CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.17405301

Available online at: http://www.iajps.com Review Article

OVERVIEW OF HOT-MELT EXTRUSION TECHNIQUE IN THE DEVELOPMENT OF FAST-DISSOLVING TABLETS

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Abstract:

Fast-dissolving tablets (FDTs), also known as orally disintegrating tablets (ODTs), represent one of the most significant patient-centric innovations in modern pharmaceutics. They are designed to disintegrate and dissolve rapidly in the mouth without the need for water, offering a more convenient dosage form for paediatric, geriatric, and dysphagic patients. The emergence of Hot-Melt Extrusion (HME) as a continuous manufacturing technology has revolutionized solid dosage formulation by enabling solvent-free processing, taste masking, and enhanced dissolution of poorly soluble drugs through amorphous solid dispersion formation. This review provides a comprehensive overview of HME and its application in developing FDTs, detailing the process principles, materials, equipment, formulation parameters, and regulatory considerations. The synergy between HME and FDT technologies offers new possibilities for patient compliance, manufacturing efficiency, and bioavailability enhancement.

Keywords: *Fast-dissolving tablets, Orally disintegrating tablets, Hot-melt extrusion, Continuous manufacturing, Amorphous solid dispersion, Taste masking, Pharmaceutical technology.*

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Please cite this article in press Lubna Nousheen et al., ***Overview Of Hot-Melt Extrusion Technique In The Development Of Fast-Dissolving Tablets****, Indo Am. J. P. Sci, 2025; 12(10).*

1. INTRODUCTION

The oral route remains the most preferred means of drug administration owing to its simplicity, non-invasiveness, and patient acceptability [1]. Conventional tablets and capsules dominate the market; however, swallowing difficulties among paediatric and geriatric populations have created a need for dosage forms that can disintegrate quickly in the oral cavity without water [2,3]. This demand led to the development of fast-dissolving tablets (FDTs), which combine the convenience of a solid dosage form with the ease of liquid administration [4].

FDTs offer numerous advantages: rapid onset of action, improved compliance, and enhanced bioavailability for drugs absorbed through the oral mucosa [5]. According to the US FDA, an orally disintegrating tablet (ODT) is "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within seconds, when placed upon the tongue" [6]. Similarly, the European Pharmacopoeia defines ODTs as tablets that disperse or disintegrate in less than three minutes [7]. Such dosage forms are especially valuable for populations with dysphagia, psychiatric disorders, motion sickness, or nausea [8].

However, achieving the balance between rapid disintegration and sufficient mechanical strength remains a challenge in FDT formulation. Conventional manufacturing methods such as lyophilisation, spray drying, sublimation, and direct compression, often involve complex processes or lead to fragile tablets [9–11]. The integration of Hot-Melt Extrusion (HME) into FDT production has recently emerged as a transformative approach to overcome these limitations [12].

HME is a continuous, solvent-free, and scalable manufacturing technique initially developed for the plastics industry and later adapted for pharmaceuticals [13]. The process involves the melting and mixing of a polymeric carrier with an active pharmaceutical ingredient (API) under controlled temperature and shear, followed by extrusion through a die to form a uniform solid dispersion [14]. By embedding the API within a polymeric matrix, HME can improve drug solubility, enhance dissolution rate, and facilitate taste masking key attributes for FDT development [15,16].

Moreover, HME aligns with the Quality by Design (QbD) framework and Process Analytical Technology (PAT) principles advocated by regulatory agencies such as the FDA and EMA [17]. Its continuous nature allows for real-time process monitoring, reduced variability, and improved scalability compared to batch processes [18].

This review aims to provide a detailed overview of the HME technique and its application in the development of FDTs, highlighting formulation strategies, process parameters, material selection, and emerging trends. It emphasizes the role of HME as a versatile platform capable of producing FDTs with superior performance and manufacturability.

2. FAST-DISSOLVING TABLETS (FDTs): OVERVIEW

2.1 Definition and Significance

FDTs are solid oral dosage forms that disintegrate rapidly—usually within 30 seconds—upon contact with saliva, releasing the drug for local or systemic absorption [19]. They are particularly useful for patients who have difficulty swallowing conventional tablets or capsules, such as children, elderly individuals, and psychiatric patients [20]. Additionally, FDTs allow for rapid onset of therapeutic action, making them suitable for emergency medications like antiemetics, antihistamines, and analgesics [21].

