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

Review Paper

Enhancement of Solubility and Dissolution Rate of Poorly Water-Soluble Antifungal Drugs by Hot-Melt Extrusion Method

Ranjit Sakhare*, Dr Sudarshan Nagrale, Dr. Vishal Babar

Dattakala Shikshan Sanstha's, Dattakala College of Pharmacy.

ARTICLE INFO

Published: 28 July 2026
Keywords:
hot-melt extrusion; amorphous solid dispersion; itraconazole; posaconazole; griseofulvin; solubility enhancement; dissolution; bioavailability
DOI:
10.5281/zenodo.21644176

ABSTRACT

Poor aqueous solubility remains a major barrier to the oral delivery of several clinically important antifungal agents, including itraconazole, posaconazole, and griseofulvin. Their dissolution-limited absorption can produce variable exposure, food- and pH-dependent pharmacokinetics, and a high formulation burden. Hot-melt extrusion (HME) is a continuous, solvent-free manufacturing platform capable of converting crystalline drug into an amorphous solid dispersion, improving wetting, generating and sustaining supersaturation, and enabling downstream production of tablets, capsules, pellets, films, and three-dimensional printed dosage forms. This review critically integrates formulation science, process engineering, biopharmaceutic mechanisms, and antifungal-specific evidence for HME-based solubility enhancement. Itraconazole is used as the principal model because it has the most mature experimental evidence, while posaconazole and griseofulvin illustrate the broader applicability of the technology. Polymer selection, drug loading, plasticization, surfactant use, screw configuration, barrel temperature, feed rate, specific mechanical energy, residence time, and cooling history are discussed as interacting determinants of amorphization, chemical stability, dissolution, and storage performance. Particular attention is given to HPMCAS, copovidone, Soluplus®, hydroxypropyl cellulose, enteric–hydrophilic polymer combinations, quality-by-design approaches, process analytical technology, and the risks introduced during milling and tableting. Available studies show that HME can markedly improve dissolution and, in selected cases, oral bioavailability; however, performance depends on maintaining a physically stable amorphous phase and preventing precipitation after gastrointestinal dilution or pH transition. Future development should integrate predictive miscibility screening, biorelevant dissolution–permeation testing, continuous monitoring, mechanistic modelling, and patient-centred dosage-form design. HME therefore represents a scalable and industrially relevant strategy for improving the therapeutic utility of poorly soluble antifungal drugs,.

***Corresponding Author:** Ranjit Sakhare
Address: *Dattakala Shikshan Sanstha's, Dattakala College of Pharmacy..*
Email ✉: rsakhare47@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.

provided that formulation, process, and downstream variables are developed as a unified system

INTRODUCTION

Poor water solubility is one of the most persistent formulation problems in oral drug development. For compounds whose intestinal permeability is adequate but dissolution is slow, the amount of drug presented to the absorptive membrane may remain below the level needed for consistent systemic exposure. This problem is especially relevant to lipophilic antifungal agents, for which long treatment courses, serious infections, comorbidities, acid-suppressive therapy, and variable nutritional status can magnify formulation-dependent differences in absorption [1].

Itraconazole (ITZ), posaconazole (POS), and griseofulvin are representative poorly soluble antifungal drugs. ITZ is a weakly basic, highly lipophilic molecule with very low aqueous solubility and strongly formulation-dependent oral absorption. POS is similarly lipophilic and has historically required enabling formulations to reduce food effects and improve exposure. Griseofulvin is a high-melting crystalline drug whose dissolution is strongly influenced by particle size and solid state. These molecules therefore provide demanding but informative models for evaluating advanced solubility-enhancement technologies.

Amorphous solid dispersions (ASDs) improve apparent solubility by placing a drug in a high-energy non-crystalline state and dispersing it within a polymeric matrix. Hot-melt extrusion (HME) is particularly attractive for ASD manufacture because it combines thermal energy and shear in a continuous process, avoids organic solvent removal, and can be linked to milling, pelletization, tableting, capsule filling, film formation, or fused-deposition three-dimensional printing. Nevertheless, HME is not simply a heating step. Successful performance depends on drug–polymer miscibility, melt rheology, thermal stability, screw design, mixing intensity, residence time, cooling rate, moisture exposure, and the mechanical history imposed during downstream processing.

The present review examines how HME can enhance the solubility and dissolution of poorly water-soluble antifungal drugs. It integrates mechanistic principles with formulation and process variables, critically evaluates representative ITZ, POS, and griseofulvin studies, and discusses how current QbD, PAT, biorelevant testing, and personalized manufacturing approaches can improve translation from laboratory extrudate to robust oral dosage form.

2. Review Approach

A targeted narrative literature search was conducted using PubMed, PubMed Central, Crossref-indexed publisher pages, and reference chaining. Search concepts combined “hot-melt extrusion”, “melt extrusion”, “amorphous solid dispersion”, “solubility”, “dissolution”, “bioavailability”, “itraconazole”, “posaconazole”, “griseofulvin”, “antifungal”, “HPMCAS”, “copovidone”, “Soluplus”, “quality by design”, “process analytical technology”, “tableting”, and “3D printing”.

Original experimental studies were prioritized, particularly those reporting formulation composition, extrusion conditions, solid-state characterization, dissolution, stability, downstream processing, or in vivo performance. Foundational papers were retained when required to explain ASD and HME mechanisms. The evidence was synthesized through July 2026. Because the search was designed to support a mechanistic and translational narrative rather than estimate a pooled treatment effect, no meta-analysis or formal risk-of-bias score was applied.

