

Hot Melt Extrusion an Emerging Pharmaceutical Technology

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Abstract

Review Article

Hot Melt Extrusion technology offers an opportunity to acquire intellectual property, evident from the increasing number of patents and publications that have integrated it as an emerging pharmaceutical formulation technology over the last decades. Industrial adaptability has allowed hot-melt extrusion (HME) to gain wide recognition over the last decades and has already established its place in a wide range of manufacturing operations and advancements in pharmaceutical research. This study addressed the importance of the use of a quality-based strategy, based on a holistic approach to equipment, materials processing methods, novel formulation design and advancements, and its various applications for oral drug delivery systems. In drug discovery and development, the industry estimates that more than 50% of the active pharmaceutical ingredient used is part of the Biopharmaceutical Classification System II, defined as water-insoluble compounds, leading to formulations having less bioavailability. The pharmaceutical industry needs to develop formulations that will improve the solubility and ultimately the bioavailability of these compounds. Hot Melt Extrusion has already been shown to be robust, novel and powerful technique for improved bioavailability as well as taste masking of bitter active pharmaceutical ingredients (APIs). This paper examines the many benefits of Hot Melt Extrusion, based on a holistic approach to equipment, material processing methods, novel design and advancements.

Keywords: Hot Melt Extrusion, Solid-dispersion, Bioavailability, Application.

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INTRODUCTION

Extrusion is a process in which the homogeneous product is formed by converting the powder into a molten mass through accurate control of the processing condition. Hot Melt Extrusion (HME) has emerged as a novel processing technique in the development of molecular dispersion through various polymer or lipid matrices of active pharmaceutical ingredients, resulting in time-controlled, prolonged and targeted drug delivery [1-3]. HME has now provided the opportunity to use materials to mask the bitter taste and enhance the solubility of active substances. In 1797 Joseph Bramah patented the first extrusion process for the production of soft metal pipes [4]. It involved preheating the metal and then forcing it through a die through a hand-driven plunger. In 1820, Thomas Burr carried out this process for the hydraulic press lead pipe (also invented by Joseph Bramah) and at that time the process was called "squirting." In 1894, Alexander Dick extended the process of extrusion to copper and brass alloys [5, 6].

In the 1930s, the industrial application of the extrusion process quickly became the most widely used

processing technology in the plastics, rubber and food industries [7, 8]. The application of extrusion expanded to the pharmaceutical industry at the beginning of the 1970s and was used in formulation and product development as well as manufacturing. HME technology was firstly introduced into the pharmaceutical industry in 1991 when Warner-Lambert used HME to enhance the solubility of Troglitazone which is very poorly soluble drug [9, 10]. The company had bought an early phase medication product Troglitazone two years ago, utilizing a spray drying method to improve drug material solubility by the creation of amorphous solid dispersion. HME has received considerable attention from both the pharmaceutical industry and academics to the development of pharmaceutical dosage forms such as tablets, capsules, film and drug delivery implants via oral, transdermal and Trans muscular routes [11, 12]. This makes the HME an ideal alternative to other conventionally accessible roll spinning and spray drying techniques. HME also fulfills the U.S. Food and Drug Administration's mission, which is focused on a comprehensive view of its multiple elements, manufacturing techniques and resources, and the

innovative nature and creation of new formulations in its complex use in the oral drug delivery system [13, 14]. As part of the development of the pharmaceutical formulation, HME has made available sophisticated equipment such as customized downstream auxiliary extruders and monitoring tools for use in performance

and product quality assessments. This increased availability has supported the growth of this innovative technology in pharmaceutical manufacturing processes using single and twin-screw extruders [15]. The approved formulation in market by hot melt extrusion proves shown in Table No I.

