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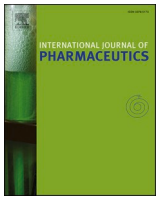

Review

HME as a transformative platform in pharmaceutics: from molecular dispersion engineering to personalized drug delivery

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ABSTRACT

Hot melt extrusion (HME) has become a major continuous manufacturing approach for producing amorphous solid dispersions (ASDs) that address the poor solubility and limited bioavailability of many contemporary drug candidates. Through controlled application of heat and mechanical shear, HME enables uniform molecular dispersion of the drug within a polymer carrier, converting crystalline APIs into kinetically stable amorphous systems with improved dissolution profiles and enhanced supersaturation. The performance of these extrudates is determined by essential Critical Quality Attributes (CQAs) such as glass transition temperature (T_g), residual crystallinity, dissolution behaviour and impurity levels which in turn depend on Critical Material Attributes (CMAs) including polymer properties, drug loading, hygroscopicity and particle size, as well as Critical Process Parameters (CPPs) like screw speed, barrel temperature, residence time and specific mechanical energy (SME).

A Quality by Design (QbD) framework provides a structured basis for formulation and process optimization by mapping the relationships between CQAs, CMAs and CPPs to establish a robust design space. Modern implementation strategies increasingly incorporate Process Analytical Technology (PAT) tools and real–time release testing (RTRT), allowing continuous monitoring of amorphization, mixing efficiency and chemical stability in alignment with FDA, EMA, and ICH regulatory expectations. Emerging case studies highlight the broad applicability of HME beyond traditional bioavailability enhancement, with successful use in taste–masked paediatric formulations, abuse–deterrent platforms, fixed–dose combinations (FDCs), and gastro–retentive systems. Together, these developments reinforce HME as a mature, solvent–free, and industrially scalable technology for manufacturing advanced oral drug products with consistently high performance and improved patient outcomes.

1. Introduction

HME is a versatile and efficient technology that has been widely used in pharmaceutical manufacturing to enhance the solubility and bioavailability of poorly water-soluble drugs. During the extrusion process, the melting/mixing of active pharmaceutical ingredients (APIs) and polymeric matrix leads to the production of solid dispersions (SDs) that improve drug solubility. Since the 1930s, when HME was first developed for commercial use in the plastics and food sectors, it has been utilised in pharmaceutical manufacturing (Patil et al., 2015). HME has been largely acknowledged as a suitable technique for processing pharmaceuticals, aiming to enhance the physicochemical properties of challenging drug candidates, such as biopharmaceutics classification system II (BCS class-II) molecules via the formation of SDs. In recent decades, HME technologies have evolved into a sophisticated platform for the production of different drug delivery systems. Since its beginnings in the early 1970s, HME has been used to develop several drug delivery methods such as enhancing solubility, SDs, implants, oral disintegration mechanisms, ophthalmic delivery, controlled, sustained release drug delivery, granules, cocrystals, taste masking, concealing flavour, and formulating films and strips using environmentally friendly technology that avoids organic solvents, minimises manufacturing steps,

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and is easily scalable (Tambe et al., 2021).

The HME process involves feeding a physical blend into the extruder barrel, where it is conveyed, mixed, melted and dispersed under controlled torque and pressure to produce SDs (S. Li et al., 2024). The primary components of the extruder include the feeder, barrel, screw and die (Fig. 1). As a continuous pharmaceutical manufacturing technique, HME processes polymeric materials using a rotating screw at temperatures above their T_g and, in some cases, above their melting temperature (T_m), enabling molecular–level mixing of active compounds with thermoplastic binders such as Hypromellose, hydroxypropyl cellulose and polyethylene oxide (PEO). These materials soften upon heating and resolidify upon cooling without undergoing chemical transformation, making them suitable carriers for ASDs. Another significant advantage of HME is its formulation flexibility. A wide range of pharmaceutical excipients can be incorporated, including high-molecular-weight polymers that serve as matrix formers or stabilizers, as well as low-molecular-weight additives such as sugar alcohols, waxes, plasticizers, and surfactants. This broad excipient compatibility enables extensive formulation design possibilities and facilitates the development of customized drug delivery systems tailored to specific therapeutic or processing requirements.

This cutting-edge technology also promotes continuous manufacturing (Abu Diak, 2009) and process monitoring with integration of downstream auxiliary equipment or instruments such as process analytical tool (PAT), such as Raman spectroscopy & near-infrared spectroscopy (NIR) for evaluating the manufacturing process and product quality (da Silva Júnior et al., 2017); (Leister et al., 2012); (Wahl et al., 2013).

HME has emerged as an attractive alternative to conventional pharmaceutical manufacturing processes due to its versatility, efficiency, and ability to support modern formulation strategies. Advances in pharmaceutical-grade extruder design have enabled improved control over mixing, melting, and dispersion processes, allowing APIs to be effectively combined with polymeric carriers and functional excipients. As a result, HME has become a valuable platform for the production of a wide range of solid dosage forms, including granules, pellets, films, and filaments for downstream processing.

One of the key advantages of HME lies in its ability to produce granules or pellets with uniform size, shape, and density while ensuring excellent drug content uniformity. The continuous mixing and controlled thermal environment within the extruder promote homogeneous distribution of one or more APIs within the carrier matrix. This capability is particularly beneficial for formulations requiring consistent dose accuracy and reproducible product performance, especially when processing poorly soluble drugs or developing advanced drug delivery systems.

More recently, HME has gained considerable attention as a continuous granulation technology capable of supporting both wet and solvent-free melt granulation processes. In addition to its processing versatility, HME offers several operational and environmental benefits. It is considered a green manufacturing technology due to the absence of organic solvents and reduced waste generation. Continuous processing

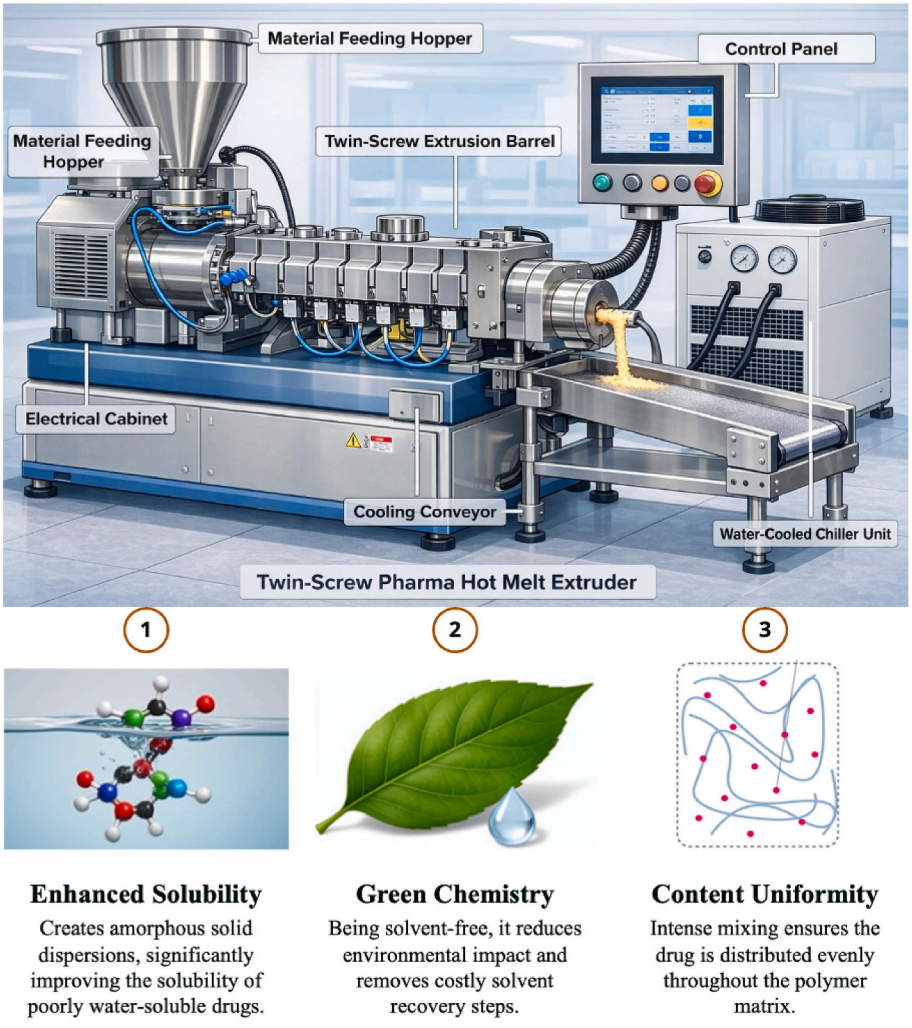

Fig. 1. HME process highlighting key advantages, including improved drug solubility, environmentally sustainable processing, and enhanced content uniformity.

improves equipment utilization, reduces production footprint, and lowers energy consumption. Furthermore, HME simplifies scale-up, minimizes manual intervention, enhances process safety, and shortens development timelines, ultimately contributing to reduced manufacturing costs and faster time to market for pharmaceutical products (Kolipaka et al., 2024).

Although numerous reviews have discussed individual aspects of HME, including ASDs, polymer selection, or extrusion processing, a comprehensive framework integrating formulation science, process engineering, QbD, PAT, stability assessment, and emerging applications such as 3D printing and personalized drug delivery remains limited. This review aims to bridge these areas by presenting HME as a transformative pharmaceutical manufacturing platform rather than solely a solubility-enhancement technology. Particular emphasis is placed on the interplay between CMAs, CPPs, and CQAs, alongside a mechanistic understanding of ASD formation, stabilization strategies, continuous manufacturing considerations, and future translational opportunities. By integrating these perspectives, the review provides a modern and process-oriented roadmap for the rational development of advanced HME-based drug delivery systems.

2. Overview of HME

Extrusion is the process of changing the physicochemical properties of substances by passing them through a heated barrel under pressure with rotating screws. As shown in Fig. 2, during this process, the material is softened or melted, mixed, conveyed, and forced through a die (feed rate, screw speed, and temperature) to form strands, pellets, granules, films, or filaments according to the materials' melting and miscibility characteristics, followed by extrusion of the processed material (Crowley, Zhang, Repka, Thumma, Upadhye, Kumar Battu, et al., 2007); (Patil et al., 2015). During HME processing, the materials undergo transformations that involve the combined effects of thermal and mechanical energy, as well as the development of pressure.

2.1. Thermal energy input: Polymer softening and drug dissolution mechanisms

Thermal energy enables polymer transitions above its glass transition (Tg) or melting point (Tm), thereby creating the molecular mobility required for drug incorporation into the carrier matrix and the formation of homogeneous systems, particularly ASDs (Hancock and Zografi, 1997); (Leuner and Dressman, 2000a). Precise temperature control defines the processing window and ensures product stability, performance, and regulatory compliance. Key considerations include polymer softening and viscosity reduction, drug distribution within the molten matrix, crystalline-to-amorphous transformation, Drug–polymer miscibility, and prevention of API thermal degradation (Baghel et al., 2016).

2.2. Mechanical energy contribution: Shear-induced mixing and homogenization

Mechanical energy generated by screw rotation provides essential distributive and dispersive mixing, ensuring uniform drug distribution and consistent product quality. SME serves as a key process parameter for monitoring mixing efficiency and batch reproducibility in continuous manufacturing (Kshirsagar et al., 2025). Critical functions include deagglomeration of API particles, enhancement of drug–polymer interfacial contact, promotion of amorphization, control of residence time and mixing intensity, and contribution to viscous dissipation heating (Maniruzzaman, Boateng, et al., 2012).

2.3. Pressure development and melt conveying behaviour

Pressure generated along the screw channel enables continuous material conveying and controlled die shaping, ensuring dimensional and structural consistency of the extrudate (Martin, 2013). Effective pressure control supports scalable, reproducible pharmaceutical manufacturing. Important process aspects include stable melt flow toward the die, control of extrudate morphology and surface quality,

Fig. 2. Schematic representation of the HME process flow, including material feeding, melting and mixing within the extruder, shaping through the die, and subsequent cooling of the extrudate.

influence on strand or filament diameter uniformity, impact on downstream processing efficiency, and maintenance of process robustness under continuous operation (Crowley, Zhang, Repka, Thumma, Upadhye, Kumar Battu, et al., 2007).

3. Theoretical considerations

The theoretical framework underpinning HME is critical for rational formulation design, prediction of physical stability, and process optimization. Solid-state transformations during HME are governed by thermodynamics (miscibility and phase behaviour), molecular mobility, and kinetic stabilization during cooling. A mechanistic understanding of these principles supports robust development of ASDs or SDs and advanced delivery systems.

3.1. Classification of SDs

SDs formed by HME vary based on drug–carrier miscibility and processing conditions, ranging from crystalline eutectic systems to fully amorphous dispersions (Fig. 3). Proper classification is essential to predict dissolution performance, stability, and overall formulation behaviour (Leuner and Dressman, 2000a). The classifications are as follows:

3.1.1. Eutectic mixtures

Eutectic mixtures form when the drug and polymer are miscible in the molten state but crystallize on cooling as two distinct phases with negligible miscibility. Their microstructure differs from that of either pure component. Eutectic combinations of poorly soluble APIs with water–soluble carriers are known to enhance dissolution through improved wettability and reduced particle size (Craig, 2002) Classical eutectic systems are typically associated with low-molecular-weight compounds or conformers, such as sulfathiazole-urea and piroxicam-urea systems. In contrast, polymer-based HME formulations predominantly form amorphous solid dispersions rather than true eutectic systems, although eutectic-like behaviour may occur in partially miscible drug–polymer combinations (Sekiguchi and Obi, 1961). (Chiou & Niazi, 1971) (Pedro et al., 2021).

3.1.2. Glass solutions

Glass solutions consist of an amorphous carrier in which solute molecules are molecularly dispersed. When the drug concentration does not exceed its solubility in the carrier, the system is thermodynamically stable. Supersaturation can trigger phase separation, including recrystallization and precipitation. Glass solutions represent homogeneous single-phase amorphous systems in which drug molecules are molecularly dispersed within the polymer matrix and typically exhibit a single T_g in DSC analysis (Hancock and Zografi, 1997) Itraconazole–HPMC and indomethacin-PVP systems are representative glass solutions that exhibit homogeneous amorphous behaviour and typically show a single T_g in DSC analysis due to molecular-level drug dispersion (Taylor and Zografi, 1997).

3.1.3. Glass suspensions

Glass suspensions form when the drug separates into a distinct amorphous phase, often drug–rich, within an amorphous carrier. Although still amorphous, these phases show a high propensity for recrystallization. Glass suspensions are heterogeneous amorphous systems containing phase-separated drug-rich and polymer-rich domains, often resulting in multiple T_g values corresponding to the individual amorphous phases (Qian et al., 2022) Felodipine-polymer dispersions have been described as glass suspensions with phase-separated amorphous domains and multiple Tg values, indicating heterogeneous amorphous structures (Sarpal et al., 2019) (Baird and Taylor, 2012).

3.1.4. Solid solutions

Solid solutions occur when a solute is incorporated non–stoichiometrically into the crystal lattice of the solvent. They are classified by solubility behaviour or the molecular distribution within the lattice (Hilfiker, 2006).

- Continuous solid solutions exhibit miscibility over the full composition range.
- Discontinuous solid solutions show solubility only at specific compositions.

3.1.4.1. Substitutional solid solutions. In substitutional solid solutions, the solute molecule replaces a solvent molecule in the lattice. This

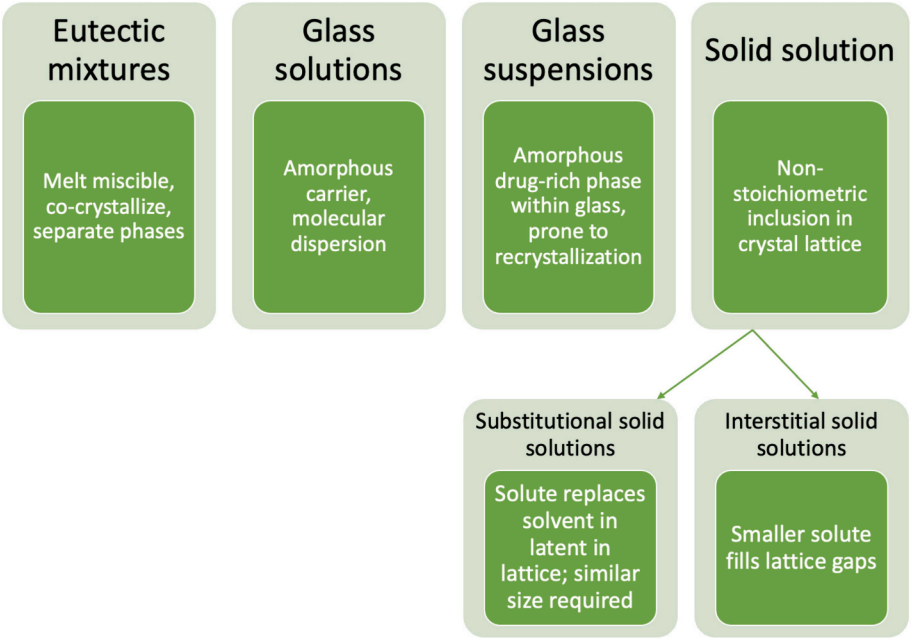

Fig. 3. Classification of SDs.

typically requires similar molecular or ionic sizes to maintain lattice stability (Rethwisch et al., 2020).

3.1.4.2. Interstitial solid solutions. Interstitial solid solutions occur when smaller solute molecules occupy interstitial spaces within the lattice of larger solvent molecules (West, 2022).

Solid solution systems such as griseofulvin–succinic acid demonstrate molecular incorporation within the crystal lattice, contributing to improved dissolution performance (Goldberg et al., 1966).

3.2. Drug–polymer miscibility

Drug–polymer miscibility determines ASD stability, dissolution behaviour, and manufacturability. While high processing temperatures during HME promote mixing, long-term stability depends on thermodynamic compatibility at storage conditions (Bhatta et al., 2025).

