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Pharmaceutical applications of hot melt extrusion technology: An overview

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Abstract
Hot-melt extrusion (HME) has emerged as a promising technique to develop several types of pharmaceutical dosage forms and drug delivery systems. The absence of solvents, fast processing, simple and continuous operation, high degree of automation, and ability to process poorly compactable material into tablet form are some of the advantages offered over conventional processing by this innovative technique. The basic steps involved in this technique are mixing and melting an active pharmaceutical ingredient (API), polymer, and other excipients in a melt extruder and then forcing it through dies with one or more rotating screws to obtain the desired product. The materials used in hot melt extruded products must possess some degree of thermal stability in addition to acceptable physical and chemical stability. Interest in HME as a pharmaceutical process continues to grow and recent success of this technique have made it worthy of consideration as a drug delivery solution.

Keywords: Hot-melt extrusion; Manufacturing operations; Applications of HME as drug delivery

Introduction
Hot melt extrusion (HME) technology is one of the emerging technologies that offer many advantages over conventional solid dosage form unit operations [1]. Although this technology has been used in rubber and plastic industry for a long time, but its application to the field of pharmaceutical product development is relatively new. In the recent past, much work has been done for the improvement in this technology. More than 100 articles have been published in the scientific literature and the number of HME patents has increased steadily [2-3]. This technology, no doubt, offers to be the technology of the future with a wide range of applications in the production of various dosage forms [4]. Initially used only in production of tablets and films, it is now being explored for the purpose of producing capsules, sustained release products and implantable devices [5-6]. Given that detailed description of HME its pharmaceutical applications have been extensively reviewed in the scientific literature and the aim of this review article is to provide a basic introduction to HME, the extrusion equipment, fundamental principles of operation and to discuss and identify the most recent applications within the field of drug delivery.

Instrumentation
The main components of an extruder are feeding hopper, a screw driving system, a barrel, a rotating screw and an extrusion die. The extrusion drive system consists of motor, gearbox and linkages. It is responsible for moving the screws inside the barrel at the required rate. An auxillary system may also be present which consists of a provision for heating or cooling of barrels [1]. The primary function of screws is to mix the ingredients properly and convey the melt to the die. These may vary in number and arrangement inside the barrel. A single screw extruder consists of a single screw whereas there are two screws in a twin screw system. The length and diameter of these screws play an important role in the extrusion process. The length/diameter ratio may vary from 20 to 40:1. This parameter is decided by the type of product and amount of product to be obtained from the extruder. An extruder is also equipped with a temperature gauge and a pressure gauge to keep a check on temperature and pressure respectively. Normally, the heating is done electrically and thermocouples assist in sensing the temperature. The maintenance of an optimum temperature is essential because higher temperature may degrade the ingredients and lower temperature may not lead to proper melting and hence improper mixing. The screws are designed in such a fashion that the pressure increases along the length of the extruder [7].

Hot melt-extrusion process

The hot melt extrusion integrates the conventional methods of melting, mixing, kneading, venting and extrusion. This process can be divided into different phases:

a) feeding the extruder
b) mixing and size reduction
c) passing the melt through the die
d) down stream processing

In this process, the drug, polymer and drug release modifiers are mixed and the physical mixture is fed into the equipment with a hopper. Subsequently, it gets heated inside the barrel. This melt is properly mixed by the screw inside to obtain a homogenous mass which is then forced through the die. The tablets or pellets may be obtained by cutting the extruded product in desired shape. The product may also be grounded to get the granules which after mixing with the excepients can be compressed to get the tablets [5, 7].

Single screw extruder

In a single screw extruder as shown in figure 1, there is only one screw and is relatively simpler in design. The polymer melt is forced through the die or injected into the mould. Although this is a simple process, it has been more or less replaced by the more efficient twin screw extrusion process.

Twin screw extruder:

The twin screw extruder has a pair of extruders arranged in different manners for the same purpose. The two screws may either co-rotate or counter-rotate for the purpose of mixing. In a design, the two screws are fixed respectively to two screw shafts at an angle which gives the equipment a conical shape.

