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Review Article

BEYOND THE HORIZON: RECENT ADVANCES IN HOT MELT EXTRUSION TECHNIQUES AND TECHNOLOGIES

MAGED MOHAMMED ABDO MOHSEN[a], AMIT B. PATIL[a*], MAGED ALKANAD[b], DARSHAN PATIL[a]

[a]Department of Pharmaceutics, JSS College of Pharmacy, Mysuru, Karnataka, India. [b]Department of Pharmacognosy, Sri. Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B. G. Nagara, Mandya, Karnataka, India
*Corresponding author: Amit B. Patil; *Email: amitbpatil@jssuni.edu.in

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ABSTRACT

This review article aims to explore the dynamic landscape of Hot Melt Extrusion (HME) technology, focusing on the spectrum of materials and machinery shaping innovation in the field. Polyethylene Oxide (PEO), Polyvinylpyrrolidones (PVP), Polypropylene (PP), Polyvinyl Acetate (PVA), and Polycaprolactone (PCL) play pivotal roles in HME and contribute to advancements in pharmaceutical manufacturing. This review sheds light on their unique contributions to HME tapestry. This review meticulously explored the machinery that orchestrates HME, including single- and double-screw extruders, as well as Extrusion Spheronization (ES). The search criteria were based on a comprehensive analysis of previous studies since the discovery of the HME, including new patented discoveries. We utilized various scholarly resources such as Google Scholar, Google Books, PubMed, Elsevier, Nature, Springer, ScienceDirect, and other indexed search engines. Case studies highlighted the real-world impact of HME in Continuous Manufacturing (CM) scenarios, emphasizing its importance in pharmaceutical production. The review also discusses the specifics of extrusion and co-extrusion, explaining how compound droplets are formed and collected, which is very important for making capsules-extrusion has emerged as a protagonist in the pharmaceutical industry, with 3D printing driving innovation beyond conventional boundaries. The amalgamation of HME and 3D printing offers new possibilities for drug delivery. This review sheds light on the diverse polymers involved in hot melt and emphasizes their importance in pharmaceutical manufacturing. This study provides valuable insights into the applications, methodologies, and future advancements of HME.

Keywords: Hot melt extrusion, Polyethylene oxide, Polyvinylpyrrolidones, Single-screw extruder, Double-screw extruder, Spheronization, Continuous manufacturing, Co-extrusion, 3D printing in hot melt extrusion, Smart polymer

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INTRODUCTION

HME is a promising technology. Its primary focus is the formulation of pharmaceutical products. Over 50% of therapeutic molecules are classified as BCS II owing to their low water solubility, leading to formulations with reduced bioavailability. This highlights the need of the pharmaceutical industry to improve its solubility and bioavailability. HME has recently emerged as a precise technology for the development of molecular dispersions of Active Pharmaceutical Ingredients (API) in polymer or lipid matrices. This enables the creation of time-controlled, modified, extended, and targeted drug delivery systems [1-3].

The inception of HME processing dates back to the beginning of the 1930s. With swift integration as the prevailing processing technology in the domain of plastics, this technology is rapidly gaining widespread acceptance in the rubber and food industries. While initially gaining prominence in these sectors, the application of the HME extended to the pharmaceutical industry in the early 1970s. Its application in formulation, product evolution, and production has emerged as a crucial factor in establishing HME as a versatile and impactful method in the pharmaceutical arena [4].

HME represents a continuous pharmaceutical processing method wherein polymeric materials are propelled through a circular motion of screws at high temperatures, at which they undergo a transition in their glassy state (glass transition temperature Tg) and occasionally exceed the temperature at which they undergo melting (melting temperature Tm). This process is designed to achieve thorough blending of the active compound at the molecular level with binders with thermoplastic properties, polymer-based binders, or a combination of both. This complex approach has proven instrumental in achieving homogeneous blends essential for pharmaceutical applications [5, 6].

Our search criteria were based on previous studies since HME's discovery and recent patented discoveries. We used keywords such as Twin-Screw Extrusion (TSE), twin screw granulation, hot-melt extrusion, twin screw extrusion pharmaceutical applications, hot-melt extrusion with scale-up, HME-coupled fused deposition modelling 3D printing, HME with CM, and HME with Process Analytical Technology (PAT) tools. Additionally, we reviewed the relevant literature and Google patents to identify formulations manufactured using hot-melt extrusion that were already on the market.

In summary, HME represents a promising avenue for improving drug solubility, bioavailability, and CM, making it a crucial technology in the pharmaceutical arena. This review aims to delve deeper into the potential of TSE for various new applications, building upon existing knowledge and innovations.

