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The Hot Melt Extrusion (HME) in Pharmaceutical Technology: A Comprehensive Review

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ABSTRACT

Hot Melt Extrusion (HME) is an innovative and versatile technology that has significantly impacted pharmaceutical formulation and drug delivery. Originally developed for the plastics industry, HME has been successfully adapted for pharmaceutical use due to its solvent-free and continuous processing capabilities. It is particularly beneficial for enhancing the solubility and bioavailability of poorly water-soluble drugs. The process involves the application of heat and shear force to produce homogeneous extrudates, enabling the development of solid dispersions, controlled-release formulations, and complex drug delivery systems. Twin-screw extruders are commonly preferred over single-screw systems due to their superior mixing efficiency and scalability. HME offers several advantages, including improved drug stability, enhanced patient compliance, and environmental friendliness. However, challenges such as thermal degradation of heat-sensitive drugs and the need for specialized equipment remain. Critical process parameters—including temperature, screw speed, and feed rate—must be carefully optimized. A wide range of materials, such as pharmaceutical-grade polymers and plasticizers, are employed, with appropriate selection being essential for desired drug release and stability. Characterization techniques like DSC, TGA, XRD, and FTIR help evaluate drug-polymer interactions and extrudate properties. Emerging innovations, such as 3D printing integration and real-time process monitoring, are expanding the potential of HME, particularly in personalized medicine and continuous manufacturing.

Keywords: Hot Melt Extrusion, Solid Dispersions, Drug Delivery Systems, Twin-screw extruder, Bioavailability Enhancement, Pharmaceutical polymers.

1. INTRODUCTION

Hot Melt Extrusion (HME) has surfaced as a revolutionary means of drug formulation in the pharmaceutical sector, providing wonderful opportunities in drug delivery systems.[1] Initially formulated for the plastics industry, HME consists of heating and mechanically blending active pharmaceutical ingredients (APIs) with polymeric carriers into a homogeneous solid dispersion.[2] The process is continuous and solvent free, hence attracting immense interest for its capabilities to enhance the solubility and bioavailability of poorly soluble drugs, stabilize the drugs, and allow for controlled or sustained release formulations.[3] One of the main advantages of HME is its adaptability. It can be used for a multitude of dosage forms such as tablets, pellets, films, and even implants.[4] In addition, the technology allows for the formation of amorphous solid dispersions, which solves the problem of dissolution for the drugs by dispersing them molecularly within a polymer matrix. HME's ability to provide single-step, scalable, and environmentally friendly production processes meets the need for continuous, green pharmaceutical manufacturing.[5]

This review is centered on a detailed analysis of the principles underlying hot melt extrusion technology, considering its fundamental aspects, materials, various process parameters, recent innovations, and applications in pharmaceuticals. It attempts to analyze literature along with recent technological advancements to bring forth the importance of HME in contemporary drug design and delivery systems.

2. PRINCIPLE OF HME

The principle of Hot Melt Extrusion (HME) revolves around the application of heat and mechanical force to blend and shape pharmaceutical materials into a uniform dosage form without the use of solvents. [6] In this process, a mixture of the active pharmaceutical ingredient (API) and thermoplastic polymeric excipients is introduced into an extruder, where it undergoes melting due to controlled heating and intense mixing by rotating screws.[7] As the material softens, it is thoroughly homogenized to ensure uniform distribution of the drug within the polymer matrix.[8] The molten mass is then forced through a die to form a specific shape, such as films, granules, or rods, and is subsequently cooled and solidified to retain its structure. This technique enables the formation of amorphous solid dispersions, thereby enhancing the solubility and bioavailability of poorly water-soluble drugs. Since the process is continuous and solvent-free, it is both environmentally friendly and scalable, making it a valuable technology in modern pharmaceutical manufacturing.[9]

3. ADVANTAGES

The implementation of Hot Melt Extrusion (HME) in pharmaceutical manufacturing is continuously on the rise with regard to its popularity due to:

3.1 **Sustainability:** Since HME is produced without any solvents, it is an environmentally friendly manufacturing process, improving safety and compliance measures.[10]

3.2 Improved flexibility: As a continuous process, the streamlined production resulting from lesser variability in batches and unit operations translates to streamlining in the transition from the laboratory to commercial scale production.[11]

3.3 Enhanced Efficiency: Reduction of excipients, solvents, and drying processes results in HME being an economically friendly approach to drug formulation and production.[12]

3.4 Content uniformity: The necessity of content uniformity is achieved through inline mixing and shear forces received during the drug extrusion process.HME enables homogeneous dispersion of the active drug.[13]

3.5 Classification independence: Unlike the rest of the tablet compressing methods, HME does not need an extensive number of compressible powders. Therefore, materials with poorly compressible indices can still be used. [14]

3.6 Reduced Excipients and Multifunctional Polymers: The amazing flexibility that modern polymers offer allows HME formulations to utilize less excipients, since the polymers themselves can perform several functions, such as matrix formers, solubilizers, and modifiers of release rates. [15]

3.7 Improved Drug Solubility and Bioavailability: Particularly for poorly water-soluble drugs, the technique is most beneficial due to its ability to create amorphous solid dispersions, which significantly enhance solubility and bioavailability. [16]

3.8 High Thermodynamic Stability: Products formulated via HME are less prone to thermodynamic instability and exhibit greatly reduced recrystallization tendencies in comparison to other hot-melt or solvent-based methods.[17]

3.9 Minimized Oxygen Exposure: The enclosed design of the extrusion channel reduces the drug's oxygen exposure, which is useful for oxygen-sensitive compounds.[18]

3.10 No Need for Downstream Processing: HME does not require additional steps like drying and milling, which greatly simplifies the production workflow by eliminating post-processing steps.[19]

Due to these significant advantages, HME has gained widespread adoption in the pharmaceutical industry for the development of novel drug delivery systems and enhancing the performance of existing formulations.

