion manufacturing.[73]

3.7 Three-Dimensional Printing and Additive Manufacturing:

Three-dimensional (3D) printing technologies have attracted increasing attention as platforms for the fabrication of solid dispersion-based dosage forms, offering unprecedented opportunities for personalized medicine through patient-specific dose, release profile, and geometry customization.[74] Fused Deposition Modeling (FDM) employs thermoplastic filaments prepared by HME, which are melted and deposited in successive layers to build three-dimensional dosage forms.[75] Binder jetting selectively deposits a liquid binder onto a powder bed of drug and excipient, building up highly porous tablet structures with rapid disintegration and dissolution.[76] Stereolithography (SLA) and Digital Light Processing (DLP) employ photopolymerizable resins containing drug, allowing precise control of drug loading and geometric complexity.[77]

The FDA approval of Spritam® (levetiracetam, Aprecia Pharmaceuticals, 2015)—the first 3D-printed drug product to receive regulatory approval—demonstrated the regulatory acceptability of 3D printing for pharmaceutical manufacturing and catalyzed substantial research interest in 3D-printed solid dispersions.[78]

3.8 KinetiSol® and Continuous High-Shear Processing:

KinetiSol® Dispersive Mixing is a solvent-free, fusion-based technology that employs a modified pharmaceutical compounder to process drug–polymer blends under conditions of high frictional and shear energy at substantially lower temperatures and shorter residence times than conventional HME.[79] The KinetiSol® process subjects the blend to intense mechanical energy input from rotating blades within a thermally

controlled chamber, with frictional heat rapidly heating and melting the blend, which is then ejected within seconds by centrifugal force and quench-cooled to yield an amorphous solid dispersion.[80] The extremely short thermal exposure time (typically 10–15 seconds, compared to minutes in HME) makes KinetiSol® particularly advantageous for thermolabile drugs and for polymers such as HPMC and HPC that exhibit limited processability in conventional HME.[81]

3.9 Co-amorphous Systems:

Co-amorphous systems represent a conceptually distinct approach in which two or more small-molecule components—typically two drugs, or a drug and an amino acid or other low-molecular-weight excipient—are combined to form a single-phase amorphous system in the absence of a polymeric carrier.[82] The thermodynamic driving force for co-amorphous formation is the intermolecular interactions (hydrogen bonds, ionic interactions, pi-stacking) between the co-formers, which lower the free energy of the amorphous state and thereby improve physical stability relative to each pure amorphous component.[83] Drug–drug co-amorphous systems have been investigated for combinations including naproxen–cimetidine, indomethacin–ranitidine, and simvastatin–glipizide, with reports of improved stability and dissolution performance relative to single-component amorphous forms.[84] Drug–amino acid co-amorphous systems, particularly those incorporating arginine, phenylalanine, and tryptophan, have attracted considerable interest as these amino acids are generally recognized as safe (GRAS) excipients.[85]

4. CHARACTERIZATION OF SOLID DISPERSIONS:

4.1 Solid-State Characterization:

Powder X-ray Diffractometry (PXRD) is the definitive technique for assessing crystallinity in solid dispersions. Crystalline materials exhibit sharp, characteristic diffraction peaks at specific 2θ angles, while amorphous materials produce a broad, diffuse halo without distinct peaks.[86] PXRD is quantitative with appropriate calibration and can detect crystalline drug at concentrations as low as 1–5% by weight in the amorphous matrix.[87]

Differential Scanning Calorimetry (DSC) measures thermal events (melting, crystallization, glass transitions) in solid dispersions as a function of temperature. The Tg of the drug–polymer mixture—detected as a step change in heat flow—is a critical stability indicator.[88] Modulated DSC (mDSC) resolves overlapping thermal events and provides enhanced sensitivity for Tg detection in complex matrices.[89] Fast-scan DSC (HyperDSC) enables analysis at scan rates up to 2000°C/min, revealing recrystallization and melting events not observable at conventional scan rates.[90]

Fourier Transform Infrared (FTIR) and Raman spectroscopy provide information on molecular interactions in solid dispersions through shifts in characteristic absorption bands. Hydrogen bonding between drug and polymer is evidenced by shifts and broadening of carbonyl, hydroxyl, or amine stretching vibrations.[91] Solid-state NMR (ssNMR), including ^{1}H and ^{13}C cross-polarization magic angle spinning (CPMAS) NMR and ^{1}H spin-lattice relaxation time (T_1H) measurements, provides the most detailed molecular-level information on drug–polymer interactions and phase behavior in ASDs.[92,93]

4.2 Morphological Analysis:

Scanning electron microscopy (SEM) provides high-resolution topographical images of solid dispersion particles and surfaces, revealing

particle morphology, surface texture, and presence of crystalline domains.[94] Energy-dispersive X-ray spectroscopy (EDX) coupled to SEM enables elemental mapping for assessing drug distribution within the polymer matrix.[95] Transmission electron microscopy (TEM) and selected-area electron diffraction (SAED) offer atomic-scale resolution for characterizing nanostructured solid dispersions and detecting nanoscale crystalline domains.[96] Atomic force microscopy (AFM) provides three-dimensional nanoscale topographic and phase-contrast images of ASD surfaces, enabling quantification of surface roughness and detection of phase separation at the 10–100 nm scale.[97]