Hot-melt extrusion

The HME apparatus consists of an extrusion machine, processing stages, and crucial monitoring instruments for evaluating product effectiveness and quality. The extruder, which is a central component, includes a feeding container, barrels, single or double twin screws, and a driving unit. The additional apparatus includes heating or cooling mechanisms for the barrels, a conveyor system for product cooling, and a solvent delivery pump. Integrated monitoring tools, such as temperature sensors, screw speed controllers, extrusion torque monitors, and pressure indicators, are part of the setup. This comprehensive arrangement significantly aids in facilitating and optimizing the HME process for various pharmaceutical applications [7].

As shown in fig. 1. Thermal stability is a crucial requirement for materials used in HME. While the time in the extruder is relatively short, ranging from 0.5 to 5.0 min, it is important to note that not every situation warrants the exclusion of thermolabile compounds from HME. Moreover, the suitability of these materials is also contingent. Based on the preferred attributes of the end product, materials must either mix at the molecular level or remain phase-separated. This consideration forms a key aspect of the foundation for exploring the applications and effectiveness of HME in diverse contexts within the pharmaceutical industry [9].

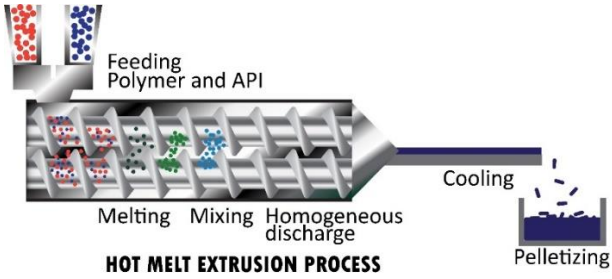

Fig. 1: Schematic representation of hot melt extrusion process, reproduced with permission from [8]

The formulation of a drug delivery system through HME incorporates an API into a carrier matrix, which may include one or more compounds or functional excipients capable of melting or fusing at specific temperatures and pressures. These carriers, integral to the HME process, can belong to either the polymer or lipid category. The polymeric materials employed may fall into the categories of either biodegradable or non-biodegradable, providing a diverse range of options for tailoring drug delivery systems based on specific application requirements. This introductory insight sets the stage for an in-depth exploration of the role and versatility of HME in crafting effective drug delivery formulations [10].

An extruder is composed of two main components: a transport system for conveying materials and achieving distributive mixing and a shaping system through the die. Extrusion is categorized into molten systems with temperature-controlled materials for viscosity control, facilitating their passage through the die; semi-solid systems encompass multiphase dispersions characterized by a significant ratio of solids to liquids [11].

Types of material suitable for hot-melt extrusion

Various industries, particularly the pharmaceutical sector, use HME as a versatile technology for the formulation and delivery of various drugs. The choice of polymers in HME is crucial for achieving the desired properties in the final product. The selection of a polymer depends on the specific requirements of the formulation, such as drug compatibility, release profile, mechanical properties, and stability. In this section, we discuss the selection of polymers with respect to major concerns.

PEO is a thermoplastic homopolymer that can be used in many ways. It is prepared by polymerizing ethylene oxide monomers in a heterogeneous catalytic manner. It is available in a wide range of molecular weights, from 100,000 to 8,000,000, which influence its physical properties and applications. PEO is highly miscible with water in any proportion owing to the hydration of its ether oxygen groups, making it useful in various aqueous applications. This semi-crystalline polymer exhibits a melting temperature range of 57–73 °C, where its crystalline regions transition to a molten state. PEO is thermally unstable when exposed to oxygen, which leads to its degradation. Under ambient conditions, PEO can degrade in both bulk and liquid forms, with degradation accelerating at higher temperatures. When stored above the melting point, particularly at approximately 80 °C, the degradation rate increased significantly.

Owing to the enhanced oxidative reactions. However, only the amorphous regions of PEO, which lack the structural stability of crystalline parts, are susceptible to oxidative degradation when stored at temperatures below 55–80 °C. This highlights the importance of appropriate storage conditions to maintain the integrity of the polymer and minimize degradation. Understanding these properties is crucial for effective utilization of PEO in various industrial and scientific applications [12].

Thermal oxidation of PEO is highly dependent on its molecular weight. When the molecular weight is lower, thermal degradation increases. Because PEO has a high viscosity and a molecular weight of more than 300,000 Da, it can only be extruded successfully with two different grades. In particular, approximately 10% of the lower molecular weight PEO N-80 was required to lower the viscosity so that PEO N-750 films (MW 300,000 Da) could be extruded evenly [13].

PEO degradation increases with lower screw speeds and higher processing temperatures. This indicates that thermal degradation, as opposed to mechanical degradation, is the predominant mechanism. The processing temperature and duration within the extruder significantly affect the degree of PEO degradation. With an increase in screw speed, polymer degradation decreased until reaching the point where the melt fracture commenced. Researchers have documented the pseudoplastic nature of PEO melt behavior [14].