Table-I: Marketed formulation by hot melt extrusion

Brand Name	Approved Year	Product	Types of System
Merck	1981	Lacrisert	Shaped Systems
Pfizer	1996	Zothromax	Sustained Release
Merck	2001	Nuva Ring	Shaped System
Purdue Pharma	2004	Palladoone	Sustained Release
Abb Vie	2005	Kaletra	Immediate Release
Merck	2006	Implanon	Shaped system
Novartis	2007	Eucreas	Immediate Release
Allegran	2009	Ozurdex	Shaped System
Abb Vie	2010	Nucynta	Sustained Release
Merck	2013	Noxafil	Delayed Release
Merck	2014	Belspmra	Immediate Release
Merck	2015	Zepatier	Immediate Release

Equipment and processing of hot melt extrusion

In Extrusion process, the drug is mixed with a suitable polymer to form the molten mass by forcing it through a heated barrel or die under controlled temperature and pressure. The Extruders are classified into three main categories Ram, Radial screen and Screwed extruder [16]. Among these, the screws Extruders in the pharmaceutical industry are the most

important as they continuously transform feed material to the finished shape such as a pipe, tube, or film. The spinning screws push the feed content against the die, and the frictional heat produced through the barrel wall softens the substance. The feed reaches the end of the screw in a viscous state and then forced through an orifice and molded into the desired shape [17] is the process of Hot melt extrusion shown in Fig No 1.

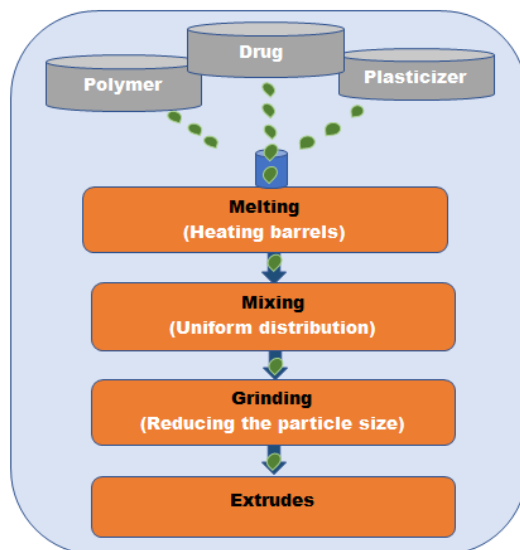


Fig-1: Hot melt extrusion process and design

PARTS OF EXTRUDER

Barrels

Extruder barrels are the housing for the screws. The barrels are generally electrically heated and water cooled. During the extrusion process the barrel temperature is monitored by thermocouples. Depending on the design and manufacturing the barrel can be either a one-piece or a modular design. Compared to the one-

piece design modular barrels are more widely used in the pharmaceutical industry due to their greater flexibility [18].

Different types of barrels [19]

The different type of barrel is used in hot melt extrusion process are shown in Fig No 2.

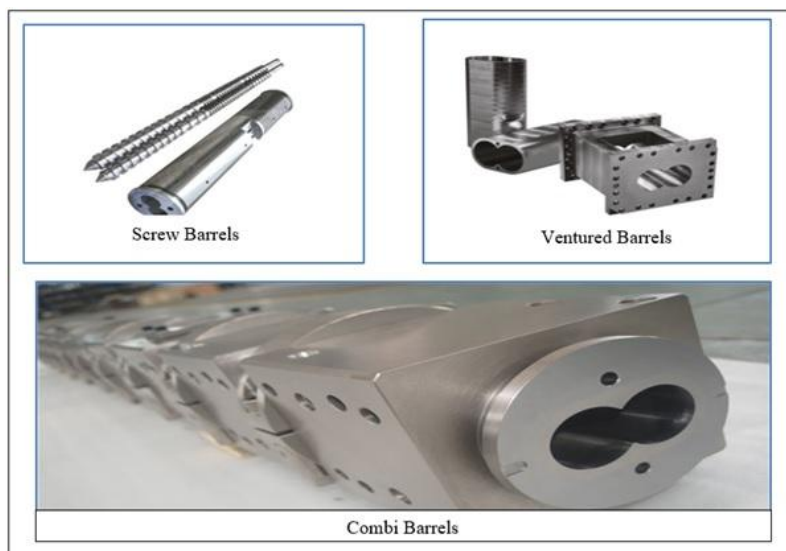


Fig-2: Different types barrels used in HME process

- Closed barrel and combo:** This type of barrels can be used for liquid feed. This type of barrels can be used for liquid feed. Used, if needed it can be introduced into the system through an injection nozzle connected to a closed barrel.
- Feed barrel:** It is either in a circular or rectangular shape. It normally kept at near to the room temperature to maximize the free volume of material to enter into the extruder.
- Vented barrel:** It is used to remove air and/or volatiles from the extruder. The process is also referred as devolatilization.