3.2.1. HME predictive approaches

During the HME process, miscibility is promoted by polymer softening above Tg or Tm, enabling drug dissolution in the molten matrix. Shear-enhanced mixing improves molecular distribution, while specific interactions (e.g., hydrogen or ionic bonding) support phase stability. Rapid cooling then kinetically stabilizes the amorphous state and limits phase separation (Lang et al., 2014). Predictive thermodynamic models are widely applied to screen carrier candidates and estimate miscibility prior to experimental trials. These approaches reduce development risk and support QbD strategies (Wang et al., 2026). The most common predictive tools are the following:

3.2.2. Flory–Huggins (F-H) interaction parameter (χ)

The lattice–based F–H theory (Flory, 1953) (Equation 1) is widely used to predict polymer–solvent and polymer–polymer interactions by (Fig. 4) evaluating the change in Gibbs free energy before and after mixing between a polymer and a low molecular weight compound using the interaction parameter (Klueppelberg et al., 2023). In pharmaceutical research, the F–H framework is frequently applied to determine the interaction parameter, χ, which reflects the strength of interactions between two components during melting. Recent studies on SDs have commonly estimated χ using melting–point depression techniques (Marsac et al., 2009); (Jelić, 2021).

The application of F–H theory to drug–polymer binary systems can provide valuable insights for the development of SDs manufactured using processes such as HME. However, one limitation of the theory is its assumption of a random distribution of molecular segments, which may not accurately represent systems dominated by strong polar interactions or specific interactions such as hydrogen bonding between blend components (Koningsveld, 2023).

To better characterize these stronger, more specific interactions, an atomic–level understanding is essential. Molecular modelling techniques serve as a powerful complement to the F–H model, enabling direct visualization of drug–polymer interactions and estimation of interaction strengths (Maniruzzaman et al., 2015). Numerous molecular mechanics (MM) and molecular dynamics (MD) studies have been conducted to examine molecular behaviour, including dissolution at crystal surfaces (O'Neill et al., 2024) and to evaluate drug–polymer miscibility in ASDs (Nambiar et al., 2022) (Barmpalexis et al., 2019) (Xiang and Anderson, 2017); (Thakral and Thakral, 2013).

$$\frac{\Delta G_{mix}}{RT} = n_d \ln\phi_d + n_p \ln\phi_p + \chi n_d \phi_p \quad (1)$$

Thakral and Thakral, 2013).where:ΔG_{mix} = Gibbs free energy of mixing.χ = Flory–Huggins interaction parameter.R and T = Universal gas constant (R) and absolute temperature (T).n_d and ϕ_d = number of moles and volume fraction of drug.n_p and ϕ_p = number of moles and volume fraction of polymer.

3.2.3. Hansen solubility parameters (HSP)

Solubility parameters, also known as cohesion energy parameters, are useful for predicting various physicochemical properties of materials, including solubility and melting behaviour (Hancock and Zografi, 1997). Cohesive energy represents the total energy arising from intermolecular forces such as van der Waals interactions, covalent bonds, hydrogen bonding and ionic interactions that hold a material together. It can also be described as the energy required to overcome these interactions, allowing atoms or molecules to separate and enabling transitions such as solid-to-liquid, liquid-to-gas, or solid-to-gas.

The cohesive energy per unit volume is referred to as the cohesive energy density (CED). Based on regular solution theory for non-polar

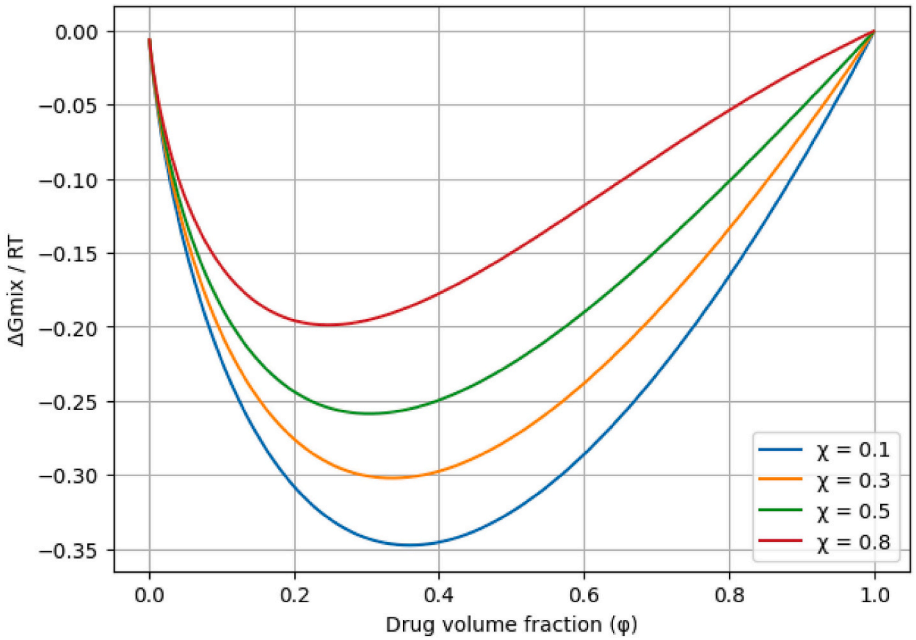

Fig. 4. Flory–Huggins free energy of mixing (ΔGmix/RT) as a function of drug volume fraction (φ) for different interaction parameters (χ). Lower χ values indicate stronger drug–polymer interactions and greater thermodynamic favourability for amorphous solid dispersion formation.

systems, the solubility parameter (δ) can be calculated directly from the CED.

Miscibility between a drug and a polymer is considered likely when the Hansen distance (Ra) between them is small. Because HSPs (δt) are straightforward to determine, they are widely used during early formulation screening, although experimental verification is still required (Milliman et al., 2012). HSP (Equation 2) divides the total cohesive energy into three components: dispersion forces (δD), polar interactions (δP), and hydrogen-bonding forces (δH).

$$\delta_t^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (2)$$

(AlQasas and Johnson, 2023).

In practical formulation screening, smaller Hansen distance (Ra) values indicate greater similarity between the intermolecular interaction profiles of the drug and polymer, suggesting improved miscibility and a higher probability of forming stable amorphous solid dispersions. Conversely, larger Ra values indicate weaker compatibility and increased risk of phase separation or recrystallization. A difference in solubility parameter values (δt) below 7 $MPa^{0.5}$ suggests favourable drug–polymer miscibility, whereas δt values greater than 10 $MPa^{0.5}$ are commonly associated with poor miscibility and increased likelihood of phase separation (Mamidi and Rohera, 2021) (Greenhalgh et al., 1999).

3.3. Glass transition temperature (T_g) modelling

Tg modelling predicts the physical stability of amorphous dispersions. The Gordon–Taylor equation (Equation 3) estimates the mixture Tg based on component Tg values and composition (Červinka and Fulem, 2021). A higher system Tg generally correlates with reduced molecular mobility and improved long-term physical stability.

$$T_g = \frac{w1\ Tg1 + kw2Tg2}{w1 + kw2} \quad (3)$$

where:T_g = glass transition temperature of the mixture (K or °C).T_g1 and T_g2 = glass transition temperatures of component 1 and component 2, respectively.W1 and w 2 = Weight fractions of component 1 and component 2, respectively.K = Gordon–Taylor constant

Phase diagram construction: Phase diagrams map drug–polymer interactions across temperature and composition ranges. They help define miscibility limits and processing windows in HME (Tian et al., 2013). Phase diagrams support rational formulation development and reduce empirical trial-and-error approaches.

Early–stage formulation development has also benefited from new methods aimed at predicting polymer suitability for ASD design while conserving limited API. Patel et al. (2023) compared theoretical miscibility predictions with small–scale experimental assessments during polymer selection for triclabendazole ASDs. Although thermodynamic modelling identified VA64 as the most compatible polymer and predicted poor miscibility with PVA, experimental preparation using a material–sparing supercritical fluid technique produced the opposite trend. Ultimately, ASDs prepared using either polymer showed dramatic solubility enhancement, but the findings illustrated the limitations of relying exclusively on theoretical prediction tools for HME–focused development. Integrating modelling with rapid experimental screening appears to provide a more accurate guide for polymer selection.

4. Formation of ASDs

The formation of ASDs (Fig. 5) via HME is a thermally and mechanically driven process in which the crystalline drug is transformed into a molecularly dispersed amorphous state within a polymer matrix (Agrawal et al., 2015a). Successful ASD formation depends on controlled melting, efficient mixing, favourable intermolecular interactions, and kinetic stabilization during cooling.

4.1. Mechanisms for the formation of ASDs

The formation of ASDs (Fig. 5) during HME is governed by interconnected thermal and mechanical processes that collectively convert a crystalline or partially crystalline drug into a molecularly dispersed amorphous phase. As the polymer is heated above its T_g or T_m, it transitions into a molten or viscoelastic state that can solubilize the API. This dissolution step is crucial, as it determines whether a true single–phase system can form. The extent of drug dissolution depends on drug–polymer miscibility, processing temperature, residence time, and the thermodynamic driving forces for mixing (Crowley et al., 2007).

For APIs with melting points near or within the extrusion temperature range, partial or complete melting may occur, promoting molecular dispersion within the polymer matrix. When the drug has a melting point significantly higher than feasible processing temperatures, dissolution may proceed through solid–state solubilization facilitated by polymer plasticization and shear–induced disruption of the crystal lattice (Qian et al., 2022); (Vasanthavada et al., 2004). In such cases, shear–assisted mixing plays a central role. The mechanical energy imparted by kneading and mixing elements enhances deagglomeration, reduces particle size and increases interfacial contact between drug and polymer, all of which accelerate dissolution kinetics and help achieve a homogeneous amorphous phase (Maniruzzaman, Boateng, et al., 2012).

Once molecular dispersion is achieved, rapid cooling at the die exit is essential to kinetically stabilize the amorphous structure. Abrupt temperature reduction lowers molecular mobility, effectively freezing the drug in the disordered state before nucleation or crystal growth can occur. Consequently, cooling rate, extrudate temperature, and downstream handling conditions strongly influence long–term physical stability (Kolipaka, Junqueira, Pathrapankal, et al., 2026) (Baird and Taylor, 2012); (Bhujbal et al., 2021). Overall, the interplay of controlled thermal input, optimized shear exposure, and efficient quenching defines the mechanistic pathway of ASD formation during HME and ultimately determines the performance and durability of the final dispersion.

4.2. Intermolecular interactions

The long-term stability of ASDs depends largely on the strength and nature of drug–polymer interactions. These interactions reduce molecular mobility and inhibit nucleation and crystal growth (Schittny et al., 2020). Key stabilizing mechanisms include hydrogen bonding between drug functional groups and polymer chains, ionic interactions in systems containing ionizable components, dipole–dipole interactions that enhance miscibility, polymer chain entanglement that restricts molecular diffusion, and high Tg matrices that reduce molecular mobility and

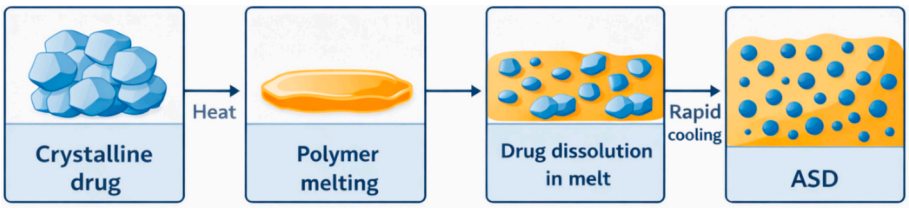

Fig. 5. Formation of ASDs.

slow recrystallization kinetics (He et al., 2015).

4.3. Factors involved

The formation and long-term stability of ASDs are governed by a complex interplay of formulation composition and process conditions. Among these variables, drug loading is one of the most critical determinants of system performance. Increasing drug concentration enhances the thermodynamic driving force for phase separation, particularly when the solubility limit of the drug in the polymer matrix is exceeded. At high loadings, the system may transition from a single-phase molecular dispersion to a biphasic structure containing amorphous drug-rich domains, which significantly increases the likelihood of nucleation and recrystallization during storage. Therefore, identification of the drug–polymer miscibility limit through phase diagrams or solubility parameter analysis is essential during formulation development.

Polymer properties, particularly T_g and molecular weight, strongly influence both processing behaviour and physical stability. Polymers with high Tg values reduce molecular mobility within the matrix, thereby suppressing nucleation and crystal growth according to the Williams–Landel–Ferry (WLF) relationship. Higher molecular weight polymers can further restrict chain mobility and enhance kinetic stabilization; however, they also increase melt viscosity, which may compromise processability, elevate torque, and require higher processing temperatures. Consequently, a balance must be achieved between stability enhancement and manufacturability, often necessitating the use of plasticizers or optimized screw configurations to maintain manageable rheological properties during extrusion.

Processing conditions, particularly cooling rate, play a decisive role in kinetically trapping the drug in its amorphous state. Rapid quenching at the die exit reduces molecular mobility before phase separation or crystallization can occur, effectively preserving the single-phase structure formed in the melt. Inadequate or slow cooling may allow structural relaxation and facilitate nucleation, especially in marginally stable systems. Downstream handling conditions therefore, become integral to ASD stabilization, particularly in continuous manufacturing settings.

Environmental factors, most notably humidity exposure, critically impact ASD stability. Moisture acts as a plasticizer, lowering the system Tg and increasing molecular mobility, which accelerates crystallization kinetics. Hygroscopic polymers are especially susceptible to this effect, and even modest increases in relative humidity can significantly reduce the physical stability window. Appropriate packaging, moisture barriers, and desiccants are therefore essential for long-term storage.

Finally, the intrinsic crystallization tendency of the API itself remains a fundamental constraint. Drugs characterized by high lattice energy, strong intermolecular interactions, or inherently high molecular mobility exhibit a greater propensity for recrystallization. Such compounds may require lower drug loading, higher Tg polymers, or stronger intermolecular drug–polymer interactions to achieve durable stabilization. Collectively, rational optimization of composition and process parameters is essential to ensure robust ASD formation and sustained amorphous stability throughout the product lifecycle.

5. Components of HME

HME components (Fig. 4) integrate controlled feeding systems, a temperature-regulated barrel, modular screw assemblies (primarily co-rotating twin-screw), a shaping die, and downstream cooling units (Patil et al., 2015). These components collectively ensure consistent mixing, stable processing, and scalable pharmaceutical manufacturing under continuous conditions.

5.1. Feeding systems

Accurate and consistent feeding is fundamental to achieving content uniformity, stable torque, and reproducible product quality in HME. Variations in feed rate directly affect residence time, SME, and melt pressure, impacting both process stability and final product performance (A. S. et al., 2019).

5.1.1. Gravimetric feeding

Gravimetric feeders operate based on real-time mass flow measurement using load cells. They continuously adjust the feed rate to maintain a preset mass throughput. Gravimetric feeding is considered the standard in pharmaceutical-scale HME. The advantages of gravimetric feeding systems are high precision and reproducibility, essential for continuous manufacturing, minimize batch-to-batch variability, and support QbD strategies (Maniruzzaman, Boateng, et al., 2012).

5.1.1.1. Volumetric feeding. Volumetric feeders deliver material based on screw speed and calibrated volume without direct mass measurement. For robust commercial manufacturing, volumetric feeding is generally replaced by gravimetric systems. The characteristics of volumetric feeding are lower precision compared to gravimetric systems, sensitive to bulk density variation and powder flow properties, and commonly used in early-stage screening or feasibility studies (Alshetaili et al., 2020a).

5.2. Extruder barrel

The extruder barrel consists of multiple segmented, temperature-controlled zones designed to regulate material transformation along the process path. Independent temperature control across zones enables optimization of the thermal profile, reducing degradation risk while ensuring adequate mixing. Modular barrel segmentation enhances process flexibility and scalability (Wesholowski et al., 2019). The extruder barrel functions include controlled polymer melting or softening, progressive mixing, homogenization, and pressure development before the die.

5.3. Extruder screws

The screw configuration is the core determinant of mixing efficiency, shear exposure, and residence time distribution (RTD) (Table 1) (Mali et al., 2019).

5.3.1. Types of screws

Co–rotating twin–screw extruders are the predominant choice in pharmaceutical HME due to their excellent distributive and dispersive mixing efficiency, modular screw configurations, and precise process control, all of which facilitate consistent production of high–quality ASDs (Bauer et al., 2023). In contrast, counter–rotating twin–screw systems generate higher pressure build–up and are advantageous for applications requiring substantial pumping capacity, but they offer comparatively weaker mixing performance and are therefore less commonly employed for complex drug–polymer matrices.

Single–screw extruders, while characterized by mechanical simplicity and suitability for processing high–viscosity melts, provide limited mixing capability and are thus generally reserved for shaping or melt–forming operations rather than for achieving the molecular–level mixing required for pharmaceutical SD manufacture (Fig. 6).

5.3.2. Screw elements

Modern co-rotating twin-screw extruders are inherently modular systems in which screw configuration can be rationally engineered to match formulation and process requirements. As highlighted by Crowley et al. (2007). The arrangement, length, and sequence of screw elements

Table 1
Comparison of extruder types used in pharmaceutical HME.

Parameter	Single screw extruder	Co-rotating twin-screw extruder	Counter-rotating twin-screw extruder
Number of Screws	One screw	Two screws rotating in the same direction	Two screws rotating in opposite directions
Mixing Efficiency	Limited (mainly distributive)	Excellent distributive and dispersive mixing	Moderate mixing; less dispersive than co-rotating
Shear Intensity	Low to moderate	High and adjustable via screw configuration	Moderate; more compressive than shear-dominant
Residence Time Control	Limited control	Good control via modular screw elements	Moderate control
Pressure Generation	Moderate	Moderate	High-pressure build-up capability
Suitability for ASDs	Limited (less efficient amorphization)	Highly suitable; industry standard for ASDs	Suitable but less commonly used for ASDs
Screw Configuration Flexibility	Fixed/simple design	Highly modular (kneading blocks, mixing, reverse elements)	Less modular compared to co-rotating systems
Process Control	Basic	Advanced; supports PAT integration	Moderate
Scalability & Continuous Manufacturing	Suitable but limited flexibility	Excellent; widely used in continuous pharma manufacturing	Suitable for specific applications
Typical Pharmaceutical Applications	Melt shaping, simple matrix systems	ASDs, controlled release, 3D-printing filaments	High-viscosity formulations, −shear sensitive systems
Industrial Prevalence in Pharma	Less common	Most widely used	Less common

determine the balance between shear stress, RTD, thermal input, and pressure generation. This level of configurational flexibility allows formulators to tailor the extrusion environment for specific objectives, such as ASD formation, polymer blending, or controlled degradation avoidance. For example, conveying elements primarily ensure forward material transport with minimal shear input, thereby stabilizing throughput and maintaining process continuity. In contrast, kneading blocks available at stagger angles of 0°, 30°, 45°, 60°, and 90° generate progressively higher shear forces, facilitating dispersive mixing and particle size reduction (Fig. 7). The choice of stagger angle directly influences energy dissipation and mechanical work input, which are critical parameters for drug amorphization and uniform API distribution.