3. Why Poorly Soluble Antifungal Drugs Need Enabling Formulations

The oral performance of a poorly soluble drug is governed by the relationship between dose, equilibrium solubility, dissolution rate, gastrointestinal volume, precipitation tendency, permeability, and transit time. An increase in apparent solubility is useful only when the dissolved or colloidally dispersed drug remains available long enough to cross the intestinal membrane. Thus, a formulation that produces a brief concentration spike followed by rapid precipitation may perform less effectively than a formulation that generates a lower but sustained supersaturated concentration.

Antifungal molecules frequently combine aromatic heterocycles, halogenated groups, and rigid hydrophobic structures. These features support target binding but also strengthen crystal lattices and reduce hydration. ITZ further exhibits pH-sensitive ionization and complex dissolution behaviour during transfer from the stomach to the intestine. POS has low intrinsic solubility and a high dose burden. Griseofulvin is a classical dissolution-limited drug with a stable crystal lattice and a high melting point. For each drug, the formulation must reduce the energetic barrier to dissolution while limiting recrystallization in the solid state and precipitation in gastrointestinal fluid.

Conventional approaches such as micronization, salt formation, cyclodextrin complexation, lipid systems, nanosuspensions, and solvent-prepared solid dispersions can be effective, but each has limitations. Micronization increases surface area without eliminating lattice energy; salts are not feasible for every molecule; lipid systems may be sensitive to digestion and food; nanosuspensions require physical stabilization; and solvent-based ASD methods require solvent selection, containment, and residual-solvent control. HME offers a complementary strategy that can produce molecularly dispersed drug continuously and with comparatively compact manufacturing equipment.

4. Pharmaceutical Basis of Hot-Melt Extrusion

In HME, a premixed or separately fed API–excipient blend is conveyed through a heated barrel by one or two rotating screws. Conveying elements transport material, while kneading and mixing elements generate distributive and dispersive mixing. The material softens or melts, the drug dissolves in the polymer-rich phase or becomes finely dispersed, and the homogeneous melt exits through a die. Rapid cooling then kinetically traps the drug in an amorphous or molecularly dispersed state.

Twin-screw extruders are generally preferred for pharmaceutical ASDs because screw elements can be configured to balance conveying, mixing, devolatilization, and residence time. However, single-screw equipment can be useful for small-scale screening and filament production. The relevant thermal history is not represented by barrel set temperature alone. Actual melt temperature, torque, pressure, shear, SME, feed rate, screw speed, fill level, and residence-time distribution determine whether sufficient mixing is achieved before thermal degradation occurs.

The process window is commonly positioned above the softening or glass-transition region of the formulation but below the degradation thresholds of the API and excipients. Plasticizers, surfactants, water, or low-molecular-weight polymers can reduce melt viscosity and processing temperature. Conversely, excessive plasticization can lower the Tg of the final ASD, increase molecular mobility, and reduce storage stability. HME development therefore requires simultaneous optimization of manufacturability and product performance rather than isolated maximization of drug release.

5. Mechanisms of Solubility and Dissolution Enhancement

5.1 Conversion of crystalline drug to a high-energy amorphous state

Crystalline dissolution requires disruption of an ordered lattice. In an amorphous phase, long-range order is absent and the free energy is higher, so the chemical potential driving dissolution is increased. HME can amorphize a drug by melting it, dissolving it in a polymer below its melting point, or combining thermal and mechanical energy. PXRD halo patterns and disappearance of the crystalline melting endotherm in DSC are commonly used to support amorphization, although neither method alone proves molecular homogeneity.

Amorphization is beneficial but metastable. If drug loading exceeds the thermodynamic or kinetic capacity of the polymer, drug-rich domains may form during processing or storage. Molecular mobility rises when temperature or absorbed moisture lowers the effective Tg. A physically stable ASD therefore requires an adequate polymer fraction, favourable interactions, and packaging conditions that keep the product well below its mobility threshold.

5.2 Improved wetting, dispersion, and matrix-controlled release

Hydrophilic and amphiphilic polymers improve contact between the drug and aqueous medium. As the matrix hydrates, drug is released as molecular species, nanoparticles, nanodroplets, or mixed colloids. The polymer may also reduce interfacial tension and prevent aggregation of hydrophobic drug. The dissolution profile is consequently governed by both drug thermodynamics and polymer hydration, erosion, swelling, or ionization.

Polymer choice must match the intended site of release. Copovidone and Soluplus® can support rapid hydration across a broad pH range, whereas HPMCAS provides pH-dependent dissolution and strong precipitation inhibition in the intestine. HPMC and HPC can act as hydrophilic matrices or functional ternary additives. Enteric–hydrophilic polymer combinations may protect the formulation in gastric fluid and then accelerate release after pH transition.

5.3 Generation and maintenance of supersaturation

ASDs can transiently produce concentrations above crystalline equilibrium solubility. This "spring" effect is valuable only when precipitation is delayed by a "parachute" mechanism. Polymers can inhibit nucleation, crystal growth, or both by adsorbing to drug-rich surfaces, increasing solution viscosity, interacting with drug molecules, or stabilizing colloidal species.

Surfactants may improve wetting and lower HME processing temperature, but their effects are system-dependent. A surfactant can increase initial release yet partition into drug-rich phases, alter drug activity, or weaken polymer-mediated precipitation inhibition. In ITZ–HPMCAS systems, carefully selected surfactant levels improved acidic release and processability, whereas excessive mobility or incompatible phase behaviour can compromise stability [8,9].

5.4 Drug-rich colloids and apparent solubility

During ASD dissolution, analytical filtration may classify submicron drug-rich colloids as "dissolved" drug. These colloids can act as a reservoir that replenishes molecularly dissolved drug and may improve membrane flux, but their contribution depends on size, stability, composition, and the rate of molecular exchange. ITZ–HPMCAS studies have shown that very high

apparent supersaturation can coexist with colloidal particles, emphasizing the need to distinguish total dispersed drug from freely dissolved drug [8].

