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PHARMACEUTICAL APPLICATIONS OF HOT MELT EXTRUSION TECHNIQUE

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ABSTRACT

Hot-melt extrusion (HME) is a widely applied technique in the plastics industry and in the recent years has been demonstrated to be a viable method to prepare several types of dosage forms and drug delivery systems. HME processes are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations. HME offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, thus less time consuming, simple and continuous operation, high degree of automation, accepted by regulatory agencies, the ability to process poorly compactable material into tablet form and the possibility of the formation of solid dispersions and improved bioavailability. The basic principle behind HME technology involves mixing and melting an active pharmaceutical ingredient (API), a pharmaceutical grade 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 selection of polymer and the establishment of extrusion conditions (extrusion temperature, screw configuration, screw speeds etc.) are critical during product development. Moreover, 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 the potential of automation and reduction of capital investment and labor costs has made this technique worthy of consideration as a drug delivery solution.

INTRODUCTION

Hot melt extrusion (HME) technology is one of the emerging technologies that offer many advantages over conventional solid dosage form unit operations. Although this technology has a long past in rubber and plastic industry, but its application to the field of pharmaceutical product development is not much old. 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 [1]. 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. 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. Given that detailed description of HME its pharmaceutical applications have been extensively reviewed in the scientific literature. The aim of this article is to provide an insight to HME, and the most recent applications within the field of drug delivery.

Process and Equipment

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 auxiliary system may also be present which consists of a provision for heating or cooling of barrels [2]. 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 can be selected based on 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 leads to improper mixing. The screws are designed in such a fashion that the pressure increases along the length of the extruder [3].

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) downstream 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 excipients can be compressed to get the tablets [4].

Single screw extruder:

In a single screw extruder, 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 [5].

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 [5].

PHARMACEUTICAL APLLICATIONS OF HME

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 to prepare sustained release wax granules [6]. 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 [7].

Pelletization involves cutting the thermoplastic strands as they emerge from the extruder's die and then processing them in a spheroniser. Follonier and co-workers investigated HME technology for the development of polymer based pellets of diltiazem HCl 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 [8]. Controlled-release theophylline containing spherical pellets were successfully produced by HME and spheronization process. A powder blend of anhydrous theophylline, eudragit preparation 4135 F, microcrystalline cellulose and polyethylene glycol 8000 powder was sieved, blended and then melt-extruded in a randcastle microtruder. The hot-melt extruded pellets were prepared by first cutting a thin, extruded composite rod into symmetrical pellets. The pellets were then spheronized in a traditional spheronizer at an elevated temperature. The rate of release of theophylline from the hot-melt extruded spherical pellets was characterized using USP 24 apparatus 2 dissolution testing after initial pellet production and after one year storage in sealed high density polyethylene containers at 25^{0}C/60% RH [9].

For moisture-proofing effect study, herbal extracts of guizhi fuling (GF) were prepared using extrusion-spheronization combined with hot-melt coating. In the process of extrusion-spheronization, pellets containing 100% GF were prepared. When the pellets were coated with a 96:4 mixture of stearic acid and PEG 6000, the cumulative drug release was over 90% at 45 min, while the moisture content was 4.9% at 75% RH within 10 days. These pellets have better moisture-proofing than those coated with opadry aqueous moisture barrier [swelling controlled system] at the same coating level due to a different moisture sorption mechanism [10]. Wang *et al.,* (2010) prepared gliclazide-loaded matrix pellets consisting of ethylcellulose, microcrystalline cellulose and sodium carboxymethyl starch by extrusion-spheronization [11].

Sustained release pellets of furosemide for oral administration were prepared by extrusion spheronization. Along with microcrystalline cellulose, drug coat L-100 was used within the pellet. The formulation was prepared with drug to polymer ratio 1:3 [12]. Mihir *et al.,* (2013) developed intestinal-targeted pellets of budesonide for the treatment of ulcerative colitis and Crohn's disease by extrusion and spheronization method. A pH-controlled intestinal-targeted pellet of budesonide was established using 3^2 full factorial design by giving an enteric coating with eudragit S100 [13]. Maddineni *et al.,* (2014) conducted the studies to develop techniques

for an abuse-deterrent platform utilizing the hot-melt extrusion process. The three formulation factors: polyox WSR301, benecel K15M and carbopol 71G; were studied at three levels on tamper-resistant attributes of the produced melt extruded pellets. Lidocaine hydrochloride was used as a model drug [14].

Retarded release pellets were developed using vegetable calcium stearate as a thermoplastic excipient. Vegetable calcium stearate was extruded at temperatures between 100-130°C. Pellets were also prepared with a drug loading of 20% paracetamol which released 11.54% of the drug after 8 h due to the great densification of the pellets. Two plasticizers glyceryl monostearate and tributyl citrate were investigated for plasticization efficiency and impact on the *in vitro* drug release. Glyceryl monostearate increased the release rate due to the formation of pores at the surface (after dissolution) and showed no influence on the process parameters. The addition of tributyl citrate increased the drug release to a higher extent [15].