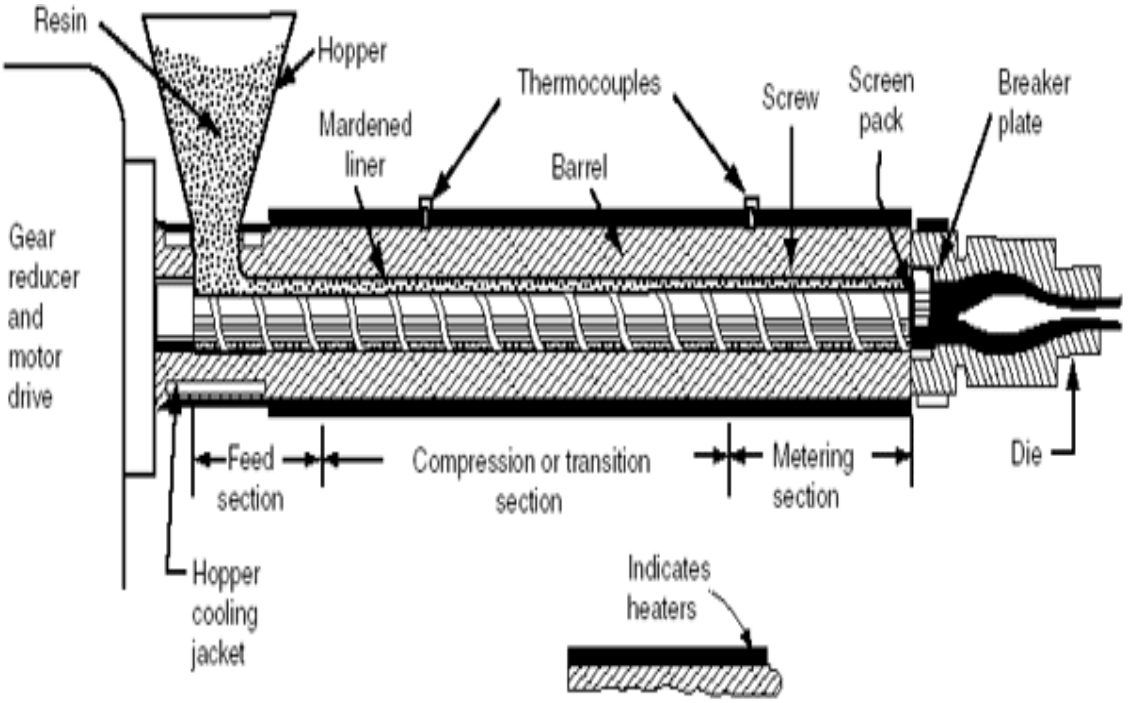

Fig 1: Components part of a single crew extruder

Pharmaceutical Applications

Granulation and pelletization

HME can be employed for the preparation of granules and pellets. Granulation, an important step in preparation of tablets is possible by extruding a combination of meltable binders, API, and other excipients at the required temperature. HME was employed by Liu et.al to prepare sustained release wax granules [8]. As compared to traditional melt granulation technique, granules prepared with HME showed excellent strength and better content uniformity. Effervescent granules were also prepared by HME which showed controllable rate of effervescence [9].

Pelletization involves cutting the thermoplastic strands as they emerge from the extruder's die and then processing them in a spheroniser. Follonier and coworkers investigated HME technology for the development of polymer based pellets of Diltiazem for incorporation into sustained release capsules. Ethylcellulose (EC), cellulose butyrate (CAB) and poly (ethylene-co-vinyl-acetate) (EVAC) were used as polymers and triacetin, diethylphthalate were used as plasticizers [10].

Tablets

HME is now being used in the development of solid dosage forms such as tablets and capsules. The extrudate can then be collected as granules that can be further processed for incorporation into tablets. The development of tablets by HME offers various advantages such as fewer processing steps, ability to process poorly compactable drugs and ability to process moisture sensitive drugs.