4. DISADVANTAGES

Even though the Hot Melt Extrusion technique has its benefits, it does pose some challenges. Some of the major shortcomings of this technology are as follows:

4.1 Inapplicable to Thermolabile Drugs: The sensitive APIs that need low temperatures undergo high thermal degradation during extrusion and therefore cannot use HME.[20]

4.2 Limited Choices of Polymers: The number of polymers that can put up with the thermal and mechanical stress of HME is very small. This restriction may be detrimental for other formulation designs, especially those targeting specific release rates of the drug. [21]

4.3 Reliance on the Flow Properties of the Material: HME harnesses the use of materials that have good flow ability so as to guarantee uninterrupted feeding and processing of the material. Poor flow properties of materials may result in feeding inconsistencies, agglomeration, or differences in the quality of the end product. [22]

From these disadvantages, it is evident that the hot melt extrusion process requires optimization of the dry blending process for the pharmaceutical industry.

5. IMPORTANCE OF HME TECHNOLOGY IN PHARMA INDUSTRY

The use of polymers in Hot Melt Extrusion (HME) determines the processability, stability, and performance of the final pharmaceutical product, highlighting their importance in HME's success. [23] Thermal stability is one of the main criteria required from polymers. The residence time in the extruder is short, generally 0.5 to 5 minutes, minimizing thermal degradation. However, the components must still withstand high and severe processing temperatures.[24] Preferentially, the use of thermolabile compounds is possible because clever design of the temperature profiles and screw configurations mitigates degradation. [25] Some of the properties of the final dosage form might require polymers to aid in the molecular level mixing with the API, which is necessary for the amorphous solid dispersions to form. Other times, the polymers may choose to remain phase-separated for specific controlled-release profiles targeting specific therapeutic needs. This multifunctionality enhances the application of HME across diverse delivery systems.[26]

Thermoplastic biodegradable polymers used in HME-based formulations, especially in long-acting and implantable drug delivery systems, are of great importance in Synthetic Biologics. [27] In this regard, poly (ortho esters) (POEs) is gaining more attention due to the relative controlled and predictable surface erosion characteristics. Compared to bulk-eroding polymers such as polylactide, POEs are superior due to surface erosion mechanisms.[28] Since the 1970s, four generations of POEs (POE I to POE IV) have been developed, each enhancing the biocompatibility, degradation profile, and mechanical properties of the polymer for pharmaceutical applications.[29]

6. TYPES OF EXTRUSION SYSTEMS

Hot Melt Extrusion (HME) systems are primarily classified based on the design and configuration of their screw mechanisms. The selected extrusion setup plays a crucial role in determining the mixing efficiency, output capacity, material residence time, and suitability for specific pharmaceutical formulations. The three major types of HME systems include single-screw, twin-screw, and multi-screw extruders. Each type offers distinct functional advantages and is chosen according to the formulation's complexity, the desired drug delivery characteristics, and production scale.

6.1 Single-Screw Extrusion

Single-screw extruders represent the most basic form of HME equipment, featuring one rotating screw housed within a heated barrel. The material is introduced into the barrel, where it undergoes melting and is then pushed through a die to shape the final product. These systems primarily utilize drag flow and are best suited for simple formulations that do not require extensive mixing.[30]

Although not commonly used for pharmaceutical applications due to their limited capacity for advanced mixing and reduced control over process variables, single-screw extruders are still relevant in specific scenarios. They are particularly useful for basic melt processing tasks and solvent removal, where minimal mixing suffices. Their straightforward design, lower operational costs, and minimal maintenance needs make them a viable choice for small-scale or early-stage development. [31]

6.2 Twin-Screw Extrusion

Twin-screw extruders are the most widely implemented type in pharmaceutical hot melt extrusion due to their adaptability and superior performance. These systems consist of two screws that may rotate in the same direction (co-rotating) or opposite directions (counter-rotating), and they can either intermesh or operate independently. Among them, co-rotating intermeshing designs are especially favored for their efficient dispersive and distributive mixing abilities.[32]

These extruders are well-suited for producing amorphous solid dispersions, which enhance the solubility and absorption of poorly water-soluble drugs. They are also employed in fabricating controlled-release formulations, taste-masked dosage forms, and oral films. The modular screw assembly allows process customization to match the physical and flow properties of the formulation components. Twin-screw systems support continuous processing and offer reliable scalability from laboratory to commercial-scale manufacturing, contributing to improved batch uniformity and process efficiency. [33]

6.3 Multi-Screw Extrusion

Multi-screw extrusion systems, which incorporate more than two screws, are designed for high-throughput applications and provide superior mixing capabilities. [34] These systems expand the contact surface within the barrel, promoting uniform blending and better thermal control. Although their use in pharmaceutical manufacturing is currently limited due to their complexity and cost, they present promising opportunities for future large-scale continuous manufacturing initiatives. [35]

They are particularly advantageous for processing formulations with high polymer loads or elevated viscosities, as well as applications that demand stringent control over thermal and mechanical processing conditions. Furthermore, multi-screw extruders can be integrated with real-time monitoring systems, such as Process Analytical Technology (PAT) tools including near-infrared (NIR) spectroscopy, to ensure consistent quality and compliance with regulatory standards.[36]

7. MONITORING AND CONTROLLING PARAMETERS

Extrusion processing requires close monitoring and understanding the various parameters: viscosity and variation of viscosity with shear rate and temperature, elasticity, and extensional flow over hot metal surfaces. Today, extruders allow in-process monitoring and control of parameters, such as the temperature in the extruder, head, and die, as well as pressure in extruder and die. The main monitoring and controlling parameters are barrel temperatures, feed rate, screw speed, motor load and melt pressure. Barrel temperature, feed rate and screw speed are controlling parameters and motor load and melt pressure are monitoring parameters.