Povidones, which are polyvinylpyrrolidones, are water-soluble polymers formed when N-vinylpyrrolidone undergoes a radical polymerization process. They are extensively used in the pharmaceutical sector as binders [15]. The Tg value of PVP is suitable for HME production for drug loading and enhances molecular dispersion stabilization by directly interacting with certain drugs. API recrystallization is impeded by PVP, which forms a network around the drug molecules or crystal surfaces, limiting API mobility. However, concerns regarding thermal degradation and hygroscopicity restrict their use. These problems can be solved by carefully studying the drug-polymer interactions during manufacturing at moderate temperatures, along with the composition and processing parameters [16]. This maintains the usefulness of the PVP. Discovered in 1954, PVP has gained widespread popularity because it is the least dense among common plastics [17]. PVP undergoes a melting process within a temperature range of 130–171 °C and determining its melting point requires identifying the highest temperature on a differential scanning calorimetry chart. The crystallinity of most commercially available PVP typically falls within an intermediate range of 40–60% [18]. Perfectly isotactic PVP exhibits a melting point of 171 °C (340 °F). The melting point of commercial isotactic PVP varies between 160 and 166 °C (320 and 331°F), depending on the presence of the atactic material and the level of crystallinity [19].

PVAc is a monomer polymerized with vinyl acetate using a free-radical polymerization technique. The side chain of the acetate ester in the backbone structure contributes to its amorphous nature. The relatively low glass transition temperature of PVAc is attributed to the highly flexible structural framework of the backbone. Despite being water-insoluble, it exhibits slight hydrophilicity and can absorb water to a limited extent. This polymer has been applied in the formulation of matrix pellets, coatings for sustained release, and systems for drug delivery to the buccal cavity [20–22]. Polyvinyl Acetate Phthalate (PVAP) is a polymer that exhibits pH-dependent solubility characteristics, and its suitability for HME is not thoroughly understood. Currently, only one study has investigated the use of PVAP in HME [23].

Mehyus *et al.* (2005) a gastro-retentive system, was formulated using PVAP, which required a substantial amount of plasticizer (40% w/w) to achieve an extrudable blend. However, this leads to compromised storage stability owing to high plasticizer content [24].

PCL is a synthetic polyester that is biodegradable and derived from crude oil. It is characterized as a hydrophobic, semi-crystalline polymer with a glass transition temperature (Tg) of 60 °C and a melting point in the range of 59–64 °C. The crystalline nature of PCL allows simple shaping at relatively low temperatures. PCL samples typically have an average molecular weight ranging from 3000 to 90,000 g/mol [25]. As the molecular weight rises, the crystallinity of

PCL tends to diminish. The favorable solubility, low melting point, and remarkable compatibility of the blends have spurred widespread exploration of their potential in the biomedical sector. PCL has diverse applications, including in medical implants and controlled drug delivery systems, highlighting the crucial significance of its crystallization and morphological properties [26].

Table 1: Comparative table of materials suitable for HME, along with some characteristic features

Material	Characteristic features	References
Polyethylene	High melt strength, good chemical resistance, excellent electrical insulating properties.	[27]
Polypropylene	High impact strength, good chemical resistance, relatively low cost, suitable for food packaging applications.	[28]
Polyethylene Oxide (PEO)	High solubility, biocompatible, suitable for controlled drug release, used in pharmaceutical formulations.	[29, 30]
Polyvinylpyrrolidone (PVP)	Excellent solubility, good film-forming properties, used as a binder in pharmaceuticals and inks.	[31]
Polypropylene	High melt strength, good chemical resistance, relatively low cost, widely used in packaging and automotive parts.	[32, 33]
Polyvinyl acetate (PVAc)	Excellent adhesion good film-forming properties, used in adhesives, coatings, and wood glue.	[34, 35]
Polycaprolactone	Biodegradable, low melting point, good mechanical properties, used in drug delivery systems and 3D printing.	[36, 37]

Overview of equipment used in HME technology

HME machines are pivotal in pharmaceutical and polymer processing and provide a versatile method for formulating various products. They utilize controlled heat and pressure to melt and mix materials, such as polymers, APIs, and excipients. Particularly valuable for drug delivery system development, HME enables the creation of solid dispersions and sustained-release formulations. Equipped with precision controls, the extruder ensures continuous and homogeneous mixing, thereby enhancing bioavailability and drug performance. The adaptability of HME machines makes them indispensable in pharmaceutical manufacturing and offers a scalable and cost-effective solution for producing innovative drug formulations.