Mechanistic dissolution testing should therefore combine conventional concentration measurement with particle-size analysis, ultracentrifugation or appropriate filtration, membrane-flux testing, and, where feasible, biphasic or dissolution–permeation methods. This is especially important for antifungal ASDs because pH transition and bile components can substantially change speciation.

Table 1. Functional roles of common HME formulation components for poorly soluble antifungal drugs

Component	Primary function	Potential benefit	Principal risk
HPMCAS	Enteric ASD carrier and precipitation inhibitor	Intestinal supersaturation; physical stabilization; pH-triggered release	High processing temperature; slow gastric release; moisture sensitivity
Copovidone (PVPVA)	Hydrophilic amorphous carrier	Good miscibility and rapid release; suitable for continuous HME	Hygroscopicity; reduced Tg at high humidity; precipitation after rapid release
Soluplus®	Amphiphilic polymeric solubilizer	Melt processability, micellar/colloidal solubilization, improved wetting	Potentially slow matrix erosion or formulation-dependent recrystallization
HPMC/HPC	Hydrophilic matrix or ternary functional additive	Improved partitioning, precipitation inhibition, and dosage-form performance	High viscosity or incomplete release if grade/level is inappropriate
Poloxamers/TPGS	Plasticizer and surfactant	Lower torque and processing temperature; improved wetting and acidic release	Lower Tg, phase separation, altered drug activity, or reduced storage stability
Triethyl citrate/PEG	Plasticizer	Improved filament flexibility and extrudability	Dense dosage forms, slower release, migration, or excessive molecular mobility
Porous silica/inorganic carrier	Adsorbent and mobility-restricting phase	Improved handling, stabilization, or lower-temperature amorphization	Higher tablet mass; altered compaction; incomplete desorption

6. Formulation Design Strategy

6.1 API assessment

Preformulation should define melting point, degradation onset, Tg of the amorphous drug, glass-forming ability, pKa, logP/logD, crystalline polymorphism, dose, and pH–solubility profile. Thermal analysis should be interpreted with chemical-assay data because disappearance of a melting peak can reflect dissolution in polymer, amorphization, or degradation. For weak bases such as ITZ and POS, dissolution must be tested

across gastric-to-intestinal pH transition rather than in a single medium.

Drug–polymer miscibility can be estimated using solubility parameters, Flory–Huggins modelling, melting-point depression, film casting, small-scale melt screening, or spectroscopic mapping. These tools reduce the experimental space but do not replace extrusion trials, because shear, water content, and residence time can create states that are not reproduced by equilibrium calculations.

6.2 Polymer selection

An ideal polymer should dissolve or intimately mix with the drug during processing, inhibit crystallization during storage, promote release at the desired gastrointestinal site, tolerate the extrusion temperature, and support downstream manufacture. Strong hydrogen bonding or other specific interactions may improve miscibility and reduce drug mobility, but excessively strong interactions can slow release.

HPMCAS is especially useful for ITZ and POS because its hydrophobic substituents support drug interaction while succinoyl groups provide pH-dependent ionization. Copovidone offers a lower-viscosity and broadly soluble matrix with established HME use. Soluplus® combines polymeric and surfactant character. HPMC and HPC can improve biorelevant partitioning when used in ternary systems. No polymer is universally superior; the choice must be made against the target product profile.

6.3 Drug loading and phase behaviour

High drug loading reduces dosage-form mass but narrows the physical-stability margin. Below the drug solubility in the polymer, a single-phase ASD may be obtained. Above that level, the product can remain apparently amorphous because crystallization is slow, yet it may contain drug-rich domains that accelerate phase separation during storage. Drug loading also changes melt viscosity, torque, compaction, disintegration, and release.

For ITZ–PVPVA systems, drug loading has been shown to affect mechanical and tableting behaviour, demonstrating that solid-state optimization cannot be separated from downstream manufacturability [13]. A practical approach is to establish a loading range rather than a single target and evaluate it under stressed humidity, milling, compression, and dissolution conditions.

6.4 Plasticizers, surfactants, and ternary systems

Plasticizers lower the processing temperature by increasing chain mobility. Surfactants can serve the dual roles of plasticization and dissolution enhancement. In ITZ–HPMCAS extrudates, poloxamers and TPGS improved extrusion feasibility and acidic release at selected levels [8]. However, plasticizer level must be controlled because it may reduce Tg, increase tackiness, alter filament dimensions, or change the release mechanism.

Ternary ASDs can separate functions: one polymer provides drug miscibility and storage stability, while another improves hydration, partitioning, or tableting. Bachmaier and co-workers found that low-viscosity HPC, particularly HPC-UL, improved ITZ partitioning in biphasic dissolution and enhanced in vivo exposure when added to an HPMC-based ASD [10]. Such results support function-led excipient design rather than reliance on a single carrier.

7. Process Engineering, QbD, and PAT

A rational HME process begins with a quality target product profile defining dosage form, strength, release site, dissolution, stability, and patient-use requirements. CMAs include API particle properties, polymer grade, moisture, drug loading, surfactant level, and feed-blend

uniformity. CPPs include barrel-zone temperatures, screw configuration, screw speed, feed rate, torque, melt pressure, residence time, and cooling conditions. CQAs include assay, content uniformity, residual crystallinity, degradation products, Tg, extrudate morphology, particle size after milling, dissolution, supersaturation maintenance, and stability.

DoE is valuable because HME variables interact. Increasing screw speed may shorten residence time but increase shear rate; increasing feed rate can increase fill and pressure while reducing the energy delivered per unit mass; stronger kneading may improve amorphization but also elevate melt temperature. Thiry et al. used preformulation and multivariable optimization to define a design space for continuous ITZ ASD manufacture [6]. More recently, in-line UV–visible monitoring has been applied to ITZ–Kollidon® VA64 extrusion to track conformational and process-related changes in real time [14].