2.2 Advantages

The benefits of FDTs extend beyond patient convenience. They include:

- **Enhanced compliance:** Especially in populations with dysphagia [22].
- **Rapid onset:** Faster dissolution and absorption compared to conventional tablets [23].
- **Improved bioavailability:** Bypassing first-pass metabolism for certain drugs [24].
- **Ease of administration:** Can be taken without water, enhancing portability and usability [25].

2.3 Limitations

Despite their advantages, FDTs pose several formulation challenges. These include taste masking of bitter drugs, maintaining adequate mechanical strength while ensuring fast disintegration, and ensuring stability against moisture [26]. Achieving a delicate balance between porosity, hardness, and dissolution rate requires careful selection of excipients and processing methods [27].

2.4 Manufacturing Approaches

Several techniques are available for FDT manufacturing (Table 1). Among them, HME stands out for its solvent-free nature, continuous operation, and capability to enhance solubility and mask taste [28,29].

Table 1. Common techniques for the manufacture of fast-dissolving tablets

Technique	Principle	Advantages	Limitations
Direct compression	Use of superdisintegrants for rapid breakup	Simple and cost-effective	Limited to low-dose drugs
Lyophilisation	Freeze-drying of drug solutions/suspensions	Very fast disintegration	Fragile tablets, costly
Sublimation	Use of volatile agents to create porosity	Improved disintegration	Limited mechanical strength
Spray drying	Produces highly porous particles	Uniform distribution	High process cost
Hot-Melt Extrusion	Melt mixing of drug-polymer matrix	Solvent-free, continuous, taste masking	Thermal sensitivity issues

3. HOT-MELT EXTRUSION (HME): TECHNOLOGY, PROCESS AND EQUIPMENT

3.1 Principle and Mechanism

Hot-melt extrusion is a continuous processing technique in which the API, polymer carrier and functional excipients are blended and conveyed through a heated barrel by rotating screws to form a homogeneous molten mass**.** The melt is then forced through a die of defined geometry, cooled, and shaped into an extrudate that may be milled or directly molded into dosage forms [30–33]. The technique enables molecular-level mixing, transforming crystalline drugs into amorphous solid dispersions with improved dissolution rates and bioavailability [34]. Because HME avoids organic solvents and batch variability, it aligns well with modern green-chemistry and continuous-manufacturing initiatives [35].

3.2 Process Zones and Flow Dynamics

A typical twin-screw extruder is divided into several functional zones [36, 37]:

1. **Feeding zone** – introduction of raw materials from a hopper; powder feeding rate must synchronize with screw torque.
2. **Conveying zone** – transport of material; primarily affects residence time.
3. **Melting/plasticizing zone** – controlled temperature causes polymer softening and drug dissolution or dispersion.
4. **Mixing/kneading zone** – ensures distributive and dispersive mixing; shear generated here must remain below the degradation threshold of the API.
5. **Devolatilization zone** – allows venting of trapped air or residual moisture.
6. **Die zone and cooling** – shape formation and solidification.

The residence-time distribution (RTD) determines drug uniformity. Short RTD enhances throughput but may cause incomplete melting; longer RTD increases thermal exposure. Optimization of screw configuration and speed maintains balance between mixing efficiency and thermal stability [38, 39].

3.3 Equipment Design

Pharmaceutical extruders are typically co-rotating, intermeshing twin-screw systems. Important design aspects include:

- **Screw configuration:** combination of conveying and kneading elements controls mixing intensity [40].
- **Barrel segmentation:** allows independent heating/cooling control per zone.
- **Torque rheometry:** monitors viscosity and melt load; deviations indicate process upsets [41].
- **Downstream units:** cooling belts, pelletizers, or granulators convert strands into flowable intermediates [42].

3.4 Critical Process Parameters (CPPs)

The most influential CPPs are **barrel temperature profile, screw speed, feed rate, torque, and die pressure** [44, 45].

- **Temperature:** Should exceed the polymer's glass-transition or melting point but remain below API degradation temperature [46].
- **Screw speed:** Higher speeds increase shear and mixing yet may cause air entrainment; typical range 50–250 rpm [47].
- **Feed rate:** Affects fill level and RTD; imbalance leads to surging or insufficient mixing [48].
- **Torque and pressure:** Indicators of viscosity changes; monitored via PAT systems [49].

Optimization often employs Design of Experiments (DoE**)** to define a *design space* where CPPs produce extrudates meeting desired Critical Quality Attributes (CQAs**)** such as content uniformity, dissolution and mechanical strength [50].