Kalivoda *et al.,* (2012) applied hot-melt extrusion to improve the solubility of the poorly water-soluble drug oxeglitazar. Copovidone, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer (PVCL-PVAc-PEG) and hypromellose 2910/5 were used as carriers. After extrusion, the extrudate was pelletized [16]. Schilling (2010) investigated the influence of three plasticizers triethyl citrate, methylparaben and PEG 8000 on the properties of hot-melt extruded eudragit S100 matrix pellets. Reduction in polymer melt viscosity was produced by all three plasticizers [17].

Maniruzzaman *et al.,* (2012) extruded granules containing high paracetamol loadings in eudragit E PO or kollidon VA64 by hot-melt extrusion. The taste masking effect of the processed formulation was evaluated *in vivo* by a panel of six healthy human volunteers. *In vitro* evaluation was carried out by an Astree e-tongue (Alpha MOS) equipped with seven sensors. The best masking effect was observed for VA64 at 30% paracetamol loading [18]. Crospovidone (polyplasdone XL-10) was compared with microcrystalline cellulose for the preparation of melt-in-mouth pellets of taste-masked fexofenadine hydrochloride [19]. Bialleck *et al*., (2011) prepared pellets based on four different starches (corn starch, waxy corn starch, pea starch and potato starch), four different active ingredients (paracetamol, ibuprofen, phenazon and tramadol-HCl) were used along with various additives. The resulting pellets exhibited a large mechanical stability and low porosity with small surface area [20].

Tablets

HME has lot of application 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;
- Ability to process moisture sensitive drugs.

Zhang *et al.*, (2000) investigated the drug release mechanism of theophylline from matrix tablets prepared by HME. 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 [9]. HME was also 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^{o}C for 1 month, 40^{o}C and 75% RH (40^{o}C/75% RH) for 1 month, and 60^{o}C for 15 days [21]. Crowley *et al*., (2004) investigated the drug release mechanism from ethyl cellulose (EC) matrix tablets prepared by either direct compression or HME of binary mixtures of water soluble drug (guaifenesin) and the polymer [22]. 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 HME. 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 showed control drug diffusion from the extrudates [23]. In 2008, Schilling *et al.,* (2008) 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 [24]. Citric acid monohydrate promoted the miscibility between the drug and eudragit RS PO during HME, resulting in the extrusion of an amorphous system with improved dissolution characteristics. 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 [25].

The thermal stability of polyethylene oxide in sustained release tablets prepared by hot-melt extrusion was investigated. The average molecular weight of the polymer was studied using gel permeation chromatography. The chemical stability of polyethylene oxide was found to be dependent on both, the storage and processing temperature and the molecular weight of the polymer [26]. Eudragit L100-55, an enteric polymerwas pre-plasticized with triethyl citrate and citric acid and subsequently dry-mixed with 5-aminosalicylic acid and an optional gelling agent (PVP K30 or carbopol 971P). These powder blends were hot-melt extruded as cylinders and were cut into tablets [27]. Michael *et al.*, (2004) investigated physicochemical properties and drug release mechanism from ethyl cellulose matrix tablets prepared by either direct compression or hot-melt extrusion of binary mixtures of water soluble drug (guaifenesin) and the polymer. Ethyl cellulose was separated into fine particle size fraction corresponding to 80-325 and coarse particle size fraction of 30-80 mesh, respectively. Tablets containing 30% guaifenesin were prepared at 10, 30, or 50 kN compaction forces and extruded at processing temperatures of 80-90°C and 90-110°C [28].

Matrix mini-tablets based on a combination of microcrystalline waxes and starch derivatives were prepared using ibuprofen as a model drug. Prior to tableting, melt granulation in a hot stage screw extruder and milling was done. The *in vitro* drug release was varied using microcrystalline waxes with a different melting range, the slowest drug release being obtained with a formulation containing a microcrystalline wax with a melting range between 68°C and 72°C. Increasing the ibuprofen concentration to 70% resulted in a faster drug release rate [29]. Liu *et al.*, (2001) investigated the influence of formulation factors on the physical properties of hot-melt extruded granules and compressed tablets containing wax as a thermal binder/retarding agent. Powder

blends of phenylpropanolamine hydrochloride, precirol with various excipients were extruded in a single-screw extruder. The extrudates were passed through a 14-mesh screen to produce granules. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and showed lower values of bulk/tap densities. Tablets containing microcrystalline cellulose or lactose granules prepared by HME exhibited higher hardness values [30].