Mixing elements further enhances distributive mixing by promoting material redistribution without excessive shear, improving compositional homogeneity across the extrudate cross-section. Reverse or backward-conveying elements are strategically incorporated to increase.

residence time and localized pressure build-up, thereby improving melt consolidation and homogenization. However, excessive use of reverse elements may elevate torque and thermal load, potentially compromising thermolabile compounds. Consequently, screw design represents a CPP in HME, where optimized configurations enable precise control over microstructure development, drug–polymer interactions, and final product performance while maintaining process robustness and scalability.

5.4. Dies

The die is a critical component of the HME system, as it governs not only the final geometry of the extrudate, such as strands, pellets, films, or filaments, but also influences flow behaviour, pressure development, and thermal history at the final stage of processing. The Die design parameters, including length-to-diameter (L/D) ratio, channel geometry, and land length, directly affect shear stress distribution and melt relaxation before exit. These factors are particularly important in pharmaceutical applications, where dimensional precision and surface quality can influence downstream operations such as palletisation, cutting, filament winding, or direct feeding into 3D printing systems. For instance, filament production for fused deposition modelling (FDM) requires tight diameter tolerances to ensure consistent feeding and dose accuracy, making die design and pressure stability especially critical.

Die pressure serves as a real-time indicator of melt viscosity, homogeneity, and overall process stability. Fluctuations in die pressure may signal variations in material feeding, incomplete melting, phase separation, or degradation phenomena. Maintaining stable die pressure ensures uniform extrudate dimensions, minimizes internal stresses, and enhances reproducibility across batches. Furthermore, controlled

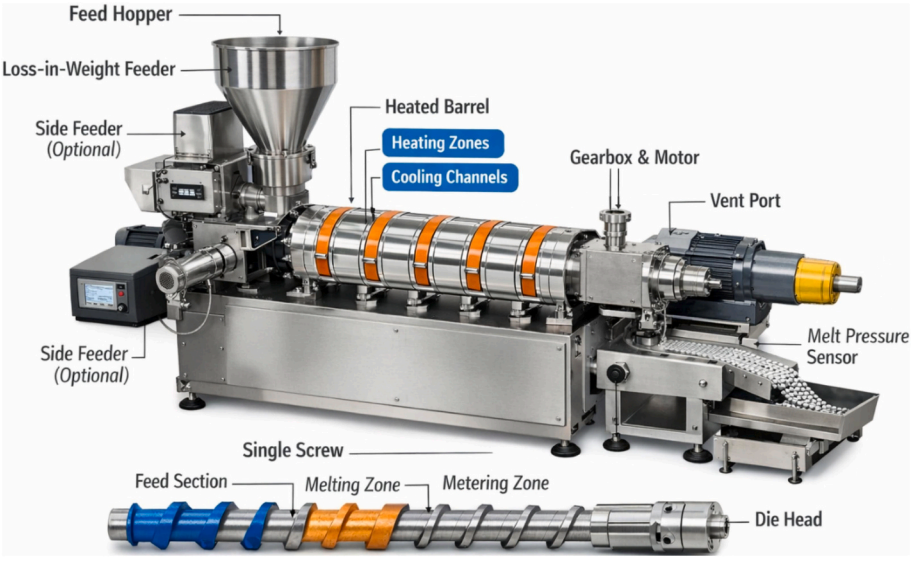

Fig. 6. Single screw hot melt extruder.

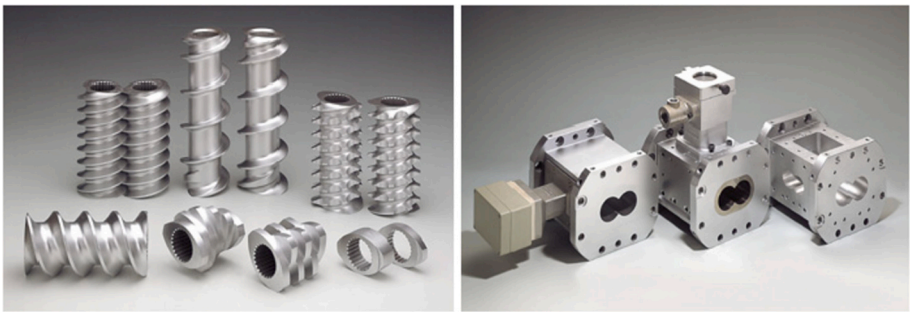

Fig. 7. Screw types that are assembled on high torques splined shafts (left) and flanged barrels electrically heated and liquid cooled (right).

pressure profiles contribute to consistent residence time and shear exposure, thereby supporting uniform drug dispersion and solid-state stability. In continuous pharmaceutical manufacturing, die pressure monitoring is therefore considered a key process analytical parameter, facilitating robust scale-up and ensuring product quality through improved process control.

5.5. Downstream components

Downstream processing plays a decisive role in preserving the physicochemical attributes imparted during HME, particularly when manufacturing ASDs. As highlighted by Grymonpré et al. (2017) Controlled cooling and solidification are essential to stabilize the amorphous state and prevent phase separation or recrystallization. The rate of heat removal directly influences molecular mobility, residual stresses, and free volume within the extrudate matrix. Rapid and uniform cooling reduces residual mobility of the drug–polymer system, thereby minimizing the risk of post-extrusion crystallization and ensuring long-term physical stability. Effective downstream design is therefore critical for maintaining product quality while supporting scalable continuous manufacturing.

Several downstream components are strategically selected depending on the intended final dosage form. Chill rolls provide rapid and uniform cooling for films and sheets, controlling thickness and surface morphology. Air-cooling systems facilitate gradual and controlled solidification of extruded strands, preventing deformation or internal stress accumulation. Pelletizers and strand cutters enable precise size reduction, ensuring narrow particle size distributions for capsule filling or further processing. Spooling systems are essential for filament production, maintaining a consistent diameter and tension for subsequent 3D printing applications. Milling units may be employed for granulation, preparing extrudates for tablet compression, or encapsulation. Collectively, optimized downstream operations ensure dimensional consistency, physical stability, and efficient integration into continuous pharmaceutical manufacturing platforms.

6. Process parameters and their influence on product quality

HME is a thermo-mechanical process in which both thermal energy and shear are applied to transform a drug–excipient blend into a homogeneous extrudate. The performance of an ASD or any HME-based product depends strongly on the selection and control of CPPs (Alshetaili et al., 2020a). These parameters govern the melt state, molecular mixing, drug dissolution within the polymer, and the final physical stability of the product (Table 2). The following subsections summarize the key parameters and their mechanistic impact on product quality attributes.

6.1. Temperature profile

The temperature profile along the barrel is often the most influential CPP in HME. It must provide sufficient thermal energy to soften or melt the polymer and enable drug incorporation without inducing thermal degradation (Winck et al., 2023). A well-designed temperature profile ensures controlled viscosity, uniform melt flow, and consistent RTD.

Table 2
Process parameters and their influence on product quality.

Process parameter	Role/effect
Temperature	Degradation / Amorphization
Screw speed	Mixing / RTD
Feed rate	Pressure / Homogeneity
Specific mechanical energy	Drug dispersion
Cooling	Recrystallization risk

If the process is carried out below the polymer softening/T_m, then inadequate mixing with high torque takes place, which leads to incomplete amorphization and drug crystals in the final product. In addition, when operating above the optimal melt temperature, there is a great risk of polymer degradation and drug decomposition, where colour changes and reduction in molecular weight (particularly for polyvinylpyrrolidone or PEO) are observed.

Polymers such as polyvinylpyrrolidone (PVP) and polyethylene oxide (PEO) are particularly susceptible to thermal and thermos-oxidative degradation during HME processing due to polymer chain scission at elevated temperatures and prolonged residence times. In PEO systems, degradation may result in molecular weight reduction and altered rheological properties, whereas PVP may undergo oxidative degradation accompanied by discoloration and viscosity changes. These degradation processes can affect processability, mechanical properties, and long-term stability of the final formulation (Maniruzzaman, Boateng, et al., 2012(Crowley et al., 2007).

Zonal control is a key element where early zones may be cooler to prevent premature melting near the feed throat, while mid-barrel zones provide the bulk of melting and mixing, and the final zone stabilizes the melt before die entry.

6.2. Screw speed (RPM)

Screw speed governs the balance between shear input and residence time. In most ASD processes, moderate to high screw speeds (100–400 RPM for laboratory equipment) facilitate drug dissolution in the polymer without overexposing the melt to heat. The higher screw speed results in lower residence time, higher shear rate and SME, improved distributive and dispersive mixing, and lower melt viscosity due to shear thinning (Douroumis, 2012). The lower screw speed results in longer residence time, higher risk of degradation (if high temperatures are used), and less intensive mixing.

6.3. Feed rate and fill level

In twin-screw extrusion, fill level refers to the proportion of the available free screw channel volume occupied by material during

processing. The commonly reported fill level range of approximately 40–80% is based on practical operating conditions used to balance material conveying, mixing efficiency, residence time, and pressure development while avoiding screw starvation or overfilling (Maniruzzaman, Boateng, et al., 2012). Very low fill levels may result in inadequate mixing and unstable feeding, whereas excessive fill levels can increase torque, pressure, and thermal exposure during HME processing. Fill level is influenced by feed rate, screw speed, material bulk density, melt viscosity, and screw configuration. In practice, fill level is not measured directly but is typically estimated using process modelling, residence time distribution studies, torque and pressure monitoring, or numerical simulation approaches employed in extrusion process development (Thompson and Sun, 2010) (Portier et al., 2021).

6.4. Specific mechanical energy (SME)

SME (kJ/kg) is a CPP in HME, representing the mechanical work transferred from the rotating screws to the material per unit mass processed. SME integrates the effects of screw speed, torque, screw configuration, and mass throughput, thereby providing a quantitative measure of the mechanical intensity experienced by the formulation (Equation 3). Because it captures both shear stress and residence-related energy input, SME is frequently used as a scale-up parameter to align laboratory- and commercial-scale extrusion systems (Domenech et al., 2013). Maintaining comparable SME values across scales can help ensure similar melt homogeneity, amorphization efficiency, and product performance, even when equipment geometry differs.

$$SME = \frac{2 \times \pi \times n \times M}{\dot{m}} \left(\frac{kWh}{Kg}\right) \quad (4)$$

where n (rpm) is the screw rotation speed, M (Nm) is the net torque, and $\dot{m}$ is the feed rate (kg/h).

Higher SME levels generally promote enhanced dispersive mixing, facilitating particle size reduction and improved molecular-level drug dispersion within the polymer matrix. This is particularly advantageous for the preparation of ASDs, where sufficient mechanical energy can compensate for lower barrel temperatures, reducing the reliance on thermal input and thereby mitigating the risk of thermally induced degradation. However, excessively high SME may increase localized shear heating and mechanical stress, potentially leading to polymer chain scission or oxidative degradation if not properly controlled. Conversely, low SME conditions may result in inadequate mixing, incomplete drug amorphization, and residual crystallinity within the extrudate. Therefore, SME must be carefully optimized to balance efficient dispersion and solid-state transformation with material stability, making it a central parameter in both process development and robust scale-up of pharmaceutical HME systems.

6.5. Residence time distribution (RTD)

RTD describes the amount of time material spends within the extruder and is a critical parameter for predicting thermal exposure, mixing efficiency, and the resulting quality attributes of hot–melt–extruded products. RTD is strongly influenced by screw configuration, specifically the balance between conveying elements,

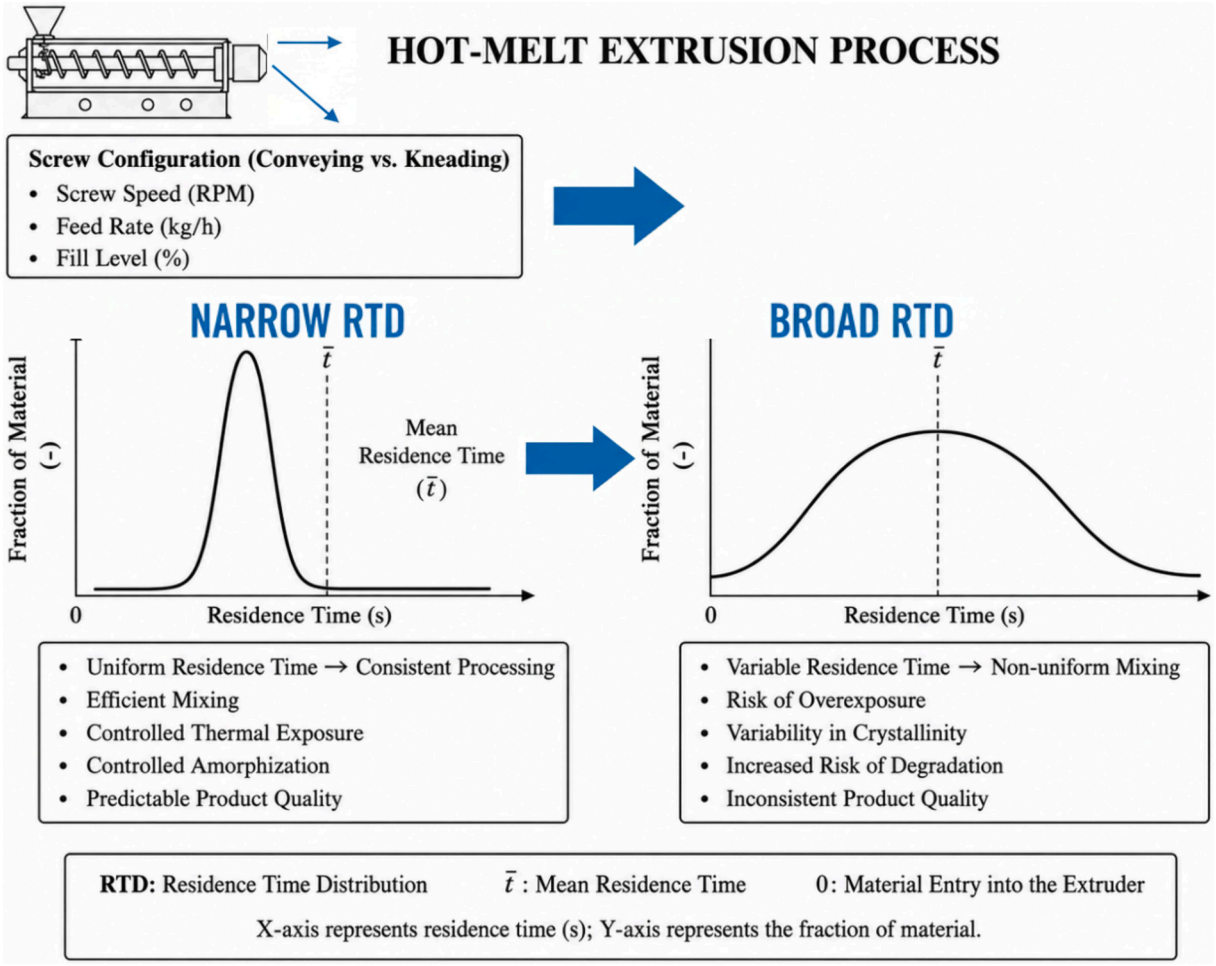

Fig. 8. A summary of RTD distribution effects on HME processing.

which promote forward transport, and kneading blocks, which introduce back–mixing and dispersive forces. As shown in Fig. 8, additional factors such as screw speed, feed rate, and barrel fill also significantly affect the breadth and shape of the RTD (Wesholowski et al., 2018a).

RTD is commonly determined using tracer-based experiments in which a pulse or step input of a detectable tracer material is introduced into the feed stream and its concentration at the extruder outlet is monitored as a function of time (Winck et al., 2023). The resulting RTD curve provides information regarding material flow behaviour, mixing efficiency, back-mixing, and the extent of thermal and mechanical exposure experienced during HME processing. Tracers may include colorants, salts, fluorescent compounds, or spectroscopically detectable materials monitored using techniques such as UV–Vis, Raman, or near-infrared spectroscopy (Wesholowski et al., 2018).

A narrowed RTD is generally advantageous for pharmaceutical HME because it promotes consistent exposure of material to thermal and mechanical energy. This results in predictable mixing behaviour, uniform amorphization of the drug, and reduced batch–to–batch variability—particularly important for APIs or polymers with thermal or mechanical sensitivity (Repka et al., 2008); (Crowley et al., 2007). In contrast, a broadened RTD indicates that different material fractions experience significantly different residence times. Material subjected to extended exposure may undergo thermal degradation, oxidative changes, or unwanted chemical transformation, while under-processed material may remain partially crystalline or inadequately mixed (Maniruzzaman, Boateng, et al., 2012). Such heterogeneity can lead to inconsistent crystallinity, degradation–related impurities, poor mechanical uniformity, and compromised performance of the final dosage form.

Furthermore, RTD plays a critical role in process scale–up. An extruder exhibiting broad RTD at a smaller scale may exhibit amplified variability when scaled up to larger equipment, complicating process control and reproducibility. Therefore, optimizing RTD is essential not only for achieving consistent product quality but also for enabling robust, scalable, and regulatory–compliant continuous manufacturing (Vargas et al., 2018).