Screw element

Screw construction may have a major effect on the functionality and efficiency of the component as it impacts mechanical shear and period of residence. For a wet granulation process, Thompson and Sun stated that modifications in the screw elements may affect the size and shape of lactose-polyvinylpyrrolidone granules. Nakamichiet *et al.* showed that kneading paddles play an important role in the preparation of amorphous solid dispersion (ASD) of nifedipine. Therefore, the special attention should be given while designing the screws. During design the process requirements and the material properties must be considered. Screw configuration can be designed as shear-intensive or shear-passive according to process requirements [20].

Dies

The die opening is attached to end of the extruder and the pressurized molten mass is passed from the barrel and enters into the die. The main function of die is to convert the pressurized molten mass into desired shape and size.

Auxiliary systems

A wide range of auxiliary systems including feeders and various downstream equipment are used in the extrusion process. The selection of feeder and downstream equipment with extruder is very important for completion of the extrusion process [21].

PROCESS PARAMETERS

Extrusion is an integrated unit operation composed of several functional zones. Process parameter plays a key role in determining the properties of the extruded product. The complexity of the material and energy properties in different functional zones thought the extruder. The product quality is controlled directly by key system parameters such as specific energy, temperature, residence time and pressure. While the common adjustable equipment and process parameters impact the product quality indirectly. Key process considerations based on the adjustable parameter (e.g. Feed rate, screw speed, temperature profiles) Table No II [22].

Table-II: Process parameter of hot melt extrusion

Function Zone	Slid feed	Slid convey	Melting	Mixing	Melt Convey	Discharge
Material State	Solid	Solid	Slid/Melt	Melt	Melt	Melt
Pressure (Bar)	1	1	1	>1	>1	>1
Conductive Energy	Out of Material	In and out of Material	Out of material	Out of Material	Out of Material	Out of Material
Energy Conversion	None	None	PED/FED	VED	VED	VED

MATERIALS USED IN HOT MELT EXTRUSION Drug

HME can be conducted below the melting point of a drug that means the melting point of a drug is depressed when there is a strong interaction between the drug and the polymer. Intermolecular interaction between drug and polymer is important for the physical stability of amorphous solid dispersion (ASD). Interaction between drug and polymer can be determined by experimentation using the melting-point depression method. Good miscibility between drug polymers manifests itself as the depression of drug melting point. The Gibbs free energy of the dissolved drug in its saturated solution in polymer melts [23].

Polymer

Polyethyleneglycol-polyvinyl caprolactam-polyvinyl acetate grafted copolymer is a newly

developed polymer commonly used in HME for drug development. The polymer has an amphiphilic structure that enables it to behave as both a polymer-forming matrix and a solubilizer for poorly soluble APIs in aqueous solutions. It has a low glass transition temperature of 70 °C. Figure 3 shows the relationship between the glass transition temperature and the polymer state. Djuris *et al.* Have demonstrated with a single screw hot-melt extruder that a mixture of carbamazepine and Polyethyleneglycol-polyvinyl caprolactam-polyvinyl acetate thermodynamic model. In another example, the oral bioavailability of Valsartan was improved by melt extrusion with this copolymer and the addition of a non-ionic surfactant, Vitamin E TPGS [24]. Table No III shows the selection of polymers based on dosage form.

Table-III: Selection of Polymer in Hot Melt Extrusion

Dosage form	Polymer
Oral / Ingestible	Polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Hydroxypropyl Cellulose (HPC), Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS), Ethyl cellulose (EC), Cellulose acetate butyrate (CAB), Cellulose Acetate Phthalate (CAP), Polyvinyl alcohol (PVA), Poly (ethylene glycol) (PEG), Poly (vinyl acetate) (PVAc), Methacrylate's.
Bioresorbable	Poly lactide (PLA), Polyglycolide (PGA), Copolymers of PLA/PGA and Polycaprolactone (PCL).
Implantable	Ethylene Vinyl Acetate (EVA), Polyurethanes (TPU), Polyethylene (PE).

