REVIEW ARTICLE

REVIEW ON THE PHARMACEUTICAL APPLICATIONS OF HOT MELT EXTRUDER

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Abstract: Compared to single-unit dosage forms, oral multi particulate drug-delivery systems like pellets, granules offer advantages in terms of a more even and predictable distribution and transportation in the gastro-intestinal tract. As the number of poorly soluble drugs has risen sharply in recent years, techniques for improving the solubility, and potentially, the bioavailability have become increasingly important. Melt extrusion technology represents an efficient pathway for increasing the solubility of poorly soluble drugs. In the drug the active forms a solid dispersion where the drug is presented in an amorphous state and molecularly dispersed in the carrier. This leads to an increase in solubility, as no lattice energy has to be overcome during dissolution. The particle size is reduced to the molecular level and the carrier increases the wetting of the drug. Scientists have tried to address such issues by various pharmaceutical interventions like various pelletizations, granulation and hot melt extrusion techniques available to prepare drug loaded spherical particles or granules. Amongst all extrusion is the most common method which utilized in formulation of beads and pellets. Limitations related to bioavailability and site specific drug delivery can be over come by this technique. This technology has gained focus because of its easy of operation and fast processing. Extrusion is widely utilized in formulation of sustained release, controlled release delivery system. Melt extrusion is considered to be an efficient technology with particular advantages over solvent processes like co-precipitation for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. This process is also useful from an ecological standpoint to produce solid dispersions efficiently without degradation. Potential drawbacks like the influence of heat stress and shear forces on the drug needs attention while doing extrusion. This review article describes the melt extrusion equipment, process and polymers used for formulation of various API using various pharmaceutical-grade polymers.

Keywords: Hot melt extrusion, HME process, extruder, excipients in HME process, formulations development.

INTRODUCTION

Extrusion process has gained world wide attention because it is a simple and fast processing technology for mixing and designing moldable materials. This process is well known in the polymer and food industry [1] and is now being used for pharmaceutical manufacture due to its financially viable and environmental advantages and the prospect to create novel new formulations [2-5].

The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method [6], embedding of drug by means of spray drying [7], co-evaporation, co-precipitation [8], freeze-drying [9], and roll-mixing or co-milling [10, 11].

In 1974, Sekiguchi and Obi were first to report the melting or fusion method as a new field of pharmaceutical technique [12] and its principles role in increasing dissolution, absorption and therapeutic efficacy of the drug [13].

The bioavailability of an orally administered drug mainly depends on its solubility and permeability. Due to introduction of high throughput screening in the drug discovery process the resultant compounds are often high molecular weight and highly lipophilic hence exhibits poor solubility. Also the controlled and sustained release of drug application within the pharmaceutical industry require consistent smooth surface with a narrow size distribution, to ensure uniform coating and accurate free flow of granules for filling operations like capsule filling , and all this can be achieved by melt extrusion technique [3]. The main objective of the extrusion is to produce pellets of uniform size with high drug loading capacity. Extrusion is a multiple process of wet mass extrusion to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon the material as well as process used for extrusion. Extrusion has been used in various industries like agrochemicals, detergent additives, sweeteners, food and more recently in pharmaceuticals. The process is useful when uniform spherical shape, uniform size, good flow properties, reproducibility in packing, high strength, low friability and smooth surface of granules is desired. The pellets or beads produced by the extrusion offer several advantages over conventional drug delivery system like; it produces spheroids with high loading capacity of active ingredient without producing extensively large particles.

In pharmaceutical industry the melt extrusion has been used for various applications like [14-16],

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
- Controlling or modifying the release of the drug.
- Masking the bitter taste of an active drug

It produces particles of uniform size with narrow size distribution and good flow properties. Successful coating is applied to spheroid because of its spherical shape and low surface area to volume ratio. Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drug at the same or different site in GI tract. Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification. It improves the safety and efficiency of active ingredient. It helps to increase bioavailability of drugs by controlling or modifying the release rate of drugs. HME offers several benefits over the traditional formulation which makes it more attractive with respect to commercialization and ease of operations [17].