Zhang *et al*. investigated the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion. A physical mixture of drug, polymer, and drug release modifiers was fed into the equipment and heated inside the barrel of the extruder. The cylindrical extrudates were either cut into tablets or ground into granules and compressed with other excipients into tablets. The release rate was shown to be dependent on the granule size, drug particle size, and drug loading in the tablets. Water-soluble polymers were demonstrated to be efficient release rate modifiers for this system [11]. Hot-melt extrusion process was employed to prepare matrix tablets of chlorpheniramine maleate (CPM) containing chitosan and xanthan gum. The HME tablets containing both chitosan and xanthan gum showed no significant change in drug release rate when stored at 40 degrees C for 1 month, 40 degrees C and 75% relative humidity (40 degrees C/75% RH) for 1 month, and 60 degrees C for 15 days [12]. Crowley *et al*.

investigated the drug release mechanism from ethyl cellulose (EC) matrix tablets prepared by either direct compression or hot-melt extrusion (HME) of binary mixtures of water soluble drug (guaifenesin) and the polymer [13]. Controlled release tablets containing a poorly water-soluble drug, indomethacin (IDM), acrylic polymers (Eudragit RD 100, Eudragit L 100, or Eudragit S 100), and triethyl citrate (TEC) were prepared by hot-melt extrusion. Indomethacin (IDM) was found to be both thermally and chemically stable following hot-melt extrusion processing and displayed a plasticizing effect on Eudragit RL PO as demonstrated by a decrease in the glass transition temperatures of the polymer Indomethacin (IDM) was transformed from a crystalline Form I into an amorphous form in the Eudragit RD 100 granules following hot-melt extrusion. The thermal processing facilitated the formation of a solid solution with a continuous matrix structure that was shown to control drug diffusion from the extrudates [14].

More recently Schilling *et al*. investigated the ability of citric acid monohydrate (CA MH) to enhance the release of diltiazem hydrochloride from melt extruded Eudragit RS PO tablets and to eliminate drug particle size effects The enhanced drug release was attributed to the amorphous character of the soluble components, improved drug dispersion in the plasticized polymer along with increased polymer permeability (14). CA MH promoted the miscibility between the drug and Eudragit RS PO during hot-melt extrusion, resulting in the extrusion of an amorphous system with improved dissolution characteristics. Hot-melt extruded tablets with enteric and sustained-release properties were prepared using ketoprofen as a model drug and Eudragit® L100 as the carrier. Ketoprofen, with a similar solubility parameter to Eudragit® L100, was homogeneously dispersed in the polymer matrix in a non-crystalline state, and was identified by differential scanning calorimetry, X-ray diffraction, and scanning electron microscopy analysis [15].

Alshetaili *et al*., prepared taste-masked mini-tablets by hot-melt extrusion technology was used to of the bitter model drug ketoprofen using Eudragit® EPO as a taste-masking polymer. Thermo gravimetric analysis studies showed that the drug was thermally stable under the employed extrusion parameters. Differential scanning calorimetry and polarized light microscopy-hot stage microscopy studies confirmed that the binary mixtures were miscible under the employed extrusion temperatures. Drug release was less than 0.5% within the first 2 min in simulated salivary fluid (pH 6.8) and more than 90% in the first 20 min in gastric media (pH 1.0).=-017. The results of the electronic tongue analysis were well correlated with the drug release results obtained for the mini-tablets in artificial saliva. SEM revealed no pores or cracks on the surface of the mini-tablets, confirming that the mini-tablets were compact solids [16].

Capsules

HME is also finding application in capsule dosage form. Mehuys *et al*. developed an alternative technique for enteric coating consisting of the hot-melt extrusion of coating polymers. An enteric coating polymer (PVAP or HPMC AS), premixed with a plasticizer, was extruded into hollow cylinders. The hollow pipes were filled with a model drug and both open ends of the cylinders were closed, yielding hot-melt extruded enteric capsules [17]. Main advantages of this new technology are the continuity of the process and its application for the formulation of moisture sensitive active ingredients. The enteric capsules showed excellent gastro-resistance, since no drug release was observed after 2 h 0.1N HCl. It was concluded that hot-melt extruded capsules could be a suitable alternative for enteric coating.

