JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

Advancements and Challenges in Hot Melt Extrusion (HME) for Pharmaceutical Applications

Saranya P*[1], Snehamayee Mahapatra[1], Rakshana V[2], Srinivasan R[3]

[1] *Student, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, India*
[2] *Assistant Professor, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, India*
[3] *Dean and Professor, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, India*

Publication history: Received on 12th March; Revised on 20th March; Accepted on 22nd March

Article DOI: 10.5281/zenodo.10950451

Abstract: Hot melt extrusion (HME) is a continuous pharmaceutical process utilizing controlled conditions to melt materials and extrude them through an aperture. Thermoplastic binders and polymers, pumped at or above their glass transition temperature (Tg) or melting temperature (Tm), facilitate molecular level mixing of active compounds and binders. HME technology has demonstrated reliability in creating solid dispersions, enhancing bioavailability, and masking the taste of bitter Active Pharmaceutical Ingredients (API). Primarily employed in rubber, plastics, and the food industry, HME is increasingly utilized in pharmaceuticals to manufacture tablets and suppositories. Through agitation, pressure, and heat applied via extrusion channels, HME combines materials. Despite authorization from the FDA, HME products have drawbacks, necessitating further steps to enhance drug solubility and dispersion. This article discusses HME screw design, 3D printing, materials, manufacturing processes, qualitative risk management strategies, scaling up processes, and current pharmaceutical applications.

Keywords: Screw Design; 3D Printing; Hot melt extrusion; HME Materials; Pharmaceutical Manufacturing.

1. Introduction

Hot-melt extrusion (HME) is a manufacturing process that was developed in the early 1930s and quickly became the most widely utilized technique in the food, rubber, and plastic industries. In the beginning of the 1970s, HME started being increasingly used in the pharmaceutical industry for product development, formulation, and manufacturing. [1] In the HME process, polymeric materials are fed into an extruder where they are pumped with a rotating screw at temperatures above their glass transition temperature (Tg) and sometimes even above their melting temperature (Tm). This achieves molecular level mixing of the active pharmaceutical ingredients with thermoplastic binders, polymers, or both. HME is a continuous pharmaceutical manufacturing process. The molecular combination of the constituents results in an amorphous solid product that has a uniform density and shape. This enhances the dissolution profile of the drug, improving bioavailability even for drugs with low aqueous solubility.[2,3]

Over the past 12 years, there has been a dramatic surge in research studies utilizing HME techniques for pharmaceutical applications, with over 100 studies being published in scientific journals. Globally, there has also been a noticeable rise in the number of patents granted for pharmaceutical HME systems since the early 1980s. According to patent data, Japan holds roughly 19% of all HME patents, while the United States and Germany collectively own about 28% of these patents.[4]

The HME process originated from the manufacture of lead pipes in the late 1700s. It was subsequently adapted to produce pipes, sheets, bags, and other products for the plastic, rubber, and food processing industries. With the advent of high-throughput screening methods, HME has been used to manufacture over half of all plastic products, including pipes, sheets, and bags. [5] The process involves melting and shaping diverse polymers into various forms for a range of household and industrial applications. Extrusion alters the physical properties of a material by forcing it through an aperture or die, or allowing it to degrade under carefully controlled conditions. Extrusion equipment can be broadly categorized into three types: ram extruders, radial screen extruders, and roll or screw extruders. Screw extruders are widely used in the pharmaceutical industry as they enable continuous conversion of raw materials into finished products such as tubes, films, and rods. In a screw extruder, the rotating screws convey the feed material forward towards the die. As the material passes through the barrel, frictional heat causes it to soften. Upon reaching the die or aperture at the end of the screw, the viscous material can be shaped into the desired form. [6]

* Corresponding author: Saranya P

The key steps in the HME process are as follows:

- The extruder is fed through a hopper.
- The feed material undergoes mixing, grinding, particle size reduction, venting, and kneading within the extruder barrel.
- The softened material is forced through the die.
- The extrudate emerging from the die undergoes downstream processing, such as cooling, cutting, or further shaping.

HME is a robust technique that enables efficient manufacturing of amorphous solid dispersions, thereby improving solubility and bioavailability of drugs. The continuous nature of the process, coupled with the absence of solvents, makes it an attractive option for pharmaceutical manufacturing [7-19].

