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Hot melt extrusion technique and its pharmaceutical applications: A review

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ABSTRACT

Significance of hot-melt extrusion techniques for pharmaceutical applications is growing rapidly over the last three decades. Industrial malleability has allowed hot-melt extrusion (HME) to gain wide acceptance and has already established its importance in manufacturing operations and pharmaceutical research developments. Hot-melt extrusion techniques provide time controlled, modified, extended, and targeted drug delivery resulting in improved bioavailability as well as taste masking of bitter active pharmaceutical ingredients (APIs). HME offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, and the possibility of the formation of solid dispersions and improved bioavailability. Hot-melt extrusion techniques are pragmatic in the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts.

Keywords: Hot-melt extrusion techniques, Targeted drug delivery, Solid dispersions, Bioavailability.

INTRODUCTION

HME has emerged as a novel processing technology in developing molecular dispersions of active pharmaceutical ingredients (APIs) into various polymer or/and lipid matrices which has led this technique to demonstrate time controlled, modified, extended, and targeted drug delivery [11]. Hot-melt extrusion is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Currently, more than half of all plastic products, including plastic bags, sheets, and pipes, are manufactured by this process [12]. HME has received considerable attention from both the pharmaceutical industry and academia in a range of applications for pharmaceutical dosage forms, such as tablets, capsules, films, and implants for drug delivery via oral, transdermal, and transmucosal routes. This makes HME an excellent alternative to other conventionally available techniques such as roll spinning and spray drying. In addition to being a proven manufacturing process, HME meets the

goal of the US Food and Drug Administration's (FDA) process analytical technology (PAT) scheme for designing, analyzing, and controlling the manufacturing process via quality control measurements during active extrusion process [13]. In this chapter, the hot-melt extrusion technique is reviewed based on a holistic perspective of its various components, processing technologies, and the materials and novel formulation design and developments in its varied applications in oral drug delivery systems.

However, the theoretical approach to understanding the melt extrusion process can be summarized by classifying the whole procedure of HME compaction into the following:

1. Feeding of the extruder through a hopper,
2. Mixing, grinding, reducing the particle size, venting, and kneading,
3. Flow through the die, and
4. Extrusion from the die and further downstream processing.

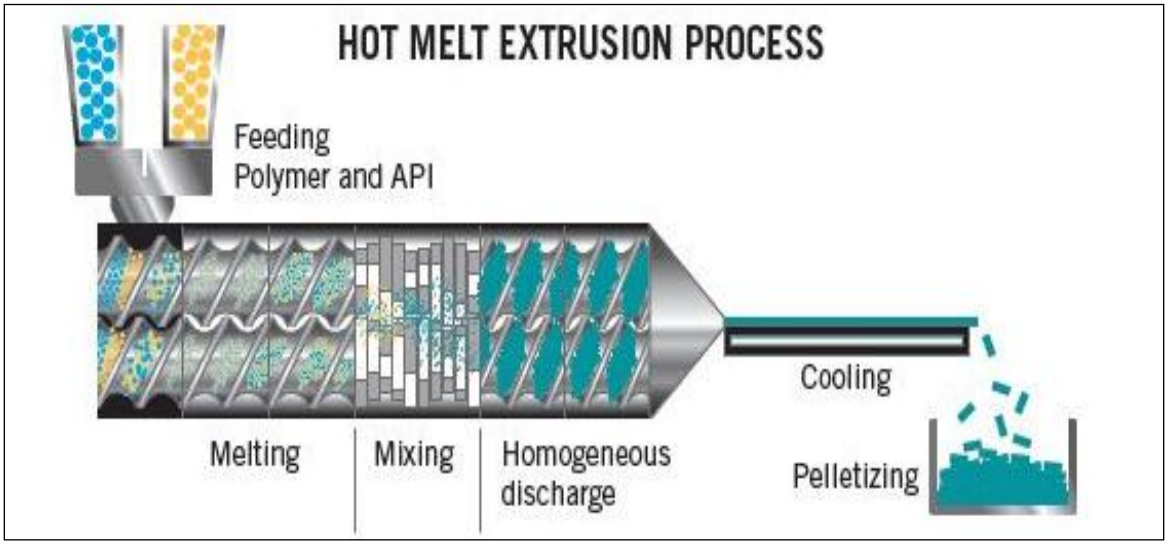

Figure 1: Schematic diagram of the HME process

Advantages

HME offers several advantages over traditional pharmaceutical processing techniques including: Enhanced bioavailability of poorly soluble compounds.