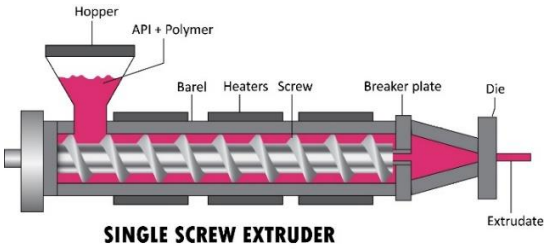

Fig. 2: Schematic representation of single screw extruder reproduced with permission from [8]

Fig. 2 shows a visual representation of a single-screw extruder. Single-screw extruders were first used for thermoplastic material extrusion in the early 1930s [38]. Single-screw extrusion is commonly described as a method of blending, homogenizing, and shaping materials by compelling them using a meticulously designed die. This type of extruder integrates a high-temperature and short-time cooking process with various other unit operations, including conveying, kneading, heating, mixing, and forming, within a singular unit [39].

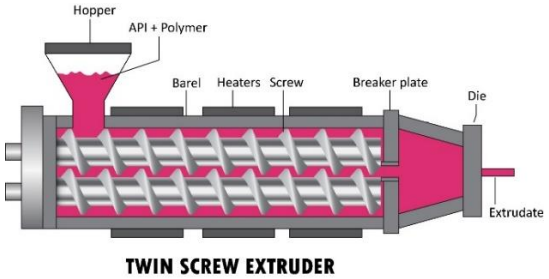

Fig. 3: Schematic representation of twin screw extruder reproduced with permission from [8]

A diagrammatic representation of the twin-screw extruder is shown in fig. 3. TSE play a crucial role in extrusion, with increasing commercial significance owing to specialized processes such as alloying, compounding, and de volatilization. Unlike single-screw extruders, which rely on frictional and viscous forces, TSE exhibit positive conveying characteristics. This distinction in conveying mechanisms contributes to the versatility and efficiency of the TSE processes [40]. The twin-screw extruder establishes precise temperature and pressure conditions in the barrel that are crucial for processing the material in a defined manner. Controlling the heat flow ensures the prescribed temperature in every barrel or zone, whereas the screw design and rotation speed adjustments modulate the pressure [41]. In a twin-screw extruder, the screws can rotate either in co-rotation, where they move in the same direction, or in counter-rotation, where they move in opposite directions. Counter-rotating extruders exert substantial pressure, compressing the material between the gaps formed by the two screws [42]. Counter-rotating TSE generally operate at a reduced speed compared to co-rotating TSE because of the necessity of creating high pressure with screws turning in opposing directions. Counter-rotating TSE have drawbacks such as air entrapment, product deterioration due to elevated pressure, and reduced material output owing to the lower

screw speed [43]. Co-rotating extruders are commonly used in the pharmaceutical industry to avoid potential material degradation and the intense pressure generated by their counter-rotating counterparts. In pharmaceutical applications, co-rotating TSE typically have an intermeshing design with automatic cleansing features. Unlike counter-rotating extruders, where screws rotate in opposite directions, co-rotating extruders with screws rotating in the same direction produce a lower pressure. To compensate for this, co-rotating screws often operate at higher speeds, thereby increasing the material output. Additionally, co-rotating extruders reduce wear and tear on screws and barrels by eliminating the pushing action that occurs when the screws rotate in opposite directions. Co-rotating TSE allow versatile arrangements of various screw elements, enabling the creation of unique screw designs for specific applications [44].

Reynolds first documented the E) technique in 1970, and Hadley and Conine independently performed the same technique in the same year. The pharmaceutical industry widely favors the ES method for pelletization because of its straightforward and rapid processing. This approach generates uniformly sized pellets with enhanced drug-loading capacity. The ES method meets the criteria for creating controlled and sustained-release dosage forms, offering the option to prepare sustained pellets without the need for coating [45]. The initial stage in an extrusion-spheronization cycle involves creating a plastic mass. The initial three processors also serve to blend the powder components, whereas diverse granulators combine the powder mixture and the liquid used in granulation. The planetary mixer is the most frequently used granulator [46, 47]. In the granulation phase, minimizing the evaporation of the fluid phase is crucial, particularly with high-shear mixers that impart a significant amount of energy that is partially converted into heat. An increase in temperature could lead to vaporization of the granulation liquid, thereby influencing the extrusion properties of the wet mass. To alleviate this concern, cooling the granulation bowl can be employed [48]. The next step involves shaping the wet mass into elongated rods via extrusion, a method widely utilized in various industries. Four main types of extruders are used: screw, sieve, basket, roll, and ram extruders. The screw extruder utilizes either one or two Archimedes screws to transport the plastic mass towards an axial or radial extrusion screen. In the axial configuration, the screen is at the end of the screw, whereas in the radial configuration, the die surrounds the screw [49].