2. Types of screw extruders

Pharmaceutical screw extruders must meet the most recent regulatory standards for the manufacturing of dosage forms, taking into account the intended extrudate. They are categorized as follows: [10]

2.1. Single-screw extruders

Crushed or pelletized pellets can be utilized as raw materials in the single-screw extruder machine, which is appropriate for pellet finishing. The screw collects granular or powdered feed from a hopper, and before melting begins, there is a first segment known as the "solids conveyance zone." The polymer then progressively melts in a region known as the "melting zone." Following this melting zone, the melt is directed to the die via the helical channel between the screw and the barrel, which is completely filled with melt. This is the final "metering zone." [11]

In this case, when the die approaches, the pressure increases. The screw and barrel's relative motion causes the metering section to produce a "drag flow" in the direction of the die. This is counteracted by the 'pressure flow' from the die to the hopper. The extruder's net output equals the difference between drag flow and pressure [12]. The mixing that occurs The quality of extrudate produced in single screw extruders is typically heavily reliant on, and the majority of analyses have focused on, the laminar shear mixing that happens in the metering zone.

2.2. Twin screw extruder

Twin-screw extruders are frequently used in high-performance processing equipment for a wide range of applications, including plastics, chemicals, food, and medicine. Extrusion, granulation, and material handling are among the applications. The twin-screw extrusion series includes co-rotating twin screw extruders with high torque, super high torque co-rotating twin screw extruders, split twin screw extruders, lab scale extruders, and so on. Furthermore, we provide a variety of options, such as single- and twin-screw extruder systems, each with its own set of benefits for overcoming problems and enhancing productivity.[13] Twin screw extruders are made up of two parallel screws that can rotate in the same or opposite directions, and they are either completely integrated. Hinge, partially intermeshed, or non-intermeshing [14]. Independent of relative rotation, non-intermeshing twin screws operate similarly to two independent single screws, with the difference that when the exit pressure is strong, more backflow can occur due to the large middle gap. Fully meshing twin screws that spin in opposing directions.

2.3. Multi screw extruder

A multi-screw extruder is one with more than three screws in the barrel. The screw can be organized as a letter or a V form. There is also an active screw, which is a planetary multi-screw extruder that drives the root-driven screw. In terms of working mechanism, the twin-screw extruder is the same as the multi-screw extruder [15]. As a result, in contrast to the single-screw extruder, the twin-screw extruder is occasionally In addition to the API, the materials used in hot UV absorbers called a multi-screw extruder. The machine makes the polymer melt have a greater specific surface, which is advantageous to the elimination of volatiles from the melt. Its primary applications include mixing, reaction extrusion, polymer refining, and polymer solution concentration. Multiple-screw machines come in many different forms, including non-intermeshing counter rotating screws, intermeshing corotating screws, and intermeshing counter-rotating screws. The screws in these machines rotate counter-clockwise, with the flight of one screw traveling inside the channel of the other. Four-screw extruders employ four screws, whereas twin-screw extruders utilize just two. A twin-screw plasticating section feeds into a twin-screw discharge section directly below it in a standard two-stage four-screw extruder. Usually, rather of using barrel diameters or L/D ratios to size the many screws, output rates (lb/hr) are utilized.[16]

3. Materials used in HME

The materials utilized in hot melt extrusion (HME) must adhere to stringent safety and purity standards akin to Active Pharmaceutical Ingredients (APIs). They must exhibit the capability to melt within the extruder and solidify to form extrudates. In

addition to APIs, the following materials find application in HME production: polymers, additives, solubility enhancers, melting temperature modifiers, physical state controllers, and thermal stabilizers [17]

3.1. Carriers

A crucial component in HME, carriers predominantly encompass polymers, although low-melting-point waxes, such as carnauba wax, are also viable options. The choice of carrier depends on the desired properties of the final product. For instance, for rapid-release formulations, polymers with high melt flow rates are preferred, while extended-release formulations necessitate polymers with low melt flow rates, such as ethyl cellulose. Manipulating the drug-to-polymer ratio offers control over the release rate of the active ingredient [18]

3.2. Fillers

Fillers are incorporated into HME formulations to augment the physical and chemical characteristics of the end product. Examples of commonly employed fillers include lactose, mannitol, microcrystalline cellulose, and silica

3.3. Additives

Additives are introduced into HME formulations to improve processing efficiency or enhance the physical properties of the product. These may include lubricants, plasticizers, flow enhancers, acids, UV absorbers, stabilizers, surfactants, and antioxidants [19]

3.4. Plasticizers

Plasticizers, comprising low molecular weight compounds, are utilized to soften polymers, thereby enhancing their flexibility and lowering the processing temperature of HME. They play a crucial role in modifying extrudate properties during or post-extrusion and impact the release characteristics of the final dosage form. Various classes of plasticizers exist, including conventional, non-traditional, and specialty plasticizers. Widely used conventional plasticizers include triacetin, citrate ester, vitamin E d-alpha tocopheryl PEG 1000 succinate (TPGS), surfactants, and low-molecular-weight polyethylene glycols [20]