- Processing in the absence of solvents and water.
- Economical process with reduced production time, fewer processing steps, and a continuous operation.
- Clinically advantaged dosage forms, such as drug abuse and dose dumping deterrent technology.
- Sustained, modified and targeted release capabilities.
- Better content uniformity was obtained from the HME process among granules of different size ranges.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.
- Reduced number of unit operations.

Process and Equipment

Hot-melt extrusion equipment consists of an extruder, auxiliary equipment for the extruder, downstream processing equipment, and other monitoring tools used for performance and product quality evaluation. The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw driving unit.

There are two types of extruders

Single-screw and twin-screw extruders.

Single Screw Extruder

The single-screw extruder has been the most widely used. Twin-screw extruders use two side-by-side screws either co-rotating or counter-rotating. There are several advantages of twin-screw extruders over

single-screw extruders such as easier material feeding and dispersion capacities, less tendency to over-heat and shorter transit times. However, single-screw extruders are more simple and cheaper. The single screw extruder is the most widely used extrusion system in the world. One screw rotates inside the barrel and is used for feeding, melting, devolatilizing, and pumping. Mixing is also accomplished for less demanding applications. Single screw extruders can be either flood or starve fed, depending upon the intended manufacturing process. Single screw extruders are continuous, high-pressure pumps for viscous materials that can generate thousands of pounds of pressure while melting and mixing. Most extruder screws are driven from the hopper end. However, once screws are reduced to less than 18 mm, the screw becomes weak and solids transportation is far less reliable [Fig 2].