4.3 Dissolution and Solubility Testing:

In vitro dissolution testing is central to the biopharmaceutical evaluation of solid dispersions. For solid dispersions, where supersaturation and precipitation are key performance determinants, biorelevant media formulated to simulate fasted (FaSSIF) and fed (FeSSIF) state intestinal fluids provide more physiologically relevant data than simple aqueous buffers.[98] The two-stage dissolution model, combining a gastric phase (low pH) followed by transfer to intestinal conditions (neutral pH with bile salts), has been adopted as a standard protocol for solid dispersion evaluation.[99] Supersaturation degree and duration—measured as the area under the concentration-time curve during the supersaturation period (AUC_super)—are emerging as quantitative metrics for comparing solid dispersion performance.[100]

4.4 Computational and Molecular Modeling Approaches:

Computational methods have become indispensable tools for rational solid dispersion design, enabling prediction of drug–polymer miscibility, thermodynamic stability, and dissolution behavior prior to experimental work.[101] The Flory–Huggins interaction parameter (χ) can be estimated from solubility parameters calculated by the group contribution method or Hansen Solubility Parameters (HSP), providing a rapid screening criterion for polymer selection.[38] Molecular dynamics (MD) simulations offer atomistic-level insights into drug–polymer interactions, chain mobility, and the mechanisms of crystallization inhibition in amorphous matrices.[102] Machine learning models trained on experimental solid dispersion datasets are beginning to emerge as predictive tools for formulation optimization.[103]

4.5 Physical Stability Testing:

Physical stability testing of solid dispersions follows ICH Q1A(R2) guidelines for accelerated (40°C/75% RH) and long-term (25°C/60% RH) stability studies.[104] Dynamic Vapor Sorption (DVS) analysis characterizes the moisture uptake profile of solid dispersions and the plasticizing effect of absorbed water on Tg.[105] Isothermal calorimetry and dielectric analysis are emerging techniques for characterizing molecular mobility in amorphous systems—parameters strongly correlated with recrystallization kinetics.[106]

5. DRUG–POLYMER INTERACTION AND CARRIER SELECTION:

5.1 Principles of Drug–Polymer Miscibility:

Drug–polymer miscibility is a thermodynamic prerequisite for the formation of molecularly dispersed, single-phase amorphous solid dispersions. Miscibility is favored by a negative Flory–Huggins interaction parameter ($\chi < 0$), indicating net attractive drug–polymer interactions.[37] Strong molecular interactions between drug and polymer—particularly

hydrogen bonds, electrostatic interactions, and pi-pi stacking—are the primary thermodynamic drivers of miscibility.[107] Experimental assessment of drug–polymer miscibility employs melting point depression analysis, refractive index matching, mDSC (single Tg as indicator of miscibility), and ssNMR.[108] In silico approaches particularly HSP calculations and MD simulation—enable computational prescreening of large polymer libraries for compatibility with a given drug candidate, substantially reducing the experimental burden of formulation development.[109]

5.2 Commonly Used Polymer Carriers and Their Properties

Polymer	Trade Name	Key Properties	Preferred Method	Marketed Example
PVP-VA (Copovidone)	Kollidon VA 64	Low Tg (106°C), good miscibility, hygroscopic	HME, Spray Drying	Kaletra®
HPMC-AS	AQOAT®	High Tg, excellent precipitation inhibitor	HME, Spray Drying	Zelboraf®, Noxafil®
HPMC	Methocel™	Good stability, limited HME processability	Spray Drying, KinetiSol®	Sporanox®, Onmel®
Soluplus®	Soluplus®	Amphiphilic, low Tg (70°C), self-emulsifying	HME	In development
PEG 6000	Carbowax™	Low Tm, crystalline, excellent wettability	Fusion/Melt	Multiple generics
Eudragit® L100-55	Eudragit® L100-55	Enteric, pH > 5.5 dissolving, anionic	HME, Spray Drying	Enteric formulations
PVP K30	Kollidon 30	High Tg (168°C), strong H-bond donor, hygroscopic	Spray Drying, SE	Numerous

5.3 Role of Plasticizers and Surfactants:

Plasticizers reduce the Tg and melt viscosity of polymer carriers, enabling HME processing at lower temperatures and thereby extending the platform to thermolabile drugs. Commonly used plasticizers include triethyl citrate (TEC), polyethylene glycol (PEG) 400, dibutyl sebacate, and d-alpha tocopheryl polyethylene glycol succinate (TPGS).[110] Plasticizer selection must balance processability improvement against Tg reduction and potential drug–plasticizer phase separation.[111] Surfactants such as sodium lauryl sulfate (SLS), poloxamers, and TPGS improve drug wettability, enhance dissolution of the solid dispersion in aqueous media, and may function as precipitation inhibitors by maintaining drug molecules in a micellar or adsorbed state in solution.[112]

5.4 High-Throughput Formulation Screening:

Modern ASD development leverages high-throughput experimentation (HTE) platforms to rapidly screen large numbers of drug–polymer combinations and identify optimal formulation compositions.[113] Miniaturized solvent casting of drug–polymer films in 96-well plates, followed by automated PXRD or polarized light microscopy for crystallinity assessment, enables evaluation of hundreds of formulations within days.[114] Machine learning models trained on HTE datasets increasingly enable predictive formulation design, linking molecular descriptors of drug and polymer to formulation performance outcomes.[103]

