

Solid Dispersion by Hot Melt Extrusion

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Abstract—Poor aqueous solubility continues to limit the successful development of many new drug candidates, particularly those classified under the Biopharmaceutics Classification System Class II category. Inadequate dissolution often results in reduced absorption, low bioavailability, and inconsistent therapeutic performance, making it a major cause of failure in drug development pipelines.

To address this issue, solid dispersion systems have gained considerable attention, especially amorphous solid dispersions (ASDs), which enhance drug dissolution by maintaining the drug in a high-energy, non-crystalline state. Among the available techniques, Hot-Melt Extrusion (HME) has emerged as an efficient, solvent-free, and scalable method for producing such formulations.

This review examines recent advances in the use of HME for developing ASDs and eutectic systems, highlighting its impact on improving drug solubility and bioavailability. Studies demonstrate substantial enhancement in drug performance, including significant increases in bioavailability for poorly soluble compounds such as Cyclosporine A. Additionally, HME offers advantages in processing flexibility and compatibility with real-time monitoring technologies.

Overall, HME provides a reliable and industrially viable approach to overcoming solubility-related challenges, supporting the development of more effective oral drug formulations.

Keywords: Hot-melt extrusion (HME), solid dispersions, amorphous solid dispersions (ASDs), solubility enhancement, bioavailability, BCS Class II drugs, eutectic mixtures, and Process Analytical Technology (PAT).

I. INTRODUCTION

1. Introduction

1.1 The Growing Challenge of Poor Solubility

Why do so many new drugs struggle to get to market? In modern drug discovery, the reason is often surprisingly simple: they don't dissolve in water. This challenge of poor aqueous solubility has become one of the biggest headaches in pharmaceutical development. [1] For a whole class of drugs, known as Biopharmaceutics Classification System (BCS) Class II, this poor solubility is the main bottleneck that stops them from being absorbed by the body. These compounds are permeable (they can pass through the gut wall) but can't dissolve in the gut's fluids first. If a drug can't dissolve, our bodies can't absorb it, leading to poor and unreliable clinical results. This single issue is a primary driver of high failure rates for promising new medicines. [2]

1.2 The Amorphous Solid Dispersion (ASD) Solution

An excellent and proven way to fix this is by creating an amorphous solid dispersion, or ASD. The concept is to convert the drug from its stable, ordered crystalline form into a "messy," high-energy amorphous state. Think of an ASD as the drug being "dissolved" while still in a solid polymer carrier. This amorphous state is thermodynamically unstable; it has more energy than its crystal counterpart and, as a result, dissolves much, much faster when it encounters water. [3]

The polymer carrier in the ASD is not just a filler; it performs two critical jobs. First, it helps the hydrophobic (water-fearing) drug get wet, improving its wettability. Second, and just as importantly, it kinetically stabilizes the drug, acting like a molecular cage that stops the drug from turning back into a stable, non-dissolving crystal during storage. This stabilization is key to the product's shelf life and success. [4]

1.3 The Evolution and Types of Solid Dispersions

To fully grasp the utility of hot-melt extrusion, it helps to understand that solid dispersions are not a single, uniform type of formulation. Historically, they have evolved through four distinct "generations" to address specific drug delivery challenges:

First-Generation (Crystalline Carriers): The earliest approach relied on co-melting a drug with a crystalline carrier, such as urea or various sugars. Eutectic mixtures fall perfectly into this category, where two combined components melt at a lower temperature than either would on its own. [5] While this method improves dissolution primarily by milling the drug down to micro-sized particles within the carrier, the crystalline nature of these systems means they generally lack the thermodynamic driving force seen in later generations.

Second-Generation (Amorphous Carriers): To achieve more dramatic solubility enhancements, formulators shifted to using amorphous polymers (like PVP, PEG, or HPMC) as carriers. These are the amorphous solid dispersions (ASDs). Instead of remaining in a stable crystal lattice, the drug is forced into a high-energy, "messy" amorphous state. The polymer acts essentially as a molecular cage, kinetically trapping the drug to prevent it from recrystallizing during storage. The Cyclosporine A formulation utilizing PVP K12 discussed later is a hallmark example of this second-generation strategy. [6]

Third-Generation (Surfactant-Based Carriers): A known limitation of second-generation ASDs is that once the highly soluble drug reaches the gastrointestinal fluids, it can rapidly precipitate out of solution before it can be absorbed. Third-generation systems mitigate this by incorporating surfactants or surface-active self-emulsifying agents into the polymer matrix. These additives improve the drug's wettability and help sustain its supersaturated state in the gut.[7]