4. HME) in Pharmaceutical Formulation Development

4.1. Formulation development

The incorporation of hot melt extrusion (HME) in the formulation development process enables the creation of amorphous solid dispersions (ASDs) for poorly soluble drug candidates. This approach amalgamates formulation and processability screening, computational predictions, experimental evaluations of biopharmaceutics and stability, and scalable production methods. It amalgamates novel academic insights with contemporary industrial practices, offering a comprehensive framework applicable not only to HME but also to alternative production routes like supercritical fluid technology, milling, congealing, and spray drying (SD). Pharmaceutical companies need to meticulously consider factors such as the drug's melting point, solubility, compatibility, thermal stability, and viscosity during drug design for HME [21]

4.2. Applications of HME

HME, originally prominent in the plastics industry, has emerged as a versatile process for formulating various dosage forms and drug delivery systems. HME-produced dosage forms exhibit intricate compositions comprising processing aids, excipients, and active pharmaceutical ingredients, offering advantages such as enhanced bioavailability, streamlined processing, continuous operation, and the ability to create solid dispersions. Notably, encapsulation using HME presents a cost-effective, solvent-minimizing approach with applications in targeted drug delivery systems [1,4]

4.3. HME & 3D Printing Technology Combination System

The integration of 3D printing and HME technologies in pharmaceutical applications offers a transformative approach to manufacturing. The synergistic utilization of these technologies streamlines traditional manufacturing processes, facilitating the creation of customized dosage forms with immediate absorption capabilities. This integrated approach holds particular promise for remote healthcare settings, where the cost-effective and efficient production of dosage forms is imperative [10].

4.4. Mechanism of Fused Deposition Modeling (FDM)

FDM, an open-source 3D printing technique, offers a cost-effective alternative to conventional printing methods. Utilizing thermoplastic materials, FDM printers construct objects layer by layer, with materials like polylactic acid (PLA) and acrylonitrile butadiene styrene (ABS) being commonly employed. Advanced thermoplastics like Polyether Ether Ketone (PEEK) and Polyether Imide (PEI) are also gaining traction, owing to their exceptional mechanical properties and high melting points [18].

4.5. Advantages and disadvantages of HME

The adoption of HME in pharmaceutical applications presents numerous advantages, including solvent-free solid dispersion formation, environmental safety, shortened manufacturing timelines, and enhanced process effectiveness. However, challenges such as energy-intensive operations, potential mechanical and thermal degradation of materials, and the need for ongoing research to address these issues underscore the necessity for comprehensive technological solutions and well-designed equipment [22]

5. Conclusion

In conclusion, the integration of hot melt extrusion (HME) into pharmaceutical formulation development represents a paradigm shift in drug manufacturing. This review has highlighted the applications of HME, ranging from the creation of amorphous solid dispersions for poorly soluble drugs to the production of customized dosage forms using 3D printing technology. By using a combination of computational predictions, experimental evaluations, and scalable production methods, pharmaceutical companies can harness the full potential of HME to overcome challenges associated with traditional manufacturing processes. Despite the undeniable advantages offered by HME, it is imperative to acknowledge and address associated drawbacks, such as energy-intensive operations and potential material degradation. Continued research efforts and technological innovations hold the key to further enhancing the efficiency, sustainability, and versatility of HME in pharmaceutical formulation development, ultimately advancing the delivery of safe and effective medications to patients worldwide.

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Author's short biography

Saranya P

Saranya P is a dedicated Bachelor of Pharmacy student with a strong interest in pharmaceutical research. Currently pursuing her undergraduate studies, she actively engages in research within the Department of Pharmacy. Saranya is enthusiastic about exploring various aspects of pharmacy and is committed to expanding her knowledge through research endeavors. With a passion for contributing to the field of pharmacy, she looks forward to undertaking further research projects and making valuable contributions to the pharmaceutical sciences.

Snehamayee Mahapatra

Snehamayee Mahapatra is a dedicated Bachelor of Pharmacy student with a keen interest in pharmaceutical research. Currently pursuing her undergraduate studies, she is actively engaged in research within the Department of Pharmacy. Snehamayee is passionate about exploring new avenues in pharmaceutical sciences and continuously strives to contribute to the field through her research endeavors. With a strong commitment to academic excellence and a drive to make meaningful contributions to the pharmacy profession, she looks forward to undertaking further research projects and expanding her knowledge in the field.

Dr. Rakshana V

Dr. Rakshana V is an Assistant Professor in the Departments of Pharmacy Practice, specializing in Doctor of Pharmacy. With a primary focus on the pharmacy practice, She has a wealth of experience and expertise in this field. Through her research projects and professional endeavors, she aims to contribute significantly to the advancement of pharmacy practice and enhance patient care.

Dr. Srinivasan R

Dean and professor, my research project /experience is mainly in the development, synthesis, characterization and application of novel polymers, multiple projects in the area of pharmaceutical analysis & Quality assurance**.**