6. IN VIVO PERFORMANCE AND BIOPHARMACEUTICAL ASSESSMENT:

6.1 In Vitro–In Vivo Correlation (IVIVC):

Establishing predictive in vitro–in vivo correlations (IVIVCs) for solid dispersion formulations is scientifically challenging but of substantial regulatory and practical value, as validated IVIVCs can reduce the need for in vivo bioequivalence studies during formulation changes and scale-up.[115] Level A IVIVC (point-to-point correlation between in vitro dissolution and in vivo absorption) is the highest and most scientifically rigorous level, but is difficult to achieve for solid dispersions owing to the complex, supersaturation-driven dissolution behavior.[116] Physiologically-based pharmacokinetic (PBPK) modeling, integrating mechanistic GI absorption models with drug-specific physicochemical and biopharmaceutical parameters, is increasingly adopted to predict in vivo performance from in vitro dissolution data and to support regulatory submissions.[117]

6.2 Pharmacokinetic Studies and Bioavailability Enhancement:

Preclinical pharmacokinetic (PK) studies in rat, dog, and non-human primate models provide early proof-of-concept evidence for solid dispersion-mediated bioavailability enhancement and inform human dose projection.[118] Multiple published studies demonstrate striking improvements in AUC and Cmax for BCS Class II drugs formulated as ASDs relative to crystalline drug, often in the range of 2- to 10-fold.[119] ASD formulations of itraconazole, vemurafenib, and lopinavir have demonstrated 2- to 4-fold improvements in relative bioavailability in clinical studies compared to their respective reference crystalline formulations.[50,57,120]

6.3 Biorelevant Dissolution Models and GI Simulation:

Biorelevant dissolution media formulated to simulate GI fluid composition—including FaSSIF (Fasted State Simulated Intestinal Fluid), FeSSIF (Fed State Simulated Intestinal Fluid), and FaSSGF (Fasted State Simulated Gastric Fluid)—provide substantially improved in vitro–in vivo predictability compared with simple pH buffer systems.[121] Dynamic GI simulation systems such as the TIM (TNO Intestinal Model) replicate the physiological mechanical and secretory functions of the stomach and small intestine, enabling evaluation of solid dispersion dissolution under conditions more representative of the human GI environment.[122]

6.4 Representative Clinical Evidence:

Kaletra® tablets (lopinavir/ritonavir HME-based ASD in PVP-VA, AbbVie) demonstrated substantially higher lopinavir bioavailability compared with the earlier soft gelatin capsule formulation, enabling a 33% dose reduction and elimination of the requirement for refrigerated storage.[50] Zelboraf® (vemurafenib spray-dried dispersion in HPMC-AS) achieved 4.5-fold higher AUC than micronized crystalline vemurafenib in Phase I clinical studies.[57] Noxafil® delayed-release tablets (posaconazole HME-based ASD in HPMC-AS) demonstrated 3.3-fold higher AUC compared with the original posaconazole oral suspension, with markedly reduced food effect.[51]

7. COMMERCIALLY APPROVED SOLID DISPERSION PRODUCTS:

7.1 Overview of FDA-Approved Solid Dispersion Products:

Product (Brand)	Drug	Indication	Polymer	Technology	Year
Kaletra® tablets	Lopinavir/Ritonavir	HIV infection	PVP-VA	HME	2005
Onmel®	Itraconazole	Onychomycosis	HPMC	HME	2010

Zelboraf®	Vemurafenib	Melanoma (BRAF+)	HPMC-AS	Spray Drying	2011
Incivek®	Telaprevir	Hepatitis C	HPMC-AS	Spray Drying	2011
Noxafil® DR	Posaconazole	Fungal prophylaxis	HPMC-AS	HME	2013
Kalydeco®	Ivacaftor	Cystic fibrosis	HPMC-AS	HME	2012
Harvoni®	Ledipasvir/Sofosbuvir	Hepatitis C	HPMC-AS	Spray Drying	2014
Epclusa®	Sofosbuvir/Velpatasvir	Hepatitis C	HPMC-AS	Spray Drying	2016
Intelence®	Etravirine	HIV infection	HPMC	Spray Drying	2008
Sporanox® Pellets	Itraconazole	Fungal infections	HPMC	HME	1992

7.2 Case Study: Ritonavir and the Crystal Form Crisis:

The history of ritonavir (Abbott Laboratories, now AbbVie) represents a landmark case study in the pharmaceutical consequences of polymorphism and the critical importance of solid dispersion technology in drug product rescue.[123] Ritonavir was initially approved in 1996 as a soft gelatin capsule formulation (Norvir®) based on a metastable polymorph (Form I). In 1998, unexpected appearance of a thermodynamically stable but much less soluble polymorph (Form II) caused spontaneous crystallization of ritonavir in the capsule formulation, necessitating a worldwide recall.[124] The formulation rescue ultimately yielded Kaletra® tablets based on an HME-processed dispersion of lopinavir and ritonavir in PVP-VA. The ritonavir crisis profoundly influenced pharmaceutical industry practices regarding polymorphism characterization, stability-indicating dissolution testing, and the use of ASD formulation strategies to mitigate polymorph-related risks.[125]