Figure 2: Single Screw Extruder

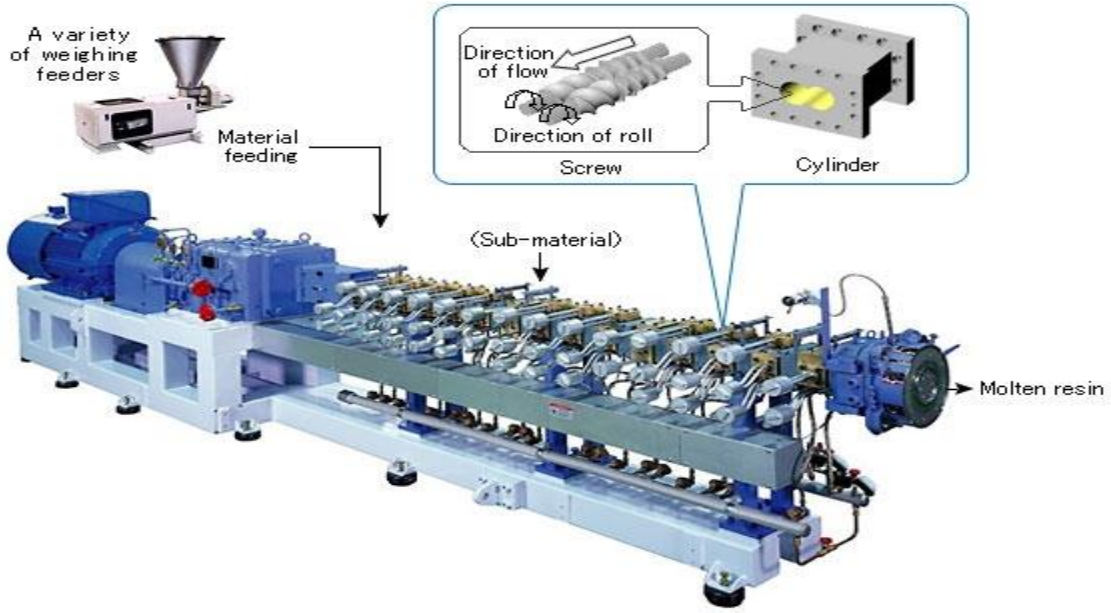

Figure 3: Twin Screw Extruder

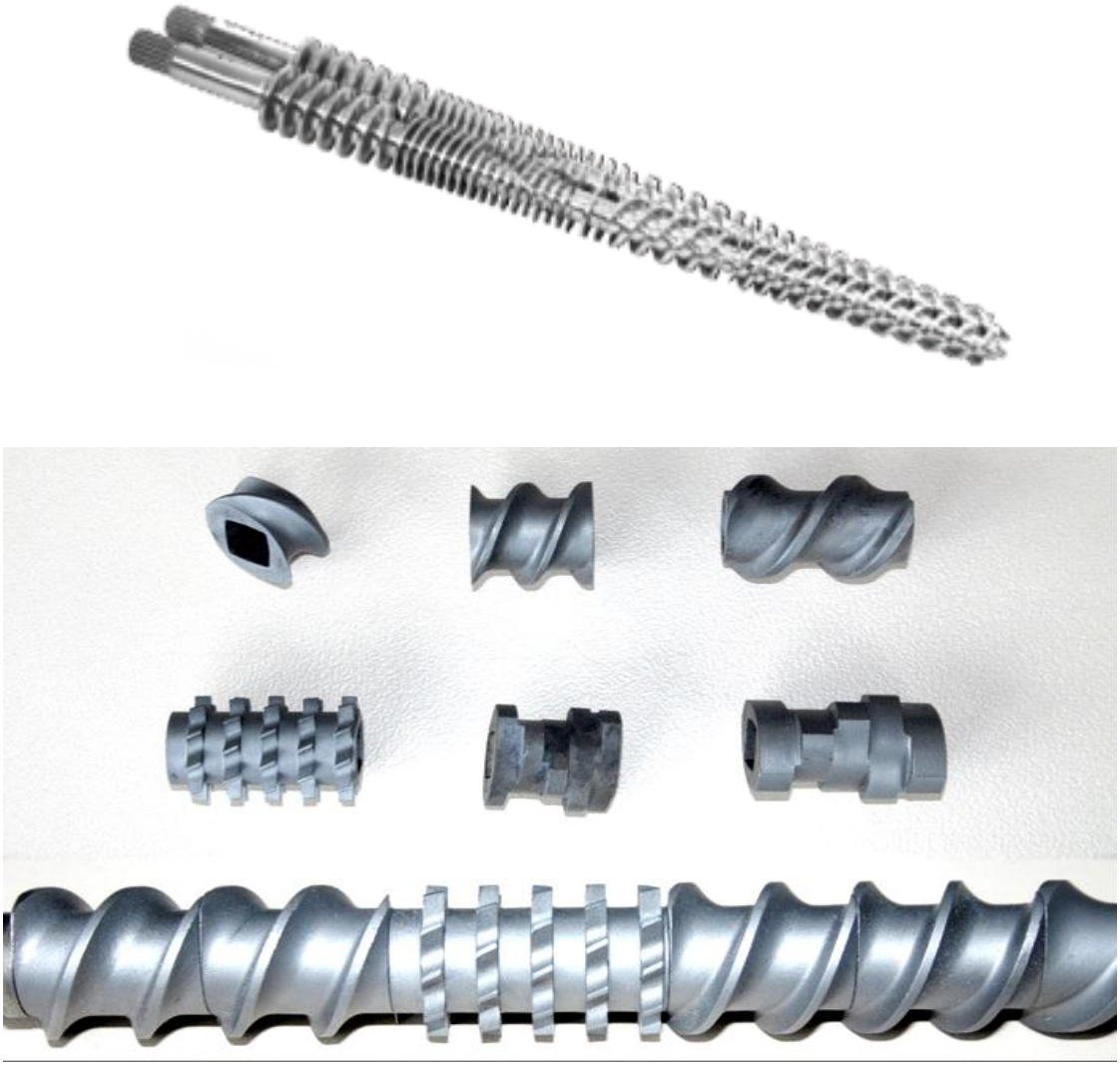

Figure 4: Twin-screw extruder and screws

Twin-screw extruder

The twin-screw extruder is characterized by the following descriptive features:

1. Short residence time: The residence time in the twin-screw extruder in a typical extrusion processes ranges from 5-10 minutes depending on the feed rate and screw speed.
2. Self-wiping screw profile: The self-wiping screw profile i.e. the flight of the one Screw wipes the root of the screw on the shaft next to it, ensures near complete emptying of the equipment and minimizes product wastage on shutdown.
3. Minimum inventory: Continuous operation of the equipment coupled with the continuous feeding of the material helps in reducing inventories of work in progress. This is important when processing valuable or potentially hazardous materials.
4. Versatility: Operating parameters can be changed easily and continuously to change extrusion rate or mixing action [Fig 3].

MATERIALS USED IN HOT-MELT EXTRUSION [1, 2, 3]

For a pharmaceutical material to be processed by HME, it must be able to deform easily inside the extruder and solidify upon its exit. The materials must meet the same levels of purity and safety as those prepared by traditional techniques. Most of the raw materials used in hot melt extruded pharmaceuticals

have been used in the production of other solid dosage forms such as tablets, pellets, granules, transdermal, and transmucosal systems [2].

Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered in this process may not limit all thermo labile compounds.

Carriers

In hot-melt extruded drug delivery systems, the active compound is embedded in a carrier formulation often comprised of one or more "meltable" substances and other functional excipients. The meltable substance is generally a polymer or low melting point wax. The selection of an appropriate carrier is important in the formulation and design of a hot-melt extruded dosage form. The physical and chemical properties of the carrier can control the release of the active compound from the final dosage form. For systems employing nonpolymeric carrier materials, the compatibility between the drug substance and carrier should be addressed. The incorporation of a low melting compound into a low melting point wax may form a eutectic mixture or reduce the melting point of the mixture preventing the formation of a solid dosage form. The production of granules using carnauba wax has been reported [3]. The use of polymeric carriers in HME often requires the incorporation of a plasticizer into the formulation to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product.

Plasticization of the polymer is generally attributed to the inter-molecular secondary valence forces between the plasticizer and the polymer.

Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains. In doing so, the ease of movement of polymer chains with respect to each other is dramatically reduced. Plasticizers were also found to facilitate the fusion process of semi-crystalline polymers. Less energy is usually required to melt semi-crystalline polymers following the addition of one or more plasticizers. With the addition of a plasticizer, a HME process can be conducted at lower temperatures and with less torque. Generally, both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions. Materials commonly used as plasticizers that are approved by the Food and Drug Administration for use in pharmaceutical dosage forms are listed in Table 1 according to their chemical structure.

Table 1: Common plasticizers used in pharmaceutical dosage forms

Type	Examples
Citrate esters	Triethyl citrate, tributyl citrate, acetyl triethylcitrate
Fatty acid esters	Butyl stearate, glycerol monostearate
Phthalate esters	Diethyl phthalate, dibutyl phthalate, dioctyl phosphate
Glycol derivatives	Polyethylene glycol, propylene glycol

Table 2: Different hot-melt extruded films

Film	Main polymer(s)	Plasticizer/additive	Main active ingredient(s)
1	Acrylic Eudragit	Triacetin Triethylcitrate	Lidocaine
2	Hydroxy propyl cellulose Polyethylene oxide	N/A	Ketoconazole
3	Hydroxy propyl cellulose Hydroxy propylmethylcellulose Polyethylene oxide	Polyethylene glycol 3350	Lidocaine
4	Hydroxy propyl cellulose	Polyethylene glycol 400	Hydrocortisone
5	Hydroxy propyl cellulose Polycarbophil	Polyethylene glycol 3350	Clotrimazole

The taste masking of bitter APIs is a major challenge especially for the development of orally disintegrating tablets (ODT). HME has been reported to be an effective technique to mask the bitter tastes of various APIs by the use of taste masking polymers that create solid dispersions to prevent bitter drugs from coming in contact with the patient's taste buds. More recently ibuprofen- and paracetamol-based taste masked formulations by HME have been reported [1].