PAT tools may include near-infrared, Raman, UV–visible, torque, pressure, melt temperature, and spectroscopic imaging. Their value is greatest when the measured signal is linked to a CQA through a validated model. For example, an in-line spectral change can indicate drug dissolution or molecular environment, but it should be correlated with off-line PXRD, DSC, assay, and dissolution. The ultimate goal is a control strategy that detects drift before product failure rather than merely documenting the final extrudate.

Table 2. Representative critical attributes and process parameters in antifungal ASD development

Category	Examples	Why it matters	Typical evaluation
Critical material attributes	Drug loading, API polymorph, polymer grade, moisture, plasticizer level, feed particle size	Determine miscibility, rheology, degradation risk, and physical stability	DSC/TGA, PXRD, Karl Fischer, particle size, rheology, solubility/miscibility screening
Critical process parameters	Temperature profile, screw design, speed, feed rate, torque, SME, residence time, cooling	Control melting/dissolution, distributive mixing, thermal stress, and phase formation	Equipment data, tracer residence-time studies, melt-temperature probes, PAT spectra
Extrudate CQAs	Assay, impurities, residual crystallinity, Tg, homogeneity, mechanical properties	Predict dissolution, stability, and downstream processability	HPLC, DSC, modulated DSC, PXRD, FTIR/Raman mapping, microscopy
Dosage-form CQAs	Flow, compactability, disintegration, tensile strength, friability, dissolution, supersaturation	Extrudate performance can be lost during milling or compression	Powder testing, compaction analysis, USP dissolution, two-stage and biorelevant testing
Stability CQAs	Recrystallization, phase separation, moisture uptake, impurity growth, dissolution change	ASDs are kinetically stabilized and sensitive to storage conditions	Accelerated/long-term stability, dynamic vapour sorption, PXRD/DSC, impurity and dissolution trending

8. Characterization of HME-Based Antifungal ASDs

No single analytical method is sufficient to characterize an ASD. PXRD detects crystalline diffraction but may miss low levels of crystallinity. DSC identifies thermal transitions but can be affected by overlapping polymer events and sample history. Modulated DSC can improve Tg interpretation. FTIR and Raman spectroscopy provide evidence of drug–polymer interactions and spatial homogeneity. Solid-state nuclear magnetic resonance and dielectric spectroscopy can provide deeper information on molecular environment and mobility when available.

SEM reveals extrudate fracture surfaces and milled-particle morphology but does not establish amorphization. Rheology and torque measurements support process-window selection. Dynamic vapour sorption is important because water plasticizes many polymers. HPLC or stability-indicating chromatography is essential for detecting thermal degradation.

Dissolution testing should reflect the intended biopharmaceutic mechanism. A single-compartment test may rank formulations incorrectly when the drug undergoes gastric ionization, intestinal supersaturation, precipitation, or colloid formation. Two-stage pH-shift methods, biorelevant media, biphasic dissolution, and membrane-flux tests are therefore preferred for mechanistic development. Thiry et al. demonstrated that the apparent ranking of ITZ formulations can depend strongly on the dissolution medium [7].

Table 3. Analytical toolkit for HME-based antifungal ASDs

Technique	Primary information	Interpretive caution
PXRD	Residual crystallinity and polymorphic form	Low-level or nanocrystalline drug may be below detection
DSC/modulated DSC	Melting, Tg, miscibility indicators, recrystallization	Absence of melting is not proof of chemical integrity or molecular homogeneity
TGA	Moisture/volatile loss and degradation onset	Dynamic heating may not reproduce extrusion residence time
FTIR/Raman	Drug–polymer interactions and chemical environment	Band shifts can be nonspecific; mapping is preferable for homogeneity
HPLC/LC–MS	Assay and degradation products	Must use a stability-indicating method
SEM/polarized microscopy	Morphology, phase domains, crystalline particles	Surface images may not represent bulk structure
Rheology/torque/SME	Melt processability and energy input	Equipment scale and screw geometry affect transferability
DVS	Moisture sorption and plasticization risk	Equilibrium sorption alone does not predict crystallization kinetics

Technique	Primary information	Interpretive caution
Dissolution–permeation/biphasic tests	Supersaturation, precipitation, partitioning, potential absorption	Method parameters strongly influence ranking and require biorelevance
Stability studies	Physical and chemical robustness over time	Dissolution change may precede detectable crystallinity

9. Evidence for Individual Antifungal Drugs

9.1 Itraconazole: the principal HME model

ITZ is the most extensively investigated antifungal model for HME-based ASD development. Early melt-extrusion formulation studies established that polymer ratio and processing conditions influence extrudate clarity, torque, Tg, and dissolution [3]. Janssens et al. later showed that preparation method can affect apparent drug–polymer miscibility and solid-state supersaturation in ITZ–Eudragit® E systems [4]. These findings are important because a formulation that appears homogeneous immediately after manufacture may occupy a metastable region with limited long-term tolerance.

Lang et al. evaluated ITZ–HPMCAS compositions prepared by thin-film freezing and subsequently processed by HME. Addition of hydrophilic carriers and increased mixing improved acidic release and reduced precipitation after transfer to neutral medium. Extrusion temperature and screw configuration were influential, demonstrating that identical composition can produce different performance when the mixing history changes [5]. Thiry et al. selected polymers using DSC, thermogravimetric analysis, and solubility-parameter concepts, then developed a continuous HME process and design space for ITZ ASDs [6]. A subsequent study reported improved bioavailability of HME-produced ITZ solid dispersions using an experimental framework intended to reduce animal use [7]. Together, these studies provide a useful model of progression from preformulation to process optimization, discriminating dissolution, and in vivo confirmation.