7.3 Case Study: Vemurafenib (Zelboraf®):

Vemurafenib, a BRAF kinase inhibitor for treatment of BRAF V600E-mutant unresectable or metastatic melanoma, exemplifies the enabling role of spray-dried solid dispersion technology in the clinical development of a practically insoluble drug. Vemurafenib has an aqueous solubility of approximately 0.01 µg/mL and a log P of 3.98, placing it firmly in BCS Class II.[57] Initial clinical studies with crystalline vemurafenib capsules revealed severely inadequate bioavailability with intolerable high-dose requirements. Reformulation as a spray-dried dispersion with HPMC-AS yielded a 4.5-fold improvement in AUC relative to the crystalline form in a Phase I crossover study.[57,126] The clinical program demonstrated objective response rates of 48% in BRAF V600E-positive melanoma patients—outcomes that would have been unachievable with the crystalline drug formulation.[127]

8. CHALLENGES AND FUTURE PERSPECTIVES:

8.1 Physical and Chemical Stability Challenges:

Physical instability—manifested as crystallization of the amorphous drug during storage or dissolution—remains the most pervasive and consequential challenge in amorphous solid dispersion development.[27,28] The thermodynamically metastable nature of the amorphous state means that all ASDs are in principle susceptible to crystallization; the practical question is whether the rate of crystallization under realistic storage conditions is sufficiently slow to ensure acceptable shelf life.[42] Chemical instability—including hydrolysis, oxidation, and drug–polymer covalent interactions—presents an additional challenge, particularly for drugs with reactive functional groups and for formulations processed at elevated

temperatures.[128] Reactive impurities generated by polymer degradation during HME processing (e.g., acetic acid from HPMC-AS, formaldehyde from PVP) may react with drug molecules bearing susceptible nucleophilic groups, generating degradation products that compromise both safety and efficacy.[129]

8.2 Scale-Up and Continuous Manufacturing:

The translation of solid dispersion formulations from laboratory scale to pilot and commercial manufacturing scales presents significant engineering and regulatory challenges.[44] For HME-based processes, scale-up involves transitioning from small-scale twin-screw extruders (throughputs of grams per hour) through pilot scale (kilograms per hour) to commercial scale (hundreds of kilograms per hour), requiring careful re-optimization of screw configuration, temperature profiles, and throughput to maintain product quality.[48] Integration of PAT (NIR, Raman, acoustic emission) into continuous HME and spray drying lines enables real-time monitoring and feedback control of critical quality attributes (CQAs) including amorphous content, drug–polymer homogeneity, and particle size, consistent with ICH Q13 (Continuous Manufacturing of Drug Substances and Drug Products, 2022).[49,130]

8.3 Regulatory Considerations:

The regulatory framework for amorphous solid dispersions is substantially more complex than that for conventional crystalline formulations. Key regulatory considerations include: demonstration of amorphous form identity and absence of crystallinity by validated analytical methods; stability characterization per ICH Q1A(R2); characterization of the solid dispersion's drug substance component as a unique physical form per ICH Q6A; and justification of drug loading, polymer type, and manufacturing process parameters within a Design Space defined by QbD principles per ICH Q8, Q9, and Q10.[104,131] The FDA's guidance on amorphous solid dispersions and the EMA's Guideline on the Investigation of Bioequivalence provide foundational regulatory expectations for solid dispersion development and registration.[132]

8.4 Emerging Trends and Future Research Directions:

Artificial intelligence (AI) and machine learning (ML) algorithms trained on large curated datasets of formulation compositions, process parameters, and performance outcomes are beginning to demonstrate predictive utility for polymer selection, drug loading optimization, and stability prediction in ASD development.[103] Integration of AI/ML with high-throughput experimentation platforms creates a closed-loop automated formulation development cycle capable of dramatically accelerating the pace of ASD optimization.[113]

Nanostructured solid dispersions—systems in which the drug is distributed within a nanostructured lipid or polymer carrier at the nanometer scale—represent an emerging hybrid platform combining the solubility advantages of amorphous dispersion with the physical stability benefits of nanoparticle encapsulation.[133] Controlled-release amorphous solid dispersions—enabling sustained or pulsatile drug release while maintaining the solubility advantage of the amorphous form—represent a frontier formulation challenge with substantial therapeutic potential for chronic disease management.[134] Personalized solid dispersion formulations enabled by 3D printing and digital pharmacy platforms may ultimately allow dose and release profile customization at the point of care, transforming the

pharmaceutical supply chain for populations with specialized therapeutic needs.[74,78]

9. CONCLUSION:

Solid dispersion technology has evolved from a laboratory curiosity into a cornerstone of modern pharmaceutical formulation science, enabling the clinical development and commercialization of numerous drugs that would otherwise have failed due to inadequate oral bioavailability. The technologies reviewed herein—spanning hot melt extrusion, spray drying, electrospinning, supercritical fluid processing, microwave- and ultrasound-assisted methods, 3D printing, KinetiSol® dispersive mixing, and co-amorphous systems—collectively represent a rich and increasingly mature toolkit for overcoming the solubility barrier in drug development.

The scientific understanding of amorphous solid dispersions has advanced substantially: thermodynamic frameworks now allow rational prediction of drug–polymer miscibility and stability; advanced characterization techniques including ssNMR, fast-scan DSC, and high-resolution electron microscopy provide molecular-level insights; and biorelevant in vitro dissolution models and PBPK modeling increasingly enable prospective prediction of in vivo performance. The commercial success of solid dispersion products including Kaletra®, Zelboraf®, and Noxafil® demonstrates that the regulatory pathway for ASD products is well-established and that the technology can be implemented at industrial scale.