6.6. Melt viscosity and rheology

Viscosity influences torque, pressure, mixing, and die swell. Drug loading strongly affects melt viscosity: high drug loadings (>40% w/w) often reduce viscosity because low-molecular-weight APIs act as plasticizers (Kimmel et al., 2024). Formulators often target a melt viscosity window of 50–500 Pa-seconds (Pa·s) (Rauwendaal, 2014)for optimal processing under shear conditions relevant to twin-screw extrusion, typically within shear rates of approximately 50–1000 s^{-1}, depending on equipment configuration and formulation design. Because polymer melts exhibit shear-thinning behaviour, apparent viscosity decreases at higher shear rates, facilitating material flow and mixing during HME processing. Monitoring rheology helps optimize mixing efficiency, dispersive capabilities, filament quality for HME-based 3D printing, and the feasibility of high-drug-load systems.

6.7. Screw configuration

As discussed in Section 4.3.2, screw configuration strongly influences shear exposure, residence time distribution, melt homogeneity, and pressure development during HME processing. Variations in conveying, kneading, and reverse elements directly affect dispersive mixing, amorphization efficiency, and thermal exposure of the formulation. Therefore, optimized screw design is critical for balancing mixing efficiency, process stability, and product quality while minimizing degradation risks (Douroumis, 2012).

6.8. Die geometry and pressure

Die geometry and die pressure significantly influence melt flow behaviour, extrudate uniformity, and dimensional consistency. Variations in die design affect pressure development, shear stress, and cooling behaviour at the die exit, which can subsequently impact strand morphology, filament diameter, and downstream processability. Continuous monitoring of die pressure also serves as an important indicator of process stability and melt homogeneity during HME processing. Narrow dies generate higher back pressure, which can enhance mixing and densification; however, excessive pressure may increase torque, thermal load, and risk of melt fracture. Wide or slit dies are typically employed for film and sheet extrusion, enabling uniform thickness and surface finish. Circular dies are preferred for producing strands, pellets, and filaments used in downstream processing, including 3D printing applications (Kolipaka, Junqueira, Garg, et al., 2026).

6.9. Cooling and downstream processing

Cooling rate and downstream processing conditions play a critical role in maintaining the amorphous stability of HME formulations. Rapid cooling reduces molecular mobility and minimizes the risk of phase separation or recrystallization, whereas slow cooling may promote structural relaxation and crystal growth. Downstream operations such as palletisation, milling, and filament spooling should therefore be carefully controlled to preserve the physicochemical integrity and performance of the extrudates (Censi et al., 2018).

7. Excipients for ASDs

Excipients are central to the successful development of ASDs prepared by HME. Among them, polymers function as the primary structural matrix, providing both molecular dispersion capability and long-term stabilization against recrystallization. The selection of excipients directly influences drug–polymer miscibility, processing feasibility, dissolution enhancement, and physical stability throughout shelf life (Alzahrani et al., 2022; He and Ho, 2015). Unlike conventional solid dosage forms, ASDs rely heavily on excipient functionality to maintain the drug in a high-energy amorphous state while ensuring manufacturability under thermal and shear stress conditions. Therefore, excipient choice must consider thermodynamic compatibility, T_g, hygroscopicity, melt rheology, and regulatory acceptability.

7.1. Functional roles of excipients

Polymers constitute the structural and functional backbone of ASDs (ASDs) prepared by HME. Frequently employed pharmaceutical polymers include PVP/VA (polyvinylpyrrolidone–vinyl acetate copolymer), HPMC, HPMCAS, PEO, Eudragit® grades, Soluplus®, and various cellulose derivatives such as HPC, HPMC, EC, and CMC (Kachrimanis and Nikolakakis, 2015). Selection of a suitable carrier is governed by critical attributes including high T_g, thermal stability under processing conditions, appropriate melt viscosity, and physicochemical compatibility with the API. These properties ensure adequate processability while maintaining the drug in a stabilized amorphous state.

Functionally, polymers enhance apparent solubility by sustaining the drug in a molecularly dispersed form and promoting favourable thermodynamic interactions, such as hydrogen bonding or ionic interactions, that improve miscibility. They suppress recrystallization by reducing molecular mobility and inhibiting nucleation and crystal growth during storage and dissolution. Furthermore, polymers support supersaturation maintenance through the “spring and parachute” mechanism, thereby prolonging drug exposure in solution. Beyond stabilization, the polymer matrix provides the mechanical integrity necessary for downstream shaping into tablets, films, or filaments.

Excipients such as plasticizers, surfactants, stabilizers, and anti-

plasticizers are often incorporated to fine-tune performance. Plasticizers reduce melt viscosity and lower processing temperatures by decreasing polymer Tg, thereby improving flow and reducing torque—particularly important for thermally labile APIs. However, excessive plasticization can increase molecular mobility and compromise long-term physical stability. Surfactants enhance wettability and dissolution by lowering interfacial tension, facilitating micellar solubilization, and improving supersaturation retention, provided they remain thermally stable and polymer-compatible during extrusion. Stabilizers mitigate chemical degradation pathways, including oxidation and moisture-induced hydrolysis, thereby extending shelf life.

Conversely, anti-plasticizers elevate the T_g of the system, reduce molecular mobility, and improve the physical stability of amorphous solid dispersions by limiting molecular diffusion and recrystallization. Common anti-plasticizing excipients include high-T_g polymers such as poly (methacrylic acid) derivatives, cellulose-based polymers, and certain inorganic carriers such as silica. These materials increase matrix rigidity and reduce free volume within the amorphous system, which is particularly advantageous for high drug-loading or hygroscopic formulations where recrystallization risk is elevated. In addition to improving stability, anti-plasticizers may also enhance mechanical strength and reduce tackiness during downstream processing and storage (Baird and Taylor, 2012) (Baghel et al., 2016) (Hancock and Zografi, 1997).

7.2. Strategic considerations in excipient selection

A rational, mechanism-based excipient strategy is essential for developing robust, high-performance ASDs suitable for commercial pharmaceutical manufacturing. Excipient selection for ASDs must balance thermodynamic compatibility, processability under HME conditions, long-term physical and chemical stability, dissolution enhancement capability, and regulatory acceptance and scalability. Some of the polymers/carriers used in HME-based ASDs and their key functions are listed in Table 3. The functional behaviour of PEO strongly depends on its molecular weight. High molecular weight grades are widely used in sustained-release matrices, whereas lower molecular weight grades, such as PEO N10 and N80, exhibit faster hydration and dissolution, making them suitable for immediate-release HME formulations (Crowley et al., 2007) (Repka et al., 2012).

Table 3
Polymers/carriers used in HME-based ASDs and their key functions.

Polymer/Carrier	Key functional attributes in ASDs
PVP/VA (Polyvinylpyrrolidone–vinyl acetate copolymer) (Danilova et al., 2025)	Strong hydrogen-bonding capability; enhances drug–polymer miscibility and solubilization; widely used for ASD formation.
HPMC (Hydroxypropyl methylcellulose) (Karandikar et al., 2015)	Provides physical stability; high Tg; suitable for sustained/controlled release applications.
HPMCAS (Hydroxypropyl methylcellulose acetate succinate) (Butreddy et al., 2022)	Enteric polymer with pH-dependent solubility; effective precipitation inhibitor; maintains supersaturation.
PEO (Polyethylene oxide) (Cantin et al., 2016)	High MW grades are commonly used in controlled-release systems, whereas low molecular weight grades, such as PEO N10 and N80, are also employed in immediate-release formulations due to their lower viscosity and rapid hydration properties.
Eudragit grades (Dos Santos et al., 2021)	Methacrylate-based polymers with pH-dependent solubility enable targeted and modified release profiles.
Soluplus (S. Li et al., 2024)	Amphiphilic graft copolymer specifically developed for ASD formation; enhances solubility and dissolution of poorly soluble drugs.
Cellulose derivatives (Chatterjee et al., 2018)	Provide mechanical strength, stability, and modulation of drug release behaviour in extruded systems.

8. Stability of ASDs

Although ASDs enhance apparent solubility and dissolution performance, their thermodynamic instability presents significant formulation challenges (AL-Japairai et al., 2023). The high-energy amorphous state tends to revert to a lower-energy crystalline form over time. Key stability concerns (Table 4) include physical stability (recrystallization), phase separation, and chemical degradation (chemical stability) during processing and storage (Martynek et al., 2025).

8.1. Physical and chemical stability

Physical instability in ASDs is fundamentally governed by molecular mobility within the amorphous matrix. In contrast to crystalline systems, the amorphous state is thermodynamically metastable and characterized by higher free energy. As molecular mobility increases, the system gains the kinetic freedom necessary to undergo structural relaxation, nucleation, and ultimately crystal growth (Corrie et al., 2023). Therefore, long-term stabilization of ASDs is primarily a kinetic challenge: maintaining sufficiently low molecular mobility throughout storage is essential to suppress recrystallization and preserve performance attributes such as enhanced solubility and dissolution rate.

T_g is one of the most critical determinants of molecular mobility. Below Tg, the amorphous matrix exists in a glassy state with restricted segmental motion; above Tg, it transitions into a rubbery state where molecular diffusion and rearrangement become significantly more rapid. For robust stability, the Tg of the ASD should remain meaningfully above the intended storage temperature, commonly by at least 20–50°Cto provide a sufficient kinetic barrier against nucleation. Systems with marginal Tg–storage temperature separation are particularly vulnerable to physical aging and crystallization over time. Humidity exposure represents a major destabilizing factor because water acts as a potent plasticizer. Moisture absorption lowers the effective Tg of the system by increasing free volume and enhancing chain mobility. Even limited water uptake can shift the matrix closer to or below storage temperature, dramatically accelerating crystallization kinetics.

Hygroscopic polymers are especially susceptible, making environmental control, protective packaging, and moisture-resistant formulations critical components of stability strategy.

Thermodynamic miscibility between drug and polymer also plays a central role. Limited compatibility promotes phase separation, leading to the formation of drug-rich amorphous domains with locally elevated mobility and reduced Tg. These domains act as preferential sites for nucleation. Similarly, higher drug loading increases the probability of exceeding the solubility limit of the API within the polymer matrix, thereby increasing the thermodynamic driving force for crystallization. Consequently, optimization of drug loading, polymer selection, and environmental protection collectively determines the ability of an ASD to maintain its amorphous state throughout its shelf life.

In addition to physical instability, ASDs may undergo chemical degradation, particularly under elevated temperature and humidity. Chemical instability can compromise product efficacy, safety, and regulatory compliance (Sarode et al., 2013). Potential degradation pathways include thermal degradation during extrusion or storage, oxidation of susceptible functional groups, hydrolysis, especially in hygroscopic systems, and polymer molecular weight reduction, which may alter mechanical and release properties.

8.2. Stabilization strategies

To enhance the stability of ASDs, a multifaceted approach that addresses both physical and chemical instability is critical for the

Table 4
Stability factors influencing HME-based ASDs.

Factor	Mechanism	Mitigation strategy	CQA (impact on product quality)
Low T_g	Increased molecular mobility enhances nucleation and crystal growth	Use high-Tg polymers; reduce drug loading; incorporate anti-plasticizers	Physical stability; crystallinity level; dissolution profile
High Drug Loading	Exceeds drug solubility in polymer matrix → phase separation and recrystallization	Optimize drug-to-polymer ratio; perform miscibility screening; apply Tg modeling	Crystallinity; dissolution rate; bioavailability
Moisture Exposure (Humidity)	Moisture plasticizes matrix → lowers Tg → increases recrystallization risk	Use moisture-protective packaging; include desiccants; select less hygroscopic polymers	Physical stability; dissolution performance; shelf life
Poor Drug–Polymer Miscibility	Limited thermodynamic compatibility → formation of drug-rich domains	Hansen solubility screening; calculate F-H χ; select interactive polymers	Phase homogeneity; dissolution; long-term stability
Thermal Degradation	Elevated temperature induces API or polymer breakdown	Optimize barrel temperature; reduce residence time; add antioxidants	Impurity levels; assay; regulatory compliance
Oxidative Degradation	Oxygen exposure causes API oxidation	Oxygen-barrier packaging; nitrogen purging; antioxidants	Impurity profile; assay potency; shelf life
Hydrolytic Degradation	Moisture-induced chemical degradation (e.g., ester/amide hydrolysis)	Control humidity; moisture-barrier packaging; stable polymer selection	Impurity levels; chemical stability; safety
Polymer Molecular Weight Reduction	Thermal/mechanical stress causes chain scission → altered matrix properties	Control SME; optimize temperature profile	Release profile; mechanical strength; content uniformity
Phase Separation During Storage	Drug-rich and polymer-rich domains form due to thermodynamic instability	Improve miscibility; reduce drug loading; rapid cooling	Dissolution consistency; bioavailability; physical stability
Inadequate Cooling Rate	Slow cooling permits molecular rearrangement and crystallization	Use rapid cooling (chill rolls/air-cooling); minimize thermal exposure	Residual crystallinity; dissolution rate; product performance

development of robust and commercially viable formulations (AL-Japairai et al., 2023). Physical stabilization focuses on limiting molecular mobility, which is a primary driver of recrystallization. This is typically achieved through the use of high-glass-transition-temperature (high-Tg) polymers, which increase the overall Tg of the system and reduce molecular diffusion. Additionally, careful control of the thermal history during processes such as HME, particularly through controlled cooling rates, can kinetically trap the drug in an amorphous state,

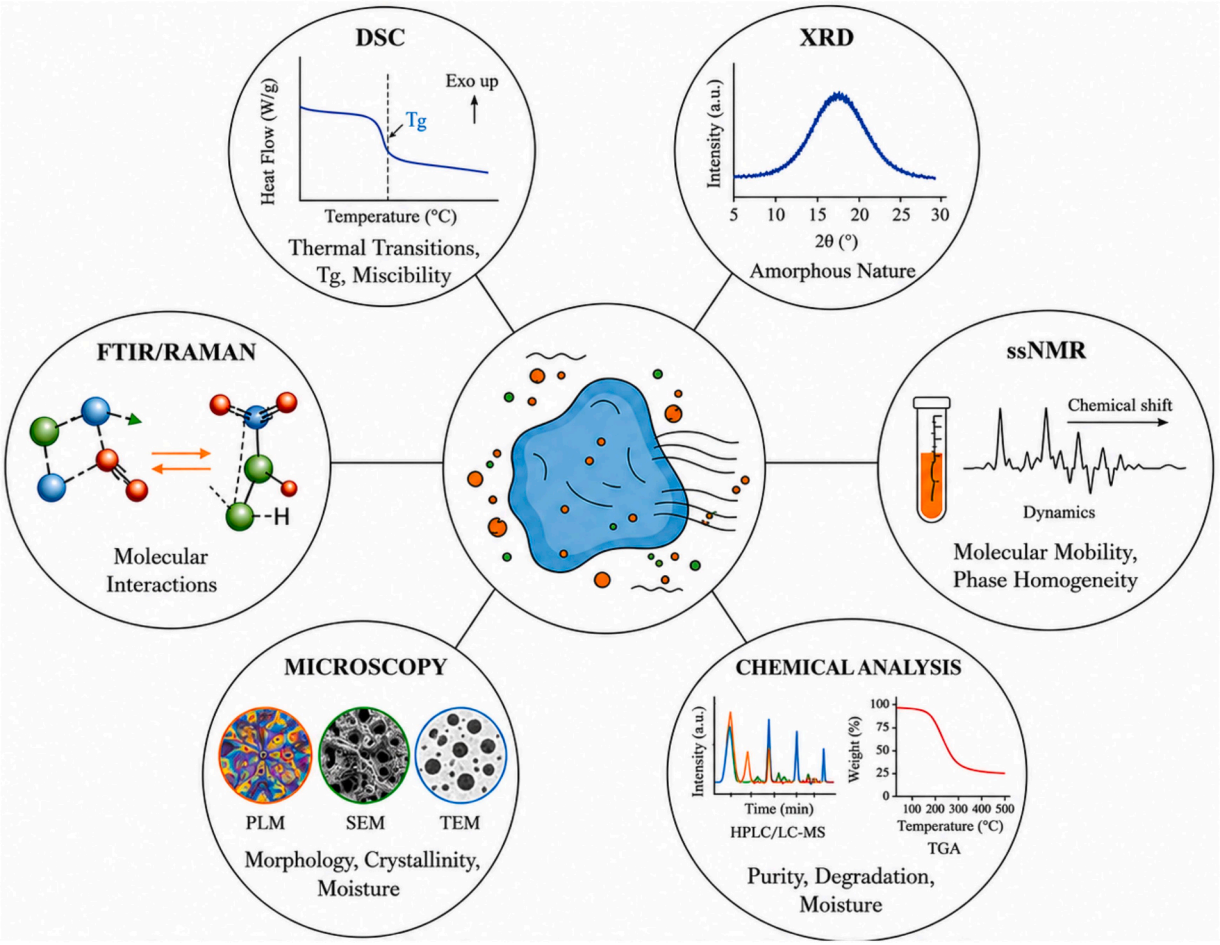

Fig. 9. Summary of analytical characterisation techniques for ASDs. DSC: Differential Scanning Calorimetry; XRD: X-ray Diffraction; FTIR: Fourier Transform Infrared Spectroscopy; RAMAN: Raman Spectroscopy; ssNMR: Solid-State Nuclear Magnetic Resonance; PLM: Polarized Light Microscopy; SEM: Scanning Electron Microscopy; TEM: Transmission Electron Microscopy; HPLC: High-Performance Liquid Chromatography; LC-MS: Liquid Chromatography–Mass Spectrometry; TGA: Thermogravimetric Analysis.

further mitigating the risk of crystallization. Formulation strategies may also include the use of polymer blends or copolymers to optimize the drug–polymer interactions and improve physical stability over the product's shelf life.

Chemical stabilization, on the other hand, targets potential degradation pathways such as oxidation, hydrolysis, or other chemical reactions. Incorporating antioxidants or other stabilizing excipients into the ASD formulation can mitigate these risks, while moisture-protective packaging prevents plasticization caused by environmental humidity, which can accelerate both chemical and physical instability. Together, these strategies create a synergistic effect, where physical stabilization reduces the likelihood of recrystallization and chemical stabilization limits molecular degradation. By combining careful polymer selection, excipient optimization, process control, and protective packaging, formulators can develop ASD products with enhanced shelf-life and reproducibility, ultimately supporting the translation of lab-scale formulations into commercially viable dosage forms.