Recent trends and innovation in HME techniques

Amidst globalization, the pharmaceutical industry faces regulatory hurdles due to shortened patent lives and decreased drug profitability. This drives a transition towards CM processes, notably via HME, to expedite drug development. HME is a solvent-free and scalable green technology that provides efficient benefits. CM guarantees improved product quality, reduced labor costs, and faster development timelines than batch processes. This review delves into the evolving applications of CM and HME, addressing manufacturing challenges in the pharmaceutical sector.

Continuous manufacturing

HME is a reliable and effective technology that is particularly suitable for mass production (fig. 4). It allows for CM with less waste and higher output. HME can create solid molecular mixtures, offering several benefits compared to methods such as spray drying and co-precipitation, which rely on solvents. In recent years, researchers have widely embraced and studied HME to create drug delivery systems with sustained, modified, and targeted effects [50].

Mechanochemical blend chemistry and mechanical engineering at a small molecular level. The HME has garnered interest for its role in mechanochemistry because it is a solvent-free method for CM. It has applications in co-crystal creation and reactive extrusion processes [51, 52].

CM involves producing goods and handling materials without interruptions and maintaining a steady flow of material input and output. Unlike batch manufacturing, materials used in continuous processes are consistently in motion, undergo chemical changes, or experience mechanical and heat treatments. Large-scale continuous processing typically operates 24/7, with regular planned maintenance shutdowns occurring on a weekly, monthly, semi-annual, or annual basis [53].

Researchers have extensively studied the use of HME-based fused deposition modeling for 3D printing in batch processes. Nonetheless, there is the potential to integrate HME technology with fused deposition modeling 3D printing for CM [54]. Conventional batch manufacturing processes suffer from various limitations, such as inadequate controllability, low yield, and challenging scalability, making them labor-intensive. Consequently, there is a concerted focus on advancing and refining continuous processes [54]. However, applying CM, automation, and control in the pharmaceutical sector remains challenging. Addressing these challenges is crucial before the successful design and implementation CM processes [55, 56].

Alice Melocchi *et al.* explored the potential of manufacturing Immediate-Release (IR) tablets using HME and Injection Molding (IM) techniques, addressing the needs of CM in the pharmaceutical sector. This study extensively evaluated polymers suitable for pharmaceutical applications, assessing their suitability as tablet-forming agents based on processability in both methods and the disintegration and dissolution traits of the resulting products. Focusing on the challenging tracer molecule furosemide, this study identifies several tablet-forming agents that consistently produce IR tablets from simple formulations. Specifically, sodium starch glycolate was found in ExplotabR CLV, and VivastarR, have surprising thermoplastic processing abilities and natural disintegration tendencies. Additionally, this study established formulation approaches using soluble, disintegrant, and effervescent additives to enhance tablet disintegration and drug dissolution. The resulting ExplotabR CLV-based units, prepared through HME and IM, meet the USP dissolution requirements for furosemide, highlighting the favorable potential of these methods in the CM of immediate-release tablets [57].

Siva Ram Munnangi *et al.,* systematically assessed five Cyclodextrins (CDs) for their ability to form inclusion complexes with Ibuprofen (IBU) using computational and experimental methods. HP β-CD successfully formed a 1:1 equimolar complex with IBU aided by HME for continuous complex formation with a polymer additive. Using Quality by Design (QbD) ideas, this study examined how barrel screw speed, temperature, and polymer concentration affect variables that are dependent on each other, such as IBU dissolution and solubility. Compared with physical mixtures, the extrusion process significantly increased the solubility of IBU saturation, with enhanced dissolution under acidic conditions. Analytical methods confirmed that IBU in the complex was in an amorphous state. This shows that the polymer matrix, rheology, and formulation variables affected the formation of the complex during extrusion when heat was applied. This case study not only advanced our understanding of thermally induced complex formation but also demonstrated its potential in addressing solubility challenges in poorly soluble drugs, thereby enhancing bioavailability and therapeutic efficacy [58].

Co-extrusion

Conventional extrusion is typically used for encapsulation and pales in comparison with coextrusion. Conventional extrusion involves applying pressure and high temperatures to push a solution or molten emulsion through a die, followed by cooling to produce a rod or fiber, which is then finely pulverized into powder. In contrast, coextrusion utilizes liquids at room temperature and is extruded through a concentric nozzle without the need for high pressure [59].