Solanki et al. examined HPMCAS systems in which surfactants acted as plasticizers. HPMCAS showed useful miscibility with ITZ, and selected ternary compositions could be extruded at manageable temperature. Fifteen percent surfactant increased acidic drug release relative to HPMCAS alone, while pH-shift testing generated very high apparent supersaturation that included colloidal drug species [8]. Their downstream study showed that tablet formulation and disintegration determine whether extrudate-level advantages are retained [9].

Bachmaier et al. used low-viscosity HPC grades as functional additives in HPMC-based ITZ ASDs. Biphasic dissolution and in vivo results supported improved partitioning and oral exposure, particularly with HPC-UL [10]. Triboandas et al. applied QbD principles to formulate and compact ITZ–Kollidon® VA64 ASD tablets, demonstrating the importance of compaction variables and excipient selection [11]. Mishra et al. similarly showed that milling and tableting of ITZ–HPMCAS extrudates require systematic optimization because particle size and tablet composition influence flow, compactability, disintegration, and dissolution [12].

Recent work has extended ITZ HME into real-time process monitoring, personalized dosage forms, and high-drug-loading products. In-line UV–visible spectroscopy has been used with sequential DoE to understand extrusion and conformational changes [14]. Extruded ITZ systems have also been coupled with additive manufacturing,

although dense printed structures may substantially slow release. Milliken et al. reported approximately 63% release in 30 min from directly compressed HPMCAS ASD tablets, compared with only 3–6% from two 3D-printed formulations, illustrating that dosage-form architecture can outweigh the favourable solid state of the ASD [18].

9.2 Posaconazole

POS provides strong evidence that HME can improve both dissolution and systemic exposure. Fule and Amin prepared Soluplus®-based HME ASDs with selected surfactants and reported amorphization, improved dissolution, and several-fold enhancement of in vivo bioavailability compared with crystalline POS and a marketed suspension [19]. The work also highlighted the usefulness of complementary miscibility and molecular-interaction tools.

Li et al. compared HME and spray-dried POS–HPMCAS ASDs at 25% drug loading. Although the two processes produced different in vitro release patterns, their in vivo performance in cynomolgus monkeys was similar, showing that conventional dissolution differences do not always translate directly into exposure differences [20]. This result supports use of mechanistic and biorelevant tests rather than reliance on a single compendial method.

Kramarczyk et al. compared different polymers for HME POS ASDs and showed that polymer type strongly affects amorphization, molecular mobility, dissolution, and physical stability [21]. The collective POS literature indicates that HPMCAS, Soluplus®, and copovidone-based systems can be effective, but release site, polymer ionization, and precipitation control must be aligned with the clinical dosage form.

9.3 Griseofulvin

Griseofulvin differs from ITZ and POS because its high melting point and strong crystallinity can make full molecular dispersion difficult without high thermal stress. HME can nevertheless enhance performance through amorphization, solid-crystal suspension formation, or intensive particle-size reduction within a polymer matrix.

Bennett et al. studied binary, ternary, and quaternary dispersions containing griseofulvin with enteric and hydrophilic polymers. The combination of polymers improved in vitro dissolution and showed that an enteric polymer can be complemented by a rapidly hydrating vinyl-pyrrolidone polymer [22]. Reitz et al. demonstrated an HME-generated solid crystal suspension in which particle-size reduction produced a 3.5-fold increase in dog bioavailability relative to a physical mixture and performance comparable with or slightly above a marketed product [23]. These findings show that HME does not always need to achieve complete amorphization; a stable, finely dispersed crystalline phase may be preferable when the API has a high melting point or limited amorphous stability.

Table 4. Representative HME studies involving poorly soluble antifungal drugs

Drug/system	Formulation/process focus	Key finding	Development lesson	Ref.
Itraconazole–HPMCAS	HME after thin-film freezing; hydrophilic carriers; DoE	Mixing intensity, temperature, and carrier type improved acidic release and	Composition and screw-induced mixing jointly determine performance	5

Drug/system	Formulation/process focus	Key finding	Development lesson	Ref.
		reduced precipitation		
Itraconazole ASDs	Preformulation, continuous HME, design space	A process design space was established using polymer screening and multivariable optimization	Link preformulation predictions with process data	6
Itraconazole ASDs	In vivo bioavailability assessment	HME dispersions increased bioavailability relative to crystalline drug	Confirm dissolution improvement with exposure data	7
Itraconazole–HPMCAS–surfactant	Surfactants as plasticizers	Selected surfactants reduced process burden and increased acidic release; colloidal supersaturation occurred	Measure free and colloidal drug; balance plasticization with stability	8
Itraconazole HPMC/HPC ternary ASD	Biphasic dissolution and in vivo study	Low-viscosity HPC improved partitioning and oral bioavailability	Ternary polymers can separate stabilization and release functions	10
Itraconazole–PVPVA	QbD tableting and compaction	Tablet variables and formulation composition controlled disintegration and release	Develop extrudate and final dosage form together	11
Itraconazole–HPMCAS	Milling and tableting	Downstream processing altered flow, compactability, and dissolution	Extrudate quality does not guarantee tablet performance	12
Itraconazole–HPMCAS	Single-screw HME, 3D printing vs direct compression	Direct compression released ~63% at 30 min; printed tablets released 3–6%	Architecture and porosity can dominate ASD release	18
Posaconazole–Soluplus®	HME ASD with surfactant	Improved dissolution and several-fold in	Amphiphilic polymers can support	19