Fourth-Generation (Controlled Release): More recently, the focus has expanded beyond immediate release to creating controlled-release dosage forms. Rather than dissolving instantly, these dispersions utilize high-molecular-weight, swellable, or non-soluble polymers (such as specific grades of HPMC or Eudragit®). When swallowed, the polymer matrix slowly swells like a gel rather than breaking apart. The drug must then slowly diffuse out, providing steady, sustained drug levels over an extended period.[8]

1.4 Hot-Melt Extrusion (HME) as a Manufacturing Platform

While there are a few ways to make ASDs, including solvent-based methods like spray drying, hot-melt extrusion (HME) is quickly becoming a favorite and is stepping up as a powerful, solvent-free solution.[9]

HME is essentially a sophisticated, high-tech 'melt-and-mix' process. . It uses a combination of intense heat and mechanical shear to blend the active drug and polymer carrier together at a molecular level.[10] This mixture is then pushed through a die to form a uniform, solid product. The best part? It's a single-step process that doesn't require any solvents. . This solvent-free nature makes it a cleaner, faster, and more efficient process that is a perfect fit for modern continuous manufacturing strategies. . It eliminates the cost, environmental impact, and safety risks associated with handling, and later removing, large volumes of organic solvents[11]

1.5 Aims and Scope of This Review

This review will take a closer look at what HME can really do. We will dig into recent studies to see HME in action, looking at how it's used for both amorphous solid dispersions (ASDs) and eutectic mixtures. This paper will analyze how HME's unique process can handle tricky formulations that other methods can't and how it can be paired with modern quality-control tools like NIR spectroscopy to monitor the product in real-time.[12] By examining key case studies—from the 7.3-fold bioavailability boost of Cyclosporine A to the processing of difficult-to-handle eutectic mixtures—this review will demonstrate that HME is a highly effective, scalable way to make poorly soluble drugs work better.

All manuscripts must be in English. These guidelines include complete descriptions of the fonts, spacing, and related information for producing your proceedings manuscripts. Please follow them.

II. METHODOLOGY

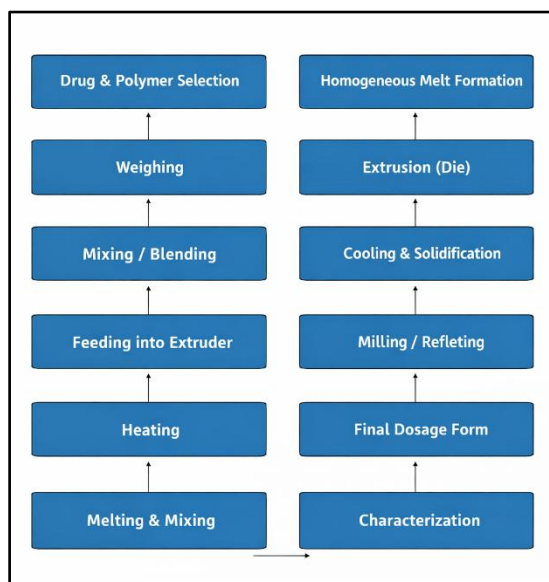


Figure II.1 Methodology of HME

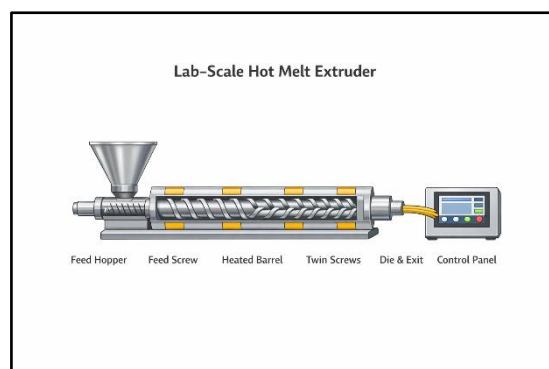


Figure II.2 Lab scale Hot Melt Extruder.