Matrix tablets of chlorpheniramine maleate containing chitosan and xanthan gum prepared by a hot-melt extrusion process was investigated to detect the influence of pH and ionic strength on the release mechanism. Drug release from hot-melt extruded tablets containing either chitosan or xanthan gum was pH and buffer species dependent and the release mechanisms were controlled by the solubility and ionic properties of the polymers. HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release [31]. Zhang *et al.,* (1999) investigated the properties of polyethylene oxide as a drug carrier and studied the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets prepared by hot-melt extrusion was. Faster release of CPM from the matrix tablets was observed in acidic medium than in purified water and phosphate buffer (pH 7.4) [32].

Influence of sodium bicarbonate on the physicochemical properties of controlled release hot-melt extruded tablets containing eudragit RS PO and/or eudragit E PO was investigated by using acetohydroxamic acid and chlorpheniramine maleate as model drugs. Sodium bicarbonate was added into the tablet formulations and the drug release properties and buoyancy in media for hot melt extruded tablets and directly compressed tablets were investigated. The hot melt extruded tablets prepared from the powder blend containing both eudragit RS PO and sodium bicarbonate exhibited sustained release properties and the tablets floated on the surface of the media for 24 h [33].

Cassidy *et al.,* (2011) formulated eudragit based drug delivery system, via hot melt extrusion, for targeting colonic release of photosensitizers. The susceptibility of *E. faecalis* and *B. fragilis* to photodynamic antimicrobial chemotherapy mediated by methylene blue, meso-tetra(N-methyl-4-pyridyl)porphine tetra-tosylate (TMP), or 5-aminolevulinic acid hexyl-ester (h-ALA) was determined with tetrachlorodecaoxide. Results showed that, for methylene blue, an average of 30% of the total drug load was released over a 6-h period. For TMP and h-ALA, these values were 50% and 16% respectively. Levels of E. faecalis and B. fragilis were reduced by up to 4.67 and 7.73 logs, respectively [34]. Ability of citric acid monohydrate to enhance the release of

diltiazem hydrochloride from melt extruded Eudragit RS PO tablets and to eliminate drug particle size effects was investigated. The addition of citric acid monohydrate to the formulation promoted the thermal processibility and matrix integrity by plasticization of the polymer. Due to citric acid monohydrate the drug release from systems with constant drug-to-polymer ratio was significantly increased as a result of enhanced pore formation. When large amounts of citric acid monohydrate were used, particle size effects were eliminated due to the loss of drug crystallinity [35].

Thommes *et al.*, (2011) formulated 800 mg of darunavir in a single unit dosage form using a corotating twin screw extruder. Extrudates of 1 mm diameter were prepared to evaluate the extrusion and dissolution behavior of darunavir. Two different poloxamers (188 and 407) were used to modify the dissolution properties of darunavir. A higher solubilization for poloxamer 188 was observed. A zero order drug release from pure darunavir extrudates was found which was modulated by the extrudate diameter. Extrudates of 13 mm diameter were cut into tablets containing 800 mg of darunavir. The formulations exhibited acceptable extrusion behavior and dissolution properties [36].

Capsules

HME is also finding application in capsule dosage form. Mehuys *et al*., (2005) 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 [37]. 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.

Klucel hydroxypropylcellulose EF and ELF polymers were evaluated for solubility enhancement using ketoprofen. Extrudates were pelletized and filled into capsules. Extrudates exhibited a carrier-dependent faster release with ELF polymer. Tablets compressed from milled extrudates exhibited rapid release owing to the increased surface area of the milled extrudate. Addition of mannitol further enhanced the release by forming micro-pores and increasing the porosity of the extrudates [38].

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. [39]. The viability of HME for production of films was investigated by Atiken-Nichol [40] and 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 films utilizing a killion extruder which had numerous advantages over the films cast from organic or aqueous solvents. It was concluded that the extruded films are not restricted by solvent concerns and offer better dissolution rates and ductility [41]. Films containing hydroxypropylcellulose 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. 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 [42].

Physical stability of the drug clotrimazole and the polymer contained within hot-melt extrusion films was enhanced using polymer blends of hydroxypropyl cellulose and polyethylene oxide. Clotimazole was found to be in solid solution within all of the extruded formulations. The physical stability of the clotrimazole and polyethylene oxide in the HME films increased with increasing hydroxypropyl cellulose concentration [43].