Transdermal/Transmucosal dosage form

HME technology is currently being explored and used in the pharmaceutical field for preparation of transdermal/transmucosal systems. In HME the polymer is shaped into film by heating method as compared to traditional solvent cast method. The transdermal systems prepared by HME offers various advantages over conventional methods of film cast from organic or aqueous solvents which includes less processing time, environment friendly approach and cost effectiveness. The viability of HME for production of films was investigated by Atiken-Nichol [18]. They found that HME was a viable method for preparing films of the acrylic resin based on dimethylaminoethyl methacrylate and neutral methacrylic acid resin esters. Repka and coworkers used HME technology to produce hydroxyl propyl cellulose (HPC) films utilizing a Killion extruder which numerous advantages over the films had cast from organic or aqueous solvents. The authors concluded that the extruded films are not restricted by solvent concerns and offer better dissolution rates and ductility [19]. Films containing hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) were prepared using a Randcastle extruder (Model 750) with and without Vitamin E TPGS (TPGS, D-alpha-tocopheryl polyethylene glycol 1000 succinate) as an additive. Conventional plasticizers including polyethylene glycol 400 (PEG 400), triethyl citrate (TEC), and acetyltributyl citrate (ATBC) were also incorporated into films containing a 50:50 blend of HPC and PEO. Hot-melt extrusion technology (HME) was used to prepare muco-adhesive matrix films containing 10% w/w clotrimazole (CT) intended for local drug delivery applications for the oral cavity [20].

Solid Dispersions

HME offers an alternative to the melt and solvent methods for developing solid dispersions and mini matrices. It requires incorporating the API into a polymer by melting or plasticizing the API and excipient with either one or two screws inside a heated barrel. When the molten material is cooled, it forms a glass solution of API and polymer. Since HME is a solvent free process, it overcomes the environmental, toxicological, and financial problems associated with the use of large amount of solvent. Because HME subjects the API-carrier mixture to elevated temperatures for a very short period, the technique can process APIs that are thermo labile [21]. Solid dispersions of 17 beta-estradiol hemi hydrate, a poorly soluble drug, were prepared by HME [22-23]. Recently it has been found that glass solutions of a lipophilic drug substance prepared by extrusion technology, on dissolution forms nanoparticles, thereby increasing the dissolution kinetics. Moreover, using hot extrusion method C-nanotubes/nanofibres can be incorporated in aluminium matrix imparting overall strength [24-25]. Solid dispersions containing 10% and 20% paracetamol in EUDRAGIT E were prepared by hot-melt extrusion into elongated strands [26].

Lakshman *et al*. reported a novel method where the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w [27]. By this means, melt extrusion could be performed much below the melting temperature of the drug substance. Since the glass transition temperature of the amorphous drug was lower than that of the polymer used, the drug substance itself served as the plasticizer for the polymer.

The addition of surfactants in the matrix enhanced dispersion and subsequent dissolution of the drug in aqueous media. The amorphous melt extrusion formulations showed higher bioavailability than formulations containing the crystalline API. There was no conversion of amorphous solid to its crystalline form during accelerated stability testing of dosage forms. Solid dispersion with carrier of Eudragit E100 or PVP-VA was prepared by hot-melt extrusion and then characterized by differential scanning calorimetry (DSC), X-ray diffraction, *in vitro* dissolution test, and *in vivo* bioavailability study. Hot-melt extrusion proved to be an excellent method to improve the dissolution and therefore the bioavailability of fenofibrate [28].

Ophthalmic Inserts

The technique of melt extrusion is also applied to the fabrication of acyclovir ocular inserts as solid polymeric rods to be placed in the cul-de-sac of the eyes. These inserts were retained in the eye for required period of time and sustained the release of the drug for 10 h. The polymer slowly released the drug via swelling and dissolved slowly in the tear fluid, thus avoiding the need to remove insert after drug administration. Further, the polymer is also non-greasy, thus potentially increasing patient acceptability [29].

Conclusion

HME is one of the latest emerging technologies in the field of pharmaceutical product development. It offers a wide range of applications in production of solid dosage forms, films and is still being explored in other fields too. Researchers are aiming to reduce the few but existing drawbacks of this technology. New designs of the screws and high efficiency barrels are also being searched for. Recent developments in this field ensure that this technology promises to be the technology of future.

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