Advantages

- Small equipment
- Economic continuous process and scale up flexibility
- Solvent-free manufacture
- High mixing efficiency
- Closed process unit to prevent cross contamination
- Short processing time
- Easily controlled process parameters
- Possibility of online analytics for process control

Disadvantages

- Thermal process (drug/polymer stability)
- Flow properties of the polymer are essential to processing
- Limited number of available polymers
- Requires high energy input
- The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved

This process is anhydrous thus avoids any potential drug degradation from hydrolysis following the addition of aq. or alcoholic

granulating media. During hot-melt extrusion, a matrix is formed due to the polymer melt acting as a thermal binder. In addition, poorly compactible materials can be incorporated into tablets produced by cutting an extruded rod thus eliminating any potential tableting problems seen in traditional compressed dosage forms.

The HME process (HME)

HME has been widely used technique in plastic processing industries and now it is used in pharmaceutical industries for developing formulation of sustained release [18], controlled release [19] and transdermal as well as transmucosal [20-22] drug delivery system. Polymer, API, equipment selection, excipients and processing conditions all play important roles in the success of a HME formulation.

Most of the compounds used in the production of hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, and transdermal film.

FDA guidance also facilitates the introduction of new technologies like HME to the pharmaceutical industry for the enhancement and modernization of formulation process using HME to improve the efficiency and effectiveness of manufacturing process design, control and quality assurance [23].

While doing HME for developing formulation ingredient like polymer, release modifying agents, bulking agents and processing agents are required with the help of which can be a the single- and twin-screw extruders [24,25]. Simple single screw arrangements consist of only a single rotating screw inside a stationary extruder barrel, whereas more advanced machines involve twin-screw systems utilizing either a co rotating or counter-rotating screw configuration. It is common for the extrusion screw to be characterized by the length/diameter (L/D) ratio, which typically ranges from 20 to 40:1. Typical pilot plant extruders have diameters ranging 18–30 mm, whereas production machines are much larger with diameters typically exceeding 50 mm. Irrespective of the complexity of the machine, the extruder must be capable of rotating the screw(s) at a selected speed while compensating for the torque generated from the material being extruded.

Single-screw extrusion is the simplest form of polymer processing mainly used to increase pressure within a polymer melt, allowing extrusion through a die or injection into a mould. Although a relatively simple process, single screw extrusion does not possess the mixing capability of a twin-screw machine and is, therefore, not the preferred approach for the production of pharmaceutical formulations [26]. While twin-screw extrusion offers a rapid, continuous process with much efficient mixing capability than single screw extrusion [26]. Also, twin screw extrusion provides a more stable melting process, shorter residence times and significantly greater output.

As an initial evaluation, the thermal, chemical, and physical properties of the drug and other ingredient must be characterized before and after processing. Depending on the physical and chemical properties of the drug substance (API) and the other ingredient in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. An extruder for HME process consists of a platform that supports a drive system, an extrusion barrel; a rotating screw arranged on a screw shaft and an extrusion die for defining product shape. Typically, process parameters are controlled via connection to a central electronic control unit. In hot melt extrusion process, extrusion channel is conventionally divided into three sections that are feed zone, transition zone, and metering zone. The monitor and controlling parameter in HME are barrel temperature, feed rate, screw speed, motor load and melt pressure. Extruder consist of two rotating screw inside a stationary cylindrical barrel. And an endplate die connected to the end of barrel determines the shape and size of extruded products. The function of the feeding section is to transfer the solid material forward into the melting section where it gradually melts as it enters the melting section. Initially, melting results from the heat transferred to the barrel from the heating devices. The geometric design of the metering section is an important factor in determining output rate of the extruder. The materials used in the production of hot-melt extruded dosage forms must meet the same levels of purity and safety as those used in traditional dosage forms and should maintain the same properties before and after the process. The state of the drug in the dosage form may have a severe impact on the heat hence cooling device is provided at the outer side of barrel. The molten mass is continuously pumped through the metering section with homogeneous mixing and passed through the die in a variety of shape and size. The thermal stability of each individual compound and the composite mixture should be sufficient to withstand the processing environments. The selection of an appropriate carrier compound is important in the formulation and design of a hot-melt extruded dosage form as the properties of the ingredient material often decide the processing conditions necessary for the production of the dosage unit, and the physical and chemical properties of the ingredient often modulate the release of the active compound from the final dosage form. To produce granules or tablets via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature because of the thermal sensitivity of most drugs (Table 1).