9. Comprehensive analytical characterization of ASDs

A rigorous analytical framework is essential for understanding the structural, physicochemical, and chemical attributes of ASDs. Because the amorphous state is inherently metastable and susceptible to crystallization, molecular mobility changes, and chemical degradation, a multifaceted characterization strategy is required to assess formulation performance, establish stability, and ensure regulatory compliance. An integrated analytical approach typically includes thermal, structural, spectroscopic, and microscopic methods in combination with chromatographic and mass–based chemical analyses (Fig. 9). Together, these techniques provide a robust assessment of amorphous structure, drug–polymer interactions, phase behaviour, crystallization risk, and chemical integrity attributes that critically determine the efficacy and stability of ASD–based drug products.

9.1. Thermal and structural characterization

Robust evaluation of thermal behaviour and solid–state structure is central to confirming amorphous conversion, miscibility, and physical stability.

9.1.1. Differential Scanning Calorimetry (DSC) and Modulated DSC (MDSC)

DSC and MDSC represent cornerstone techniques for assessing the thermal properties of ASDs. Determination of the glass–transition temperature (Tg) allows evaluation of molecular mobility and the likelihood of physical instability. A single Tg is widely interpreted as evidence of a molecularly homogeneous and miscible drug–polymer system, whereas multiple Tgs suggest partial phase separation or incomplete dispersion (Hancock and Zografi, 1997). MDSC further enhances interpretation by deconvoluting heat–capacity–related (reversing) transitions from kinetic events such as enthalpic relaxation or recrystallization (non–reversing signals), enabling greater sensitivity to low levels of residual crystallinity and subtle relaxation processes. These insights are critical during formulation screening and accelerated stability studies (Fig. 9).

9.1.1.1. X–ray diffraction (XRD/XRPD). XRPD is the most widely used technique for verifying the amorphous state of ASDs. The absence of sharp Bragg peaks and the presence of broad diffuse halos indicate loss of long–range molecular order, a hallmark of amorphous materials. XRPD provides high specificity for detecting even trace crystalline fractions, supporting identification of recrystallization phenomena during storage or thermal stress. Its non–destructive nature and high reproducibility make XRPD indispensable both in early–stage formulation development and in routine quality control.

9.2. Molecular interaction and microstructural analysis

Understanding interactions at the molecular level is essential for predicting stability and performance of ASDs, as drug–polymer interactions often govern amorphous stabilization.

9.2.1. FTIR and Raman spectroscopy

Vibrational spectroscopies such as FTIR and Raman provide rich detail about functional–group environments and intermolecular interactions. Shifts in characteristic vibrational bands can indicate hydrogen bonding, π–π interactions, or dipole–driven associations that stabilize the amorphous drug within the polymer matrix (Matić et al., 2021); (Kushwah et al., 2024). Raman spectroscopy additionally enables spatial mapping for detecting localized crystallization or phase heterogeneity, an important advantage for evaluating large–scale manufacturing processes. FTIR, particularly via ATR, supports rapid screening of interaction strength and provides indirect evidence of disruption of the crystalline lattice upon amorphization.

9.2.2. Solid–State NMR (ssNMR)

Solid–state NMR offers unparalleled insight into molecular mobility, chemical environments, and phase heterogeneity. Techniques such as magic–angle spinning (MAS) and relaxation–time measurements provide quantitative data on segmental mobility, which correlates strongly with physical stability and recrystallization tendencies (S. Li et al., 2024). ssNMR can distinguish miscible from partially phase–separated systems, characterize drug–polymer interactions at the atomic level, and detect subtle structural domains undetectable by DSC or XRPD. Although resource–intensive, ssNMR remains one of the most powerful tools for mechanistic understanding of ASD stability.

9.2.3. Microscopy (PLM, SEM, TEM)

Microscopy techniques complement thermal and spectroscopic methods by providing direct visualization of morphology and crystallinity. Polarized light microscopy (PLM) allows rapid detection of birefringent crystalline domains, useful for assessing amorphous conversion efficiency. Scanning electron microscopy (SEM) reveals surface morphology and particle architecture, offering insights into the influence of processing methods such as spray drying or HME on microstructure. Transmission electron microscopy (TEM) further enables nanoscale imaging to detect submicron crystalline domains or phase–separated regions, providing an additional layer of sensitivity for comprehensive structural assessment.

9.3. Chemical stability and degradation analysis

Beyond physical stability, chemical integrity of the API is a critical determinant of both efficacy and safety. Chemical characterization ensures that degradation pathways are identified early and controlled throughout product development.

9.3.1. Chemical integrity and regulatory Importance

Chemical stability evaluation ensures that the API remains intact within the ASD matrix and does not undergo degradation due to processing conditions, interactions with excipients, or prolonged storage. This aspect is central for regulatory approval, as chemical purity and well–defined impurity profiles are required for establishing shelf life and ensuring patient safety (Matić et al., 2020). The amorphous state may increase reactivity due to higher molecular mobility, necessitating vigilant monitoring during formulation design and stability studies.

9.3.2. High-performance liquid (HPLC) and liquid Chromatography–Mass spectrometry (LC–MS)

HPLC is the primary method for quantifying API content and assessing content uniformity in ASDs. It enables routine monitoring of purity and detection of degradants that may arise during storage or

high–temperature manufacturing processes. Liquid chromatography–mass spectrometry (LC–MS) further enhances analytical specificity by combining chromatographic separation with mass–based identification. LC–MS can detect low–level impurities, characterize degradation pathways, and identify interaction products arising from drug–polymer reactions. Because ASDs often involve processing conditions that expose the API to heat or shear, these methods are indispensable for ensuring chemical robustness of the final product.

9.4. Thermogravimetric analysis (TGA)

TGA evaluates mass loss as a function of temperature, providing critical information on moisture content and thermal degradation behaviour. Moisture has profound effects on amorphous systems, including plasticization of the matrix, reduction of Tg, and enhancement of molecular mobility, ultimately increasing the risk of recrystallization. TGA also identifies degradation onset temperatures, helping define safe processing windows and storage requirements. When interpreted alongside DSC and XRPD data, TGA contributes significantly to a holistic understanding of ASD stability.

ASDs require a comprehensive suite of analytical tools to fully characterize their physical, chemical, and structural attributes. The combination of thermal analysis, diffraction methods, vibrational spectroscopy, ssNMR, microscopy, and chromatographic techniques enables a multidimensional understanding of ASD behavior. Such a holistic analytical approach not only ensures the scientific robustness of formulation development but also supports regulatory compliance, enhances predictive stability modeling, and ultimately contributes to the successful translation of ASDs into clinically effective drug products.

Overall, the solid-state characterization confirms phase behaviour, miscibility, and structural integrity of ASDs (Table 5). The techniques mentioned below collectively validate successful amorphization and long-term structural stability (Netchacovitch et al., 2017).

9.5. Process analytical technologies (PAT)

Analytical characterization is essential for confirming amorphous structure, understanding drug–polymer interactions, and ensuring product stability in HME-based systems. Integration of PAT further enables real-time monitoring and control under continuous manufacturing frameworks (Hitzer et al., 2017).

PAT tools enable real-time monitoring and control of HME processes, supporting QbD and continuous manufacturing. Integration of advanced analytical tools with data-driven modeling enhances process robustness, reduces variability, and supports RTRT in pharmaceutical extrusion (Netchacovitch et al., 2017).

In advanced HME operations, PAT tools play an essential role in real–time monitoring and quality assurance, enabling continuous assessment of CMAs and process parameters. In–line near–infrared (NIR) spectroscopy is extensively used to evaluate blend uniformity, drug distribution, and melt state, providing immediate feedback on whether the drug is fully dispersed within the polymer matrix (Wesholowski et al., 2018a). Likewise, in–line Raman spectroscopy offers high chemical specificity and is particularly effective for detecting crystallinity, monitoring phase transitions, and identifying any residual or newly formed crystalline domains during extrusion. These spectroscopic tools, integrated directly into the extrusion barrel or die, support proactive process adjustments and ensure consistent production of ASDs.

Complementing spectroscopic monitoring, mechanical sensors such as torque and pressure transducers provide valuable indirect indicators of melt viscosity, feed consistency, and overall process stability. Changes in torque or die pressure can signal variations in material properties, onset of degradation, or deviations in feed rate, enabling operators to intervene before product quality is compromised. To fully leverage the diverse data streams generated by PAT tools, chemometric approaches such as principal component analysis (PCA) and partial least squares (PLS) modelling are routinely employed. These multivariate methods facilitate the interpretation of complex datasets, support the development of predictive control models, and enhance real–time decision–making in continuous manufacturing environments. Together, the integration of spectroscopic monitoring, mechanical sensing, and chemometrics significantly strengthens process understanding and control within HME–based pharmaceutical production.

10. Dosage form development using HME

HME is a versatile platform technology that enables the development of diverse pharmaceutical dosage forms. By producing homogeneous drug–polymer matrices, particularly ASDs, HME supports improved solubility, immediate and controlled release, and personalized medicine applications (Repka et al., 2008). Its compatibility with continuous manufacturing further enhances scalability and reproducibility.

10.1. Oral solid dosage forms

HME-derived intermediates can be processed into conventional oral solid dosage forms, including compressed tablets, capsule-filled extrudates, or milled granules, and pellets for multi-particulate systems. ASDs

Table 5
Solid-state characterization techniques used for HME-based ASDs.

Technique	Purpose	Detects	Limitation
DSC	Determine thermal transitions and miscibility	T_g, melting point (Tm), recrystallization events, residual crystallinity	Limited sensitivity for low levels of crystallinity (<1–2%); overlapping thermal events may complicate interpretation
MDSC (Modulated DSC)	Improve resolution of overlapping thermal events	Accurate Tg measurement, separation of reversible/non-reversible transitions	More complex data analysis; longer experimental time
XRPD	Confirm amorphous or crystalline state	Sharp diffraction peaks (crystalline) vs halo pattern (amorphous); polymorphic transitions	Limited detection threshold (~1–5% crystallinity); may miss nanocrystals
FTIR Spectroscopy	Evaluate drug–polymer intermolecular interactions	Hydrogen bonding, ionic interactions, functional group shifts	Interpretation can be qualitative; overlapping peaks are possible
Raman Spectroscopy	Monitor crystallinity and molecular interactions; suitable for PAT	Phase transitions, polymorphs, and crystallinity changes	Fluorescence interference requires chemometric modeling for quantitative analysis
Solid-State NMR (ssNMR)	Assess molecular mobility and phase homogeneity	Molecular-level dispersion, phase separation, and interaction strength	Expensive instrumentation; complex data interpretation
PLM	Visual identification of crystalline domains	Birefringence indicating crystal presence	Low sensitivity for very small or low-level crystals
SEM	Evaluate surface morphology	Surface structure, phase separation, particle distribution	Does not directly confirm amorphous state
TEM	High-resolution morphological analysis	Nano-scale phase separation, nanocrystals	Time-consuming sample preparation; limited bulk representativity
TGA	Evaluate thermal stability and moisture content	Weight loss due to degradation or moisture	Does not directly measure crystallinity or miscibility

prepared via HME significantly enhance dissolution rate and apparent solubility of poorly water-soluble drugs (BCS Class II and IV), leading to improved bioavailability (Maniruzzaman, Douroumis, et al., 2012). Extruded materials typically exhibit excellent content uniformity and compressibility, supporting robust downstream processing.

10.2. Immediate-release systems

HME-derived extrudates are commonly milled and incorporated into conventional immediate–release (IR) dosage forms, including compressed tablets, capsules, granules and pellets. Through the transformation of crystalline APIs into ASDs within hydrophilic polymer matrices, HME markedly increases dissolution rate and apparent solubility, enabling rapid drug release once exposed to gastrointestinal fluids. Achieving an effective IR profile depends on careful selection of hydrophilic carriers, optimization of drug loading, and appropriate downstream processing to ensure rapid release without sacrificing physical or chemical stability (AlSuwais et al., 2025). Collectively, these advantages position HME as a scalable, continuous, and solvent–free manufacturing platform for high–performance immediate–release oral dosage forms.

Immediate–release systems produced using HME offer several notable benefits:

- Rapid disintegration and dissolution
- Enhanced oral bioavailability for BCS Class II and IV compounds
- Homogeneous drug distribution and improved content uniformity
- Reduced dose–to–dose variability
- Robust and repeatable performance under continuous manufacturing conditions

A typical example includes Itraconazole, a poorly soluble BCS Class II antifungal, which has been successfully processed via HME with Hypromellose acetate succinate (HPMCAS). The resulting amorphous dispersion demonstrated a several–fold increase in dissolution rate and enabled an immediate–release capsule formulation with significantly enhanced bioavailability compared to crystalline drug forms (Ashour et al., 2016). The use of a ternary ASD tablet comprising of Hypromellose and mesoporous silica offered IR under neutral conditions with high supersaturation maintenance (Hanada et al., 2018). Similarly, Indomethacin extruded with Sepitrap produced a highly miscible amorphous dispersion exhibiting near–complete dissolution within minutes (Lacerda et al., 2024). In another study, Ritonavir, a heat–stable yet poorly soluble antiviral, was processed via HME with copovidone to generate IR granules showing dramatically improved dissolution (>80% within 15 min). The enhanced solubility and reduced variability supported effective downstream tableting for fast oral delivery (Oktay and Polli, 2025).

10.3. Controlled release systems

HME is a highly adaptable platform for developing modified–release and controlled–release drug delivery systems due to its ability to precisely engineer polymer matrices. By tailoring parameters such as polymer selection, drug loading, and matrix density, formulators can regulate diffusion pathways, erosion behaviour, and drug–polymer interactions to achieve predictable release kinetics (Kushwah et al., 2024). The capacity to manipulate both composition and geometry of the extruded matrix makes HME especially valuable for creating dosage forms with reproducible and customizable sustained–, delayed, or extended–release profiles.

Sustained–release matrix tablets have been successfully produced using hydrophilic and hydrophobic polymers to control swelling and erosion. For example, Reitz et al. (2008) developed controlled–release verapamil HCl matrix tablets using Verapamil Meltrex® technology, achieving robust 12–hour sustained release in comparison to compressed marketed formulations. Similarly, melting–extruded osmotic pump systems have been shown to provide highly stable zero–-order release. Multi-particulate systems have also benefited from HME's precision Komanduri et al. (2025) produced sustained–release pellets of theophylline with excellent dose flexibility and potential taste masking for paediatric applications. Beyond oral products, HME has been used to create extended–release implants, such as polycaprolactone–based intravaginal rings delivering antiretroviral drugs for up to 30 days (Moseson et al., 2021), highlighting its potential for long–term therapy.

Together, these case studies demonstrate the broad and growing applicability of HME for modified–release dosage forms. Whether used to develop matrix tablets, osmotic systems, multi-particulates, or long–-duration implants, HME offers a solvent–free, scalable, and highly controllable manufacturing process capable of delivering consistent and tuneable drug–release performance.

10.4. Films and transdermal systems

HME enables the efficient production of drug–loaded polymeric films with highly uniform thickness, consistent drug distribution, and tunable mechanical properties. By selecting appropriate polymers, plasticizers, and processing conditions, HME can produce films suited for diverse applications, including oral thin films, buccal delivery systems, and transdermal patches (Karki et al., 2016). Depending on the polymer's functional characteristics, these films can be engineered for rapid disintegration and immediate drug release or for sustained, controlled delivery over extended periods.

A key advantage of film–based systems produced via HME is the solvent–free nature of the process, which eliminates issues related to residual solvents and simplifies regulatory compliance. Continuous melt processing ensures homogeneous drug distribution throughout the film matrix, while extrusion dies allow precise control of film thickness, tensile properties, and flexibility. This high degree of process control makes HME–based films reproducible, scalable, and compatible with commercial manufacturing requirements.

Sawant et al. (2025) et al. (2025) used HME to prepare mucoadhesive clotrimazole films with improved mechanical strength and uniform drug loading, achieving extended drug release for vaginal candidiasis. In another study, Kasitpong and Pornsak (2020) indomethacin-loaded films via HME demonstrated enhanced dissolution rates with the drug being molecularly dispersed in the polymer matrices. Similarly, Reuther et al. (2025) produced oro-dispersible films of benzodiazepine class using HME, offering excellent stability and mechanical properties for over 12 months.

In clinical practice, these film–based dosage forms enhance patient compliance due to their ease of administration, portability, and suitability for populations with swallowing difficulties. The ability to engineer mucoadhesive characteristics or controlled–release profiles further expands their therapeutic utility, establishing HME as a powerful and flexible platform for advanced film–based drug delivery systems.

11. Applications of HME

HME has evolved from a formulation technique to a multifunctional platform technology in modern pharmaceutics. Its ability to produce homogeneous drug–polymer matrices under continuous processing conditions has enabled applications ranging from solubility enhancement to advanced and personalized drug delivery systems (Douroumis, 2007) (Patil et al., 2015).

11.1. Solubility and bioavailability enhancement

HME-based ASDs not only enhance dissolution performance but also translate these improvements into substantial gains in systemic bioavailability. When a poorly soluble drug is converted into an amorphous form and molecularly dispersed within a polymeric carrier, the

resulting system exhibits markedly higher apparent solubility. This enhanced solubility drives higher and more sustained supersaturation in gastrointestinal fluids, an essential condition for maximizing passive diffusion across the intestinal epithelium. In many cases, the polymer plays a dual role by stabilizing the amorphous drug thermodynamically and inhibiting precipitation kinetically, thereby prolonging the window of absorption. These combined effects often enable the drug to overcome permeability or dissolution–rate limitations that otherwise suppress oral bioavailability in crystalline forms. In a recent work with celecoxib–PVP and Eudragit 4155F ASDs showed that improved dissolution and excellent stability at supersaturated drug concentrations due to H-bonding interactions (Abu Diak et al., 2009), Such H-bonding interactions can provide variations in the dissolution rates depending on the selection of the polymeric carrier. In another study (Patel et al., 2023), Ibrutinib ASD prepared with Eudragit® FS 100 via HME achieved increased dissolution rates and anticancer activity for colon cancer cell studies.