The co-extrusion process involves combining diverse polymers with different properties in a single apparatus to produce a multilayer product with specific characteristics. The goal is to merge the desirable features of individual polymers while ensuring strong adhesion between the layers. This method allows for the incorporation of recycled polymer between layers of virgin polymer, thereby reducing the production costs. Coextrusion has seen significant growth, especially in packaging applications in the food industry. Initially limited to configurations with two or three layers, modern coextrusion processes can now create complex structures with up to ten layers comprising five or six different polymers [60].

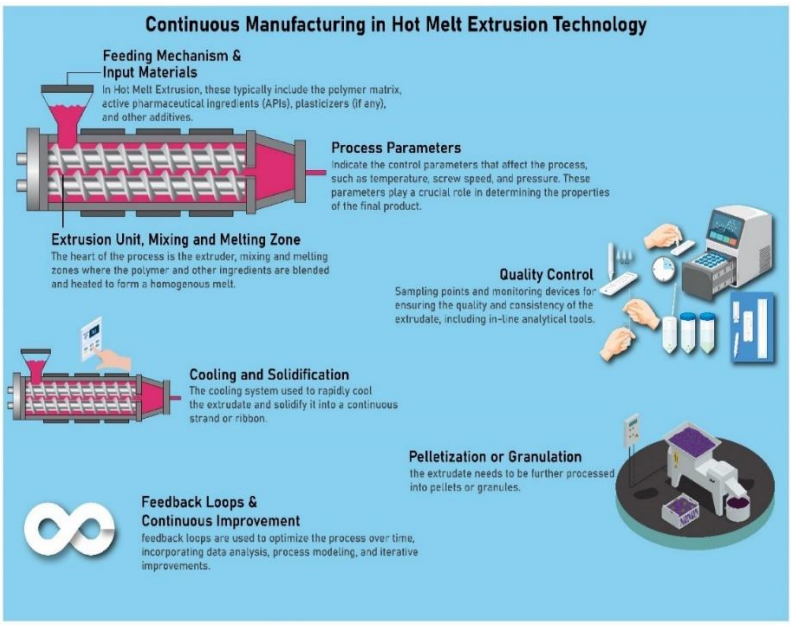

Fig. 4: Continuous manufacturing in hot melt extrusion techniques

Principles of Co-extrusion

Three fundamental steps must be considered when developing and utilizing a co-extrusion process 1) Creation of droplets from the compound, 2) formation of the outer shell, and 3) collection of capsules.

Creation of droplets from the compound

The effective creation of composite droplets depends on the accurate coordination of multiple factors. Flow rate, nozzle dimensions, nozzle length, and material characteristics are all variables that can be adjusted. The material attributes, such as viscosity, density, interfacial tension, solubility, and thermal characteristics, also play a role in this procedure. Additionally, we can employ external forces such as inertial, vibrational, centrifugal, and electrohydrodynamic forces to influence droplet formulation.

Two mechanisms regulate the formation of droplets at the nozzle tip during liquid flow. At a lower flow rate, we observe a mode characterized by drop-by-drop formation, where the liquid's surface tension adheres the droplet to the nozzle tip until its mass reaches a threshold where gravity surpasses surface tension, causing the drop to detach [61].

Nozzle dimensions impact jet formation, microcapsule size, and distribution. Larger nozzles accommodate higher flow rates, yielding larger droplets (about 1.8 times the nozzle diameter). For example, a 500 µm nozzle can generate a 900 µm droplet. Maintaining proper inner and outer nozzle size matching ensures sufficient annular space for shell material flow. Nozzle length, specifically a higher length-to-diameter (L×D) ratio, influences particle size distribution and jet breakup. A bigger L×D ratio causes more turbulence, which makes jet breakup less even and droplet size distribution wider, which could make coaxial axisymmetric breakup harder [62].

Formation of the outer shell

After composite droplet formation, the external liquid must solidify to create a shell before collection. Solidification methods include congealing, gelation, or precipitation. Congealing involves solidifying melted materials like fats or wax, while gelation occurs when cooling an aqueous solution below its gel point. For droplet formation to occur, the processing temperature must maintain viscosity. Various cooling techniques are used to initiate shell solidification after droplet creation. Spray drying produces precipitated shell materials by dissolving the shell material, which then precipitates onto the inner droplet core after solvent evaporation. Preserving core-shell morphology is vital for achieving thermodynamic stability, and surfactants can control interfacial tension to prevent core-shell structure loss before shell solidification [63].

Collection of the capsules

Various techniques for capsule collection in coextrusion include cyclones, refrigeration, liquid hardening baths, misting chambers, powdered beds, and flash volatilization chambers. These methods, often used with spray drying and spray chilling systems, disperse feed solutions into the air to form compound droplets. To prevent agglomeration or deformation, it's vital to pre-harden the shell before contacting a collection surface in misting chambers, refrigeration chambers, cyclones, and flash volatilization chambers. Cyclones use centrifugal force to collect the smallest capsules, while flash volatilization chambers, often paired with cyclones, use gentle heat to speed up solvent evaporation in a shell. Refrigeration chambers, situated around and below the coextrusion nozzle, employ cool air for droplet hardening, sometimes with misting chambers for extra cooling. During formation, misting chambers release a fine mist of cool liquid onto compound droplets, aiding rapid cooling and hardening by absorbing heat from the shell material [64].