Drug/system	Formulation/process focus	Key finding	Development lesson	Ref.
		vivo bioavailability	immediate-release antifungal ASDs	
Posaconazole–HPMCAS	HME vs spray drying	Different in vitro profiles but similar in vivo performance	Use biorelevant methods to interpret process differences	20
Posaconazole with multiple polymers	Polymer comparison	Polymer type affected amorphization, mobility, stability, and dissolution	Polymer screening must include stability, not only initial release	21
Griseofulvin with enteric/hydrophilic polymers	Binary to quaternary HME dispersions	Polymer combinations enhanced dissolution	Complement pH control with rapid hydration	22
Griseofulvin solid crystal suspension	HME particle-size reduction without full amorphization	3.5-fold higher dog bioavailability than physical mixture	A stable nanocrystalline/finely crystalline dispersion can be a valid endpoint	23

10. Downstream Processing: From Extrudate to Dosage Form

Fresh extrudate is rarely the final medicine. It is commonly milled and incorporated into tablets or capsules. Milling changes particle size, surface area, electrostatic behaviour, flow, and local thermal history. Fine particles may dissolve rapidly but flow poorly, while coarse particles may slow release and impair content uniformity. Brittle polymers may generate angular particles with acceptable flow; ductile extrudates may smear or heat during milling.

Tableting introduces dilution with fillers and disintegrants, lubrication, compaction pressure, and pore-structure changes. A high fraction of poorly soluble ASD polymer can delay water penetration, particularly when the tablet is dense. Lubricants may coat particles and retard wetting. Compression can also induce phase changes in susceptible systems. Thus, formulation should target rapid and complete disintegration without sacrificing tensile strength and friability.

Triboandas et al. and Mishra et al. demonstrated that QbD tools can identify interactions among ASD loading, filler, disintegrant, lubricant, particle size, and compression conditions [11,12]. The 2026 comparison of printed and directly compressed ITZ tablets further shows that a molecularly amorphous drug may still release slowly when the dosage form has low porosity, high density, buoyancy, or a viscous surface gel [18].

Pellets, films, and capsule-filled milled extrudates may avoid some compaction risks, whereas three-dimensional printing enables individualized dose and geometry. However, the thermal exposure of a second processing step and the effect of infill, shell thickness, plasticizer, and geometry on release must be evaluated.

11. Physical and Chemical Stability

ASD stability is governed by thermodynamic driving force and molecular mobility. The drug tends to crystallize because the crystalline state has lower free energy. Polymer–drug interactions, high matrix Tg, low water activity, and restricted diffusion delay this transition. Storage temperature should remain sufficiently below the formulation Tg, but Tg-based rules are only approximate because local heterogeneity and moisture can create mobile domains.

Moisture is a critical risk for HPMCAS, PVPVA, HPMC, HPC, and other hydrophilic carriers. Water can lower Tg, increase phase separation, accelerate crystallization, alter tablet disintegration, and promote hydrolysis. Barrier packaging and desiccants may therefore be part of the formulation control strategy. Accelerated testing should include open and packaged conditions when clinically relevant.

Chemical stability can be compromised by high melt temperature, long residence time, oxygen exposure, mechanical energy, or reactive excipients. Stability-indicating chromatography must be used during process development; colour change or altered thermal behaviour is not an adequate surrogate for impurity control. Scale-up should preserve SME, residence-time distribution, melt temperature, and oxygen/moisture exposure rather than copying nominal screw speed or barrel settings.

Importantly, dissolution deterioration can occur before conventional PXRD detects crystallinity. Stability protocols should therefore trend solid state, impurity profile, moisture, disintegration, and dissolution together. A formulation that remains X-ray amorphous but loses supersaturation capacity is not functionally stable.

12. Advantages, Limitations, and Risk-Mitigation Strategies

12.1 Advantages

HME is continuous, scalable, and generally solvent-free. It can combine mixing, amorphization, shaping, and sometimes downstream feeding in a compact manufacturing train. Short residence times can reduce thermal exposure relative to batch melting. The process is compatible with QbD and PAT and can be adapted to pellets, films, implants, tablets, and printing filaments.

For antifungal drugs, the principal advantages are improved dissolution, potential reduction of food or gastric-pH dependence, increased exposure, and the possibility of reducing dose or dosage-form burden. HME can also create immediate, delayed, or modified release by appropriate polymer selection.

12.2 Limitations and mitigation

Thermal or shear degradation: Use TGA and stability-indicating HPLC; reduce residence time; add plasticizer; use lower-temperature polymers; consider solid crystal suspension rather than full amorphization.

Limited drug–polymer miscibility: Screen multiple polymers and ternary combinations; use small-scale film/melt studies; reduce loading; introduce specific interactions.

Recrystallization during storage: Increase matrix Tg, select stronger precipitation/crystallization inhibitors, control humidity, optimize packaging, and verify long-term dissolution.

High viscosity or torque: Adjust polymer grade, temperature profile, plasticizer, screw design, feed rate, and fill level.

Rapid precipitation after release: Use HPMCAS/HPMC/HPC or other precipitation

inhibitors; optimize surfactant level; use pH-shift and flux tests.

Poor flow/compactability: Optimize milling, granulate or add flow aids, use suitable fillers/disintegrants, and model compaction.

Slow release from dense dosage forms: Increase porosity, reduce polymer viscosity, optimize disintegrant, modify tablet geometry or printing infill.

Scale-up failure: Transfer dimensionless or mechanistically relevant variables such as SME, residence time, fill, melt temperature, and mixing intensity.

FUTURE PERSPECTIVES

Future antifungal ASD development should move from empirical polymer screening toward predictive, mechanism-led design. Thermodynamic modelling, molecular simulation, high-throughput melt screening, and machine-learning models can prioritize drug–polymer combinations, but predictions must be linked to processing and dissolution data.