Clinical and preclinical studies increasingly demonstrate the translational impact of these mechanisms. Acacetin, a natural flavonoid with a melting point above 200 °C and extremely poor solubility, was successfully formulated as an ASD using a QbD framework (Wang et al., 2026). In this study, Soluplus® served as the polymeric matrix, and d α tocopherol polyethylene glycol succinate (TPGS) functioned as a plasticizer and solubilizer. The amorphous transformation of acacetin, while optimized ternary formulations achieved up to 3140-fold increases in solubility in aqueous media. Pharmacokinetic evaluation demonstrated relative bioavailability exceeding 1400 % compared with crystalline acacetin, without recrystallization after six months under stress conditions. The study exemplifies how polymer plasticizer synergy and rational design can enable extrusion of high-melting, thermally challenging compounds.

For pramipexole dihydrochloride, a short-acting, photolabile antiparkinsonian drug, HME was used to prepare sustained-release SD pellets employing ethyl cellulose and PEG 6000 as matrix carriers (Ding et al., 2025). The extrusion optimisation resulted in the formation of a molecular dispersion with hydrogen bonding interactions. The extruded pellets demonstrated a four-fold increase in systemic exposure area under the curve (AUC) compared with the commercial product Sifrol®, alongside higher brain accumulation in rats.

Nintedanib, a weakly basic drug used in idiopathic pulmonary fibrosis, exhibits poor dissolution in the intestinal environment. By employing Soluplus® and HPMCAS as polymeric matrices, two ASDs were developed via HME (Ma et al., 2025). Both formulations showed complete amorphization, and dissolution in simulated intestinal fluid increased 10–16-fold relative to the crystalline drug. In vivo studies revealed that bioavailability improved 2.5-fold for the Soluplus ASD and 7.9-fold for the HPMCAS ASD. Importantly, oral ASD administration not only enhanced antifibrotic efficacy but also caused no significant hepatic toxicity, underscoring the clinical promise of polymer driven solubility enhancement for lipophilic small molecules.

Wen et al. (2019) processed fenofibrate – PVP VA64 powder blends that were found to present excellent biocompatibility in Caco-2 cell and improved transmembrane transport with increased dissolution rates. Most importantly, pharmacokinetic analysis in animal trials (Beagle dogs) demonstrated significant bioavailability enhancement when compared the Lipanthyl® marketed product.

A particularly innovative use of HME was reported by Mujtaba et al. (2024) for a co-ASD containing the antimalarial drugs artesunate and amodiaquine with Soluplus® as the polymeric carrier and surfactants such as Lutrol F127, Lutrol F68, TPGS, and PEG 400 as plasticisers. The pharmacokinetic evaluation in rats for the extruded molecular dispersion showed 36 to 56 fold higher Cmax and 42 to 54 fold higher AUC compared to pure drugs, along with greater efficacy than the marketed product Coarsucam®.

Marketed ASD products manufactured through related technologies, such as the posaconazole ASD in *Noxafil* and lopinavir/ritonavir ASDs in *Kaletra,* provide additional evidence that amorphous systems can produce meaningful clinical benefits, including more consistent absorption profiles, reduced fed–state effects, and improved therapeutic outcomes.

HME continues to evolve as one of the most versatile solvents–free manufacturing technologies for enhancing the solubility, processability, and therapeutic performance of poorly water–soluble APIs. Recent studies highlight a series of formulation innovations ranging from acid–base super-solubilization strategies to material–sparing screening methods and hybrid HME–injection moulding workflows that collectively expand what can be achieved with ASDs. Together, these findings illustrate not only the central role of HME in enabling drug delivery for challenging molecules but also the emergence of new conceptual frameworks for rational formulation design.

One of the most notable advances is the application of the acid–base super-solubilization (ABS) principle to facilitate the melt processing of otherwise intractable drugs. Raje et al. (2026) Applied the ABS approach to delamanid, a highly lipophilic molecule with a high melting point and poor dissolution in its marketed form. By pairing delamanid with malic acid, the authors achieved dramatic increases in solubility across biorelevant media and enabled extrusion at temperatures far below the drug's melting point due to reduced viscosity. The resulting ASDs were fully amorphous at low drug loadings and demonstrated substantial dissolution improvement, exceeding 80–90% release depending on formulation. A related ABS–based strategy was reported by Raje et al. (2026) who used tromethamine to enhance the solubility and melt processability of the weakly acidic drug indomethacin. Tromethamine increased indomethacin's solubility by several orders of magnitude and lowered its T_m in the solid state, allowing extrusion at only 80 °C. The authors demonstrated rapid and nearly complete dissolution across acidic and neutral pH conditions, highlighting the potential of ABS interactions for broadening HME applicability.

HME's utility has also expanded beyond traditional ASD manufacture into integrated, efficiency–focused process designs. Wood et al. (2025) developed a combined HME–injection moulding (IM) workflow intended to streamline the multistep production of immediate–release ASD tablets. Using moxidectin as a model compound, the team generated porous moulded tablets that met USP quality specifications and released over 90% of the active within 1 h. The ability to mould tablets directly from the extrudate using both standard and custom geometries suggests HME–IM may serve as a scalable platform for creating mechanically robust tablets, including abuse–deterrent formats.

For thermolabile drugs, which often degrade under the thermal and shear stresses of conventional HME, alternative melt–free or low–heat technologies are gaining prominence. (Singh and Van de, Mooter (2016) evaluated HME, spray drying, and KinetiSol processing for fenbendazole, a molecule with poor solubility in both aqueous and organic systems and a strong tendency toward thermal degradation. HME produced extensive degradation products, while spray drying was limited by insufficient drug solubility in the required solvent system. In contrast, early–terminated KinetiSol processing produced powder–discharged samples that minimized degradation and improved dissolution performance due to reduced particle size, despite traces of crystallinity. These results demonstrate the value of short–duration, high–shear processing for otherwise HME–incompatible drugs.

Beyond classical small–molecule solubility enhancement, HME has recently been shown to improve the biological performance of botanical extracts. Kim H-M et al. used HME to prepare a processed Platycodon grandiflorus extract, which displayed significantly stronger anti–dermatitic activity than the conventionally prepared extract across both murine and cell–based models. The enhanced activity was associated with reduced TLR4 abundance and suppression of NF–κB signaling, suggesting that HME may modulate component dispersion or interactions in a manner that strengthens pharmacological effects. Such findings highlight the potential for HME in modernizing traditional medicinal preparations.

Finally, HME continues to show strong relevance for improving the solubility of BCS class II compounds. Muhindo et al. (2023) prepared raloxifene hydrochloride ASDs using PVP–based carrier systems and demonstrated more than 80% drug release within 30 min and nearly complete release within 1 h. Similarly, Althobaiti et al. produced curcumin–piperine SDs via HME and observed up to nine–fold improvements in drug release compared with crystalline curcumin. In both cases, DSC and PXRD confirmed complete amorphization, reinforcing the robustness of HME as a solubility–enhancing platform.

Collectively, these results reinforce that HME–based ASDs not only improve physicochemical performance but also provide tangible, clinically relevant enhancements in bioavailability and patient response. As modern drug pipelines continue to shift toward more challenging molecular architectures, these advances position HME as a scientifically adaptable and industrially scalable solution for next–generation oral drug delivery.

11.2. Advanced oral delivery

HME enables the development of multifunctional oral dosage forms by offering precise control over matrix architecture, polymer selection, and drug–excipient interactions ((Douroumis, 2007). Through targeted manipulation of mechanical, thermal, and release–modifying properties, HME supports several advanced pharmaceutical applications that go beyond conventional dissolution enhancement. These include taste–masking, abuse–deterrent designs, FDCs, and gastro–retentive systems, all of which benefit from the technology's ability to create uniform, solvent–free, and customizable drug–polymer matrices (Table 6).

Taste–masking is one of the most established specialized applications of HME, particularly valuable for paediatric and geriatric populations. By embedding bitter APIs within hydrophilic or taste–neutral polymer matrices, HME suppresses drug release in the oral cavity while enabling rapid release once the dosage form reaches the gastrointestinal tract. A notable example is the taste–masked acetaminophen–ethyl cellulose extrudates developed for orally disintegrating paediatric formulations, which demonstrated complete taste suppression in human panel testing (Maniruzzaman et al., 2013). Similarly, HME–processed ibuprofen–Eudragit EPO formulations provide successful taste–masking while maintaining fast gastric dissolution, supporting improved patient compliance.

Abuse–deterrent formulations (ADFs) also benefit from the mechanical robustness and thermal plasticity enabled by HME. By selecting polymers that form hard, crush–resistant matrices or gels upon contact with solvents, HME helps deter mechanical manipulation and parenteral misuse of controlled substances. The oxycodone ADF prototypes manufactured via HME using PEO and gelling agents demonstrated significant resistance to crushing and rapid gel formation in aqueous media, preventing syringeability and dose dumping. This approach aligns with FDA expectations for abuse–deterrent opioid technologies and showcases HME's ability to engineer tamper–resistant dosage forms.

HME also supports the creation of FDCs by providing uniform dispersion of two or more APIs within a single matrix. This is particularly beneficial for therapeutic areas requiring combination therapy, such as chronic pain, infectious disease or metabolic disorders. A successful example is the HME–produced Artesunate and Amodiaquine-Soluplus® FDC, where uniform API distribution and excellent stability after the addition of surfactant (Mujtaba et al., 2024). Most importantly, pharmacokinetic data demonstrated that for a FDCs of 50:135 mg of both APIs the oral bioavailability was significantly increased by enhancing Cmax and AUC. The ability to co–process multiple drugs into a single extrudate improves dosing accuracy, reduces pill burden, and enhances patient adherence, especially in long–term therapies.

Finally, gastro–retentive systems leverage HME to create floating, expanding or swellable matrices capable of prolonging gastric residence time. These systems are particularly valuable for drugs with narrow absorption windows in the upper gastrointestinal tract. For instance, HME–generated floating matrices of metronidazole using

Table 6
Typical examples of advanced HME extruded formulations.

Application area	Product status	API / Product	Polymer / Matrix	Reference/Year
Taste masking	Original Research	Acetaminophen	Ethyl cellulose	(Maniruzzaman, Boateng, et al., 2012)
	Original Research	Ibuprofen	Eudragit EPO	(Gryczke et al., 2011)
	Original Research	Azithromycin	Eudragit RLPO	(Li et al., 2022)
	Original Research	Caffeine	Ethyl cellulose/HPC	(Pimparade et al., 2015)
Abuse Deterrent Formulations	Commercial	Oxycodone HCl ADF Hydrocodone Oxymorphone MorphineSulfate TapentadolHCl	Polyethylene oxide	(Darji et al., 2024)
	Original Research	Tramadol ADF	PEO/Hydroxypropylcellulose (HPC-SL, MW 100,000 Da and HPC-L, MW 140,000 Da)	(Ong et al., 2020a)
Fixed Dose Combinations	Original Research	Acetaminophen/ ibuprofen	Eudragit S100/ hydroxy propyl cellulose (HPC-LF) and Eudragit EPO	(Oh and Park, 2024)
	Original Research	Artesunate/Amodiaquine	Soluplus and surfactant	(Mujtaba et al., 2024)
	Original Research	Curcumine/Piperine	Soluplus	(Althobaiti et al., 2022)
	Original Research	Rifampicin/Isoniazid	Hydroxypropyl methylcellulose acetate succinate (HMPCAS, AQOAT, and AS-LMP/HPC Klucel EF)	(Ghanizadeh Tabriz et al., 2021)
	Commercial	Lopinavir/Ritonavir	Copovidone	(Crowley et al., 2007).
Gastro-Retentive Systems	Original Research	Metronidazole self-Floating Tablets	Hydroxypropyl methylcellulose (HPMC) E50, K4M, K15M, K100M, and K250M	(Wook Huh et al., 2021)
	Original Research	Levodopa Floating Tubes	Vinylpyrrolidone-vinyl acetate copolymer 60:40 (PVP-VA)/ Ethylene-vinyl acetate copolymer 82:18 (EVA)	(Windolf et al., 2022)
	Original Research	Pramipexole HCl	Polyvinyl alcohol (PVA)	(Windolf et al., 2022)
	Original Research	Metformin	Hydroxypropylcellulose (HPC) Nisso H	(Vaingankar & Amin, 2017)

hydroxypropyl cellulose (HPC) demonstrated prolonged buoyancy and extended drug release over 12 h, improving bioavailability for drugs absorbed primarily in the proximal intestine (Sana et al., 2023). Another example includes gabapentin swellable HME matrices, designed to enhance gastric retention and maintain therapeutic plasma levels for extended durations.

Together, these examples illustrate how HME extends beyond traditional solubility enhancement and supports the development of innovative, multifunctional oral drug delivery systems. Through strategic polymer selection and matrix engineering, HME continues to expand its utility across complex formulation challenges and diverse therapeutic needs.

11.3. 3D-Printing and HME

HME is the primary method for producing drug-loaded filaments used in FDM 3D printing. These filaments serve as feedstock for fabricating personalized dosage forms (Douroumis, 2019). The integration of HME with 3D printing represents a major advancement toward patient-specific medicine and decentralized pharmaceutical manufacturing (Fig. 10).

Recent advances in HME have increasingly focused on producing drug-loaded filaments for fused-deposition modelling (FDM) 3D printing, enabling personalized dosage forms with tunable geometry and drug release profiles. One of the most notable developments has been the use of HME to generate filaments containing high drug loads while maintaining printability and mechanical integrity. Goyanes et al. (2016) demonstrated one of the first successful integrations of HME and FDM by producing paracetamol-loaded filaments capable of being printed into tablets with individualized shapes and doses. This work established the feasibility of combining continuous manufacturing with additive manufacturing to produce patient-specific oral dosage forms. Building upon this foundation, (Uboldi et al., 2022); (Auriemma et al., 2022) expanded the applicability of HME for filament fabrication by developing polymeric matrices with enhanced thermal stability and flexibility, enabling the extrusion of filaments incorporating thermolabile drugs and complex release-modifying excipients.

More recent studies have moved beyond conventional polymers to explore innovative carrier systems designed specifically for HME-based filament production. (Zamboulis et al., 2022)introduced amphiphilic polymer blends formulated to promote drug solubilization while preserving the mechanical characteristics required for FDM. Their work revealed that tailored polymer combinations could improve filament homogeneity, drug distribution, and print reliability, even at elevated drug loadings. Another significant innovation was provided by Milliken et al. (2024) who utilized HME to produce filaments incorporating nanostructured drug carriers, enabling multi-scale control over drug release kinetics. This hybrid strategy combined the benefits of ASD formation with nanoscale engineering, resulting in filaments with enhanced dissolution rates and customizable release profiles.

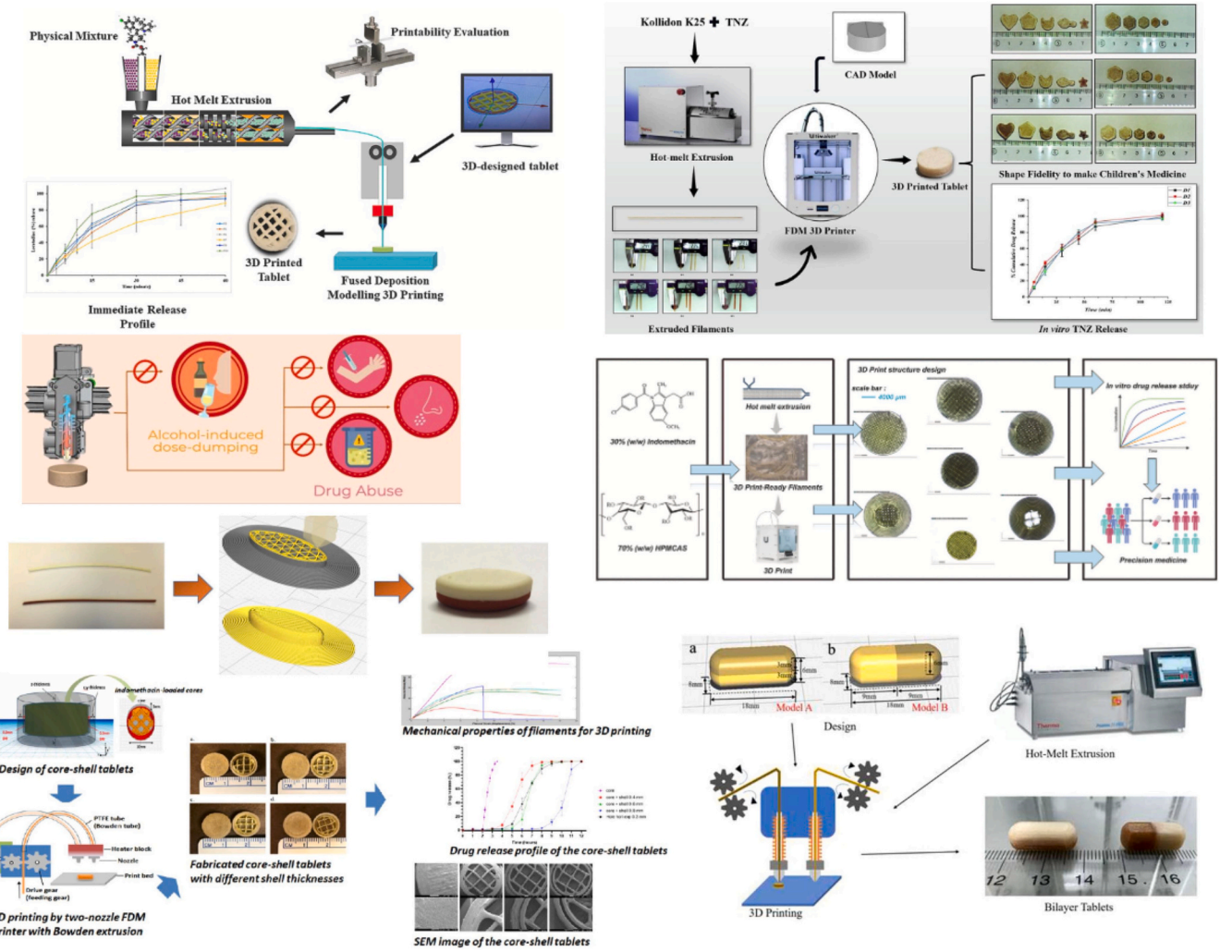

Fig. 10. Array of 3D printing applications combining HME and printing technologies – Reprinted with permission from (Huang et al., 2024; Pawar et al., 2024; Omari et al., 2022; Zhang et al., 2022; Ong et al., 2020; Pandey et al., 2020).