Application of coextrusion in the pharmaceutical field

Medical professionals have long used extrusion to create tubing for minimally invasive diagnostic and therapeutic procedures, including balloon catheters and single-or multi-lumen tubes. Recent technological advancements now extend to co-extrusion, allowing the creation of tubing with multiple layers comprising different materials or featuring colored stripes of identical material. Co-extruded tubing is particularly valuable in medical interventions like angioplasty, stent placement, catheter guidance, and dialysis [65]. Scientists are looking into how nanolayer coextruded fibers and mats could be used in different ways because they are strong mechanically and have a lot of open spaces on their surface. Adjusting polymer and process parameters allows for desired fiber characteristics while reducing the need for organic solvents promotes environmental sustainability. Researchers widely use conventional spinning methods such as electrospinning and melt spinning [66–70]. In biomedical technologies, the increased specific surface area of polymer fibers, compared to solid substrates, has recently gained considerable attention. Conventional spinning techniques, including electrospinning, co-electrospinning, melt electrospinning, rotary jet spinning, melt blowing, and solution blow spinning, have been extensively applied for crafting polymer fibers utilized in various applications such as drug delivery, tissue engineering, scaffolds for cell growth, and wound-healing patches [71–77].

3D printing with HME technology

3D printing, also referred to as additive manufacturing, involves the incremental fabrication of 3D objects based on digital designs. The equipment and materials for this process were initially created in the early 1980s, primarily for research in fields such as chemistry, optics, and robotics [78, 79]. Sachs *et al.* presented the first instance of free-form powder-based fabrication using 3D printing methods at the Massachusetts Institute of Technology (MIT) in 1993. This approach utilized a standard inkjet head to administer binders to unbound powders within a powder bed [80]. In contrast to conventional methods for producing dosage forms, 3D printing enables the fabrication of intricate, personalized, and immediately consumable products [81]. The traditional pharmaceutical manufacturing process involves a complex downstream sequence, including milling extrudates, sifting, compacting, and applying coatings. However, integrating 3D printing with HME can streamline these procedures. This combined continuous process is better than the old way of doing things because it improves drug solubility and bioavailability, makes it possible to make complex personalized drug products and dosage forms and makes the downstream process more efficient and cost-effective. Additionally, the FDA advocates for manufacturers to create orally administered solid dosage forms meeting growing requirements for bioavailability and controlled release through a regulated and CM process [82]. Drawing on the benefits of integrating both technologies, the fundamental steps in the continuous HME-3D printing process for the production of dosage forms are: 1) Creating the appropriate dosage form and converting it into a format that the printer can read; 2) preparing raw materials, including particulates, powders, pastes, or granules; 3) creating hot-melt extruded filaments; 4) cooling the filaments; 5) 3D printing; and 6) removing the printed material, followed by downstream processes like cooling, drying, and packing. In continuous pharmaceutical product manufacturing with HME and 3D printing, the crucial elementary steps include extruding 3D-printable filaments, dissolving poorly water-soluble APIs in molten polymeric excipients, and blending them to enhance API bioavailability [83].

Leveraging 3D printing techniques could potentially enable the development of medicine with higher precision, striving to customize therapeutic approaches to align with the distinctive lifestyle and physiological requirements of individual patients [84]. 3D printing offers advantages over traditional tablet manufacturing methods, such as customization, enhanced product complexity, and the ability for on-demand production [79]. This technology facilitates the customization of medication doses based on factors such as the patient's body's genetic variations, metabolism, mass index, and other concurrent health illnesses. Additionally, it will begin creating medicinal products with personalized designs and release profiles. The technology permits the consolidation of medications prescribed for the patient's daily regimen into a singular polypill or multi-drug dose, possibly improving compliance with the treatment, particularly for geriatric and pediatric patients. Moreover, in manufacturing applications, 3-D printing can be employed to manufacture implants such as bone grafts, tracheal splints, and implants containing multiple drugs for chemotherapy [85,86]. It provides a straightforward and consistent drug formulation that can readily attain a specific release profile. The ability to print in various shapes is appealing to the pediatric demographic, addressing challenges in treatment adherence. Another significant benefit of 3D printing lies in its capability for on-demand manufacturing, particularly in situations with limited time and resources, such as military operations, emergency rooms, and disaster areas. This technology allows the successful printing of drug products tailored to specific needs [87].