4. MATERIALS USED IN HME FOR FDT FORMULATION:

4.1 Polymeric Carriers

Polymers act as carriers, matrix formers and solubilizers.
Common choices [51–54]:

Polymer	Characteristics / Suitability
PVP K30, PVP VA64 (crospovidone)	Amorphous stabilizer, rapid dissolution; ideal for FDTs
HPMC E5/E15	Film-forming, provides mechanical strength
PVA	Excellent melt-processability, non-hygroscopic
PEG 4000–8000 / PEO	Plasticizer and hydrophilic carrier
Eudragit EPO	Taste-masking cationic polymer
Soluplus®	Amphiphilic polymer designed for HME – enhances solubility of BCS II drugs

Polymer selection must balance extrudability**,** drug miscibility, and rapid dissolution of the matrix in saliva.

4.2 Plasticizers and Surfactants

Plasticizers (triethyl citrate, glycerol, PEG) lower melt viscosity and processing temperature [55]. Surfactants (Poloxamer 188, Tween 80, SLS) promote wetting and dissolution [56]. Their levels must be optimized because excessive plasticization can soften tablets and delay disintegration [57].

4.3 Super-Disintegrants and Taste-Masking Agents

To ensure fast disintegration, extruded granules are often blended with **super-disintegrants** such as crospovidone, croscarmellose sodium, or sodium starch glycolate [58]. **Ion-exchange resins** (e.g., Indion 414) incorporated via HME effectively mask bitterness [59].

5. APPLICATION OF HME IN THE DEVELOPMENT OF FAST-DISSOLVING TABLETS

5.1 Rationale

The combination of HME and FDT leverages HME's ability to enhance solubility and produce uniform dispersions with the rapid disintegration demanded by FDTs [60]. Extruded granules or pellets demonstrate excellent compressibility**,** enabling robust tablets that still disintegrate within seconds [61].

5.2 Formulation Workflows:

1. Physical screening of API-polymer miscibility by DSC or FTIR.
2. Melt extrusion under optimized temperature/speed profile.
3. Cooling and milling of extrudate into granules (150–500 µm).
4. Blending with super-disintegrant, sweeteners, flavors and lubricant.
5. Compression into tablets using rotary press.
6. Evaluation: hardness, friability, disintegration, dissolution, taste-masking and stability.

5.3 Case Examples

Drug	Carrier/Polymer	Outcome	Reference
Ibuprofen	Copovidone (PVP-VA64)	Enhanced dissolution, smooth mouthfeel	[64]
Meloxicam	PEG 6000	Improved solubility & FDT disintegration < 30 s	[65]
Caffeine	PVP K30	Taste-masked, rapid release	[66]
Paracetamol	Soluplus® + Crospovidone	Uniform extrudate, fast dissolution	[67]
Loratadine	Eudragit EPO matrix	Complete bitterness suppression	[68]

5.4 Process Analytical Technology (PAT)

Integration of near-infrared (NIR) or Raman spectroscopy during extrusion allows real-time monitoring of melt temperature, homogeneity and API crystallinity [69, 70]. Such in-line control enables Real-Time Release Testing (RTRT) reducing end-product testing and aligning with QbD principles [71].
Modern extruders also include torque-feedback loops and predictive analytics for early fault detection [72]

5.5 Advantages of HME for FDT Manufacturing

- **Continuous & scalable** – seamless integration into CM lines [73].
- **Solvent-free** – eliminates solvent-residue concerns [74].
- **Taste-masking** via polymer embedding [59, 68].
- **Enhanced dissolution** through amorphous dispersion [60].
- **Uniformity & reproducibility** due to steady-state processing [75].

- **QbD/PAT-ready** – real-time monitoring and control [69–72].

5.6 Limitations and Challenges

Despite advantages, HME demands thermal stability of the API**,** precise temperature control**,** and costly equipment [76]. Not all polymers are extrudable; some may degrade or discolor under heat [77]. Additionally, scale-up requires maintaining equivalent specific mechanical energy *and* residence time, *which* can be complex [78]. Moisture uptake during storage may trigger re-crystallisation of amorphous APIs [79]. Mitigation includes polymer selection with anti-plasticization effects**,** moisture-barrier packaging**,** and inclusion of stabilizers like PVP or HPMC [80].

6. REGULATORY, QUALITY-BY-DESIGN (QbD) AND SCALE-UP ASPECTS

6.1 Quality-by-Design (QbD) Framework

Quality-by-Design (QbD) has become an integral part of pharmaceutical development, emphasizing designing quality into the product rather than testing it afterward [81].
In the context of HME-based FDTs**,** QbD facilitates understanding of how Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) influence Critical Quality Attributes (CQAs**)** such as hardness, disintegration time, dissolution rate, and content uniformity [82,83].

