Expert Opinion

Melt extrusion: process to product

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Introduction: Niche applicability and industrial adaptability have led hot melt extrusion (HME) techniques to gain wide acceptance and have, therefore, solidified their place in the array of pharmaceutical research and manufacturing operations. Melt extrusion's momentum has resulted in extensive research publications, reviews and patents on the subject for over a decade. Currently, > 50% of the new drug candidates are speculated to be highly lipophilic and thus poorly bioavailable. HME is a key technology for these and other formulation and processing issues.

Areas covered: Various approaches have been addressed using HME in developing solid molecular dispersions and have demonstrated viability to provide sustained, modified and targeted drug delivery resulting in improved bioavailability. This review provides a holistic perspective on HME from equipment, processing and materials to its varied applications in oral delivery (immediate release, sustained release, taste masking, enteric and targeted release, as well as trans-drug delivery), oral mucosal, dermal, ungual and intravaginal systems.

Expert opinion: Interest in HME as a pharmaceutical process continues to grow and the potential of automation and reduction of capital investment and labor costs has earned this technique a necessary consideration as a drug delivery solution.

Keywords: bioadhesion, bioavailability, controlled release, drug delivery systems, hot melt extrusion, melt extruded films, melt extruded tablets, solid dispersion, sustained release

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1. Introduction

Although hot melt extrusion (HME) has been a mainstay technology in the plastics industry for ~ 70 years, research and manufacturing within the pharmaceutical industry over the past 2 decades have propelled HME as an alternative 'platform' for numerous solid dosage forms. Over the last 15 years, hundreds of research papers and extensive reviews have been published on this subject [1-4]. Moreover, issued HME patents have continuously increased worldwide.

Due to the emergence of high-throughput screening in drug discovery, it is speculated that at least 50% of the new chemical entities (NCEs) under development will have very poor solubility and hence low bioavailability [5]. It is a challenging task for the pharmaceutical scientist to increase the solubility of these new compounds, as well as reformulated generic drugs. Several new approaches have been used to address this issue including solid dispersions [6].

HME is a technology that can be applied to the preparation of solid dispersions. Raw materials or blends can be mixed and extruded under defined conditions as a continuous process. There are some parameters such as feeding rate, shear, temperature and screw rotating speed that can be varied to generate a final product of uniform size, shape and content. HME offers some distinct advantages over other traditional methods. For example, it is solvent-free, entails a continuous operation (necessitating fewer processing steps), requires no compression and can improve bioavailability due

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Article highlights.

- Innovation in formulation, polymer manufacturing science and equipment processing technology has revolutionized the advancement of hot melt extrusion techniques. Industrial acceptability and adaptability continue to influence the development of improved and scalable equipment. The present review provides the latest information on equipment, processing and materials used, as well as various applications including oral, transdermal and implants in the hot melt extrusion arena.
- Among different types of pharmaceutical grade hot melt extruders available, the most popular twin-screw (co-rotating/counter-rotating) extruders are discussed in detail, including a list of commercially available extruders. In addition, processing in terms of effect of different screw designs and configurations, screw speeds, hopper-feeding rates and processing temperatures on product attributes is discussed. Advantages of in-line process analytical technology and co-extrusion processing have also been provided.
- Hot melt extrusion applications in the field of oral, trans-delivery and implant delivery are comprehensively discussed. Utility of a new polymer (Soluplus®) and newer polymer grades, such as low-molecular-mass Klucel™, to improve the oral bioavailability of lipophilic drugs is examined. In addition, differing polymer properties were instrumental in demonstrating varied modified and targeted drug release profiles for oral and trans-drug delivery. The developmental aspect of the structurally and functionally intricate FDA approved intravaginal ring manufactured using hot melt extrusion encourage innovation in the field of medical devices such as implants.

This box summarizes key points contained in the article.

to dispersion of the drug at the molecular level in the final dosage form [7-9]. Few drawbacks limit the use of HME in the pharmaceutical industry. For instance, it needs a higher energy input compared to other techniques and may exclude some thermolabile compounds due to high processing temperatures. However, the combination of HME with other technologies such as nanotechnology [10], powder coating [11] and complexation (e.g., cyclodextrins) [12,13] has demonstrated the versatility of HME.

In the HME process, the active component is embedded in a carrier system, usually comprised of one or more thermoplastic polymers [14-17], low melting waxes [18], sugar alcohols [19] or starch [20]. Molten polymers or waxes during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants on cooling and solidification. Other functional excipients such as plasticizers [21-28], fillers [16,29], pH and release modifiers [30,31], stabilizers [32], surfactants [32,33], antioxidants [26,27] and processing aids [18,34] can also be included in the HME process. Intense mixing and agitation imposed by the rotating screws cause de-aggregation of suspended drug particles in the molten polymer, resulting in a more uniform dispersion, a solid solution or a combination of the two in the final product. The physical state of the active moiety will have a significant effect on processing, drug release properties and the stability of the drug in the final extrudates.