7.1 Barrel temperatures: The glass transition or melting temperatures of polymers and drug usually determines the barrel temperature [37]

7.2 Feed rate and screw speed: The constant feeding rate and screw speed throughout the process is important as the combination of these two factors establishes the level of fill in extruder. This is critical to the process because it governs the balance between the weak and strong mass transfer mode. Due to constant feed rate and screw speed, there will be a constant amount of material in the extruder and thus the shear stress and residence time applied to material remains constant [38]

7.3 The motor load and melt pressure: These parameters depend on feed rate and screw speed. With constant feed rate and screw speed these parameters depend upon the molecular weight of polymer and drug as well as polymer miscibility in binary mixtures. [39]

8. MATERIALS USED IN HME

A pharmaceutical component requires a tendency to readily deform inside the extruder unit and solidify upon exiting in order to be treated by HME. The ingredients ought to be as pure and safe as those made using conventional methods. The following attributes ought to be incorporated into the formulation of any HME employed in pharmaceutical applications: an intricate combination of active substances and numerous important excipients. Detailed pre-formulation evaluation of different drug delivery methods is essential for the appropriate choice of an API, carrier, and additives for the flawless and consistent operation of the HME procedure to produce the desired outcome. Despite materials remain inside the heated barrel of the equipment for approximately 10 seconds to 10 minutes (depending on the L/D, screw design, type of extruder, and speed of operation), it would always be desirable to have higher standards of thermal stability to reduce the likelihood of any potential degradation. [40,41]

These functional excipients fall into the following general categories: antioxidants, plasticizers, matrix carriers, fillers, release-modifying agents, stabilising agents, heat lubricants, and other additives. Hot-melt extruded medications can acquire particular qualities that are comparable to those obtained with conventional dosage forms by carefully choosing and utilising a variety of excipients.

8.1 Carrier System

A formulation containing a meltable material and a functional excipient serves as a vehicle for the active component to be embedded. Depending on what is needed, the carrier can be polymeric or non-polymeric. Low melting waxes or lipids, which are typically utilised in semi-solids and lipid-based drug delivery systems, are examples of non-polymeric systems.[42]

Water-insoluble polymers and waxes, such as ethyl cellulose or carnauba wax, which allow for diffusion-controlled drug release, have been employed as carriers in hot-melt extruded dosage forms. Hydroxypropyl cellulose, polyethylene oxide, and poly (vinyl pyrrolidone) are examples of water-soluble polymers in which the medication is released through a mechanism of diffusion and erosion. Frequently utilised polymeric carriers are Hydroxypropyl cellulose, Hydroxypropyl Methylcellulose Phthalate, Poly (vinyl pyrrolidone), Carbomer, Microcrystalline Wax, Carnauba Wax, Pectin, Epoxy resin containing secondary amine, Xanthan gum, Povidone, Sodium Bicarbonate, Hydrogenated Castor & Soybean Oil [43,44]

8.2 Plasticizers

In general, plasticizers are low molecular weight compounds that work to soften polymers and increase their flexibility. Their mechanism of action involves increasing the space between polymer chains, which lowers a polymer's T_g and melt viscosity. [45]

Numerous plasticizers have been investigated to ensure the seamless processing of HME. they are as follows Vitamin E TPGS (Dα-tocopherol polyethylene glycol 1000 succinate), Phthalate esters (dimethyl, diethyl, dibutyl, dioctyl phthalate), Citrate esters (triethyl, tributyl, acetyl triethyl, acetyl

tributyl citrate), Carbon dioxide, Surfactants (polysorbates, docusate sodium, polyethylene glycol monostearate), Fatty acid esters (butyl stearate, glycerol monostearate) During the HME process, pressured CO2, which is known to function as a foaming agent, has also shown to have a plasticizing impact. [46]

8.3 Other Processing Aids

Based on their mode of action, antioxidants are categorised as either chain-breaking or preventative antioxidants. Antioxidants that work to stop the start of free radical chain reactions are referred to be preventive antioxidants. Because they preferentially undergo oxidation, reducing substances like ascorbic acid can interfere with autoxidation in a preventive way. [47]

The two main classes of chain-breaking antioxidants that prevent free radical chain reactions are phenols and aromatic amines. Commonly used antioxidants that inhibit phenols include butylated hydroxyanisole, vitamin E, and butylated hydroxytoluene. generally used other processing aids are Methyl Paraben, d-α-tocopherol (Vitamin E), Saccharose monopalmitate, Mixture of hydrogenated castor oil and soybean oil. [48]

8.4 API (Active Pharmaceutical Ingredients)

The pharmaceutical scientist's selections for formulation and processing when developing dosage forms are frequently constrained by the characteristics of the active ingredient in the medicine.

The active ingredient in the formulation has the potential to enhance or impair the performance of the other ingredients. It was demonstrated that under HME processing conditions, oxprenolol hydrochloride will melt, reducing the extrudate's viscosity and producing a material with poor handling qualities.[49]

9. CHARACTERIZATION OF EXTRUDATES

9.1 DSC

DSC-PYRIS-1, PerkinElmer, and USA (Shelton, CT, USA) were used in DSC research. In tightly sealed aluminium pans, samples were prepared by sealing 3-5 mg of pure API and milled extrudates. The pans were then heated between 30 and 180 C at a rate of 20 C/min in an inert nitrogen environment, with a flow rate of 20 ml/min. The drug's polymer interactions and thermal performance were determined by the study. The nitrogen atmosphere used for the trials was dry. [50]

9.2 TGA

TGA studies were performed using Pyris 1 TGA, Perkin-Elmer Inc., Wellesley, MA, United States, analysis was performed using thermogravimetry, with a heating rate of 10 °C/min and a nitrogen purge rate of 30 ml/min and TGA was performed using open pans with a sample weight of around 10 mg. [51]

9.3 X-RAY

An X-ray diffractometer (Bruker D8 Advance, WI, USA) was used to analyse the physical states of ARS and milled extrudes using X-ray diffraction at a scan speed of 2/min over a range of 5–60 (2u). [52]