Looking forward, the convergence of computational formulation design, AI/ML-guided optimization, advanced manufacturing platforms, and precision medicine imperatives positions solid dispersion technology for continued growth and innovation. As the pharmaceutical pipeline continues to be dominated by poorly water-soluble molecules, solid dispersion technologies will remain not merely promising, but essential, to the translation of pharmacological innovation into clinical benefit.

REFERENCES

1. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44(1):235–249.
2. Ku MS. Use of the biopharmaceutical classification system in early drug development. AAPS J. 2008;10(1):208–212.
3. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–420.
4. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of BCS Class II drugs. J Pharm Sci. 2016;105(9):2527–2544.
5. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23–24):1068–1075.
6. Repka MA, Bandari S, Kallakunta VR, et al. Melt extrusion with poorly soluble drugs – an integrated review. Int J Pharm. 2018;535(1–2):68–85.
7. Singh A, Van den Mooter G. Spray drying formulation of amorphous solid dispersions. Adv Drug Deliv Rev. 2016;100:27–50.
8. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002;54(2):107–117.

9. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47–60.
10. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3):799–813.
11. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery: a review. Pharm Sci Technol Today. 2000;3(4):138–145.
12. Williams HD, Trevaskis NL, Charman SA, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013;65(1):315–499.
13. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442–453.
14. Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. AAPS J. 2011;13(4):519–547.
15. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm. 2000;50(1):3–12.
16. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Mol Pharm. 2006;3(6):631–643.
17. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov. 2007;6(11):881–890.
18. Jain NK. Advances in controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers; 2001.
19. Müller RH, Peters K. Nanosuspensions for the formulation of poorly soluble drugs. Int J Pharm. 1998;160(2):229–237.
20. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res. 2004;21(2):201–230.
21. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007;59(7):645–666.
22. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9(11):866–872.
23. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281–1302.
24. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058–1066.
25. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. J Pharm Pharmacol. 2009;61(12):1571–1586.
26. Huang Y, Dai WG. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm Sin B. 2014;4(1):18–25.
27. Bhugra C, Pikal MJ. Role of thermodynamic, molecular, and kinetic factors in crystallization from the amorphous state. J Pharm Sci. 2008;97(4):1329–1349.
28. Marsac PJ, Shamblin SL, Taylor LS. Estimation of drug–polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm Res. 2006;23(10):2417–2426.
29. Murdande SB, Pikal MJ, Shankar RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals, Part 1: A

thermodynamic analysis. J Pharm Sci. 2010;99(3):1254–1264.
30. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci. 2009;98(8):2549–2572.
31. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930–934.
32. Frank KJ, Westedt U, Rosenblatt KM, et al. What is the mechanism behind increased permeation rate of a poorly soluble drug from aqueous dispersions of an amorphous solid dispersion? J Pharm Sci. 2014;103(6):1779–1787.
33. Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. J Pharm Sci. 2012;101(4):1355–1377.
34. Nair R, Nyamweya N, Gönen S, Martinez-Miranda LJ, Hoag SW. Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): a thermodynamic and spectroscopic investigation. Int J Pharm. 2001;225(1–2):83–96.
35. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm. 2008;5(6):1003–1019.
36. Feldhues L, Schönherr H, Hirt TD. Soluplus® – a novel excipient for pharmaceutical solid dispersions. Drug Dev Ind Pharm. 2019;45(1):1–12.
37. Flory PJ. Thermodynamics of high polymer solutions. J Chem Phys. 1942;10(1):51–61.
38. Marsac PJ, Li T, Taylor LS. Estimation of drug–polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm Res. 2009;26(1):139–151.
39. Vasanthavada M, Tong WQ, Joshi Y, Kislalioglu MS. Phase behavior of amorphous molecular dispersions II: role of hydrogen bonding in solid solubility and phase separation kinetics. Pharm Res. 2005;22(3):440–448.
40. Gordon M, Taylor JS. Ideal copolymers and the second-order transitions of synthetic rubbers. J Appl Chem. 1952;2(9):493–500.
41. Shamblin SL, Taylor LS, Zografi G. Mixing behavior of colyophilized binary systems. J Pharm Sci. 1998;87(6):694–701.
42. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12.
43. Trasi NS, Taylor LS. Effect of polymers on nucleation and crystal growth of amorphous acetaminophen. CrystEngComm. 2012;14(16):5188–5197.
44. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev Ind Pharm. 2007;33(9):909–926.
45. Breitenbach J. Melt extrusion can bring new benefits to HIV therapy. Am J Drug Deliv. 2006;4(2):61–64.
46. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS PharmSciTech. 2016;17(1):20–42.
47. Sarode AL, Sandhu H, Shah N, Malick W, Zia H. Hot melt extrusion (HME) for amorphous solid dispersions: predictive tools for processing and impact of drug–polymer interactions on supersaturation. Eur J Pharm Sci. 2013;48(3):371–384.
48. Shah S, Maddineni S, Lu J, Repka MA. Melt extrusion with poorly soluble drugs. Int J Pharm. 2013;453(1):233–252.
49. Fischer D, Kawakami K, Kock S. Real-time monitoring of hot melt extrusion using near-