PRISMA Study Selection

1. Identification: Total records identified through database searching: (n = 120)

2. Screening: Records remaining after duplicates removed: (n = 100)

Records screened by title and abstract: (n = 65)

Records excluded based on title/abstract (e.g., wrong topic, irrelevant application): (n = 5)

3. Eligibility: Full-text articles assessed for eligibility: (n = 60) Full-text articles excluded for not meeting inclusion criteria (e.g., wrong study design, conference abstract only, different manufacturing process): (n = 15)

4. Included: Studies included in the qualitative synthesis (the final review): (n = 45)

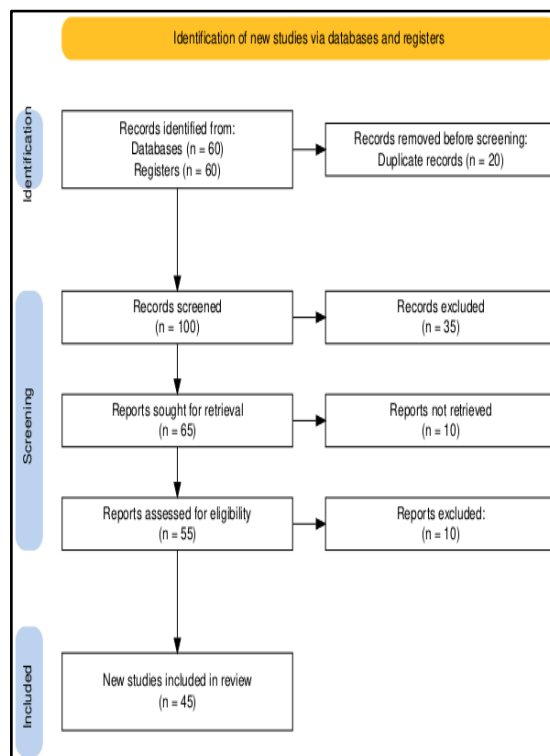


Figure II.3 PRISMA Study

III. COMPREHENSIVE ANALYSIS OF STUDIES

Looking at the research, it's clear HME is a versatile and powerful tool. It's not just about one thing; it's about improving bioavailability, solving tough processing challenges, and ensuring quality. The following case studies demonstrate the breadth of HME's capabilities.[13]

Enhancing Bioavailability: Cyclosporine A ASD. A major challenge with many drugs is simply getting them into the bloodstream. A study by Jiang et al. took on Cyclosporine A (CsA), a notoriously hard-to-dissolve, high-molecular-weight drug. **Formulation:** The researchers tested several polymers to find one that could both dissolve CsA at high temperatures and, critically, stop it from recrystallizing upon cooling and storage. They identified PVP K12 as the best choice for keeping the drug in a stable, ready-to-dissolve, supersaturated state.

Characterization: Advanced tests confirmed their success. Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction (PXRD) showed that the final HME product was fully amorphous. The analysis found a single glass transition temperature (T_g), which is the classic sign of a well-mixed, homogenous dispersion where the drug and polymer are dissolved in each other. Furthermore, FT-IR scans suggested the drug and polymer were "holding hands" via hydrogen bonds—a key molecular interaction that provides the thermodynamic stability needed to keep the amorphous form stable.

Performance: The results spoke for themselves.[14] The HME-made tablets dissolved quickly in vitro. But the in vivo animal studies were the real showstopper: the HME formulation boosted the drug's bioavailability (AUC) by an incredible 7.3-fold compared to the original drug powder. It was also 3.1-fold better than just a simple physical mix of the drug and polymer, proving that the molecular dispersion created by HME was the key to success.

Process-Specific Advantages: Eutectic Mixtures

A study by Schlosser and Bunjes. highlights a unique benefit of HME that goes beyond just making amorphous dispersions. .

Processability: They compared HME to traditional "melt casting" for making eutectic mixtures (where two components mixed together melt at a lower temperature than either one alone).[15] They found that HME could successfully manufacture formulations that traditional casting simply couldn't. One specific mixture (IBU-PEG40ST) was a processing nightmare—it was tacky and just wouldn't solidify properly in a mold.

HME's Unique Solution: HME handled it perfectly. The study found that the intense friction and shear inside the extruder's screws actually forced the mixture to crystallize and solidify.[16] This shear-induced crystallization is a unique feature of the HME process, turning a processing bug into a feature and allowing a difficult product to be manufactured.

Dissolution: Both methods led to "considerably higher" dissolution rates than the pure drugs. This was because the process milled the drug down to tiny micro-sized particles (d50 of ~6–9 µm) inside the carrier. This study perfectly illustrates how HME is not just a heater, but a powerful mechanical processing tool.