9.4 RESIDENCE TIME ATOMIC FORCE MICROSCOPY (AFM)

Using a razor blade to cut through the extrudate and then breaking it to reveal the cross section, samples for AFM were made. After that, carbon adhesive was used to adhere the samples to a glass slide. The Veeco Dimension 3100 (Santa Barbara, CA, USA) and Nanoscope V controller were used for AFM imaging in tapping mode using Nano sensors SSS-NCHR (Neuchatel, Switzerland) cantilevers. With a 5% offset from the amplitude at resonance, the cantilevers were driven. To achieve good surface tracking, the drive amplitude, amplitude setpoint, and feedback gains were optimised for each sample. 1.2 Hz scan rates were employed, and 512 × 512 resolution pictures were taken for each image.[53]

Some photos were subjected to a first-order flattening method in order to account for sample tilt. The software (Nanoscope 7.30) point and shoot feature was used to collect force versus displacement curves across a user-drawn line on the image in order to perform force spectroscopy. Force measurements were used to calibrate the sensitivity of the photodiode detector on a sanitised glass slide. Veeco RFESP cantilevers were utilised for force spectroscopy, and the thermal tune method in the programme was utilised to estimate the spring constant. A load-unload cycle of 1 Hz was used for force measurements, with a maximum force of 700 nN.[54]

9.5 RAMAN SPECTROSCOPY

A LabRamHR800 (Horiba Jovan Yvon, UK) fitted with a 633-nm Ar-Ne laser was used to record the Raman spectra. A SYNAPSE CCD detector (1024 pixels) was used for obtaining Raman spectra. In order to enable relatively quick mapping for the milled extrudate compact, maps were obtained across 8–10 min 2800–3000 cm^1 sections utilising a fixed grating. Repeatable outputs were achieved by recording the spectra several times. To comprehend the drug distribution pattern inside the polymer matrix and verify its uniformity, Raman mapping or imaging was performed. [55, 56]

10. TYPES OF PROCESSES IN PHARMA INDUSTRY FOR HME

10.1 Solid Dispersion Manufacturing

Hot melt extrusion is commonly utilized to create solid dispersions aimed at increasing the solubility and absorption of drugs with low water solubility. This process involves incorporating the active drug at a molecular scale into a polymer matrix, resulting in an amorphous system. The absence of crystalline structures significantly improves the dissolution rate, which in turn enhances bioavailability. This technique is especially useful for poorly soluble drugs, as it enables uniform distribution of the drug in the carrier and minimizes the risk of recrystallization.[57]

10.2 Granulation

In pharmaceutical manufacturing, hot melt extrusion offers a solvent-free method for producing granules from powder blends. This technique involves melting a binder and blending it with active ingredients and excipients to produce granules that solidify upon cooling. These granules exhibit excellent flowability, uniformity, and compressibility, making them ideal for use in tablet or capsule production. Compared to traditional granulation methods, HME-based granulation reduces processing steps and improves consistency.[58]

10.3 Taste Masking

HME provides an effective solution for masking the unpleasant taste of bitter drugs, particularly in Pediatric formulations or fast-dissolving oral dosage forms. During the extrusion process, the active drug is embedded within a polymer matrix that prevents its immediate interaction with taste buds. This encapsulation ensures the drug remains palatable without affecting its release or therapeutic activity after administration, thus improving patient compliance.[59]

10.4 Controlled and Sustained Release Formulations

Controlled and extended-release dosage forms can be efficiently produced using hot melt extrusion by incorporating the drug into a polymeric matrix designed to regulate its release. By selecting appropriate polymers and adjusting processing parameters, the release rate of the drug can be modulated over an extended period. This approach helps maintain steady drug levels in the body, reduces the frequency of administration, and enhances therapeutic effectiveness.[60]

10.5 Implant and Device Fabrication

HME is also employed in the development of drug-eluting implants and medical devices that provide prolonged drug delivery. The process involves mixing drugs with biodegradable polymers and extruding them into specific shapes such as rods or films. These implantable systems release the drug gradually over days, weeks, or even months and are often used in treatments requiring localized, long-term therapy, such as cancer or hormonal conditions. [61, 62]

10.6 Film Formation (Oral and Transdermal Films)

The technology is also useful in producing thin, flexible drug-loaded films for oral or dermal application. Through hot melt extrusion, active drugs and film-forming agents are blended and extruded into uniform sheets. [63] These films offer quick or controlled drug release, depending on the formulation, and are suitable for patients who have difficulty swallowing pills. This dosage form enhances convenience and compliance while allowing precise dosing.[64]

10.7 Co-extrusion (Multi-Layered Systems)

Co-extrusion is a specialized application of HME where multiple layers are extruded simultaneously, each potentially containing different drugs or polymers. This method is particularly beneficial for creating combination products or achieving complex release patterns, such as immediate and delayed release in one formulation. [65] Multi-layered structures also help protect sensitive ingredients and allow for more sophisticated drug delivery strategies in a single dosage form. [66]

11. APPLICATIONS OF HME FOR DRUG DELIVERY

11.1 Solubility/bioavailability enhancement:

Maddineni et.al., used HME to create a solid dispersion of nifedipine, enhancing its bioavailability despite its low water solubility. This study examined how process and formulation parameters affected the solubility and stability of nifedipine in Kollidon® VA 64 hot melt extrudates. DSC and X-ray diffraction analysis showed that hot melt extrusion of the drug-polymer mixture produced solid dispersions and improved powder flow characteristics, regardless of drug load. The scientists found that

HME technology, along with Kollidon ® VA 64, successfully produced extrudates due to their physical and chemical stability throughout time. [67]

11.2 Co-crystallization by HME

Boksa et.al., introduced MAC as a new method of producing cocrystals. The authors successfully synthesised 1:1 carbamazepine-nicotinamide co-crystals with 20% (w/w) Soluplus® matrix former. The processing temperatures were adjusted to melt the polymer or matrix in which the co-crystals are embedded. Matrix-assisted co-crystals exhibited similar quality attributes to reference co-crystals made using solvent evaporation. The incorporation of Soluplus® in the matrix significantly enhanced the in vitro dissolving profile. [68]