Mididoddi *et al.,* (2006) investigared the influence of tartaric acid (TTA) on the the properties like bioadhesiveness, moisture sorption, and mechanical properties of hot melt extruded hydroxypropyl cellulose films containing polymer additives. Two klucel EF and LF batches (HPC, MW: 80000 and 95000, respectively) containing the drug ketoconazole (one batch of each MW with and without TTA 4%) were prepared into films by HME using a killion extruder. The bioadhesive properties of the hydroxypropyl cellulose films, with and without tartaric acid, were investigated *ex vivo* on the human nails [44]. Particles composed of mixtures of the

hyperbranched poly(esteramide) hybrane S1200 and hydrochlorothiazide drug were produced by hot melt extrusion at 90°C temparature without addition of a plasticizer [45]. Hot melt extruded buccal film formulations of domperidone containing polyethylene oxide N10 and its combination with HPMC E5 LV or eudragit RL100 as polymeric carriers and PEG3350 as a plasticizer, was characterized by both *in vitro* and *in vivo* techniques. The blends were prepared at a screw speed of 50 rpm with the barrel temperatures ranging from 120-160°C utilizing a bench top co-rotating twin-screw hot-melt extruder using a transverse-slit die [46].

The effect of aqueous film coating on the recrystallization of guaifenesin from acrylic, hot-melt extruded matrix tablets was investigated. After hot-melt extrusion, matrix tablets were film-coated with either hypromellose or ethylcellulose. Hypromellose prolonged the crystallization for longer period (3 or 6 months in tablets stored at 40°C or 25°C) than guaifenesin, (crystal growth on tablets cured for 2 hours at 60°C occurred within 3 weeks, whereas uncoated tablets displayed surface crystal growth after 30 min [47].

Repka *et al.,* (2001) prepared hydroxypropylcellulos films containing chlorpheniramine maleate in concentrations of 1, 5, and 10% weight, by hot-melt extrusion utilizing a randcastle microtruder. All three concentrations of extruded films exhibited a 10-12 fold decrease in tensile strength in contrast to a fourfold increase in percent elongation when testing was performed perpendicular to flow vs. in the direction of flow [48]. *In vivo* bioadhesive properties of hydroxypropylcellulose films containing seven polymer additives were investigated on the epidermis of 12 human subjects. Hydroxypropylcellulose films containing polyethylene glycol 3350 alone, vitamin E TPGS 5%, sodium starch glycolate 5%, eudragit E-100 5%, carbomer 971P 5%, and polycarbophil 5%, all with and without plasticizer, were prepared by hot-melt extrusion. Bioadhesion testing was performed using a chatillon digital force gauge DFGS50 attached to a chatillon TCD-200 motorized test stand to determine force of adhesion (FA), elongation at adhesive failure (EAF), and modulus of adhesion (MA) for the 12 films tested. The TPGS incorporated film exhibited a two-fold increase in force of adhesion when compared to the control film containing the PEG 3350 5%. The carbomer 971P and polycarbophil containing films were determined to have the highest force of adhesion and elongation at adhesive failure, and the lowest MA of all films tested [49].

Ravina *et al.,* (2014) prepared the extrudates of hyperbranched polymer hybrane H1500 by hot melt extrusion, with particle size ranges from <250μm to 1.5-2.0 mm and drug contents of (10,

20 and 30%) of acetaminophen or caffeine. Hybrane H1500 extrudates experienced a very slow hydration, with a limited swelling capacity. HME provokes the conversion of the acetaminophen into an amorphous state inside the extrudates, but in caffeine containing extrudes, some crystals remain for the highest drug proportions (20 and 30%) [50].

Six 250 g batches of hydroxypropyl cellulose and/or poly (ethylene oxide) films containing ketoconazole (20%) were extruded using a killion extruder (Model KLB-100). The theoretical post-extrusion content of ketoconazole remaining in the six film batches ranged from 90.3% (±2.2) to 102.4% (±9.0) for up to 6 months and from 83.9% (±3.6) to 91.6% (±3.0) for up to 12 months [51].

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 [52]. Solid dispersions of 17 beta-estradiol hemi hydrate, a poorly soluble drug, were prepared by HME. [53,54]. Dissolution rate of the formulation containing 10% 17 beta estradiol, 50% PVP and 40% gelucirew 44/14 increased 30 times. The solid dispersions were then processed into tablets. Moreover, using hot extrusion method carbon nanotubes/nanofibres can be incorporated in aluminium matrix imparting overall strength [55, 56]. Solid dispersions containing 10% and 20% paracetamol in eudragit E were prepared by hot-melt extrusion into elongated strands [57].

Lakshman *et al*., (2008) 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. 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. [58]. 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 [59].

Melt extrudates of ritonavir were prepared by molecular dispersions of drug in a polymer/surfactant matrix. Particulate dispersions were produced in water from both drug and placebo extrudates [60]. Geert *et al.*, (2003) prepared solid dispersions containing different ratios of itraconazole and hydroxypropylmethylcellulose by solvent casting. A drug/polymer ratio of 40/60 w/w was selected in order to prepare dispersions by melt extrusion [61].

Two hot melt extrusion HME compositions of venlafaxine HCl with eudragit RS PO as the matrix polymer and either citric acid monohydrate or lutrol F127 as plasticisers were compared. It has been found that citric acid monohydrate and lutrol have different reactivities towards venlafaxine HCl and also different plasticising mechanisms for eudragit RS PO because of hydrogen bonding [62].