In-Line Process Monitoring: Carbamazepine ASD

One of the biggest worries with amorphous dispersions is stability. Will it stay amorphous?

Problem: Even a tiny bit of the original crystal (less than 1%) left behind can act like a seed. This seed can cause the whole product to recrystallize during storage, ruining all the hard work and destroying the product's effectiveness.[17]

Method (PAT): Lim et al. explored using near-infrared spectroscopy (NIRS) as a "live" quality control tool. The idea is to mount the NIRS probe right on the HME production line to check for residual crystals in real-time. This concept is known as Process Analytical Technology (PAT).

Findings: The study was a success. The NIRS system, paired with smart math (chemometrics), was able to spot the amorphous drug and tell the different crystal forms apart. Interestingly, they also found that the HME process itself (at 160°C) caused the drug, carbamazepine, to change its crystal form (from Form III to a mix of Form I and III). This is huge because it proves two things: 1) the HME process is complex and can induce physical changes, and 2) HME can be paired with modern PAT tools for real-time quality assurance to monitor and control these changes.[18]

Expanding HME's Role: Controlled and Targeted Release

Beyond immediate release, HME is a leading platform for creating controlled-release dosage forms. This involves using specific polymers that don't dissolve instantly but rather release the drug over a long period (e.g., 12 or 24 hours) or in a specific location (e.g., the colon).[19]

Formulation (Matrix Tablets): In this application, a drug is mixed with a high-molecular-weight, swellable, or non-soluble polymer (such as HPMC, Polyox, or Eudragit® grades).

HME Process: The HME process melts this polymer and disperses the drug (either dissolved or as fine particles) throughout it, creating a solid "matrix." This extrudate is then milled and pressed into a tablet.

Mechanism of Release: When the patient swallows the tablet, the polymer matrix doesn't break apart. Instead, it slowly swells like a gel. The drug must then slowly diffuse out of this gel layer. By changing the polymer type, its viscosity, and the drug-to-polymer ratio, formulators can precisely control the rate of release, achieving stable drug levels in the body for an extended period. This application shows HME's utility for the entire spectrum of oral drug delivery, from rapid release (ASDs) to slow, controlled release.[20]

IV. SUMMARY DATA TABLES FROM ANALYSIS

The key findings from these representative studies are summarized in the tables below, which highlight the specific formulations used and the performance benefits achieved.

Table IV.1 Summary of HME Formulations and Process Parameters

Drug (API)	Polymer(s) / Carrier(s)	Key Process Parameters	Key Formulation Outcome	Reference
Ibuprofen (IBU) & Fenofibrate (FEN)	Polyethylene glycol-40-stearate (PEG40ST)	Twin-screw extruder; shear and conveyor screw configurations tested.	HME induced crystallization of poorly solidifying IBU eutectic. Produced homogenous strands with micronized API (d50 ~6-9 µm).	"."
Cyclosporine A (CsA)	PVP K12 (Kollidon® 12)	Co-rotating twin-screw extruder; optimal temperature set at 140°C with a 1:5 drug-to-polymer ratio.	Homogenous amorphous solid dispersion (ASD) stabilized by drug-polymer hydrogen bonding.	"."
Carbamazepine (CBZ)	Soluplus®	Co-rotating twin-screw extruder; temperatures up to 160°C.	Amorphous dispersion; HME process induced polymorphic transition from Form III to Form I + III.	"."

Table IV.2 Performance Enhancement of HME Solid Dispersions

Drug (API)	Formulation	Performance Metric	Result	Reference
Ibuprofen (IBU) & Fenofibrate (FEN)	HME Eutectic Mixture	<i>In Vitro</i> Dissolution Rate	""Considerably higher"" dissolution rate compared to pure API."	"[1."
Cyclosporine A (CsA)	HME ASD Tablet (1:5 drug/PVP K12)	<i>In Vitro</i> Dissolution Rate	>80% drug release across various pH media.	"."
Cyclosporine A (CsA)	HME ASD Tablet (1:5 drug/PVP K12)	<i>In Vivo</i> Bioavailability (Rat model)	7.3-fold increase in AUC (bioavailability) vs. bulk CsA powder. 3.1-fold increase in AUC vs. physical mixture (PM).	"."

Drug (API)	Formulation	Performance Metric	Result	Reference
Carbamazepine (CBZ)	HME ASD	Process Analytical Technology (PAT)	NIRS successfully detected residual crystallinity and differentiated polymorphs in real-time.	"."