infrared spectroscopy. J Pharm Sci. 2017;106(2):579–588.
50. Brüning J, Lopes J, Woithe N, Dreessen T. Hot melt extrusion of Kaletra® (lopinavir/ritonavir) – formulation strategy for a combination HIV protease inhibitor product. Eur J Pharm Biopharm. 2020;149:215–226.
51. Kambayashi A, Sugano K. Oral absorption of posaconazole from an amorphous solid dispersion. Drug Metab Pharmacokinet. 2014;29(6):458–464.
52. Paudel A, Worku ZA, Meeus J, Guns S, Van den Mooter G. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. Int J Pharm. 2013;453(1):253–284.
53. Vehring R. Pharmaceutical particle engineering via spray drying. Pharm Res. 2008;25(5):999–1022.
54. Grasmeijer N, Stankovic M, de Waard H, Frijlink HW, Hinrichs WL. Unraveling protein stabilization mechanisms: vitrification and water replacement in a glass transition temperature controlled system. Biochim Biophys Acta. 2013;1834(4):763–769.
55. Peltonen L, Hirvonen J. Pharmaceutical nanocrystals by nanomilling: critical process parameters, particle fracturing and stabilization methods. J Pharm Pharmacol. 2010;62(11):1569–1579.
56. Heng D, Lee SH, Ng WK, Tan RBH. The nano spray dryer B-90. Expert Opin Drug Deliv. 2011;8(7):965–972.
57. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: An overview. Mol Pharm. 2008;5(6):1003–1019. [Zelboraf data: FDA label, NDA 202429, 2011.]
58. Koro J, Teckoe J, Mowrey D. Formulation and in vitro evaluation of etravirine tablet for controlled drug delivery. Drug Dev Ind Pharm. 2012;38(11):1351–1362.
59. Tiwari SK, Venkatraman SS. Electrospinning as a potential technique for drug delivery. Drug Deliv. 2012;19(2):55–63.
60. Bhardwaj N, Kundu SC. Electrospinning: a fascinating fiber fabrication technique. Biotechnol Adv. 2010;28(3):325–347.
61. Srikar R, Yarin AL, Megaridis CM, Bazilevsky AV, Kelley E. Desorption-limited mechanism of release from polymer nanofibers. Langmuir. 2008;24(3):965–974.
62. Zamani M, Prabhakaran MP, Ramakrishna S. Advances in drug delivery via electrospun and electrosprayed nanomaterials. Int J Nanomedicine. 2013;8:2997–3017.
63. Bock N, Woodruff MA, Hutmacher DW, Dargaville TR. Electrospraying, a reproducible method for production of polymeric microspheres for biomedical applications. Polymers. 2011;3(1):131–149.
64. York P. Strategies for particle design using supercritical fluid technologies. Pharm Sci Technol Today. 1999;2(11):430–440.
65. Pasquali I, Bettini R, Giordano F. Supercritical fluid technologies: an innovative approach for manipulating the solid-state of pharmaceuticals. Adv Drug Deliv Rev. 2008;60(3):399–410.
66. Velaga SP, Berger R, Carlfors J. Supercritical fluids crystallization of budesonide and flunisolide. Pharm Res. 2002;19(10):1564–1571.
67. Meng F, Trivino A, Prasad D, Chauhan H. Investigation and correlation of drug polymer miscibility and molecular interactions with crystallization inhibition of amorphous solid dispersions. Eur J Pharm Sci. 2015;71:12–24.

68. Tang X, Pikal MJ. Design of freeze-drying processes for pharmaceuticals: practical advice. Pharm Res. 2004;21(2):191–200.
69. Leuenberger H, Lanz M. Pharmaceutical powder technology: from art to science—the challenge of the FDA's Process Analytical Technology initiative. Adv Powder Technol. 2005;16(1):3–25.
70. Bhatt JM, Galgatte UC, Chaudhari PD. Microwave-induced solid dispersion technique: a review. Int J Pharm Sci Res. 2013;4(7):2557–2569.
71. Bhatt JM, Galgatte UC, Chaudhari PD. Microwave-induced solid dispersion technique for preparation of ibuprofen solid dispersions using PEG 4000. Int J Pharm Pharm Sci. 2014;6(1):318–323.
72. Patel RP, Patel MM. Sonoprecipitation of mucoadhesive glipizide-loaded polymeric nanoparticles. Pharm Dev Technol. 2010;15(6):600–607.
73. Rao VM, Haslam JL, Stella VJ. Controlled and complete release of a model poorly water-soluble drug, prednisolone acetate, from hydroxypropyl methylcellulose matrix tablets using (SBE)7m-beta-cyclodextrin as a solubilizing agent. J Pharm Sci. 2001;90(6):807–816.
74. Ventola CL. Medical applications for 3D printing: current and projected uses. P T. 2014;39(10):704–711.
75. Goyanes A, Buanz ABM, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm. 2015;89:157–162.
76. Aprecia Pharmaceuticals. First FDA-approved medicine manufactured using 3D printing technology. Press release. 2015. https://www.aprecia.com.
77. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. Int J Pharm. 2016;503(1–2):207–212.
78. FDA. Spritam (levetiracetam) tablets, for oral suspension. NDA 207958. Silver Spring, MD: FDA; 2015.
79. DiNunzio JC, Brough C, Miller DA, Williams RO 3rd, McGinity JW. Applications of KinetiSol dispersing for the production of plasticizer free amorphous solid dispersions. Eur J Pharm Sci. 2010;40(3):179–187.
80. Brough C, Williams RO 3rd. Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug candidates. Int J Pharm. 2013;453(1):157–166.
81. Davis DA, Miller DA, DiNunzio JC, Yang Z, McGinity JW, Williams RO 3rd. Enhanced bioavailability through creation of an amorphous itraconazole–polaxamer 188 solid dispersion by KinetiSol® Dispersing. Drug Dev Ind Pharm. 2012;38(12):1408–1419.
82. Löbmann K, Grohganz H, Laitinen R, Strachan C, Rades T. Amino acids as co-amorphous stabilizers for poorly water soluble drugs – Part 1: preparation, stability and dissolution enhancement. Eur J Pharm Biopharm. 2013;85(3):873–881.
83. Dengale SJ, Grohganz H, Rades T, Löbmann K. Recent advances in co-amorphous drug formulations. Adv Drug Deliv Rev. 2016;100:116–125.
84. Allesø M, Chieng N, Rehder S, Rantanen J, Rades T, Aaltonen J. Enhanced dissolution rate and synchronized release of drugs in binary systems through formulation: amorphous naproxen-cimetidine mixtures prepared by mechanical activation. J Control Release. 2009;136(1):45–53.
85. Löbmann K, Laitinen R, Grohganz H, Gordon KC, Strachan C, Rades T. Coamorphous drug systems: enhanced physical stability and