HME is continuous process as it does not require a lengthy drying stage since it does not involve addition of water or other solvent. The absence of water may prevent drug degradation as many drugs are unstable in presence of water. It produces a spherical shape pellets with narrow range particle size distribution. Reduce the loss of coating material during the coating process associated with wet mass extrusion process. It is a convenient technology for preparation of solid dispersion and solid solution for delivery of poorly soluble drug as it offers an advantage of solvent free formulation of solid dispersion. It helps to mask the bitter taste of the active ingredient. Poorly compatible materials can be incorporated into tablets produced by cutting an extruded rod.

Formulation development by HME

The selection of an appropriate carrier compound is important in the formulation and design of a hot-melt extruded dosage form. Depending on the physical and chemical properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product. The thermal stability of each individual compound and the composite mixture should be sufficient to withstand the production process. The properties of the carrier material often dictate the processing conditions necessary for the production of the dosage unit, and the physical and chemical properties of the carrier often modulate the release of the active compound from the final dosage form. To produce granules or tablets via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature because of the thermal sensitivity of most drugs. The selection of polymer for hot-melt extrusion process mainly depends on drug–polymer miscibility, polymer stability and function of final dosage form. A variety of carrier systems have been studied or used in hot-melt extrusion dosage forms.

Many commercially available, pharmaceutical-grade polymers like synthetic cellulose derivatives (ethyl cellulose [35], hypromellose [36], hydroxypropylmethyl cellulose [37], cellulose acetate butyrate [38]), methacrylates [39], polyethylene oxides [40], polyvinylacetate [41], poly(lactide–co-glycolide) [42, 43], starch [44], lipids [45], waxes [46] (possibly in combination with a plasticizer to optimize the thermoplastic properties of the polymer) etc are known for drug delivery and also used in HME formulations. Hot-melt extruded dosage forms are complex mixtures of active drug and functional excipients like matrix carriers, release–modifying agents, bulking agents, and various additives. The excipients can impart specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form (Table 2).

Initially projected as significant disadvantages of HME process like residence time within the extruder and high processing temperatures to melt the polymeric carrier were resolved by modification of screw configuration, coupled with the use of plasticizing agents and the introduction of twin screw extruders, removed such concerns. Typical plasticizing agents for HME include PEGs [47], triacetin [48], citrate esters [49], and citric acid [50].Typically, conventional plasticizer such as triacetin or polyethylene glycol is used in concentration range of 5-30 % weight of the extrudate that lowers the processing temperature. Carbon dioxide can act as temporary plasticizer. During extrusion carbon dioxide is transformed in gaseous phase. As a consequence carbon dioxide escapes from extrudate and does not appear in final product. In some of the cases API have been reported as effective plasticizers which occupy sites along the polymer chain, reduce polymer–polymer chain secondary bonding and provide more mobility for the macromolecules, resulting in a softer, more easily deformable mass [51, 52] thus improving process ability.

Various studies have been conducted using this technique to produce sustained release pellets of diltiazem HCl [53], using polymers such as ethyl cellulose, cellulose acetate butyrate, poly ethylene co vinyl acetate.