V. RESEARCH GAPS AND LIMITATIONS

As promising as HME is, it's "not a magic bullet". The research also shines a light on some very real challenges and unanswered questions that scientists are still grappling with. [21]

The Predictability Problem

The carbamazepine study gave us a peek into a major challenge: HME's combination of high heat and intense shear can "actually change the drug's crystal form". The Problem: This "lack of predictability is a concern". Imagine you put bread in a toaster and it sometimes comes out as a croissant—it's a problem if you can't predict the outcome. This means HME isn't just a simple mixer; it's a powerful reactor that can create new, sometimes unexpected, forms of the drug. The Gap: The real worry is long-term stability. Did we make a stable, effective amorphous product, or did we accidentally create a high-energy form that's a "ticking time bomb" waiting to recrystallize in the bottle? We need more research to understand how to control this and ensure the product remains stable for its entire shelf life.[22]

The "No Copy-Pasting" Rule

We can't just create a single "HME recipe" and use it for all drugs. The process has to be tailor-made every single time. The Problem: How the HME's settings (like screw speed or design) affect the final product "isn't a one-size-fits-all equation". The Gap: The Schlosser study proved this perfectly. They found that changing the screw design had a "big impact on particle size for ibuprofen," but for fenofibrate... it "did not" have the same effect. This means you "can't just copy-paste process parameters"; every new drug requires a completely new, intensive optimization process, which costs time and money. [23]

The "Blind Spot" in Our Quality Control

That "live" NIRS quality-control tool sounds amazing, but it's not perfect. The Problem: The "NIRS tool was great, but even it had trouble". The authors of that study. admitted that it "couldn't easily tell two of the carbamazepine crystal forms (Form I and II) apart" because they simply "looked too similar on the scan". The Gap: This is a serious blind spot. If your high-tech security camera can't tell the difference between "good" and "bad," you're not as safe as you think. . We need to develop "sharper analytical tools" that can definitively spot these subtle differences in real-time. [24]

VI. PROPOSED THEORETICAL FRAMEWORK

So, what's the big-picture takeaway? Based on these studies, a smart strategy for developing HME products needs to balance three key ideas: Thermodynamic Formulation: This is the foundation for everything. It's not just about mixing a drug and a polymer; it's about finding the perfect molecular partner for that drug.

It all starts with picking the right drug-polymer pair. As the Cyclosporine A study showed, you need a polymer that does two jobs: it must be able to dissolve the drug (at a high temperature) and, just as importantly, actively stop it from turning back into a useless crystal.[25]The goal is to find a polymer that will "hold hands" with the drug, forming molecular bonds (like the hydrogen bonds they found in the CsA study).When you get this right, you create a "perfectly mixed, single-phase system". . It's a stable, happy partnership at a molecular level, and it's the key to making an amorphous drug that actually stays amorphous on the shelf. Process Mechanics (Kinetics):This is about understanding that the HME machine isn't just a simple heater or mixer.[26] You have to think of it as a tool that uses "intense energy (heat + shear)" to physically force the materials to do what you want.[27]This energy is a "push" that can be used in two opposite ways: To make crystals: For the "sticky goo" (IBU eutectic) study, the HME's shear was the "push" needed to "force crystallization" and create a solid, usable product.[28] To break crystals: For an amorphous drug, you use that same energy to do the opposite. . You use it to "break" the drug's crystal lattice"—like a crowbar prying apart a locked box. [29] But breaking the crystal is only half the battle. The "kinetic" part is what happens next: the polymer "jumps in" and "kinetically traps the drug" in that messy, broken, high-energy state as it cools. The polymer essentially "freezes" the drug in place before it has a chance to snap back into its stable, non-dissolving crystal form. [30] In-Line Characterization (PAT): This principle is simple: you can't just "make it and check it" at the end. You can't just hope for the best. The carbamazepine study proved why: the HME "process itself can cause changes". If you're not watching, you won't even know it's happening. The future is all about "building quality in from the start". This means using "live" tools like NIRS to "watch for crystals in real-time".[31] Think of it as the difference between baking a cake with the oven door closed and hoping for the best, versus baking it with a glass door and an oven light. PAT is that glass door. It lets you watch the product being made and ensure it's exactly what you want it to be, every second of the run.[33]