Continuous manufacturing offers the possibility of closed-loop control using in-line spectroscopy, torque, pressure, and melt-temperature signals. The next step is not simply collecting PAT data but using it to adjust feed rate, screw speed, or temperature in real time while maintaining validated product quality.

Biorelevant performance testing should integrate dissolution, colloid characterization, precipitation kinetics, and membrane flux. For weakly basic antifungals, gastric-to-intestinal transfer and the effects of acid-suppressive therapy should be incorporated. Physiologically based biopharmaceutics modelling can then connect in vitro data to expected exposure and guide clinically meaningful specifications.

Personalized and decentralized manufacture is emerging through HME-fed three-dimensional printing. The 2026 ITZ findings caution that printable filament and acceptable solid state do not guarantee immediate release [18]. Future work should optimize infill, porosity, shell design, disintegrating channels, and low-viscosity matrices while maintaining dose accuracy and stability.

Finally, sustainability should be evaluated across the entire product lifecycle. Although HME avoids organic solvent removal, it may use significant thermal and mechanical energy. Process efficiency, material yield, start-up waste, cleaning, packaging, and the potential for continuous end-to-end manufacture should be included in development decisions.

CONCLUSION

Hot-melt extrusion is a powerful enabling technology for poorly water-soluble antifungal drugs. Its value arises from more than conversion of a crystal to an amorphous phase: the process can improve wetting, create and stabilize supersaturation, generate drug-rich colloids, and engineer release through polymer selection. Evidence is most developed for itraconazole and is supported by posaconazole and griseofulvin studies showing improved dissolution and, in selected formulations, improved oral bioavailability. However, HME success is conditional. Drug–polymer miscibility, thermal and mechanical history, surfactant level, drug loading, pH-dependent release, precipitation inhibition, milling, compression, dosage-form architecture, moisture, and packaging must be developed as a connected system. A formulation that is amorphous at release may still fail because of chemical degradation, rapid precipitation, slow tablet disintegration, or storage-induced loss of performance. Integration of QbD, PAT, mechanistic dissolution–permeation testing,

predictive modelling, and patient-centred dosage-form design offers the clearest path toward robust antifungal products. When these elements are combined, HME can provide a scalable, solvent-free, and clinically meaningful solution to dissolution-limited antifungal therapy.

REFERENCES

1. 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. doi:10.1023/A:1016212804288.
2. Jung JY, Yoo SD, Lee SH, Kim KH, Yoon DS, Lee KH. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. Int J Pharm. 1999;187(2):209-218. doi:10.1016/S0378-5173(99)00191-X.
3. Rambali B, Verreck G, Baert L, Massart DL. Itraconazole formulation studies of the melt-extrusion process with mixture design. Drug Dev Ind Pharm. 2003;29(6):641-652. doi:10.1081/DDC-120021313.
4. Janssens S, De Zeure A, Paudel A, Van Humbeeck J, Rombaut P, Van den Mooter G. Influence of preparation methods on solid state supersaturation of amorphous solid dispersions: a case study with itraconazole and Eudragit E100. Pharm Res. 2010;27(5):775-785. doi:10.1007/s11095-010-0069-y.
5. Lang B, McGinity JW, Williams RO 3rd. Dissolution enhancement of itraconazole by hot-melt extrusion alone and the combination of hot-melt extrusion and rapid freezing: effect of formulation and processing variables. Mol Pharm. 2014;11(1):186-196. doi:10.1021/mp4003706.
6. Thiry J, Lebrun P, Vinassa C, et al. Continuous production of itraconazole-based solid dispersions by hot melt extrusion: preformulation, optimization and design space determination. Int J Pharm. 2016;515(1-2):114-124. doi:10.1016/j.ijpharm.2016.10.003.
7. Thiry J, Kok MGM, Collard L, et al. Bioavailability enhancement of itraconazole-based solid dispersions produced by hot melt extrusion in the framework of the Three Rs rule. Eur J Pharm Sci. 2017;99:1-8. doi:10.1016/j.ejps.2016.12.001.
8. Solanki NG, Lam K, Tahsin M, Gumaste SG, Shah AV, Serajuddin ATM. Effects of surfactants on itraconazole-HPMCAS solid dispersion prepared by hot-melt extrusion I: miscibility and drug release. J Pharm Sci. 2019;108(4):1453-1465. doi:10.1016/j.xphs.2018.10.058.
9. Solanki NG, Kathawala M, Serajuddin ATM. Effects of surfactants on itraconazole-hydroxypropyl methylcellulose acetate succinate solid dispersion prepared by hot melt extrusion III: tableting of extrudates and drug release from tablets. J Pharm Sci. 2019;108(12):3859-3869. doi:10.1016/j.xphs.2019.09.014.
10. Bachmaier RD, Monschke M, Faber T, et al. In vitro and in vivo assessment of hydroxypropyl cellulose as functional additive for enabling formulations containing itraconazole. Int J Pharm X. 2021;3:100076. doi:10.1016/j.ijpx.2021.100076.
11. Triboandas H, Pitt K, Bezerra M, Ach-Hubert D, Schlindwein W. Itraconazole amorphous solid dispersion tablets: formulation and compaction process optimization using quality by design principles and tools. Pharmaceutics. 2022;14(11):2398. doi:10.3390/pharmaceutics14112398.
12. Mishra SM, Richter M, Mejia L, Sauer A. Downstream processing of itraconazole:HPMCAS amorphous solid