Plasticizer

For plastics and pharmaceutical industries, the application of a plasticizer to promote the cycle of hot melt-extrusion is well known. A plasticizer is a low molecular weight material which is capable of polymer softening, the polymer more robust along with

elongation and strength. Plasticization of polymer is due to the inter molecular secondary valance force between plasticizer which leads to increase free volume between polymer chain and decrease in the glass transition temperature [25-30]. Table No IV shows the examples of plasticizers.

Table-IV: Example of Plasticizer

Class	Examples
Polyhydric Alcohols	Propylene glycol, Glycerol, Polyethylene glycols
Acetate Esters	Glyceryl triacetate, Acetyl triethyl citrate
Phthalate Esters	Diethyl Phthalate
Glycerides	Acetylated Monoglycerides
Oils	Castor oil, Mineral oil

Factors affecting the selection of plasticizer [31-34]

- Efficiency:** The quantity of plasticizer required to lower the glass transition temperature, (T_g) and produce desired effects indicates the

efficiency of plasticizer. The diffusion rate of plasticizer is directly proportional to efficiency shown in Fig No 3.

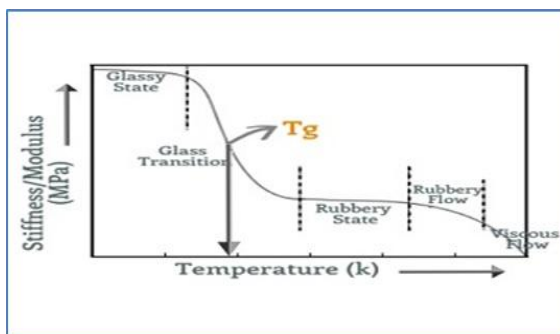


Fig-3: Glass transition temperature (T_g)

2. **Compatibility:** The compatibility of Plasticizer with polymer is depends on its phytochemical parameter such as Polarity, Structural configuration and Molecular weight of plasticizer. The compatibility of plasticizer is determined by the rule “like dissolved like” with the help of Hildebrand solubility and Hansen solubility determination methods.
3. **Permanence:** The permanence is a process of expulsion of plasticizer due to its higher volatility, which result plasticizer to come out of the polymer matrix. e. g. large alkyl moieties such as phthalates have increased hydrophobicity.

Advantages of hot melt extrusion [35-40]

HME has several benefits over conventionally accessible pharmaceutical processing methods.

1. Upgrades bioavailability of poorly soluble compound.
2. HME is economical, practical procedure with diminished creation time, less handling advances and a continued activity.
3. HME avoids dose dumping and clinically helpful in drug abuse.
4. HME can deliver drugs in a sustained manner and targeted drug delivery.
5. HME Produces various size ranges and geometries as well as show better content uniformity.
6. Compressibility of an active ingredient is not necessary.
7. HME process shows uniform dispersion of fine particles and also has good stability at varying pH and moisture level.
8. Reduced number of unit operations.
9. The process can be carried out in absence of solvents.

Limitation of hot melt extrusion [41-43]

Difficulties in maintaining stability for thermo sensitive drug and polymer

Required food flow property for polymer employed.

There are a limited number of polymers that used for HME.

The HME process requires high energy input.

Pharmaceutical applications of hot melt extrusion

The initial research concentrated on the impact of the development and processing variables on attributes of the finished dosage form.

Modified release formulation

The sustained release of drug with combination of polymer formulated into solid dispersion by fusion method. e.g. In hot melt extrusion Sucrose esters are applied as processing carriers because of their low melting points and their surfactant properties. It was investigated by performing ibuprofen and sucrose ester used as promising carrier. Ibuprofen is a safe non-steroidal anti-inflammatory drug [44] and it has a short elimination half-life 2-3 hours, oral dose is 1.2 to 2.4 g daily in divided. This short half-life necessitates the frequent drug administration. Consequently, a sustained release dosage form would reduce the frequent drug administration and may enhance patient compliance [45].