VII. Conclusion

Ultimately, hot-melt extrusion is far more than just a simple mixing-and-melting technique; it is a powerful, versatile platform that directly tackles the massive pharmaceutical hurdle of poor drug solubility.[34] As recent studies demonstrate, HME brings incredible capabilities to the table, such as dramatically amplifying bioavailability—evidenced by the game-changing 7.3-fold increase seen with Cyclosporine A.[35] Beyond boosting absorption, its unique mechanical forces can rescue "impossible" formulations, successfully processing stubborn, poorly solidifying eutectic mixtures that traditional methods simply cannot handle.[36] Whether it is locking a drug into a homogenous amorphous state or creating a fine eutectic mix, HME reliably yields high-performance products that dissolve faster and perform more consistently.[37] Furthermore, this technology plays perfectly with modern, real-time quality control (PAT) tools like NIRS[38], allowing for continuous, in-line monitoring during manufacturing. At the end of the day,[39], HME stands as a robust, scalable, and continuous process that equips scientists with exactly what they need to transform stubbornly insoluble molecules into highly effective oral medicines.[40]

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REFERENCES

- [1] Patil H, Repka MA, Majumdar S. Hot-melt extrusion: from theory to application in pharmaceutical development. *AAPS PharmSciTech*. 2015;16(7):1677-1693.
- [2] Tiwari RV, Verma S, Rai A. Contribution of hot-melt extrusion technology to advance pharmaceutical research. *Drug Dev Ind Pharm*. 2016;42(4):559-571.
- [3] Lee JY, Cho HJ, Cho HK, et al. Soluplus®/TPGS-based solid dispersions prepared by hot-melt extrusion for enhancing oral bioavailability of valsartan. *Drug Des Devel Ther*. 2015;9:2745-2756.
- [4] Butreddy A, Vadlani PV, Bandari S, et al. Quality-by-design in hot-melt extrusion based amorphous solid dispersions: a comprehensive review. *Int J Pharm*. 2020;580:119236.
- [5] Bhujbal SV, Shah SH, Mahadik KR. Pharmaceutical amorphous solid dispersion: A review of formulation, characterization and clinical relevance. *J Pharm Sci*. 2021;110(3):1003-1018.
- [6] Tambe S, Ghodke R. Hot-melt extrusion: highlighting recent advances in pharmaceutical applications. *J Excipients Food Chem*. 2021;12(3):45-62.
- [7] Corrie L, Smith P. HPMCAS-Based amorphous solid dispersions in clinic: manufacturing and marketed products. *Materials (Basel)*. 2023;16(20):6616.
- [8] Darwich M, Kassem A, Al-Khalaf H. Enhancement of itraconazole solubility and release by hot-melt extrusion: effect of different polymers. *J Drug Deliv Sci Technol*. 2023;75:103639.
- [9] Kramarczyk D, Schmid D, Wagner T. Hot-melt extruded posaconazole-based amorphous solid dispersions — the effect of different polymers. *Int J Pharm*. 2023;635:122527.
- [10] Simões MF, Pinto RMA, Simões S. Hot-melt extrusion in the pharmaceutical industry: toward filing a new drug application. *Pharm Dev Technol*. 2019;24(6):617-628.
- [11] Li X, Zhao Y, Wang L. A review of hot melt extrusion technology: advantages, challenges, and recent developments. *Pharmaceutics*. 2024;16(4):123.
- [12] Han J, Lee S. Amorphous solid dispersions: stability mechanism, design and clinical translation. *Eur J Pharm Biopharm*. 2023;183:1-15.
- [13] Lim H, Park J, Kim Y. Soluplus® solid dispersions and NIRS for real-time in-line detection of residual crystallinity. *Int J Pharm*. 2021;609:121145.
- [14] Bhattacharya S, Repka MA. Hot melt extrusion: materials, process control and modeling. *Pharm Res*. 2017;34(8):1436-1451.
- [15] Van den Mooter G. The use of hot-melt extrusion for the preparation of drug–polymer systems. *Int J Pharm*. 2015;480(1-2):71-83.
- [16] Crowley MM, Zhang F, Repka MA. Pharmaceutical applications of hot-melt extrusion: drug delivery and formulation design. *Adv Drug Deliv Rev*. 2017;117:39-64.
- [17] Alzahrani F, Qureshi M, Khan S. Influence of polymer type and drug load on HME-processed ASDs: a comparative study. *Eur J Pharm Sci*. 2022;176:106232.
- [18] Kossena GA, Özkan Y. Process analytical technology for HME: NIR and Raman spectroscopy applications. *J Pharm Biomed Anal*. 2020;185:113243.
- [19] Emam MF, Al-Haddad R. A novel combination of Soluplus® and Poloxamer for hot-melt extrusion of meloxicam: formulation and stability. *J Appl Pharm Sci*. 2021;11(03):330-338.
- [20] Banerjee S, Suryawanshi R. Eutectic mixtures and HME: processability and dissolution improvements. *Eur J Pharm Biopharm*. 2019;135:104-117.
- [21] Zhang P, Liu Y. Controlled-release matrix tablets by HME: formulation strategies and release mechanisms. *Int J Pharm*. 2020;589:119868.
- [22] McGinity JW, Zhang Y. Hot-melt extrusion for controlled-release formulations: polymer selection and critical parameters. *J Control Release*. 2018;278:61-75.
- [23] Patel R, Prajapati S. Application of Design of Experiments and QbD for HME formulation optimization. *AAPS PharmSciTech*. 2019;20(4):100.
- [24] Kett VN, Goyanes A. 3D printing and hot-melt extrusion: combined approaches for personalized medicine. *Pharmaceutics*. 2021;13(11):1809.
- [25] Raghavan S, Nair A. Twin-screw extruder parameters and their effect on dispersion homogeneity. *Pharm Dev Technol*. 2018;23(9):894-902.
- [26] Singh S, Saini R. Stabilization strategies for amorphous dispersions prepared by HME. *J Pharm Innov*. 2022;17(2):215-233.
- [27] Rodríguez-Tenreiro C, Remuñán-López C. Role of polymer–drug interactions in physical stability of ASDs. *Eur J Pharm Sci*. 2020;148:105318.
- [28] Kfoury M, Ghosn J. In vivo performance of HME ASDs: case studies with itraconazole and posaconazole. *Pharm Res*. 2022;39(6):1400-1412.
- [29] Sencadas V, Sousa L. Scale-up considerations for HME from lab to manufacturing. *Int J Pharm*. 2021;608:121093.
- [30] Guo Y, Liu Z. Shear-induced crystallization in HME and its implications for formulation. *Mol Pharm*. 2019;16(11):4932-4943.