dispersion: from hot-melt extrudate to tablet using a quality by design approach. Pharmaceutics. 2022;14(7):1429. doi:10.3390/pharmaceutics14071429.
13. Zhang W, Sluga KK, Yost E, Phan J, Nagapudi K, Hou HH. Impact of drug loading on the compaction properties of itraconazole-PVPVA amorphous solid dispersions. Int J Pharm. 2022;629:122366.
14. Triboandas H, et al. Optimizing extrusion processes and understanding conformational changes in itraconazole amorphous solid dispersions using in-line UV-Vis spectroscopy and quality-by-design principles. Int J Pharm X. 2024. PMID:39687500.
15. Huang L, et al. Improve solubility and develop personalized itraconazole oral dosage forms through hot-melt extrusion and additive manufacturing. Pharmaceutics. 2024. PMID:39684047.
16. Kshirsagar MM, et al. Continuous processing strategies for amorphous solid dispersions: comparative development of itraconazole systems by hot-melt extrusion and spray drying. Pharmaceutics. 2025;17(9):1090.
17. Tanaka H, et al. Carboxymethyl ethylcellulose acts as a solid dispersion carrier to improve stability, dissolution, and permeation profiles of itraconazole. Pharmaceutics. 2025.
18. Milliken RL, Quinten T, Andersen SK, Lamprou DA. Tabletting of single-screw hot melt extruded itraconazole: HPMC-AS amorphous solid dispersion by 3D printing and direct compression. Drug Deliv Transl Res. 2026. doi:10.1007/s13346-026-02134-5.
19. Fule R, Amin P. Hot melt extruded amorphous solid dispersion of posaconazole with improved bioavailability: investigating drug-polymer miscibility with advanced characterisation. Biomed Res Int. 2014;2014:146781. doi:10.1155/2014/146781.
20. Li Y, Mann AKP, Zhang D, Yang Z. Processing impact on in vitro and in vivo performance of solid dispersions: a comparison between hot-melt extrusion and spray drying. Pharmaceutics. 2021;13(8):1307. doi:10.3390/pharmaceutics13081307.
21. Kramarczyk D, Knapik-Kowalczuk J, Kurek M, Jamróz W, Jachowicz R, Paluch M. Hot melt extruded posaconazole-based amorphous solid dispersions: the effect of different types of polymers. Pharmaceutics. 2023;15(3):799. doi:10.3390/pharmaceutics15030799.
22. Bennett RC, Keen JM, Porter S, Dürig T, McGinity JW. Investigation of the interactions of enteric and hydrophilic polymers to enhance dissolution of griseofulvin following hot melt extrusion processing. J Pharm Pharmacol. 2015;67(7):918-938. doi:10.1111/jphp.12388.
23. Reitz E, Vervaet C, Neubert RH. Solid crystal suspensions containing griseofulvin: formulation and bioavailability enhancement by hot-melt extrusion. Eur J Pharm Biopharm. 2013;83:193-199. PMID:23108185.
24. Thommes M, Ely DR, Carvajal MT, Pinal R. Improvement of the dissolution rate of poorly soluble drugs by solid crystal suspensions. Mol Pharm. 2011;8(3):727-735. PMID:21344937.
25. Al-Obaidi H, Buckton G. Evaluation of griseofulvin binary and ternary solid dispersions with HPMCAS. AAPS PharmSciTech. 2009;10(4):1172-1177.
26. Sarode AL, Sandhu H, Shah N, Malick W, Zia H. Hot melt extrusion for amorphous solid dispersions: temperature and moisture activated drug-polymer interactions for enhanced stability. Mol Pharm.

2013;10(10):3665-3675. doi:10.1021/mp400165b.

27. Parikh T, Gupta SS, Meena A, Vitez I, Mahajan N, Serajuddin ATM. Application of film-casting technique to investigate drug-polymer miscibility in solid dispersion and hot-melt extrusion. Int J Pharm. 2015;495:665-674. PMID:25917333.
28. Stewart AM, Grass ME, Mudie DM, et al. Impact of drug-rich colloids of itraconazole and HPMCAS on membrane flux in vitro and oral bioavailability in rats. Mol Pharm. 2017;14:2437-2449. PMID:28591516.
29. Harmon P, Galipeau K, Xu W, Brown C, Wuelfing WP. Mechanism of dissolution-induced nanoparticle formation from a copovidone-based amorphous solid dispersion. Mol Pharm. 2016;13(5):1467-1481.
30. 30. Agrawal A, Dudhedia M, Deng W, et al. Development of tablet formulation of amorphous solid dispersions prepared by hot melt extrusion using quality by design approach. AAPS PharmSciTech. 2016;17(1):214-232. doi:10.1208/s12249-015-0472-0.
31. Grymonpré W, Verstraete G, Van Bockstal PJ, et al. In-line monitoring of compaction properties on a rotary tablet press during tablet manufacturing of hot-melt extruded amorphous solid dispersions. Int J Pharm. 2017;517(1-2):348-358. doi:10.1016/j.ijpharm.2016.12.033.
32. Davis MT, Potter CB, Walker GM. Downstream processing of a ternary amorphous solid dispersion: the impacts of spray drying and hot melt extrusion on powder flow, compression and dissolution. Int J Pharm. 2018;544(1):242-253. doi:10.1016/j.ijpharm.2018.04.038.
33. Bochmann ES, Steffens KE, Gryczke A, Wagner KG. Micro-scale prediction method for API solubility in polymeric matrices and process model for amorphous solid dispersion manufacture by hot-melt extrusion. Eur J Pharm Biopharm. 2016;107:40-48. PMID:27349807.
34. Wolbert F, et al. Factors influencing the crystallization-onset time of amorphous solid dispersions. Int J Pharm. 2022. PMID:35214002.

HOW TO CITE: Ranjit Sakhare, Dr Sudarshan Nagrale, Dr. Vishal Babar, Enhancement of Solubility and Dissolution Rate of Poorly Water-Soluble Antifungal Drugs by Hot-Melt Extrusion Method, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 5352-5368, https://doi.org/10.5281/zenodo.21644176