11.3 Taste masking

Pimparade et.al., used HME to conceal the bitter taste of caffeine citrate. They extruded a blend of caffeine citrate, ethylcellulose, triethyl citrate (TEC), and mannitol to increase drug release. [69]

11.4 HME in pharmaceutical multicomponent systems

According to Karimi-Jafari et.al., solvent-free solid-state procedures such as HME and mechanochemical grinding are utilised to generate co-crystals with minimal or no solvent. Methods for solvent-based cocrystallisation include liquid-assisted grinding, high-shear granulation, spray-drying, antisolvent cocrystallisation, supercritical carbon dioxide processing, freeze-drying, microfluidic and jet dispensing, and ultrasound crystallisation.[70]

11.5 Nanotechnology

Khinast et.al., used HME and nano-extrusion to create a one-step process for converting a liquid-stabilised nano-suspension into a solid formulation. This allows for the continuous production of solid nanoformulations.[71]

11.6 Self-emulsifying drug delivery systems (SEDDS) and HME

Silva et al. created carvedilol solid SEDDS with an extruder. They compared it to a standard liquid SEDDS formulation. Solid SEDDS combines Velsan® CCT, Plurol®, and Transcutol HP® with solid carriers. HME processing resulted in extrudates containing an amorphous API. The maximum drug release was achieved with the lowest drug load, the highest temperature, and longest processing time.[72]

11.7 Targeted drug delivery systems

Miller et.al., improved the oral administration of itraconazole by using hot-melt extrusion (HME). They created an amorphous solid dispersion using carbopol and eudragit, resulting in delayed and steady drug release. Animal experiments confirmed lower absorption variability. This shows that HME is a good method for targeted delivery of itraconazole in the intestines.[73]

11.8 Shaped drug delivery systems

Park et.al., employed HME to produce stable antifungal denture films (10% clotrimazole or nystatin) for oral candidiasis. HPC and/or PEO matrices produced films with amorphous APIs, resulting in increased

antifungal activity (up to 5x) and a 38% reduction in fungal adherence, even without medicines. This shows that HME could improve oral candidiasis treatment.[74]

12. INNOVATIONS IN HME:

12.1 Tamper-Resistant Formulations

Maddineni et.al., studied the effects of formulation variables on lidocaine HCl anti-deterrent pellet dosage form using HME. Examples of AD/TR formulations include Embeda®, a morphine sulphate extended-release formulation with naltrexone, and Oxecta®, an immediate-release oxycodone formulation with unpleasant excipients that can cause mucosal irritation when inhaled. [75]

12.2 Three-dimensional printing

HME is a popular process for creating fused filaments, which may be utilised in 3D printers to achieve the necessary shape and geometry for pharmaceutical dosage forms. Pietrzak et.al., created a flexible-dose dispenser for 3D-printed tablets by combining HME and 3D printing. They developed HME-theophylline extrudate filaments from methacrylic and cellulose-based polymers, allowing theophylline tablets to be released immediately and for a longer period of time.[75]

12.3 Co-crystallization

Dhumal et.al., used HME to co-crystallise ibuprofen and nicotinamide, focusing on key factors like screw configuration, speed, and extrusion temperature. High shear mixing, higher temperatures, and lower screw speeds yielded high-quality co-crystals. [76]

Moradiya et.al., effectively obtained co-crystals of carbamazepine and saccharin using HME in a 1:1 ratio and compared the results to a solvent-based prototype. The co-crystals had identical characteristics to the prototypes but enhanced carbamazepine dissolving rates. [77]

12.4 Co-Extrusion

Co-extrusion is a technique for heating two or more drug-loaded formulations through a single die, resulting in multiple-layer extrudates. It is gaining popularity in the field of medicine due to its ability to produce fixed-dose combinations consistently. [78]

13. FUTURE ADVANCEMENTS / OPPORTUNITIES FOR HME IN PHARMACEUTICAL INDUSTRY

Global market growth is primarily driven by manufacturers' recognition of the advantages of pharmaceutical HME over traditional processing procedures. HME manufacturing often involves rapid changes to functional characteristics. Extrudates can be used in a multitude of ways due to their adaptable screw designs and die plates. [79] HME's advantages have helped it scale significantly, resulting in market growth. In 2015, the global commercial market for pharmaceutical HME was valued at approximately $26.6 million. The market is expected to reach US$36.4 million by 2024, growing at a CAGR of 3.90% between 2016 and 2024. [80]

The global market is projected to grow at a CAGR of about 4.7% over the same period. The pharmaceutical HME market is segmented into five regions: Asia Pacific, North America, Europe, Latin

America, and Middle East Africa. North America dominated the market in 2018 and is expected to continue to do so during the projected period. Europe is projected to be the second largest market in terms of profit in the coming years, after only North America. The European HME market is steadily expanding due to the growing need for enhanced clinical facilities and equipment. [81]

The global pharmaceutical HME market is dominated by Coperion GmbH, Baker Perkins Ltd., Gabler GmbH & Co. KG, Milacron Holdings Corp., Thermo Fisher Scientific Inc., Leist Ritz AG, and Xtrutech Ltd. The market is expected to grow with the introduction of novel drug delivery systems through various routes of administration. The market has many commercial HME-derived items, indicating that this method can lead to more effective solutions for various purposes. [82]

CONCLUSION:

Hot Melt Extrusion (HME) has emerged as a transformative technique in pharmaceutical science, offering a solvent-free, continuous manufacturing platform that aligns with modern regulatory and quality-by-design (QbD) principles. Initially developed for polymer processing in the plastics industry, HME has been successfully adapted for drug delivery applications, particularly for enhancing the performance of poorly water-soluble compounds. Through the application of heat and mechanical shear, this technique produces uniform extrudates, facilitating the development of various dosage forms such as amorphous solid dispersions, modified-release systems, taste-masked formulations, and personalized therapeutics. A key advantage of HME is its capability to improve the dissolution and bioavailability of drugs classified under BCS Class II and IV. By converting crystalline APIs into their amorphous counterparts within a polymer matrix, HME enables higher drug solubility and faster dissolution profiles. Its elimination of organic solvents further adds to its appeal by promoting environmental sustainability and minimizing the risk of residual solvent toxicity. Twin-screw extruders are predominantly employed due to their superior mixing, feeding consistency, and scalability, which are crucial for robust process performance. However, the implementation of HME in pharmaceutical manufacturing requires meticulous control over several process parameters, including temperature profiles, screw speed, feed rate, and screw design. These factors critically influence the thermal and mechanical stresses imposed on the formulation, which can affect drug stability, particularly in the case of thermally labile substances. Therefore, careful selection and optimization of excipients such as polymers and plasticizers are essential to maintain product integrity and achieve targeted release characteristics.

Comprehensive characterization is necessary to ensure product performance and stability. Techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR) are widely utilized to evaluate drug-excipient compatibility, crystallinity, and molecular interactions in extruded products. Recent technological advancements, including real-time process analytical technologies (PAT), integration with additive manufacturing (3D printing), and continuous production strategies are expanding the potential applications of HME. These innovations are paving the way for more flexible, efficient, and patient-centric drug manufacturing models. In summary, HME represents a versatile and increasingly indispensable tool in the formulation scientist's arsenal, offering significant promise for advancing drug delivery systems and supporting the evolution of continuous pharmaceutical manufacturing.

DECLARATION OF COMPETING INTEREST

The authors confirm that there are no known competing financial interests or personal relationships that could have influenced the findings presented in this paper.

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REFERENCES

1. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert opinion on drug delivery. 2016 Mar 3;13(3):451-64.

2. Pereira GG, Figueiredo S, Fernandes AI, Pinto JF. Polymer selection for hot-melt extrusion coupled to fused deposition modelling in pharmaceutics. Pharmaceutics. 2020 Aug 22;12(9):795.

3. Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, Bansal KK, Kurmi BD. Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. Life. 2023 Apr 27;13(5):1099.

4. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS Pharm SciTech. 2016 Feb; 17:20-42.

5. Matić J, Paudel A, Bauer H, Garcia RA, Biedrzycka K, Khinast JG. Developing HME-based drug products using emerging science: a fast-track roadmap from concept to clinical batch. AAPS Pharm SciTech. 2020 Jul; 21:1-8.

6. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. Aaps Pharmscitech. 2016 Feb;17:20-42.

7. Kachrimanis K, Nikolakakis I. Polymers as Formulation Excipients for Hot-Melt Extrusion Processing of Pharmaceuticals. Handbook of Polymers for Pharmaceutical Technologies: Processing and Applications. 2015 Aug 10;2:121-49.

8. Cerea M, Maroni A, Palugan L, Moutaharrik S, Melocchi A, Zema L, Foppoli A, Gazzaniga A. Oral hydrophilic matrices having non uniform drug distribution for zero-order release: A literature review. Journal of Controlled Release. 2020 Sep 10;325:72-83.

9. Rogers L, Jensen KF. Continuous manufacturing–the Green Chemistry promise?. Green chemistry. 2019;21(13):3481-98.

10. Hessel V, Tran NN, Asrami MR, Tran QD, Long NV, Escribà-Gelonch M, Tejada JO, Linke S, Sundmacher K. Sustainability of green solvents–review and perspective. Green Chemistry. 2022;24(2):410-37.

11. Srai JS, Badman C, Krumme M, Futran M, Johnston C. Future supply chains enabled by continuous processing—Opportunities and challenges. May 20–21, 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences. 2015 Mar;104(3):840-9.

12. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert opinion on drug delivery. 2016 Mar 3;13(3):451-64.

13. Maniruzzaman M, editor. Practical Guide to Hot-Melt Extrusion. Smithers Rapra; 2015 Jul 22.

14. Patel S, Kaushal AM, Bansal AK. Compression physics in the formulation development of tablets. Critical Reviews™ in therapeutic drug carrier systems. 2006;23(1).

15. Stanković M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug Discovery Today. 2015 Jul 1;20(7):812-23.

16. Gurunath S, Kumar SP, Basavaraj NK, Patil PA. Amorphous solid dispersion method for improving oral bioavailability of poorly water-soluble drugs. journal of pharmacy research. 2013 Apr 1;6(4):476-80.

17. Tan DK, Davis Jr DA, Miller DA, Williams III RO, Nokhodchi A. Innovations in thermal processing: hot-melt extrusion and KinetiSol® dispersing. Aaps Pharmscitech. 2020 Nov 8;21(8):312.

18. Rivera KR, Yokus MA, Erb PD, Pozdin VA, Daniele M. Measuring and regulating oxygen levels in microphysiological systems: Design, material, and sensor considerations. Analyst. 2019;144(10):3190-215.

19. Zhou H, Cheng X, Jiang X, Zheng G, Zhang J, Li Y, Tang M, Lv F. Green manufacturing-oriented polyetheretherketone additive manufacturing and dry milling post-processing process research. Processes. 2022 Dec 1;10(12):2561.

20. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. Aaps Pharmscitech. 2016 Feb;17:20-42.

21. Stanković M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug Discovery Today. 2015 Jul 1;20(7):812-23.

22. Ennis BJ. Agglomeration technology: Equipment selection. Chemical Engineering. 2010 May 1;117(5):50-4.

23. Censi R, Gigliobianco MR, Casadidio C, Di Martino P. Hot melt extrusion: Highlighting physicochemical factors to be investigated while designing and optimizing a hot melt extrusion process. Pharmaceutics. 2018 Jul 11;10(3):89.

24. Capone C, Di Landro L, Inzoli F, Penco M, Sartore L. Thermal and mechanical degradation during polymer extrusion processing. Polymer Engineering & Science. 2007 Nov;47(11):1813-9.