Feng *et al.*, (2012) prepared solid dispersions containing bifendate in different polymers, including plasdone S-630, eudragit E PO and kollidon VA 64 by hot-melt extrusion. Finally, the oral bioavailability of bifendate dosage forms with bifendate-plasdone S-630, bifendate-eudragit E PO and bifendate-kollidon VA 64 solid dispersion in beagle dogs was compared with that of commercially available benfidate pills [63]. The influence of antiretroviral drugs [zidovudine and lamivudine] and plasticizers [triethylcitrate and PEG-6000] on the rheological and thermal characteristics of ethyl cellulose formulations intended for hot melt extrusion has been investigated. The viscosity of physical mixtures containing both drugs was lower than observed for pure ethyl cellulose, indicating plasticizing effect of drugs [64]. Fule and Amin developed lafutidine solid dispersion using HME technique. Amphiphilic soluplus used as a primary solubilizing agent, with different concentrations of surfactants like PEG 400, lutrol F127 and lutrol F68 were used to investigate their influence on formulation preparation via HME. Prepared amorphous glassy solid dispersion was found to be thermodynamically and physicochemically stable [65].

Carbamazepine (CBZ) solid dispersions was prepared and combinations of kollidon VA64 (VA64), soluplus (SOL) and eudragit E PO (E PO) were utilized as carriers. The result showed that drug-polymer miscibility at temperatures below the melting point(Tm) of CBZ was improved by combining E PO with VA64 or SOL. With 30% drug loading in a solid dispersion in SOL:E PO (1:1, w/w), CBZ was mainly present in an amorphous form accompanied by a small amount of a microcrystalline form [66]. Hot melt extrusion was used to manufacture an amorphous solid dispersion of kollidon VA 64 and mannitol [67].

Using a mixture of eudragit E PO and polyvinylpyrrolidone/vinyl acetate copolymer (kollidon VA64) as carriers, a nimodipine solid dispersion was prepared by HME to achieve high dissolution. The dissolution profiles in 900 ml 0.1 mol/L HCl showed that the drug release of nimodipine solid dispersion reached 90% in 1 h. Nimodipine solid dispersion tablets were compressed by wet granulation and direct compression, respectively. The results of stability studies of tablets showed that the dissolution of tablets was slightly reduced after 2 months storage (40°C, RH 75%) [68].

Pressurized carbon dioxide was combined with hot stage extrusion during manufacturing of solid dispersions of the thermally labile p-aminosalicylic acid (p-ASA) and ethylcellulose 20 cps (EC 20 cps) and to evaluate the ability of the pressurized gas to act as a temporary plasticizer. Pressurized carbon dioxide was injected into a leistritz micro 18 intermeshing co-rotating twin-screw melt extruder using an ISCO 260D syringe pump [69]. Properties of solid dispersions of felodipine for oral bioavailability enhancement using two different polymers, polyvinylpyrrolidone and hydroxypropyl methylcellulose acetate succinate, by hot-melt extrusion and spray drying were compared. Spray-dried formulations were found to release felodipine faster than melt extruded formulations for both polymer matrices [70].

Dissolution rate of efavirenz was improved by formulating a physically stable dispersion in eudragit E PO or plasdone S-630 using hot-melt extrusion. Thermal and rheological studies revealed that the drug is miscible with both polymers. Decrease in melt viscosity was observed as the drug concentration increased. The dissolution rate of efavirenz from the extrudates was substantially higher than the crystalline drug [71]. Kalivoda *et al.,* (2012) applied hot-melt extrusion to improve dissolution behavior of poorly soluble drug fenofibrate. Different polymers were used as carrier: copovidone, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer (PVCL-PVAc-PEG) and hypromellose 2910/5 (HPMC). The dissolution rate from

extrudates was significantly increased when compared to pure fenofibrate powder or physical mixture of the components [72].

Ibuprofen was embedded in a methacrylate copolymer (eudragit E PO) matrix to produce solid dispersions by hot-melt extrusion process. The granules were incorporated in orally disintegrating tablets, which were developed by varying the ratio of sodium crosscarmellose and crosslinked polyvinylpyrrolidone. The properties of the compressed tablets like porosity, hardness, friability and dissolution profiles were compared with nurofen meltlet ODTs. The taste and sensory evaluation in human volunteers demonstrated excellence in masking the bitter active and improved tablet palatability [73]. Studies were carried out to investigate and identify the interactions within solid dispersions of cationic drugs and anionic polymers processed by hot-melt extrusion technique. Propranolol HCl and diphenhydramine HCl were used as model cationic active substances while pH sensitive anionic methacrylic acid based methyl methacrylate copolymers eudragit L100 and ethyl acrylate copolymer eudragit L100-55 (Acryl EZE) were used as polymeric carriers [74]. Djuris *et al.*, (2014) prepared carbamazepine solid dispersions using polyethyleneglycol-polyvinyl caprolactam-polyvinyl acetate grafted copolymer (soluplus, BASF, Germany) and polyoxyethylene-polyoxypropylene block copolymer (poloxamer 407). All hot-melt extrudates displayed an improvement in the release rate compared to the pure CBZ [75].