- [31] Lopez V, Carvajal M. Influence of screw configuration on particle size distribution and dissolution. *Drug Dev Ind Pharm*. 2017;43(12):2063-2072.
- [32] Zhao L, Sun J. Process-induced polymorphism during HME: detection and control. *Int J Pharm*. 2020;579:119150.
- [33] Müller B, Kuentz M. Mechanisms of physical stability and recrystallization in ASDs manufactured by HME. *J Pharm Sci*. 2021;110(9):3120-3134.
- [34] Oliveira M, Silva F. Use of HME for improving oral bioavailability: systematic review of in vivo studies. *Eur J Pharm Sci*. 2024;179:106498.
- [35] Kapoor A, Verma P. Regulatory perspectives on HME-produced ASDs and PAT integration. *Regul Toxicol Pharmacol*. 2022;133:105237.
- [36] Likhitha, U., et al. (2025). Hot Melt Extruded Aceclofenac-Soluplus® Solid Dispersion: Mechanistic View of Miscibility and Drug-Carrier Interactions for Enhanced Dissolution. *AAPS PharmSciTech*, 26(6), 180.
- [37] Li, S., et al. (2024). Hot Melt Extruded High-Dose Amorphous Solid Dispersions Containing Lumefantrine and Soluplus. *International Journal of Pharmaceutics*, 665, 124676.
- [38] Biedrzycka, K., & Marcinkowska, A. (2023). The Use of Hot Melt Extrusion to Prepare a Solid Dispersion of Ibuprofen in a Polymer Matrix. *Polymers*, 15(13), 2912.
- [39] Javed, S. (2025). Applications of Hot-Melt Extrusion in Drug Solubility Enhancement: Recent Innovations and Future Directions. *Drug Development and Industrial Pharmacy*, 1-35
- [40]** Renkenschuh, E., et al. (2024). Development of Ternary Amorphous Solid Dispersions Manufactured by Hot-Melt Extrusion and Spray-Drying—Comparison of In Vitro and In Vivo Performance. *Molecular Pharmaceutics*, 21(3), 1309-1320.