25. Capone C, Di Landro L, Inzoli F, Penco M, Sartore L. Thermal and mechanical degradation during polymer extrusion processing. Polymer Engineering & Science. 2007 Nov;47(11):1813-9.

26. Nair AR, Lakshman YD, Anand VS, Sree KN, Bhat K, Dengale SJ. Overview of extensively employed polymeric carriers in solid dispersion technology. AAPS PharmSciTech. 2020 Nov;21:1-20.

27. Stanković M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug Discovery Today. 2015 Jul 1;20(7):812-23.

28. Tschan MJ, Ieong NS, Todd R, Everson J, Dove AP. Unlocking the Potential of Poly (Ortho Ester) s: A General Catalytic Approach to the Synthesis of Surface-Erodible Materials. Angewandte Chemie. 2017 Dec 22;129(52):16891-5.

29. Einmahl S, Capancioni S, Schwach-Abdellaoui K, Moeller M, Behar-Cohen F, Gurny R. Therapeutic applications of viscous and injectable poly (ortho esters). Advanced drug delivery reviews. 2001 Dec 3;53(1):45-73.

30. Yacu W. Extruder screw, barrel, and die assembly: General design principles and operation. InExtrusion cooking 2020 Jan 1 (pp. 73-117). Woodhead Publishing.

31. Abeykoon C. Single screw extrusion control: A comprehensive review and directions for improvements. Control Engineering Practice. 2016 Jun 1;51:69-80.

32. Leister D, Geilen T, Geissler T. Twin-screw extruders for pharmaceutical hot-melt extrusion: Technology, techniques and practices. Wileey; 2012 Apr 24.

33. Jacob S, Boddu SH, Bhandare R, Ahmad SS, Nair AB. Orodispersible films: current innovations and emerging trends. Pharmaceutics. 2023 Dec 11;15(12):2753.

34. Morott J. *The Influence of Screw Configuration and Other Mechanistic Approaches on the Morphology and Release of Drugs from Polymeric Matrices Utilizing Hot-Melt Extrusion Technology* (Doctoral dissertation, The University of Mississippi).

35. Srai JS, Badman C, Krumme M, Futran M, Johnston C. Future supply chains enabled by continuous processing—Opportunities and challenges. May 20–21, 2014 Continuous Manufacturing Symposium. Journal of pharmaceutical sciences. 2015 Mar;104(3):840-9.

36. Patil H, Vemula SK, Narala S, Lakkala P, Munnangi SR, Narala N, Jara MO, Williams III RO, Terefe H, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation AAPS PharmSciTech. 2024 Feb 14;25(2):37.

37. Dudowicz J, Freed KF, Douglas JF. The glass transition temperature of polymer melts. The Journal of Physical Chemistry B. 2005 Nov 17;109(45):21285-92.

38. Suparno M, Dolan KD, Ng PK, Steffe JF. Average shear rate in a twin-screw extruder as a function of degree of fill, flow behavior index, screw speed and screw configuration. Journal of Food Process Engineering. 2011 Aug;34(4):961-82.

39. Albdiry M. Effect of melt blending processing on mechanical properties of polymer nanocomposites: a review. Polymer Bulletin. 2024 May;81(7):5793-821.

40. Wilson M, Williams MA, Jones DS, Andrews GP. Hot-melt extrusion technology and pharmaceutical application. Therapeutic delivery. 2012 Jun 1;3(6):787-97.

41. Giles Jr HF, Mount III EM, Wagner Jr JR. Extrusion: the definitive processing guide and handbook. William Andrew; 2004 Dec 31.

42. Chaudhary KV. *Development and Analysis of Long-Acting Parenteral Formulation* (Doctoral dissertation, Institute of Pharmacy, Nirma University, A'bad).

43. Lefnaoui S, Yahoum MM. Carnauba wax as a promising excipient in melt granulation targeting the preparation of tablets for sustained release of highly soluble antihyperglycemic drug. Algerian Journal of Pharmaceutical Engineering. 2023 Mar 30:24-9.

44. Costa ML. Polymers for the Production of Conventional Dosage Forms. Materials Research Foundations. 2025;172.

45. Marcilla A, Beltran M. Mechanisms of plasticizers action. Handbook of plasticizers. 2004; 3:119-34.

46. Höfer R, Hinrichs K. Additives for the Manufacture and Processing of Polymers. Polymers-Opportunities and Risks II: Sustainability, Product Design and Processing. 2010:97-145.

47. Gulcin İ. Antioxidants and antioxidant methods: An updated overview. Archives of toxicology. 2020 Mar;94(3):651-715.

48. Hacısevki A. An overview of ascorbic acid biochemistry. Journal of Faculty of Pharmacy of Ankara University. 2009;38(3):233-55.

49. Allen Jr LV. Dosage form design and development. Clinical therapeutics. 2008 Nov 1;30(11):2102-11.

50. Fule R, Paithankar V, Amin P. Hot melt extrusion based solid solution approach: Exploring polymer comparison, physicochemical characterization and in-vivo evaluation. International journal of pharmaceutics. 2016 Feb 29;499(1-2):280-94.

51. Dong Z, Chatterji A, Sandhu H, Choi DS, Chokshi H, Shah N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. International journal of pharmaceutics. 2008 May 1;355(1-2):141-9.

52. Fule R, Paithankar V, Amin P. Hot melt extrusion based solid solution approach: Exploring polymer comparison, physicochemical characterization and in-vivo evaluation. International journal of pharmaceutics. 2016 Feb 29;499(1-2):280-94.

53. Effah B. The use of Atomic Force Microscopy to determine intermolecular adhesive forces in wood based composite materials (Doctoral dissertation).

54. Avilovas L. Micro electro-mechanical system design, fabrication and application for atomic force microscopy probe elasticity characterisation (Doctoral dissertation, University of Glasgow).