Three binary solid solutions were prepared by hot-melt extrusion process with kollidon VA 64, eudragit E, PEG 8000 with a cannabinoid type 1 (CB-1) antagonist. *In vitro* dissolution properties were investigated. Supersaturation dissolution study demonstrated that HME formulations composed by eudragit E and kollidon VA64 increased the drug solubility [76].

Pellet consisting of furosemide solid dispersion was prepared and evaluated. Solid dispersion for oral administration prepared by extrusion/spheronization [77]. Hot melt extrudates of indomethacin with eudragit EPO and kollidon VA 64 and those of itraconazole with HPMCAS-LF and Kollidon VA 64 were manufactured using a leistritz twin screw extruder [78]. DiNunzio *et al.*, (2008) investigated kinetisol dispersing using itraconazole as drug, while eudragit L100-55 and carbomer 974P were used as model solid dispersion carriers. Triethyl citrate was used as necessary as a model plasticizer. They also characterized benefits of kinetisol dispersing for the production of solid dispersions by using hydrocortisone drug [79]. Solid dispersions of nimodipine (NMD) with hydroxypropyl methylcellulose (HPMC, Methocel E5),

polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA, plasdone S630), and ethyl acrylate, methyl methacrylate polymer (eudragit E PO) were prepared and characterized. The dissolution results indicated that three polymers are suitable carriers to enhance the *in vitro* dissolution rate of nimodipine in pH 4.5 medium. Nimodipine acted as a plasticizer for PVP/VA and EPO and was miscible with the polymers as well as 10% NMD-HPMC systems [76].

HME was used to manufacture glass solutions containing celecoxib and polyvinylpyrrolidone and supercritical carbon dioxide as a pore-forming agent to enhance drug release. The drug-release rate from extrudates after supercritical carbon dioxide exposure was significantly higher [77]. Interactions between drugs and polymers were utilized to lower the processing temperature of hot-melt extrusion, and thus minimize the thermal degradation of heat-sensitive drugs during preparation of amorphous solid dispersions. Diflunisal (DIF) was selected as a model drug. Hydrogen bonds between diflunisal and polymeric carriers (PVP K30, PVP VA64, hydroxypropyl methylcellulose and soluplus) were revealed by differential scanning calorimetry and fourier transform infrared spectroscopy **.**The results of hot-stage polar microscopy indicated that DIF was dissolved in molten polymers at 160°C and amorphous solid dispersions were successfully produced by HME [78]. Fukuda *et al.*, investigated the influence of sulfobutyl ether beta-cyclodextrin (SBE(7)-beta-CD; captisol on the dissolution properties of ketoprofen from extrudates prepared by hot-melt extrusion. The dissolution rate of ketoprofen from samples prepared by hot-melt extrusion with SBE (7)-beta-CD was significantly faster than both the physical mixture and the hot-melt extrudates prepared with the parent beta-CD. Samples prepared by melt extrusion were least affected by exposure to elevated humidity [79].

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 [80]. For suprachoroidal drainage, the multifunctional polymeric microstent devices has been designed and fabricated with tailorable internal diameters (50-300 μm) by solventless, continuous hot melt extrusion from blends of poly[(ε-caprolactone)-co-glycolide] and poly(ε-caprolactone) [81].

Cocrystals

Dominick *et al*., (2011) investigated the application of twin screw extrusion as a scalable and green process for the manufacture of cocrystals. They selected four model cocrystal forming systems of theophylline-citric acid, caffeine-oxalic acid, carbamazepine-saccharin and nicotinamide-trans cinnamic acid. The use of catalytic amount of benign solvents led to a lowering of processing temperatures required to form the cocrystal in the extruder [82].

Beads

Wax-incorporated pectin-based emulsion gel beads of metronidazole were prepared using a modified emulsion-gelation method. The mixture was hot-melted, homogenized and extruded into calcium chloride solution. After extrusion the beads were washed with distilled water and dried for 12 h [83].

Rings

Clark *et al.,* (2012) prepared and developed microbicide intravaginal rings (IVRs) from polyether urethane (PU) elastomers for the sustained delivery of UC781 by hot-melt extrusion process. *In vitro* release studies confirmed that UC781 release profiles are loading dependent and resemble matrix-type diffusion-limited kinetics [84]. Antiretroviral pyrimidinediones IQP-0528 and IQP-0532 were formulated in polyurethane intravaginal rings as prophylactic drug delivery systems to prevent the transmission of HIV-1 [85].