Polymer blend engineering has emerged as a promising strategy for enhancing ASD performance beyond the limitations of single–polymer systems. Patel G and Minko et al. conducted a detailed multiscale assessment of Copovidone/HPMC ASLF and Copovidone/Eudragit EPO polymer blends for ASD and FDM applications. Their work showed that Copovidone/HPMCAS-LF formed a fully miscible, single–phase system characterized by a single T_g and exceptional mechanical properties—toughness and flexural strength values exceeding 400 MPa—making it highly suitable for 3D printing. In contrast, the Copovidone/Eudragit EPO blend exhibited phase separation and inferior mechanical integrity, emphasizing how polymer miscibility directly affects filament quality and printability.

The pairing of HME with FDM 3D printing has also demonstrated strong potential for individualized oral dosage forms. Chung et al. (2023). developed indomethacin–loaded HME filaments that were printed into programmable structures capable of modulating drug release. Indomethacin was molecularly dispersed in HPMCAS, resulting in ASDs with tuneable release kinetics controlled by tablet geometry. The resulting models showed excellent predictive accuracy ($R^2 \approx 0.996$), illustrating the feasibility of precision on–demand therapy for paediatric patients with juvenile idiopathic arthritis.

Further progress in immediate–release systems was shown by the formulation of Mahmood and Hussain (2020) loratadine–based filaments using various polymer carriers and super–disintegrants. Six formulations met mechanical requirements for FDM printing, and the resulting tablets achieved rapid drug release (86–97% within 30 min). These results reinforce the versatility of HME–derived filaments for rapid–acting oral therapies.

The flexibility of HME–3D printing extends beyond oral dosage forms to localized drug delivery systems. Sanil et al. (2024) addressed the heat sensitivity of disulfiram while producing extended–release vaginal films for cervical cancer management. By optimizing extrusion and printing temperatures, particularly print speed, the authors achieved films with acceptable drug content, good mechanical performance, and sustained release over 24 h. This approach highlights the capability of HME–FDM hybrid systems to handle thermosensitive APIs while generating personalized, application–specific dosage formats.

A noteworthy advancement in paediatric formulation science was introduced by Kolipaka et al., who developed a continuous HME–coupled direct–extrusion 3D printing platform to manufacture chewable, gummy–like paediatric tablets. Their work demonstrated that adjusting infill density (30–50%), tablet geometry, and polymer composition could tailor both texture and dissolution behaviour, with optimized formulations achieving nearly 90% drug release within 30 min. Rheological analysis confirmed stable shear–thinning behaviour conducive to smooth extrusion, while sensory studies validated effective taste masking achieved through hydrogen–bond–mediated interactions and optimized sweetener–flavour ratios. This study provides a compelling demonstration of how 3D printing can enhance paediatric compliance through dosage personalization and improved palatability.

As a result, these novel studies highlight the growing applications of HME-based filament manufacturing, demonstrating its potential to support fully personalized medicine, expand the innovative space for poorly soluble drugs, and accelerate the development of on-demand pharmaceuticals. As polymer science, extrusion engineering, and additive manufacturing continue to converge, HME-produced filaments represent one of the most promising frontiers in advanced drug delivery.

12. QbD and design of experiments (DoE)

HME development benefits significantly from a structured QbD framework. QbD promotes a science- and risk-based approach to formulation and process optimization, ensuring consistent product quality, regulatory compliance, and scalable manufacturing (Table 7) (Yu et al., 2014) (Butreddy et al., 2021) (Lee et al., 2015). By systematically identifying critical attributes (Quality and Material attributes) and process parameters, manufacturers can establish a robust control strategy and define an operational design space (Fig. 11).

Table 7
Critical process parameters (CPPs) and their impact in HME.

CPP	Increase effect	Decrease effect	Associated risk
Barrel Temperature	→ Improved polymer softening and drug dissolution → Reduced melt viscosity → Enhanced amorphization	→ Incomplete melting →Poor mixing → Residual crystallinity	→ API degradation →Polymer degradation → Color change or impurity formation
Screw Speed (RPM)	→ Higher shear rate → Improved distributive/ dispersive mixing → Reduced residence time → Lower apparent viscosity (shear thinning)	→ Longer residence time → Lower shear input → Potential incomplete mixing	→ Overheating from excessive shear → Drug degradation (low RPM + high temperature) → Poor homogeneity
Feed Rate	→ Higher throughput → Increased barrel fill and die pressure	→ Lower torque → Higher residence time	→ Overfilling → incomplete melting → Underfilling → overexposure to heat/shear → Variability in extrudate dimensions
Specific Mechanical Energy (SME)	→ Enhanced drug dispersion → Improved amorphization • Better homogeneity	→ Insufficient mixing → Higher residual crystallinity	→ Polymer chain scission (high SME) → Thermal/ mechanical degradation
Residence Time	→ Greater mixing and dissolution (if optimized)	→ Insufficient melting or dispersion	→ Overexposure → degradation → Underexposure → incomplete amorphization
Barrel Fill Level	→ Improved pressure generation → Better mixing efficiency	→ Reduced melt pressure → Lower mixing efficiency	→ Instability in torque and pressure → Poor content uniformity
Die Pressure	→ Improved densification → Better dimensional uniformity	→ Irregular extrudate shape	→ Melt fracture → Equipment strain → Process instability
Cooling Rate	→ Rapid kinetic stabilization → Reduced recrystallization	→ Increased molecular mobility	→ Phase separation → Post-extrusion recrystallization

12.1. Critical quality attributes (CQAs)

CQAs are measurable physical, chemical, or performance–related properties that must remain within predefined limits to ensure that an HME–based ASD delivers the intended safety, efficacy, and product-quality profile. For ASDs, one of the most important CQAs is the T_g, which provides insight into molecular mobility and physical stability. A sufficiently high Tg relative to storage temperature minimizes the risk of molecular rearrangement and recrystallization. For example, Moseson and Taylor demonstrated that HPMCAS–based ritonavir ASDs, formulations with a Tg above 60°C showed significantly improved long–term stability under ICH accelerated conditions.

Another essential CQA is the degree of crystallinity, which confirms the success of amorphization during extrusion. Even small amounts of residual crystallinity can lead to incomplete dissolution, supersaturation failure, or long–term instability. In a recent case study involving celecoxib–PVP/TPGS ASDs (Santiago et al., 2020), DSC and X-ray diffraction confirmed complete amorphization due to the synergistic effect of the

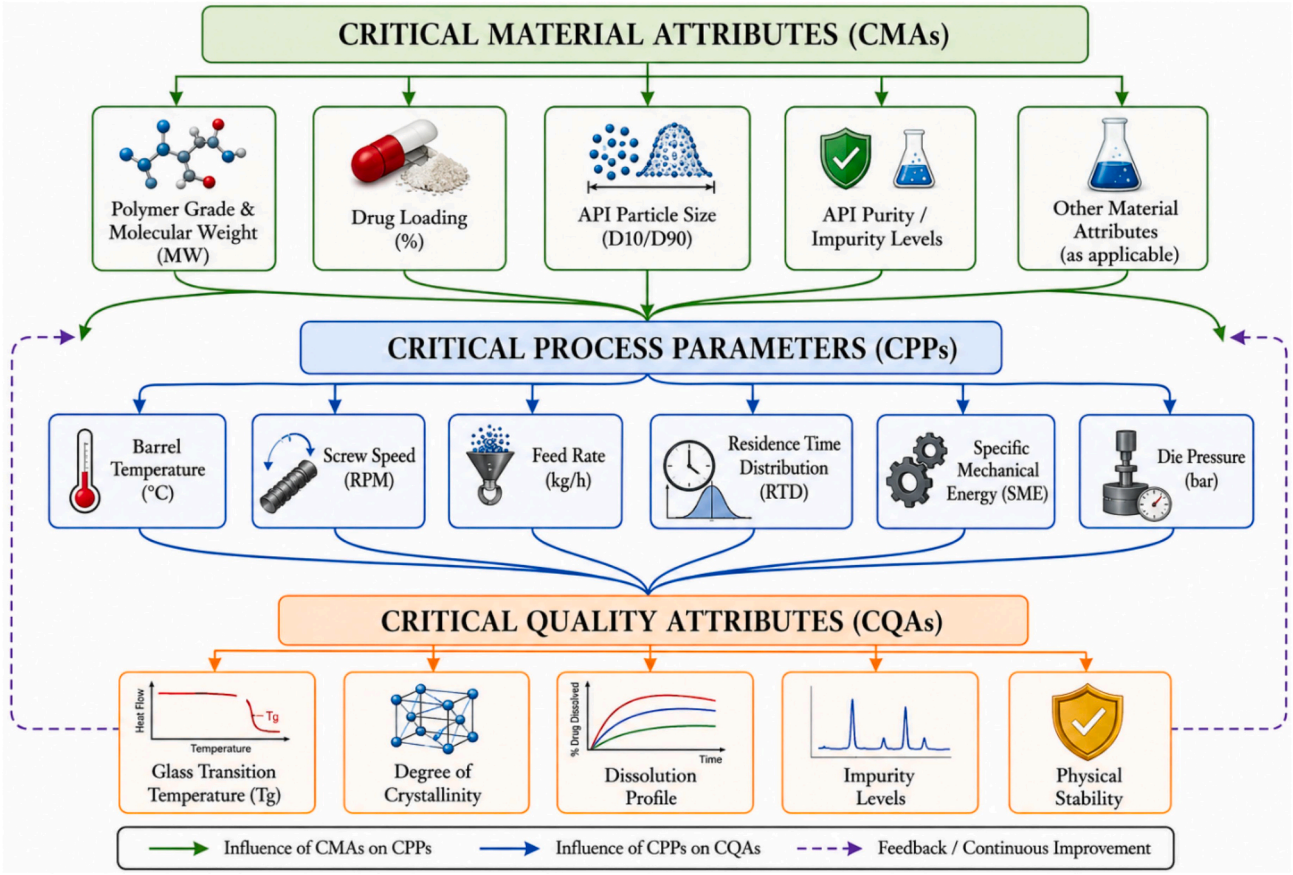

Fig. 11. Summary of CQAs, CMAs and CPPs for HME processing.

surfactant-polymer selection to inhibit recrystallization.

The dissolution profile is also a core CQA because it determines the supersaturation kinetics that control intestinal absorption. For poorly soluble drugs, dissolution improvement directly translates into higher systemic exposure. For instance, Moseson et al. (2021) demonstrated that an HME–processed ibrutinib ASD exhibited a fourfold increase in dissolution rate compared to its crystalline form, resulting in markedly improved preclinical bioavailability.

Lastly, impurity and degradation levels are critical CQAs, reflecting chemical stability and regulatory compliance. HME involves elevated thermal and mechanical energy, making API degradation a potential risk. Impurity formation during HME has emerged as a critical factor influencing the safety, stability, and performance of ASDs. Recent studies (Kushwah et al., 2024) have shown that excipient purity and processing conditions play decisive roles in determining the extent and type of impurities formed. In the case of copovidone-based ASDs, higher initial peroxide levels in excipients such as Kollidon VA 64 and Plasdone S630 were found to promote oxidative degradation of the drug, whereas formulations processed at higher barrel temperatures exhibited lower impurity levels due to decomposition of peroxides during extrusion. The inclusion of colloidal silicon dioxide improved the physical stability of extrudates but simultaneously increased oxidative degradation and hydroxylation of the drug substance, underscoring the delicate balance between stabilization and chemical reactivity. Similarly, investigation of atorvastatin extruded with hydroxypropyl methylcellulose phthalate (HPMCP-55) revealed formation of multiple drug–polymer interactions and degradation products (Mittal et al., 2025). These were identified and structurally characterized using ATR-IR and LC-HRMS analyses, and their potential toxicity was evaluated in silico. Collectively, these findings highlight that reactive impurities, whether originating from polymer grade, additives, or extrusion conditions, must be carefully controlled and characterized to ensure chemical stability and product safety in HME-processed pharmaceuticals. Together, these CQAs guide formulation optimization and ensure that HME–based ASDs consistently deliver the intended therapeutic performance.

12.2. *Critical material attributes (CMAs)*

CMAs refer to the physical and chemical properties of raw materials, such as polymer grade, molecular weight, drug particle size, hygroscopicity, and drug loading, that significantly influence product performance. Early recognition of CMAs supports quality–by–design (QbD) development and informed risk assessment (Yu, 2008).

Polymer grade and molecular weight determine viscosity, miscibility, and stabilization efficiency (Badruddoza et al., 2024) (Censi et al., 2018). Meena et al. (2014)reported that the T_g and viscoelastic behaviour of the polymers were strongly influenced by their structural characteristics, specifically the chain length, molecular weight, and degree of substitution along the main chain. They noted that increasing either chain length or molecular weight led to higher T_g and greater viscosity. Drug particle size and thermodynamic properties influence melting, mixing, and dissolution into the polymeric matrix. Drug particle size plays a decisive role in the processability and quality of HME formulations. Smaller drug particles improve dispersion uniformity, reduce extrusion torque, and promote complete amorphization by increasing surface contact with the polymer melt.

Hygroscopicity is another critical CMA, as moisture uptake (Sarode et al., 2013) can depress Tg, increase molecular mobility, and cause premature recrystallization. For example, itraconazole and indomethacin showed moisture and temperature-activated drug-polymer interactions when processed by various polymers such as Eudragit EPO, Kollidon VA 64, and HPMCAS-LF. Drug loading strongly affects

miscibility and stability. High drug loading can push systems beyond the miscibility limit, increasing crystallization risk. For instance, indomethacin ASDs were found to recrystallize during storage when processed via spray-drying, while presenting superior stability for the extruded formulations (Martynek et al., 2025). Understanding these CMAs ensures that material selection supports robust processing and long–term stability for HME–ASDs.

12.3. Identification of critical process parameters (CPPs)

CPPs are process variables that must be controlled to produce consistent CQAs (Fig. 11). In HME, CPPs include barrel temperature profile, screw configuration and speed, feed rate, SME, RTD and die pressure (Maniruzzaman et al., 2017). Temperature control is fundamental since inadequate melting hinders drug–polymer mixing, while excessive heating risks degradation. The temperature profile also determines the extent of polymer softening or melting and the dissolution of the drug within the polymeric carrier. Temperatures must be sufficiently high to enable polymer flow and drug diffusion while remaining below degradation thresholds for both components. For example, in the manufacture of itraconazole ASDs, tight control over zone temperatures prevented thermal decomposition and achieved complete amorphization by using a range of plasticisers (Solanki et al., 2019).

Screw speed and configuration influence shear and mixing efficiency. Kneading blocks enhance distributive and dispersive mixing but may raise SME. A 2021 study on atorvastatin–ezetimibe FDCs (Arafa et al., 2021) showed that modifying screw configuration improved miscibility and prevented API–API segregation. It has been found that aggressive screw configurations generally raise the SME because additional energy is needed to overcome the higher-pressure gradients created within each mixing or kneading section. Screw speed affects both the shear forces applied to the formulation and the residence time of the material in the barrel. Higher screw speeds generally increase shear and distributive mixing, which can promote drug dissolution into the polymer matrix; however, excessively high speeds may reduce residence time and limit the complete amorphization of the drug.

Feed rate and RTD affect the balance between exposure time and thermal load. Feed rate also plays a critical role, as higher feed rates can increase barrel fill and pressure, potentially improving mixing efficiency, but may simultaneously reduce residence time and thermal exposure, which are necessary for effective drug–polymer homogenization.

In addition, screw configuration, particularly the arrangement of conveying elements, kneading blocks, and mixing sections, directly influences the degree of distributive and dispersive mixing achieved during extrusion.

Configurations with kneading or mixing elements increase shear stress and improve drug dispersion within the polymer, facilitating the formation of a homogeneous amorphous system. However, excessive shear and thermal stress can lead to degradation or instability, highlighting the need to optimize screw design alongside other processing parameters to achieve consistent and stable ASD formation. As shown in Fig. 11 by mapping these CPPs to CQAs and CMAs, robust process control strategies can be developed, allowing reproducible performance and regulatory compliance for HME–based ASDs.

12.4. Design of experiments (DoE) and design space development

Design of Experiments (DoE) applies statistical methodologies to systematically evaluate the relationships between CQAs, CMAs, and CPPs. Multivariate models identify significant factors, interaction effects, and optimal processing conditions. Benefits of DoE in HME include quantitative understanding of parameter interactions, optimization of drug loading and processing temperature, minimization of variability, and establishment of a regulatory-compliant design space (Maniruzzaman et al., 2017) (Stocker et al., 2017). The design space defines the multidimensional space of combinations of material attributes and process parameters that consistently produce acceptable product quality. Operating within this approved space provides manufacturing flexibility while maintaining regulatory assurance. Together, QbD and DoE strengthen process robustness, support continuous manufacturing strategies, and facilitate efficient regulatory submissions for HME-based pharmaceutical products (Grymonpré et al., 2017).

13. Scale-Up and continuous manufacturing

HME is inherently suited for continuous manufacturing (Fig. 12); however, successful scale-up from laboratory to commercial production requires careful control of process dynamics, material behaviour, and regulatory compliance (Wesholowski et al., 2019). Maintaining product quality during scale transition depends on preserving key thermomechanical conditions and process consistency.