55. Fule R, Dhamecha D, Maniruzzaman M, Khale A, Amin P. Development of hot melt co-formulated antimalarial solid dispersion system in fixed dose form (ARLUMELT): Evaluating amorphous state and in vivo performance. International journal of pharmaceutics. 2015 Dec 30;496(1):137-56.

56. Tang Y, Wang X, Zhou G, Guo S, Li Z, Hu Y, Li W. Research progress of Raman spectroscopy and imaging techniques for the pharmaceutical analysis. Journal of Analysis and Testing. 2025 Mar;9(1):136-52.

57. Tran PH, Lee BJ, Tran TT. Recent studies on the processes and formulation impacts in the development of solid dispersions by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2021 Jul 1;164:13-9.

58. Patil H, Vemula SK, Narala S, Lakkala P, Munnangi SR, Narala N, Jara MO, Williams III RO, Terefe H, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation—where are we now?. AAPS PharmSciTech. 2024 Feb 14;25(2):37.

59. Maniruzzaman M, Boateng JS, Chowdhry BZ, Snowden MJ, Douroumis D. A review on the taste masking of bitter APIs: hot-melt extrusion (HME) evaluation. Drug development and industrial pharmacy. 2014 Feb 1;40(2):145-56.

60. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert opinion on drug delivery. 2016 Mar 3;13(3):451-64.

61. Loxley A. Devices and implants prepared using hot melt extrusion. InMelt Extrusion: Materials, Technology and Drug Product Design 2013 Oct 11 (pp. 281-298). New York, NY: Springer New York.

62. Kumar A, Pillai J. Implantable drug delivery systems: An overview. Nanostructures for the engineering of cells, tissues and organs. 2018 Jan 1:473-511.

63. Joshi R, Akram W, Chauhan R, Garud N. Thin films: a promising approach for drug delivery system. InDrug carriers 2022 Mar 27. IntechOpen.

64. Lau ET, Steadman KJ, Cichero JA, Nissen LM. Dosage form modification and oral drug delivery in older people. Advanced drug delivery reviews. 2018 Oct 1;135:75-84.

65. Stanković M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug Discovery Today. 2015 Jul 1;20(7):812-23.

66. Abdul S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. Journal of controlled release. 2004 Jul 7;97(3):393-405.

67. Maddineni S. Characterization of different hydrophilic polymers and their applicability in hot melt extrusion technology.

68. Boksa K, Otte A, Pinal R. Matrix-assisted cocrystallization (MAC) simultaneous production and formulation of pharmaceutical cocrystals by hot-melt extrusion. Journal of pharmaceutical sciences. 2014 Sep 1;103(9):2904-10.

69. Pimparade MB, Morott JT, Park JB, Kulkarni VI, Majumdar S, Murthy SN, Lian Z, Pinto E, Bi V, Durig T, Murthy R. Development of taste masked caffeine citrate formulations utilizing hot melt extrusion technology and in vitro–in vivo evaluations. International journal of pharmaceutics. 2015 Jun 20;487(1-2):167-76.

70. Solares-Briones M, Coyote-Dotor G, Páez-Franco JC, Zermeño-Ortega MR, de la O Contreras CM, Canseco-González D, Avila-Sorrosa A, Morales-Morales D, Germán-Acacio JM. Mechanochemistry: A green approach in the preparation of pharmaceutical cocrystals. Pharmaceutics. 2021 May 25;13(6):790.

71. Rantanen J, Khinast J. The future of pharmaceutical manufacturing sciences. Journal of pharmaceutical sciences. 2015 Nov 1;104(11):3612-38.

72. Silva LA, Cintra ER, Alonso EC, Alves GL, Lima EM, Taveira SF, da Cunha-Filho MS, Marreto RN. Selection of excipients for the development of carvedilol loaded lipid-based drug delivery systems. Journal of thermal analysis and calorimetry. 2017 Dec; 130:1593-604.

73. Chivate A, Garkal A, Hariharan K, Mehta T. Exploring novel carrier for improving bioavailability of Itraconazole: Solid dispersion through hot-melt extrusion. Journal of Drug Delivery Science and Technology. 2021 Jun 1; 63:102541.

74. Park JB, Prodduturi S, Morott J, Kulkarni VI, Jacob MR, Khan SI, Stodghill SP, Repka MA. Development of an antifungal denture adhesive film for oral candidiasis utilizing hot melt extrusion technology. Expert opinion on drug delivery. 2015 Jan 2;12(1):1-3.

75. Shah S, Maddineni S, Lu J, Repka MA. Melt extrusion with poorly soluble drugs. International journal of pharmaceutics. 2013 Aug 30;453(1):233-52.

76. Alwati AA. Ultrasound Assisted Processing of Solid State Pharmaceuticals. The application of ultrasonic energy in novel solid state pharmaceutical applications, including solvent free co-crystallisation (SFCC) and enhanced compressibility (Doctoral dissertation, University of Bradford).

77. Kalantri SS, Yadav MD. Advances in Carbamazepine Cocrystals: A Review. Crystal Research and Technology. 2024 Apr;59(4):2300296.

78. Vynckier AK, Dierickx L, Voorspoels J, Gonnissen Y, Remon JP, Vervaet C. Hot-melt co-extrusion: requirements, challenges and opportunities for pharmaceutical applications. Journal of pharmacy and pharmacology. 2014 Feb;66(2):167-79.

79. Repka MA, Shah S, Lu J, Maddineni S, Morott J, Patwardhan K, Mohammed NN. Melt extrusion: process to product. Expert opinion on drug delivery. 2012 Jan 1;9(1):105-25.

80. Przywara, R. Versions of De-industrialization: A model-based analysis of structural change (1973-2008) (Doctoral dissertation, University of Gloucestershire).

81. Abou Abbas A. Marketing strategies of international pharmaceutical companies in the Middle East and North Africa region (Doctoral dissertation, Walden University).

82. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert opinion on drug delivery. 2016 Mar 3;13(3):451-64.