It has been demonstrated that HME technology is an innovative and viable approach in the preparation of various pharmaceutical drug delivery systems such as pellets [20], granules [18], immediate and modified release tablets [26,35], oral fast dissolving systems [35], transdermal [24,36] and transmucosal delivery systems, transungual delivery systems [37,38] and implants [17]. The physical and chemical stability of hot melt extrudates have been shown related to the nature of the polymer and excipients, the physical state of the drug in the final extrudates, storage and packaging conditions. Although melt extruded dosage forms tend to demonstrate good long-term stability, at times recrystallization of the actives has been observed during their storage. This physical instability is one of the common problems observed with crystalline drugs processed via HME wherein the drug is first converted to an amorphous state during extrusion and reverts into the crystalline state on storage [39]. To overcome such problems, several crystallization inhibitors such as polycarbophil, polyvinyl pyrrolidone (PVP) K25 and hydroxypropyl methyl cellulose (HPMC) have been introduced into formulations as functional excipients. These additives have been shown to either prevent or reduce the recrystallization of drugs in HME formulations to a significant extent [40].

In addition to a continuous process, process analytical technology (PAT) has already been introduced for HME techniques to optimize design, analysis and control within the manufacturing process. Many analytical technologies have been incorporated into the systems including Raman spectroscopy and near-infrared spectroscopy (NIR).

Currently, there are only a few commercialized products using HME technology in the pharmaceutical market, which is a contrast to the rapidly increasing interest in HME. In this review, the authors address this 'lag time' and emphasize the future of HME as it pertains to pharmaceutical dosage forms and design.

2. Equipment

Over the past 2 decades, hot melt extruders have evolved to meet the specific demands of the pharmaceutical industry. Although the equipment and the unit operations involved are not different from the hot melt extruders utilized by the plastic industry, the manufacturing companies have had to take special precautions while designing a pharmaceutical grade extruder that is in accordance with current good manufacturing practices. Pharmaceutical extrusion, being relatively new, is still in the process of optimizing documentation regarding instrument specifications and validation. Complete written procedures with in-depth knowledge of

the processes along with a documented training program are essential for validating, operating, cleaning, calibrating and maintaining extrusion equipment. Manufacturers must utilize FDA approved lubricating oils, jacketed water-cooled tubing and ensure absence of 'dead spots'. Individual parts of a pharmaceutical grade melt extruder are built from specially coated stainless steel that is non-reactive, non-absorptive and non-toxic. However, extruder manufacturers have also responded to industry's need for smaller, development scale equipment that requires a lesser amount of material. For example, an 11 mm parallel twin screw was just released to the market (Thermo Scientific), as well as a 16 mm extruder (Leistritz), which became available a few years ago (**Table 1**).

An extruder is comprised of the feeder, barrel with screws or ram, control panel, torque sensors, heating/cooling device, assorted dies and downstream processing machinery (**Figure 1**). The type of feeder and downstream processing equipment are selected after close consideration of the material characteristics, desired dosage form, type of process (batch or continuous) and speed of processing. On-line and in-line quality control tools such as NIR [41] or a combination of NIR, Raman, ultrasonic and dielectric spectroscopy [42] can be built into the extruder monitoring equipment for real time quality assessment of the product.

Two types of pharmaceutical grade extruders are available, ram type or screw type. In addition, screw extruders are available as single or twin screw. Most applicable to pharma are twin-screw extruders and so this review's discussion is limited to such extruders.

2.1 Twin-screw extruders

The vast majority of the extruders manufactured for pharmaceutical needs are of twin-screw type (**Table 1**). Twin-screw extrusion has several advantages over single screw as it offers intense mixing of the components. The two screws create an environment of controlled temperature and pressure inside the barrel in which the material is processed. For higher capacity extruders, each zone has independent heating/cooling units and temperature sensors that can efficiently maintain the individual zones at preset temperatures. The pressure arises from the friction of the moving material against the barrel walls and eventually assists the ejection of material through the die cavity.

The two screws can be oriented in a number of configurations depending on the desired level of shear and speed of operation [43]. According to the required intensity of mixing, the two screws can be designed to rotate in the same direction (co-rotating) or in the opposite direction (counter-rotating). Co-rotating screws are primarily used in pharmaceutical manufacturing. Ferns demonstrated the mixing abilities of single screw and twin-screw extruders by addition of color pigment. The single screw extrudates showed streaks and shaded areas indicating incomplete mixing whereas material processed using twin-screw extrusion was homogeneously mixed [44].