Various polymers are used in the HME technique

HME technology uses the biodegradable polymers listed in table 2 because they can decompose over time into simpler, environmentally friendly substances. The use of biodegradable polymers in HME is particularly relevant in applications where sustainability and reduced environmental impact are priorities.

Table 2: Biodegradable polymers used in the HME process

Polymer	Melting point (C)	Glass transition temperature (C)	Solubility	Reference
Polylactic acid (PLA)	155 °C	~60 °C	Insoluble in water and soluble in organic solvent.	[88, 89]
Polyhydroxyalkanoates (PHA)	40-180 °C	The glass transition temperature (Tg) of polyhydroxyalkanoates (PHAs) can vary depending on the specific type of PHA, its molecular weight, and the presence of different monomeric units.	Insoluble in Water, Soluble in Chlorinated Solvents	[90, 91]
Polycaprolactone	60 °C	-60 to-50 °C	Soluble in organic solvents	[92, 93]
Poly (lactic-co-glycolic acid)	Lacks a distinct melting point. Instead, it undergoes a gradual softening	40-60 °C	PLGA is soluble organic solvents (Dichloromethane, Chloroform, Tetrahydrofuran, Acetone)	[94, 95]

Smart polymers, also known as stimuli-responsive or environmentally responsive polymers, undergo reversible changes in response to external stimuli like temperature, pH, light, or specific ions. Designed to exhibit specific responses under certain conditions, they find applications in drug delivery, sensors, and controlled release systems. In HME, a processing technique for thermoplastic polymers, smart polymers can be incorporated to achieve specific functionalities, chosen based on the desired response and application. Table no. 3 shows various polymers used as smart polymers.

Polymer composites for HME mentioned in table 4 involve combining polymers with other materials to enhance or modify the properties of the resulting extruded product. HME is a processing technique where a material is melted and then extruded through a die to create a continuous profile.

Table 3: Smart polymers used in the HME process

Polymer	Melting point (C)	Glass transition temperature (C)	Solubility	Reference
Poly(N-isopropyl acrylamide)	~97 °C	32 °C	Below LCST (Lower Critical Solution Temperature) Soluble in water, Above LCST Insoluble in Water	[96, 97]
Poly (diethylamino ethyl methacrylate) PDEA	~100 °C	35-40 °C	Soluble in water at lower pH values	[98, 99]
Poly (N-vinyl caprolactam) PNVCL	~175 °C	32 °C	Below LCST (Soluble), Above LCST (Insoluble)	[100, 101]

Table 4: Polymer composites used in the HME process

Polymer	Melting point (°C)	Glass transition temperature (°C)	Solubility	Reference
Polylactic acid PLA/Hydroxyapatite	PLA: 150-160 °C, HAp: 1100 °C	57-63 °C	PLA/hydroxyapatite composites are expected to have limited solubility in common solvents due to the presence of the ceramic hydroxyapatite component	[102, 103]
PEO, and graphene oxide (GO)	PEO with a molecular weight of around 200 g/mol 30-40 °C, 20,000 g/mol and above have a melting range above 70 °C	Graphene oxide to PEO can influence the thermal and mechanical properties of the composite. It may affect the crystallinity of PEO and alter the overall behavior of the material. glass transition temperature of a composite formed by combining PEO with graphene oxide depends on the interactions between PEO and GO, as well as the ratio of the two components	interaction between PEO and GO, such as hydrogen bonding or van der Waals forces, can affect the overall solubility of the composite, well-dispersed GO in PEO is expected to maintain solubility in water	[104, 105]

CONCLUSION

This review article has provided a comprehensive overview of the diverse landscape of HME technology. Through an exploration of various types of extruders and an in-depth discussion of polymers suitable for HME, we have highlighted the versatility and flexibility of this processing technique. The incorporation of recent advancements in HME technology, including innovative screw designs, process monitoring systems, and real-time control strategies, underscores the continuous evolution of this field. Furthermore, our exploration of diverse applications, ranging from pharmaceuticals and food to materials science, emphasizes the broad impact and potential of HME in various industries. As HME continues to gain prominence, the integration of cutting-edge technologies and a deeper understanding of polymer behavior will undoubtedly contribute to further advancements and novel applications, positioning HME as a pivotal technique for the future of manufacturing and material development.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

AUTHORS CONTRIBUTIONS

Maged Mohammed Abdo Mohsen: Conceptualization, methodology, data curation, writing-original draft preparation. Amit B Patil: validation and formal analysis, investigation, resources, Maged alkanad: methodology, software, data curation, writing-review and editing, Darshan Patil: software, investigation, writing-review and editing.

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