Quality Target Product Profile (QTPP) defines performance goals for FDTs this includes:

- Disintegration ≤ 60 seconds
- Pleasant mouthfeel
- Adequate mechanical strength (≥3 kg/cm² hardness)
- Assured dose uniformity
- Stability under ICH conditions

Through Design of Experiments (DoE)**,** developers can establish a *design space* linking screw speed, temperature, and polymer ratio to tablet CQAs [85]. Once validated, this design space becomes part of the regulatory submission dossier, aligning with ICH Q8–Q10 guidelines.

6.2 Process Analytical Technology (PAT)

PAT tools such as near-infrared (NIR)**,** Raman**,** and ultrasound sensors allow real-time process monitoring of the melt viscosity, drug distribution, and crystallinity during extrusion [86,87].By integrating PAT, manufacturers can achieve Real-Time Release Testing (RTRT)**,** minimizing the need for end-product QC testing[88].FDA's Emerging Technology Program actively supports such continuous-manufacturing innovations**,** recognizing HME as a model technology [89].

6.3 Regulatory Perspective

Regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)**,** now encourage continuous manufacturing (CM) approaches [90].HME aligns perfectly with CM because it allows a consistent feed of materials, continuous monitoring, and minimal batch-to-batch variation [91].The FDA Guidance on Orally Disintegrating Tablets (updated 2018) also defines specific evaluation parameters such as disintegration time, water uptake, and in vitro dissolution methods [92].Globally, authorities acknowledge that HME can serve as an enabling technology for difficult-to-formulate drugs, and its integration with FDT design supports both patient-centric and sustainable manufacturing [93,94].

7. STABILITY AND PACKAGING CONSIDERATIONS

HME-FDTs often contain amorphous drug dispersions susceptible to recrystallization, particularly under humid conditions[95]. To ensure long-term stability:

- Use polymers with anti-plasticizing properties such as PVP K90 **or** HPMC **[**96].
- Add moisture scavengers like colloidal silica or magnesium carbonate.
- Store tablets in aluminium–aluminium blisters with desiccants [97].
- Conduct accelerated stability testing (40 °C/75 % RH for 6 months) to verify retention of dissolution and disintegration performance [98].

Studies show that PVA**-** and Soluplus-based HME matrices exhibit high physical stability even after 12 months storage under intermediate conditions [99].

8. CHALLENGES AND FUTURE PERSPECTIVES

Despite rapid progress, several challenges remain for industrial adoption of HME-FDT manufacturing:

1. **Thermal degradation of APIs:** Many drugs melt or degrade below polymer processing temperatures; development of **low-melting or plasticized polymer systems** is ongoing [100].
2. **Equipment cost and expertise:** Pharmaceutical-grade twin-screw extruders and PAT integration require high capital investment [101].
3. **Scale-up reproducibility:** Maintaining equivalent shear and residence time across lab and production extruders demands robust mathematical modeling [102].
4. **Moisture sensitivity:** FDTs are prone to softening and recrystallization under humidity [103].

The future outlook is promising, with trends including:

- **Integration of HME with 3D printing** to produce personalized FDTs [104].
- **Hybrid continuous lines** combining extrusion, granulation, and direct compression [105].

- **Biopolymer-based FDTs** using natural carriers such as pullulan or starch derivatives [106].
- **Digital twins and AI models** for predictive process control and virtual validation [107].

9. CONCLUSION:

Hot-Melt Extrusion has revolutionized pharmaceutical manufacturing by offering a continuous, solvent-free, and versatile process that enhances the solubility, taste, and bioavailability of drugs. When integrated with the fast-dissolving tablet platform**,** it enables the development of dosage forms that are rapidly disintegrating, palatable, and patient-friendly**.** By embedding poorly soluble APIs into hydrophilic polymer matrices, HME provides both physical stability and enhanced dissolution kinetics, addressing one of the primary challenges of oral drug delivery.Moreover, the alignment of HME with QbD and PAT frameworks positions it as a future-ready technology compatible with regulatory expectations for continuous manufacturing. As innovation continues in polymer design, process control, and hybrid production systems, HME-based FDTs are poised to become a mainstay in next-generation oral dosage development.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the Principal, Dr. A. Venkateshawar Reddy, and the Management of Anwarul Uloom College of Pharmacy, Hyderabad**,** for their constant encouragement and for providing the necessary facilities and institutional support to carry out this review work. The authors also extend their gratitude to the faculty members of the Department of Pharmaceutics for their valuable guidance and cooperation throughout the preparation of this manuscript.

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