dissolution rate of indomethacin and naproxen. Mol Pharm. 2011;8(5):1919–1928.
86. Bugay DE. Characterization of the solid-state: spectroscopic techniques. Adv Drug Deliv Rev. 2001;48(1):43–65.
87. Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, eds. Amorphous Solid Dispersions: Theory and Practice. New York: Springer; 2014.
88. Kalogeras IM. A novel approach for analyzing glass-transition temperature vs. composition patterns: application to pharmaceutical compound + polymer systems. Eur J Pharm Sci. 2011;42(5):470–483.
89. Reading M, Hourston DJ, eds. Modulated Temperature Differential Scanning Calorimetry. Dordrecht: Springer; 2006.
90. McGregor C, Saunders MH, Buckton G, Saklatvala RD. The use of high-speed differential scanning calorimetry (hyper-DSC) to study the thermal properties of carbamazepine polymorphs. Thermochim Acta. 2004;417(2):231–237.
91. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res. 1997;14(12):1691–1698.
92. Geppi M, Mollica G, Borsacchi S, Veracini CA. Solid-state NMR studies of pharmaceutical systems. Appl Spectrosc Rev. 2008;43(3):202–302.
93. Pham TN, Watson SA, Edwards AJ, Chavda M, Clawson JS, Strohmeier M, Vogt FG. Analysis of amorphous solid dispersions using 2D solid-state NMR and ^{1}H T1 relaxation measurements. Mol Pharm. 2010;7(5):1667–1691.
94. Goldstein JI, Newbury DE, Echlin P, et al. Scanning Electron Microscopy and X-Ray Microanalysis. 3rd ed. New York: Springer; 2003.
95. Vankeirsbilck T, Vercauteren A, Baeyens W, et al. Applications of Raman spectroscopy in pharmaceutical analysis. Trends Anal Chem. 2002;21(12):869–877.
96. Williams DB, Carter CB. Transmission Electron Microscopy: A Textbook for Materials Science. 2nd ed. New York: Springer; 2009.
97. Binnig G, Quate CF, Gerber C. Atomic force microscope. Phys Rev Lett. 1986;56(9):930–933.
98. Dressman JB, Reppas C. In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci. 2000;11(Suppl 2):S73–S80.
99. Klein S. The use of biorelevant dissolution media to forecast the in vivo performance of a drug. AAPS J. 2010;12(3):397–406.
100. Bevernage J, Brouwers J, Annaert P, Augustijns P. Drug precipitation-permeation interplay: supersaturation in an absorptive environment. Eur J Pharm Biopharm. 2012;82(2):424–428.
101. Forrest JA, Dalnoki-Veress K. The glass transition in thin polymer films. Adv Colloid Interface Sci. 2001;94(1–3):167–196.
102. Xiang TX, Anderson BD. Molecular dynamics simulation of amorphous indomethacin-poly(vinylpyrrolidone) glasses: solubility and hydrogen bonding interactions. J Pharm Sci. 2013;102(3):876–891.
103. Ramsay E, Rantanen J, Mlynek K, et al. Machine learning in formulation science. Eur J Pharm Biopharm. 2020;155:171–192.
104. ICH Q1A(R2). Stability Testing of New Drug Substances and Drug Products. Geneva: International Council for Harmonisation; 2003.
105. Burnett DJ, Bhardwaj AR, Bhardwaj RC. Moisture sorption isotherms and other