EVALUATION [4, 5]

The evaluation methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier.

Differential Scanning Calorimetry (DSC)

Thermo analytical methods include those that examine the system as a function of temperature. Differential scanning calorimetry (DSC) has been widely used to study the thermal properties of materials used in hot melt extrusion.

Thermo Gravimetric Analysis (TGA)

TGA is a measure of thermally induced weight loss of a material as a function of applied temperature.

X-Ray Diffraction (XRD)

XRD is also used to characterize the crystalline properties of hot-melt extruded dosage forms. The principle of XRD is based on Bragg's law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of molecules in the lattice. Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern. If the fingerprints of the drug and carrier do not overlay one another, the crystallinity of the drug and polymer following hot-melt extrusion can be determined.

Microscopy

Microscopy is one of the best methods to study the crystalline properties of hot-melt extrudates. Both optical and electron methods are suitable to examine the surface morphology of samples to probe for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques.

FUTURE TRENDS

The application of HME technology in the pharmaceutical industry has tended to focus on the development of bio-enhanced formulations to increase the efficacy of poorly water soluble compounds. There has also been an increase in the application of HME for the development of controlled release formulations, in the form of pellets, beads or mini matrices, and as a means to facilitate the continuous processing of products to reduce the number of manufacturing unit operations.

MARKETED PRODUCTS

The interest in HME is growing rapidly. The US and Germany hold approximately more than half (56%) of all issued patents. In spite of this increased interest, there are few commercialized HME pharmaceutical products currently marketed. There is no. of companies using HME as a drug delivery technology including Pharma Form (TX, USA) and SOLIQS (Germany). SOLIQS has developed a proprietary Meltrex formulation and redeveloped aprotease inhibitor combination product, Kaletra, for the treatment of human immunodeficiency virus (HIV). Moreover, HME Kaletra tablets were shown to have significant advantages for the patient compared with the previous soft gel capsule formulation, such as reduced dosing frequency and improved stability. SOLIQS has also developed a fast-onset ibuprofen system and a sustained release formulation of verapamil (Isoptin SRE) that was the first directly shaped HME product on the market.

HME in commercial products

HME related patents which have been issued for pharmaceutical systems have steadily increased since the early 1980's. So far, the USA and Germany hold approximately more than half (56%) of all issued patents for HME in the market. Despite this increased interest, only a handful of commercialized HME pharmaceutical products are currently marketed. Several companies have been recognized to specialize in the use of HME as a drug delivery technology, such as PharmaForm and SOLIQS (Abbott). Recently, SOLIQS has developed a proprietary formulation which is known as Meltrex® and re-developed a

protease-inhibitor combination product, Kaletra®. Kaletra is mainly used for the treatment of human immunodeficiency virus (HIV) infections. The formulated, melt extruded product was shown to have a significant enhancement in the bioavailability of active substances [5]. Furthermore, HME Kaletra® tablets were shown to have significant advantages for patient compliance (i.e. reduced dosing frequency and improved stability) compared to the previous soft-gel capsule formulation as recognized by the FDA decision to fast-track approval. Additionally, Nurofen (Meltlets® lemon) is available on the market as a fast dissolving tablet prepared by HME [6]. Ibuprofen has been used as active substance in the Meltlets® tablets where its bitter taste was successfully masked by similar technique to HME. Moreover, SOLIQS has also developed a fast-onset ibuprofen system and a sustained-release formulation of verapamil (Isoptin® SR-E) through a HME related technology called 'Calendaring' that was the first directly shaped HME product on the market.

CONCLUSION

HME has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in the pharmaceutical industry enlarging the scope to include a range of polymers and APIs that can be processed with or without plasticizers. It has also been documented that HME is a solvent-free, robust, quick and economy favoured manufacturing process for the production of a large variety of pharmaceutical dosage forms.

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