An ethylene vinyl acetate copolymer ring releasing progesterone *in vitro* at about 12.05 ± 8.91 mg/day was successfully designed by hot melt extrusion. The rate of drug release is similar to that observed for progering, which is made up of silicone and intended for contraception therapies during lactation. It was observed that as the initial hormone load increases, the rate of release also increases [86]. Pedro *et al.,* (2012) assessed the anti-HIV and anti-HSV activity of tenofovir and tenofovir DF in cell and explants models. Cumulative tenofovir DF release and stability from silicone IVRs, polyether urethane and ethylene-co-vinyl acetate were compared. The activity and safety of drug released were evaluated in cervical explants and in a polarized dual-chamber model. Tenofovir DF inhibited HIV and HSV at 100-fold lower concentrations than tenofovir and retained activity in the presence of semen [87].

Matrix systems Verhoeven *et al.,* (2006) developed mini-matrices (multiple-unit dosage form) with release-sustaining properties by means of hot-melt extrusion using ibuprofen as the model

drug and ethylcellulose as sustained-release agent. Xanthan gum was added to the formulation to increase the drug release since ibuprofen release from the ibuprofen/ethylcellulose matrices (60/40, w/w) was too slow (20% in 24 h). Higher xanthan gum concentrations caused a faster drug release due to a higher liquid uptake and swelling [88].

Verhoeven *et al.,* (2008) developed mini matrices of metoprolol tartrate using ethylcellulose as sustained-release agent. Plasticizer used was dibutyl sebacate and its concentration was optimized to 50% (w/w) of the ethylcellulose concentration. Xanthan gum was added to the formulation to increase drug release [89]. Different ethylene vinyl acetate grades (EVA9, EVA15, EVA28 and EVA40 having a vinyl acetate content of 9%, 15%, 28% and 40%, respectively) were characterized via differential scanning calorimetry. Polymer flexibility, melting point, glass transition temperature and polymer crystallinity were positively affected by the vinyl acetate quantity. The processability of EVA-based formulations produced by means of hot-melt extrusion (2 mm die) was evaluated in function of vinyl acetate content, extrusion temperature (60-140°C) and metoprolol tartrate concentration (10-60%). Matrices containing 50% metoprolol tartrate resulted in smooth-surfaced extrudates, whereas at 60% drug content severe surface defects like shark skinning were observed [90]. Lyons *et al.,* (2006) used agar and microcrystalline cellulose as novel filler material in a hot melt extruded polymer matrix using diclofenac sodium as drug. The parallel plate rheometry analysis concluded that due to fillers, the matrix viscosity increased [91].

Cylindrical co-extrudates of theophylline were developed, which were characterized by an *in vivo* sustained release profile. Co-extrudate was made up of two concentric extruded matrices. The inner matrix was hydrophilic in nature, based on polyethylene glycol, and the outer matrix was lipophilic in nature, based on microcrystalline wax [92]. Lyons *et al.,* (2007) investigated the use of a supercritical CO_2 assisted extrusion process in the preparation of a hot melt extruded monolithic polymer matrix for oral drug delivery. Matrix material batches were prepared with carvedilol. These batches were subsequently extruded both with and without supercritical CO_2 incorporation. Dissolution analysis showed that the use of supercritical CO_2 during the extrusion process resulted in a faster dissolution of API when compared with unassisted extrusion [93]. Hydroxypropylcellulose matrices of fenofibrate were produced by hot-melt extrusion to improve dissolution rate and to enhance stability. Dissolution rate of fenofibrate from melt extruded pellets was faster than that of the pure drug. Fenofibrate release rates was increased by

incorporation of sugars .Various polymers like polyvinylpyrrolidone 17PF and amino methacrylate copolymer exhibited a significant inhibitory effect on fenofibrate recrystallization in the hot-melt extrudates [94]. Sustained release solid lipid matrices of diclofenac sodium processed by hot melt extrusion and subsequent compression into tablets were developed. Different extrusion processing approaches such as "cold", "hot" and pre-mixed formulations were used to develop the compritol 888 ATO lipid matrices. The lipid matrices developed by HME provided sustained release of pre-mixed formulations for 12 h mainly controlled by diffusion [95].

A double matrix system consisting of a hot stage extruded starch pipe surrounding a hot stage extruded and drug-containing starch core, was developed. Initial slower release phase was avoided by loading the starch pipe with a small amount of drug [96]. Brabander *et al*., (2004) tested the bioavailability of ibuprofen from hot-melt extruded mini-matrices based on ethyl cellulose and a hydrophilic excipient. During the *in vivo* evaluation an oral dose of 300 mg ibuprofen was administered to healthy volunteers (n=9) in a randomized cross-over study and compared with a commercially available sustained release product (Ibu-slow) [97]. A study was conducted to investigate the physicochemical properties of melt-extruded dosage forms based on acryl-EZE and to determine the influence of gelling agents on the mechanisms and kinetics of drug release from thermally processed matrices. Korsmeyer-Peppas model was used to determine mechanism of drug release [98].