13.1. Similarity principles

Successful scale-up of HME operations relies on maintaining critical process similarities between laboratory-scale and commercial-scale equipment to ensure that the final product exhibits consistent solid-state and performance characteristics. Because scale transitions inherently modify heat-transfer efficiency, torque behaviour, and pressure profiles within the extruder, preserving dynamic similarity is essential to avoid unintended recrystallization, degradation, or variability in drug–polymer mixing. Central to this process is the alignment of SME, a parameter that reflects the shear and mechanical work imparted to the material. Matching SME across scales ensures that the degree of amorphization, dispersive and distributive mixing, and drug–polymer interactions remain comparable, thereby reducing the risk of scale-induced deviations in CQAs (Djuris et al., 2013).

Equally important is the maintenance of a similar RTD, which governs the duration of material exposure to thermal and mechanical energy. Discrepancies in RTD can result in insufficient amorphization, variable dissolution performance, or thermal degradation, especially for heat-sensitive drugs or polymers. Strategies to preserve RTD typically include matching screw speed, feed rate ratios, and screw element arrangements while adjusting barrel temperature profiles to account for

Fig. 12. A continuous HME line at industrial scale.

scale-dependent heat transfer differences. Geometric similarity, including consistent screw configurations, length-to-diameter ratios, and the spatial arrangement of kneading blocks, further supports predictable mixing behaviour and enables more reliable translation from bench-top to commercial production (Crowley et al., 2007). Together, these scale-up principles help ensure robust process performance and product uniformity across manufacturing scales.

13.2. Pilot to commercial transition

Transitioning from pilot-scale to commercial-scale extruders (Fig. 11) often requires parameter adjustments due to differences in barrel diameter, throughput capacity, and thermal mass. A structured scale-up strategy minimizes development risk and supports regulatory approval (Agrawal et al., 2015b). Critical considerations include optimization of screw design to maintain mixing efficiency, adjustment of feed rate and screw speed to balance SME and RTD, refinement of barrel temperature profiles to prevent overheating or incomplete melting, and monitoring torque and die pressure to ensure process stability (Wesholowski et al., 2019).

13.3. Cleaning and GMP considerations

For commercial HME operations, compliance with Good Manufacturing Practice (GMP) standards is essential. Effective GMP implementation ensures product safety, regulatory compliance, and sustainable large-scale manufacturing of HME-based formulations. Important aspects are cleaning validation to remove polymeric residues and prevent carryover, cross-contamination, particularly for potent or highly active compounds, integration of extrusion units into a continuous manufacturing line, including feeders, blenders, and PAT systems; documentation, and process control aligned with regulatory expectations (Bhujbal et al., 2021).

14. Regulatory considerations

Regulatory expectations for HME-based products emphasize a science and risk-based approach aligned with QbD principles and continuous manufacturing guidelines. Agencies require a comprehensive understanding and control of both material attributes and process parameters to ensure consistent product performance and long-term stability. HME-based products are increasingly well accepted by regulatory authorities (Wesholowski et al., 2019). Several commercially approved ASDs are manufactured using HME, reflecting regulatory confidence in the technology when supported by robust scientific justification, validated control strategies, and comprehensive stability data (Amidon et al., 2011).

In addition, regulatory assessments emphasize a comprehensive understanding of the amorphous form, including solid–state characterization, molecular mobility, phase separation risks, and recrystallization tendencies. Regulators such as the FDA and EMA expect robust evidence demonstrating that the ASD remains physically and chemically stable over shelf life, with consistent performance across all manufacturing scales.

Process analytical technologies (PAT) and quality–by–design (QbD) frameworks are increasingly encouraged to ensure control over critical parameters such as drug–polymer miscibility, extruder temperature profiles, and RTD. Additionally, regulators often require detailed supersaturation and precipitation–inhibition studies to support biopharmaceutic claims associated with enhanced absorption.

Together, these marketed examples and regulatory considerations underscore the maturity of ASD technology and the growing confidence in HME as a reliable, scalable platform. The demonstrated ability of HME–ASDs to provide higher bioavailability, reduced pharmacokinetic variability and improved clinical performance continues to position them as a valuable strategy for modern development of poorly water–soluble drugs.

15. Case studies and marketed products

The translation of hot HME from development laboratories to commercial manufacturing underscores its maturity as a pharmaceutical platform technology. Marketed products (Table 8) demonstrate HME's versatility in addressing solubility limitations, enabling controlled release, improving stability, and enhancing patient compliance (Agrawal et al., 2015a). These real-world examples provide practical insight into formulation design, process optimization, and regulatory acceptance (Matić et al., 2020).

15.1. Commercially marketed products

Kaletra: One of the most cited examples of HME-based commercialization, Kaletra® utilizes HME to produce a SD of lopinavir and ritonavir within a polymeric matrix (Meltrex). The formulation improved solubility and oral bioavailability while eliminating the refrigeration requirement associated with earlier soft-gel formulations. This product demonstrated how HME can improve stability, simplify supply chains, and enhance patient adherence (Crowley et al., 2007).

Isoptin SR: An example of HME-enabled sustained-release matrix design using verapamil hydrochloride within a polymer matrix (hydroxypropyl cellulose/hydroxypropyl methyl cellulose/sodium alginate) (Vajna et al., 2011). Isoptin SR® uses polymer-controlled diffusion to regulate drug release over extended periods. The extrusion process ensures uniform drug distribution within the matrix, enabling predictable and reproducible release kinetics.

Nurofen Meltlets Orally Disintegrating Tablet (ODT): HME-enabled heating and mixing of the active ingredient (ibuprofen) with excipients, amorphous, high-surface-area granules that dissolve more quickly in the mouth. This applied to rapid disintegration dosage forms, enhancing patient compliance through ease of administration and improved palatability (Gryczke et al., 2011).

Generic HME-based products: Numerous generic formulations now utilize HME for producing ASDs or modified-release matrices. The adoption by generics manufacturers reflects confidence in the scalability, cost-efficiency, and regulatory familiarity of extrusion technology (S. Li et al., 2023).

15.2. Market and industrial impact

HME has evolved from a formulation development technique to a mature pharmaceutical manufacturing platform with significant industrial and commercial impact. The technology is widely recognized for its ability to enable the production of ASDs (ASDs) that improve the solubility and bioavailability of poorly water-soluble drugs, a challenge that affects a large proportion of modern drug candidates. Several marketed products manufactured using HME, such as formulations of lopinavir/ritonavir and extended-release verapamil, demonstrate that the process is capable of delivering robust, scalable pharmaceutical products across diverse therapeutic areas, including antivirals, cardiovascular drugs, and analgesics. Importantly, HME is a solvent-free process, eliminating the need for organic solvents commonly required in spray drying or solvent evaporation methods. This reduces environmental burden, simplifies downstream processing, and eliminates the need for solvent recovery and residual solvent testing, thereby improving sustainability and regulatory compliance (Repka et al., 2012) (Maniruzzaman, Douroumis, et al., 2012).

From a manufacturing perspective, HME aligns closely with the pharmaceutical industry's transition toward continuous manufacturing and advanced process control. Twin-screw extrusion systems operate in a continuous mode, allowing consistent feeding, melting, mixing, and shaping of drug–polymer formulations with minimal interruptions. This continuous operation improves process efficiency, reproducibility, and

Table 8
Commercial pharmaceutical products manufactured using HME.

Product	API(s)	Polymer / Matrix system	Indication	Release type	Approval year
Kaletra®	Lopinavir + Ritonavir	Copovidone-based SD (Meltrex® technology)	HIV-1 infection	Immediate release (enhanced solubility ASD)	2000 (US tablet reformulation 2005)
Isoptin® SR	Verapamil HCl	HPMC / HPC / alginate matrix	Hypertension, angina, arrhythmia	Sustained release	1980s
Nurofen® Meltlets	Ibuprofen	Polymer-based extruded amorphous granules	Pain, inflammation, fever	Rapid disintegration / immediate release	~2010
NuvaRing®	Etonogestrel + Ethinyl oestradiol	Poly (ethylene–vinyl acetate) (EVA) elastomer	Contraception	Controlled-release vaginal ring	2001
Estring®	Estradiol	EVA membrane system	Menopausal vaginal atrophy	Controlled release vaginal ring	1996
Femring®	Estradiol acetate	EVA-based vaginal ring	Menopausal symptoms	Controlled release vaginal ring	2003
Implanon® / Nexplanon®	Etonogestrel	EVA subdermal implant	Contraception	Long-acting implant (3 years)	2006 (Implanon US), 2011 (Nexplanon US)

scalability, while reducing batch-to-batch variability compared with traditional batch-based manufacturing processes. Furthermore, the integration of PAT tools such as near-infrared (NIR) spectroscopy or Raman spectroscopy enables real-time monitoring of CQAs, supporting the implementation of Quality-by-Design (QbD) frameworks and RTRT strategies (Crowley et al., 2007) (Lee et al., 2015).

The industrial relevance of HME is further reinforced by its strong regulatory acceptance and expanding commercial adoption. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recognize HME as a robust enabling technology, particularly within the context of continuous manufacturing initiatives and advanced pharmaceutical manufacturing programs. The technology supports supply chain resilience by enabling compact manufacturing footprints, simplified processing steps, and improved control of product quality. Consequently, HME has become a cornerstone technology in modern pharmaceutical development pipelines, especially for poorly soluble drug candidates. As the industry increasingly adopts digital process monitoring, predictive modelling, and continuous manufacturing strategies, the role of HME is expected to expand further, reinforcing its position as a key industrial platform for next-generation drug product manufacturing (Repka et al., 2008) (S. Li et al., 2024).

16. Challenges and future perspectives

HME continues to advance as a key enabling technology for modern drug delivery, yet several scientific and operational barriers constrain its full potential. As the pharmaceutical landscape shifts toward increasingly complex molecules, ranging from poorly soluble lipophilic compounds to peptides and high–dose therapeutics, HME formulations must evolve accordingly. Addressing current gaps will require innovation across polymer science, predictive modelling, and advanced process engineering.

A central technical challenge involves the processing of thermolabile APIs. Many next–generation APIs, including peptide–mimetics and highly functionalized small molecules, degrade even under short periods of heat exposure. HME typically necessitates temperatures above the polymer's glass transition or melting point to ensure adequate molecular dispersion, but these conditions can initiate chemical degradation, impurity formation, or conformational changes that reduce potency. While mitigation strategies such as incorporating plasticizers, applying low–melting auxiliary excipients, or reducing residence time have shown value, they often introduce trade–offs, including compromised mechanical strength, reduced storage stability, or increased hygroscopicity. Consequently, extending HME to thermosensitive compounds remains an active research frontier. Emerging solutions include low–temperature extrusion grades of polymers, real–time thermal mapping inside the barrel, and hybrid short–exposure technologies such as KinetiSol or microwave–assisted extrusion, which collectively aim to minimize thermal load while maintaining dispersion quality.

Achieving high drug loading in ASDs poses another significant challenge. Commercially viable formulations often require elevated drug content to reduce pill burden and manufacturing costs. However, increasing the drug fraction narrows the miscibility window, heightens the risk of amorphous phase instability, and decreases the overall T_g of the system. This combination increases molecular mobility, promoting recrystallization during storage or even during downstream processing steps such as milling or tableting. High drug loading also elevates melt viscosity, complicating screw torque control, reducing throughput, and amplifying sensitivity to process fluctuations. To overcome these hurdles, ongoing research is focusing on novel polymer designs with enhanced interaction potentials, polymer blends capable of synergistic stabilization, and nanostructured excipient systems that immobilize the drug through spatial confinement. Furthermore, machine–learning–assisted miscibility prediction is emerging as a promising tool to identify stabilizing polymer–drug combinations before large-scale experimentation.

Predicting long–term stability remains one of the most persistent limitations in ASD development. While traditional thermodynamic approaches, including F-H interaction parameters and Tg–based mobility models, provide useful early–stage guidance, they rarely capture the full complexity of real-world aging. Moisture uptake, in particular, remains a dominant destabilizing factor: water acts as a potent plasticizer, lowering Tg, increasing molecular mobility, and enabling micro–phase separation even in systems that appear initially homogeneous. As highlighted by Moffat et al., (2014), humidity–induced structural relaxation and sub–Tg transitions can accelerate recrystallization in ways not predicted by conventional models. Improving long–term stability prediction will require more robust frameworks that couple molecular mobility analysis, humidity–dependent sorption behaviour, and real–time structural monitoring. Current efforts include MD simulations to map drug–polymer interactions, accelerated stability modeling using humidity–cycling protocols, and in situ characterization tools such as low-frequency Raman and dielectric spectroscopy.

Looking forward, the next phase of HME innovation will likely come from greater integration of computational design, smart materials, and continuous manufacturing. Digital twins, for example, could allow formulators to simulate process dynamics and stability outcomes before entering the lab, reducing development time and cost. Similarly, responsive polymers with tunable interactions may offer new pathways to stabilize high–load or thermosensitive APIs. As HME becomes increasingly embedded in end–to–end continuous production systems, advanced sensors and multivariate control algorithms will help ensure consistent product quality even in formulations that push current technical limits. Taken together, these advancements will enable broader application of HME across future drug pipelines, supporting the development of more challenging, patient–centred therapies.

16.1. Emerging technologies

A range of emerging technologies is reshaping the future landscape of HME, offering new pathways to overcome thermal limitations, enhance formulation design, and integrate HME more effectively into advanced manufacturing ecosystems. These innovations bridge polymer science, process engineering, computational modeling, and hybrid processing approaches, creating a more flexible and predictive environment for developing complex drug products.

Machine learning and data–driven modeling have recently gained significant momentum as powerful tools in HME formulation design. Jiang et al. (2023) demonstrated how large–scale datasets containing polymer properties, drug physicochemical descriptors, and historical processing outcomes can be used to train predictive models capable of identifying promising drug–polymer pairs with high miscibility. Such tools reduce reliance on iterative experimental screening, directly shortening development timelines and resource consumption. In addition, ML approaches are increasingly being integrated with PAT sensors, including NIR spectroscopy, torque monitoring, and in–line rheology, to support adaptive control strategies. By analysing data streams in real time, AI–based models may eventually recognize early signs of process drift and automatically adjust barrel temperatures, screw speed, or feed rate, moving HME closer to a fully autonomous continuous manufacturing platform.

Hybrid HME–spray drying systems represent another promising frontier. As highlighted by Poozesh and Bilgili (2019), combining extrusion with spray–based technologies can merge the scalability and robustness of HME with the fine particle–level control inherent to spray drying. In practice, such hybrid systems may operate sequentially or in parallel, for example, preparing a partially dispersed API–polymer matrix via low–temperature extrusion, followed by spray drying to produce optimized particles with defined surface morphology and improved redispersibility. This approach could prove particularly valuable for high–dose ASDs or formulations requiring enhanced dissolution, where particle engineering plays a critical role in performance. Additionally, hybrid processing may enable more efficient incorporation of thermolabile actives by reducing the thermal burden placed on each individual step.

CO_2–assisted extrusion offers yet another strategy to broaden the applicability of HME to temperature–sensitive drug molecules. As shown by Almutairi et al. (2022), subcritical or supercritical CO_2 can serve as a transient plasticizer during extrusion, significantly reducing melt viscosity and lowering processing temperatures. The gas diffuses into the polymer matrix during extrusion and rapidly dissipates upon depressurization, leaving behind porous or foam–like structures. These highly porous extrudates can dramatically improve wettability and dissolution rates, which is particularly advantageous for immediate–release formulations. Moreover, this technique provides a viable processing route for APIs that would otherwise degrade under conventional extrusion temperatures, extending HME utility to more fragile chemotypes.

Finally, custom–designed polymers represent one of the most transformative areas of technological progress. Traditional HME polymers were not originally developed with extrusion-specific performance in mind. In contrast, next–generation materials are now being engineered with tailored T_g, optimized interaction potentials, and tunable rheological properties to meet the demands of emerging drug pipelines. Pereira et al. (2020) describe how amphiphilic and multifunctional polymers can improve both miscibility and supersaturation maintenance by offering multiple interaction motifs—hydrogen bonding, hydrophobic binding, ionic pairing—in a single molecular framework. These engineered polymers may also suppress molecular mobility more effectively than conventional matrices, improving long–term amorphous stability and reducing recrystallization risks even at elevated drug loadings. As polymer design continues to evolve, the availability of extrusion–optimized excipients is expected to expand significantly, enabling more robust and versatile HME formulations.

These emerging technologies signal a shift toward a more predictive, customizable, and thermally efficient extrusion environment. Integrating machine learning, hybrid processing, CO_2–assisted plasticization, and advanced polymer design will not only address long–standing challenges in HME but may also unlock entirely new formulation strategies suited to future drug development pipelines.

16.2. Future outlook

The future of HME lies in its integration with continuous manufacturing, PAT-driven RTRT, digital twins, and personalized medicine platforms. As regulatory frameworks increasingly support advanced manufacturing technologies, HME is expected to play a central role in decentralized production, 3D printing applications, and next-generation drug delivery systems. Addressing current technical gaps through materials innovation, predictive modeling, and process digitalization will further solidify HME as a cornerstone technology in modern pharmaceutics.

17. Conclusions

HME has emerged as a versatile and industrially validated platform technology in modern pharmaceutics. Its ability to produce homogeneous ASDs in a solvent-free and continuous manner makes it highly effective for enhancing the solubility and bioavailability of poorly water-soluble drugs. As a green manufacturing approach, HME reduces solvent use, waste generation, and environmental impact, supporting sustainable pharmaceutical production.

From an industrial standpoint, HME aligns with QbD, continuous manufacturing, and PAT-enabled process control, enabling robust scale-up and regulatory flexibility. Its applicability across immediate-release, controlled-release, taste-masked, implantable, and 3D-printed dosage forms highlights its broad formulation versatility. While challenges such as thermolabile drug processing and long-term stability prediction remain, advances in polymer science and digital modeling are expanding its potential. Overall, HME represents a scalable, sustainable, and future-ready technology for efficient and patient-centric pharmaceutical manufacturing.

CRediT authorship contribution statement

Siva S. Kolipaka: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Atabak Ghanizadeh Tabriz:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Vivek Garg:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Vivek Trivedi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation. **Dennis Douroumis:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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