Table 1. Various excipients and drugs used in HME process

Excipients used	Drug used	Reference no.
PEG 6000, PVP or a vinylpyrrolidone-vinylacetate-copolymer	17β-Estradiol hemihydrate (17β-E2)	27
Hydroxypropylmethylcellulose	Itraconazole	28
Hydroxypropyl cellulose and poly(ethylene oxide)	Clotrimazole	29
Polyethylene oxide	Chlorpheniramine maleate	30
Ethylcellulose, Polyethylene glycol and polyethylene oxide	Metoprolol tartrate	31
Polysorbate 80, sodium lauryl sulfate, citric acid and malic acid	Itraconazole	32
Ethyl cellulose	Ibuprofen	33
Polyethylene oxide and hydroxy propylcellulose	Tetrahydrocannabinol (THC)	34

Table 1. Properties of polymers used in HME

Polymers	Properties
Poly(ethylene) oxide	Is a white hydrophilic powder with 100,000-7,000,000-Da M.Wt. used for controlled-release, solid-dose matrix systems, transdermal delivery systems, and mucosal bioadhesive. It has a broad processing window with melting point is ~70 °C, and does not exhibit weight loss until ~350 °C, eg. Polyox® WSR.
Ethylcellulose	Is a hydrophobic ethyl ether of cellulose used for encapsulation of API, controlled-release systems, taste masking, solvent and extrusion granulation, tablet binding, and for coating for tablets and beads. EC is available in various molecular weights, and has a T_g of 129–133 °C and a melting point ~180 °C, eg. Ethocel®
Hypromellose	It is hydrophilic cellulose ether that is available in a range of viscosities and substitutions and used for controlled-release matrices, tablet coatings, and granulation binders. HM a narrow processing window because of a high T_g of 160–210 °C .
poly (ethylene-co-vinyl acetate) (EVA)	It is polar copolymers with low processing temperature. Their properties depend mainly on ration of ethylene to vinyl acetate. Thus, VA content is an important parameter of the copolymer, and needs to be known before the material is put into use. Its T_g is ~36 °C, Elvax® .
cellulose acetate butyrate (CAB)	The functional properties of CAB depend upon its degree of substitution as well as the distribution pattern of the two ester substituent groups on the (1→ 4)-d-glucopyranosyl residues of the polysaccharide. CAB is water insoluble polymer, T_g of 125–127 °C.

The resulting pellets exhibited smooth surface, low porosity and showed slow drug release [29]. Utilization of a ram extruder in the preparation of fast release dosage form with uniform shape and density, containing carbamazepine as poorly soluble model drug and PEG 4000 as a hydrophilic carrier and low melting binder, revealed that the extruded mixture of equal composition exhibited more rapid release than simple physical mixture [54].

Controlled release theophylline pellets were prepared by hot melt extrusion method using eudragit, microcrystalline cellulose and poly ethylene glycol 8000 [55-56] powder. The evaluation studies showed that pellet follows diffusion controlled drug release which is influenced by polymer swelling and pH dependent dissolution. Sustained release matrix tablets of chlorpheniramine maleate were prepared by hot melt extrusion method using polyethylene oxide as drug carrier, the evaluation studies revealed that drug release was controlled by erosion of matrix and the diffusion of drug took place through swollen gel layer at surface of the tablet.

CONCLUSION

Today melt extrusion technology represents an efficient pathway for manufacture of drug delivery systems. Incorporation of a drug in a polymer matrix is often used to sustain drug release. To produce these sustained-release matrices, HME is becoming a widely-used technology in the pharmaceutical industry. Its major advantage over conventional techniques for manufacturing of sustained-release matrices is the continuity of the hot stage extrusion technique as the different process steps like mixing, melting, homogenizing and shaping can be carried out on a single machine. This offers many opportunities for automation of the production process, allows a high throughput, limits material loss and yields matrices with excellent homogeneity.

In addition, the physical state of the drug in an extrudate can be modified with help of process engineering and the use of various polymers. The drug can be present in crystalline form for sustain release applications or dissolved in a polymer to improve dissolution of poorly water-soluble drugs. The possible use of a broad selection of polymers starting from high molecular weight polymers to low molecular weight polymers and various plasticizers has opened a wide field of numerous combinations for formulation research. The design of screw assemblies and extruder dies are two the major areas, which have significant impact on product quality and degradation of API due to mechanical, thermal and oxidative-degradation associated with the high energy input mainly required for the to shear forces and temperature. Work in this field is increasing and the literature published reveals many novel aspects to overcome issues related with HME technology.

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