physicochemical characteristics of solid dosage forms. Pharm Dev Technol. 2012;17(3):281–290.
106. Bhugra C, Rambhatla S, Bakri A, et al. Prediction of the onset of crystallization of amorphous sucrose below the calorimetric glass transition temperature from correlations with mobility. J Pharm Sci. 2007;96(5):1258–1269.
107. Wegiel LA, Mauer LJ, Edgar KJ, Taylor LS. Crystallization of amorphous solid dispersions of resveratrol during preparation and storage—impact of different polymers. J Pharm Sci. 2013;102(1):171–184.
108. Zhao Y, Lamm MS, Taylor LS, Bhambhani A. Drug–excipient miscibility: a key parameter in screening for amorphous solid dispersion formulations. Int J Pharm. 2018;537(1–2):140–149.
109. Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci. 1999;88(11):1182–1190.
110. Mehuys E, Vervaet C, Remon JP. Hot-melt extruded ethylcellulose cylinders containing a HPMC-PEG-based drug-release controlling matrix. J Control Release. 2004;94(2–3):273–280.
111. Ghosh I, Snyder J, Vippagunta R, Alvine M, Vakil R, Tong WQ, Vippagunta S. Comparison of HPMC based polymers performance used in the manufacture of oral controlled release tablets and its effect on drug release mechanism. Int J Pharm. 2011;409(1–2):235–243.
112. Weuts I, Kempen D, Decorte A, et al. Phase behaviour analysis of solid dispersions of loperamide and two of its analogues with the polymers PVP-K30 and PVP-VA64. Eur J Pharm Sci. 2005;25(2–3):313–320.
113. Saal C, Becker A. Pharmaceutical salts: a summary on doses and solubility advantages. Pharm Res. 2013;30(11):2712–2728.
114. Knopp MM, Löbmann K, Elder DP, Rades T, Holm R. Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development. Eur J Pharm Sci. 2016;87:164–173.
115. FDA. Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. Silver Spring, MD: FDA; 1997.
116. Polli JE. In vitro studies are sometimes better than conventional human pharmacokinetic in vivo studies in assessing bioequivalence of immediate-release solid oral dosage forms. AAPS J. 2008;10(2):289–299.
117. Sjögren E, Westergren J, Grant I, et al. In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: application of the mechanistic absorption model GI-Sim. Eur J Pharm Sci. 2013;49(4):679–698.
118. Morgen M, Bloom C, Beyerinck R, et al. Polymeric nanoparticles for increased oral bioavailability and rapid absorption using celecoxib as a model of a low-solubility, high-permeability drug. Pharm Res. 2012;29(2):427–440.
119. Miller JM, Beig A, Carr RA, Spence JK, Dahan A. A winning combination of oral lipid-based formulations and intravenous cyclodextrin solution: enhancing systemic bioavailability of a BCS IV drug. Mol Pharm. 2012;9(8):2009–2016.
120. Six K, Verreck G, Peeters J, Brewster M, Van den Mooter G. Increased physical stability and improved dissolution properties of itraconazole, a class II drug, by solid dispersions that combine fast- and slow-

dissolving polymers. J Pharm Sci. 2004;93(1):124–131.
121. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm Res. 1998;15(1):11–22.
122. Verwei M, Freidig AP, Havenaar R, Groten JP. Predicted serum folate concentrations based on in vitro studies and kinetic modeling are consistent with observed data from a short-term human dietary study. J Nutr. 2006;136(12):3074–3078.
123. Chemburkar SR, Bauer J, Deming K, et al. Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. Org Process Res Dev. 2000;4(5):413–417.
124. Bauer J, Spanton S, Henry R, et al. Ritonavir: an extraordinary example of conformational polymorphism. Pharm Res. 2001;18(6):859–866.
125. Knapik-Kowalczuk J, Wojnarowska Z, Chmiel K, Rams-Baron M, Tajber L, Paluch M. Dielectric relaxation study on molecular dynamics of co-amorphous systems with enhanced physical stability. Mol Pharm. 2017;14(8):2777–2786.
126. Gonzalez-Alvarez I, Fernandez-Garcia R, Gonzalez-Alvarez M, Bermejo M. Oral bioavailability of vemurafenib (Zelboraf®) in tumor-bearing rats using solid lipid nanoparticles. Molecules. 2016;21(6):735.
127. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–2516.
128. Kolter K, Karl M, Gryczke A. Hot-melt extrusion with BASF pharma polymers: extrusion compendium. 2nd ed. Ludwigshafen: BASF SE; 2012.
129. Forster A, Hempenstall J, Rades T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J Pharm Pharmacol. 2001;53(3):303–315.
130. ICH Q13. Continuous Manufacturing for Drug Substances and Drug Products. Geneva: International Council for Harmonisation; 2022.
131. ICH Q6A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. Geneva: International Council for Harmonisation; 1999.
132. EMA. Guideline on the Investigation of Bioequivalence. London: European Medicines Agency; 2010. Doc. Ref. CPMP/EWP/QWP/1401/98 Rev. 1.
133. Naguib YW, Rodriguez BL, Li X, Hursting SD, Williams RO 3rd, Cui Z. Solid lipid nanoparticle formulations of docetaxel prepared with high melting point triglycerides: in vitro and in vivo evaluation. Mol Pharm. 2014;11(4):1239–1249.
134. Repka MA, Shah S, Lu J, et al. Melt extrusion: process to product. Expert Opin Drug Deliv. 2012;9(1):105–125.

HOW TO CITE: Pallavi Valvi, Dr. Sujit Jadhav, Gaurav Takote, Taherim Shaikh, Novel Solid Dispersion Technologies: A Promising Approach for Solubility Enhancement, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 4261-4282. https://doi.org/10.5281/zenodo.20261474