Targeted drug delivery system

The transdermal and transmucosal dosage form like film and patch are produced more frequently by solvent casting method [46]. However, there are several problems with the solvent casting technique like physical aging effect on mechanical strength and increased film tensile strength [47]. This mechanical instability was related to the relaxation of the polymer chains as they moved towards a state of equilibrium. It directly affects the dissolution [48]. Rebekah *et al.* discussed the numerous disadvantages of solvent casting methods for preparing transdermal films [49]. Rothen-Weinhold developed long-acting pull (lactic acid) implants are comprised vapreotide, an equivalent somatostatin through extrusion from the hot melt. The authors reported that the peptide degraded during processing with the formation of a lactyl-vapreotide conjugate. The authors determined that residual lactide in the polylactic acid significantly influenced the formation of the peptide impurity, illustrating that carrier purity impacts the quality of the dosage form [50, 51].

Improve solubility and bioavailability

HME is recently used in healthcare industry to manufacture medical devices to enhance bioavailability of poorly soluble drug which belongs to BCS class II and IV. It has been successfully achieved through the formation of solid dispersion of drug in a polymeric

carrier matrix. HME may be classified as solid crystalline dispersions, solid amorphous dispersions, and solid solutions. Amorphous material dispersion gives not only the intrinsic free energy advantages but also optimum surface area rises and solubility of saturation [52].

Taste masking by HME approach

It is a bigger challenge to mask the taste of bitter active pharmaceutical ingredients in formulation and development of oral dosage form. The taste masking of bitter drug can be achieved by HME via various mechanisms such as the formation of solid dispersions and inter-molecular interactions [53].

Evaluation hot melt extrudes [54]

Thermal and chemical stability of extrudes: Thermal transitions of the polymers are also indicative of the temperature of the extrusion. The glass transition temperatures and melting points were measured using a differential calorimeter. For stability testing of the polymers, three types of methods were considered, i.e. thermogravimetry, preliminary extrusion tests and high-performance liquid chromatography. With the first one the temperature profile weight loss was recorded using thermobalance.

Differential Scanning Calorimetry: DSC was widely used to study the thermal properties of the material used in HME. It can be used to determine the TG and Tm in which energy is required or released. It also used in drug excipient incompatibility studies. It was also used to distinguish between amorphous and crystalline forms.

Thermo Gravimetric Analysis: TGA is a measure of thermally caused material weight loss as a function of applied temperature. TGA is severely limited to, research involving either weight gain or loss and its frequency used for the research of desolvation and decomposition.

Infrared Spectroscopy: IR can be used to identify changes in linkages between functional groups due to structural modifications or absence of crystal structure.

Physical state of extrudes

XRD: It is used to characterize the crystalline characteristics of hot melt extruded dosage forms. The XRD principle is based on Bragg's in which parallel incident X-rays strike crystal surfaces and then diffract at angles linked to the spacing between planes of molecules in the lattice. Crystallinity is represented in the diffraction pattern by the distinctive fingerprint region. However, the sensitivity of the XRD technique is limited and cannot usually detect crystallinity of less than 10%.

Microscopy: Is one of the best techniques for studying the crystalline characteristics of hot-melt extrudates. Both optical and electron techniques are appropriate for examining the surface morphology of the sample to be tested for the existence of crystalline particles or amorphous domains. Reliable data on particle size can also be obtained using these methods.

CONCLUSION

Hot Melt Extrusion has been well explored and documented as a steady, solvent-free, fast and cost-effective manufacturing method for the production of a broad range of pharmaceutical dosage forms, including oral, topical film, implants and ophthalmic inserts. HME has demonstrated to be a robust method of producing a number of drug delivery system. There is increasing interest in HME technology as it is appropriate for both elevated and very powerful low-dose compounds, as well as the equipment is commonly accessible.

Conflict of Interest

All Authors declare that they have no conflict of interest

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