Kollidon SR as a drug carrier and two model drugs, ibuprofen and theophylline, were studied by hot-melt extrusion. Differential scanning calorimetry and X-ray diffraction analysis showed that ibuprofen remained in an amorphous or dissolved state in the extrudates containing drug up to 35%, whereas theophylline was dispersed in the polymer matrix by addition of klucel LF as a water-soluble additive to the hot-melt extruded matrices, ibuprofen and theophylline release rates were increased [99]. Hasa *et al.*, (2011) prepared and evaluated helical and cylindrical extrudates of theophylline by melt extrusion for their potential as sustained release dosage form. Microcrystalline wax was used as thermoplastic binder [100].

Properties of methylparaben were investigated as a solid-state plasticizer for eudragit RS PO polymer. Matrices containing different levels of methylparaben and eudragit RS PO, were prepared by hot melt extrusion. The results demonstrated that the glass transition temperature of the eudragit RS PO decreased with increasing levels of methylparaben in the extrudate, due to an

increase in the chain mobility of eudragit RS PO. At increasing levels of methylparaben in the extrudates, a decrease in the melt viscosity was seen due to a plasticization of the polymer [101]. Suitability of citric acid as a solid plasticizer for the preparation of eudragit RS PO extended-release matrix systems by a melt extrusion technique was evaluated. The monohydrate form was found to distinctly facilitate the extrusion of eudragit RS PO, whereas the addition of anhydrous citric acid to the polymer powder was less effective. The dissolution of citric acid from the matrix tablets followed an extended-release profile, with citric acid monohydrate exhibited a faster dissolution rate than the anhydrous form [102].

Implants

Characterization of the protein release from PLGA-based implants prepared by hot-melt extrusion with special emphasis on identifying reasons for incomplete release was studied. Biodegradable PLGA-implants loaded with BSA were prepared with a syringe-die extrusion equipment [103]. Gosau *et al.,* (2013) prepared, analysed and compared biodegradable poly(lactic-co-glycolic acid) implants loaded with gentamicin sulphate to the marketed product septopal (Biomet, Darmstadt, Germany), which consists of polymethylmethacrylate beads loaded with gentamicin sulphate [104]. Model protein (lysozyme)-loaded PLGA implants were prepared with a screw extruder and a self-built syringe-die device as a rapid screening tool for HME formulation optimization. Pure PLGA implants with up to 20% lysozyme loading could be formulated without initial bursting. Addition of PEG 400 reduced the initial burst at drug loadings in excess of 20% [105]. A series of praziquantel loaded implants based on PEG/PCL blends are fabricated by a combination of hot melt extrusion and twin-screw mixing [106].

For content uniformity and distribution behavior analysis, limaprost, tamsulosin and glimepiride were used as model drugs. Very low amount of coumarin-6 was used to visualize distribution images using confocal laser scanning microscope. Poloxamer188 and polyethylene glycol 6000, were chosen as carriers. The melt extrusion was carried out around 50°C, at which both carriers were easily dissolved but model drugs remained in solid form [107]. Kindermann *et al*., (2011) studied formulation of polyelectrolyte complexes composed of poorly water-soluble acid drugs and basic polymethacrylates by hot-melt extrusion enabling a tailor-made release pattern by the addition of inorganic salts. Poorly water-soluble model drugs naproxen and furosemide were applied in their non-ionic form. The complexes did not dissolve in demineralized water.

Dissolution profiles were realized by controlled electrolyte triggering. Maximal effects were achieved by concentrations of 0.05-0.15 M NaCl [108].

Nanocomposites

Composites of paracetamol loaded poly(epsilon-caprolactone) with layered silicates (nanoclays) were prepared using hot-melt extrusion. The layered silicates and paracetamol crystals produced both intercalated and partially exfoliated nanocomposite morphologies depending on composition. Nanoclay slightly retarded the dissolution and initial burst effect [109]. Ibuprofen loaded poly (epsilon-caprolactone) (PCL) layered silicate nanocomposites were prepared by hot-melt extrusion. Exhaustive examination across the length scales revealed the composite to have both an intercalated and exfoliated morphology with ibuprofen well distributed throughout the PCL matrix. The dissolution of ibuprofen from PCL can be retarded by addition of layered silicates (nanoclays) to the polymer matrix [110].

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 minor drawbacks of this technology. 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. 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. HME process can easily facilitate the scale-up from the laboratory to the commercial scale. This attractive feature of scalability exhibited by HME is expected to increase the demand for extrusion processes in pharmaceutical manufacturing in the future.

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