2.2 Downstream processing equipment

A variety of formulations can be fabricated using melt extrusion technology (**Figure 2**) [45]. A wide preference for the selection of die shapes and sizes is available for the formulation scientist. Flat dies are utilized for production of films and patches, circular dies are used for pelletization and spheronization whereas the annular dies are used for medical devices and tubing. Generally, the cross-section of the extrudates will increase on exiting the die, which is partly due to the viscoelastic properties of the material and partly due to the pressure in the barrel. This phenomenon is called die swelling. This entropy driven event occurs when the individual polymer chains recover from the mechanical stresses induced by the rotating screws.

The molten drug–polymer mixture can also be filled into molds using injection molding. These molds can be formed to yield the classic tablet, capsule shapes or custom designed shapes to suit the needs of various body cavities such as denture adhesives, vaginal tablets, ear inserts or pediatric friendly designs. Some of the dosage forms that have been studied previously are films [36,46], pellets, spherical pellets [47], punched tablets [48], injection molded tablets [49], rods and granules [50].

3. HME processing

From the standpoint of processing, HME can be theoretically divided into five steps: i) feeding, ii) melting and plasticizing, iii) conveying and mixing, iv) venting and v) stripping and downstream processing [51]. Each elementary section may affect the properties of the final extrudates.

The different zones of the barrel are pre-set to specific temperatures prior to the extrusion process. The material to be extruded is introduced into the feed section of extruder via a hopper. It is essential that the angle of the feed hopper is always exceeding the angle of repose of the feed material in order to assure good flow properties of the feedstock. When this prerequisite is not met, the material tends to form a solid bridge at the throat of the hopper resulting in an erratic flow. Also, a force-feeding device such as a mass flow feeder or side stuffer can be used to direct the feedstock onto the rotating screw [52].

The feedstock will be transported along the length of the barrel, where it gets melted, plasticized, mixed and compressed, while thermal energy is generated by shearing, imposed by the rotating screw and from conduction from the barrel via electrical heating bands. Mixing plays an important role during HME process and is classified as distributive mixing and dispersive mixing. Distributive mixing is a reference to the content uniformity of a particular ingredient (e.g. active pharmaceutical ingredient (API)) whereas dispersive mixing is related to the size reduction and distribution [51]. For a more detailed discussion about mixing, a recently published review paper is recommended to the reader [53].

Table 1. Partial list of commercially available pharmaceutical grade extruders.

Company	Name of extruder	Capacity* (kg/h)	Screw diameter (mm)	Screw assembly
Thermo Scientific	Pharma *mini*-HME micro-compounder	0.01 – 0.2	Variable diameter	Co- and counter-rotating
	11 mm Parallel twin-screw extruder	0.02 – 2.5	11 mm	Co-rotating multiple elements
	HAAKE MiniLab II micro-compounder	0.01 – 0.2	Variable diameter	Conical co- and counter-rotating
	EuroLab 16 XL	0.2 – 10	16	Parallel co-rotating
	HAAKE Rheomex PTW 16 OS	0.2 – 10	16	Parallel co-rotating
	HAAKE Rheomex PTW 24 OS	0.5 – 50	24	Parallel co-rotating
	HAAKE Rheomex PTW 100 OS	0.2 – 5	Variable diameter	Conical counter-rotating
	Pharma 16 HME	0.2 – 5	16	Parallel co-rotating
	TSE 24 MC	0.2 – 50	24	Parallel co-rotating
Leistritz	Nano 16	0.2 – 0.8	16	Co-rotating
	ZSE 18 HP PH	0.5 – 7	18	Co-rotating
	ZSE 27 HP PH	2 – 60	27	Co-rotating
	ZSE 40 HP PH	20 – 180	40	Co-rotating
	ZSE 50 HP PH	60 – 300	50	Co-rotating
Gabler	DE 40	5 – 100	40	Co-rotating
	DE 100	80 – 800	100	Co-rotating
	DE 120	300 – 1000	120	Co-rotating
Coperion	ZSK18 -70 Twin screw	–	18 – 70	Co-rotating
Brabender	Stand-alone TSE 20/40	–	20	Co-rotating

*Actual values depend on the formulation design and excipients used.

Figure 1. Illustration of a hot melt extrusion film assembly. Courtesy of Thermo Electron Corp.

Solubility parameters are widely used to calculate the cohesive force within materials and predict the miscibility of two materials. In the case of HME, the miscibility of polymers and drugs is evaluated. The use of solubility parameters has been illustrated by Crowley *et al.* wherein the miscibility of guaifenesin and ketoprofen (KTP) in polyethylene oxide (PEO) was predicted by calculating the Hansen solubility parameter using the method of Hoftyzer and van Krevelen [25]. Improved miscibility prediction methods are being developed, such as the MEMFIS™ system [54]. However, it should be noted that the predication of miscibility is based on limited experimental data and mathematical calculations.

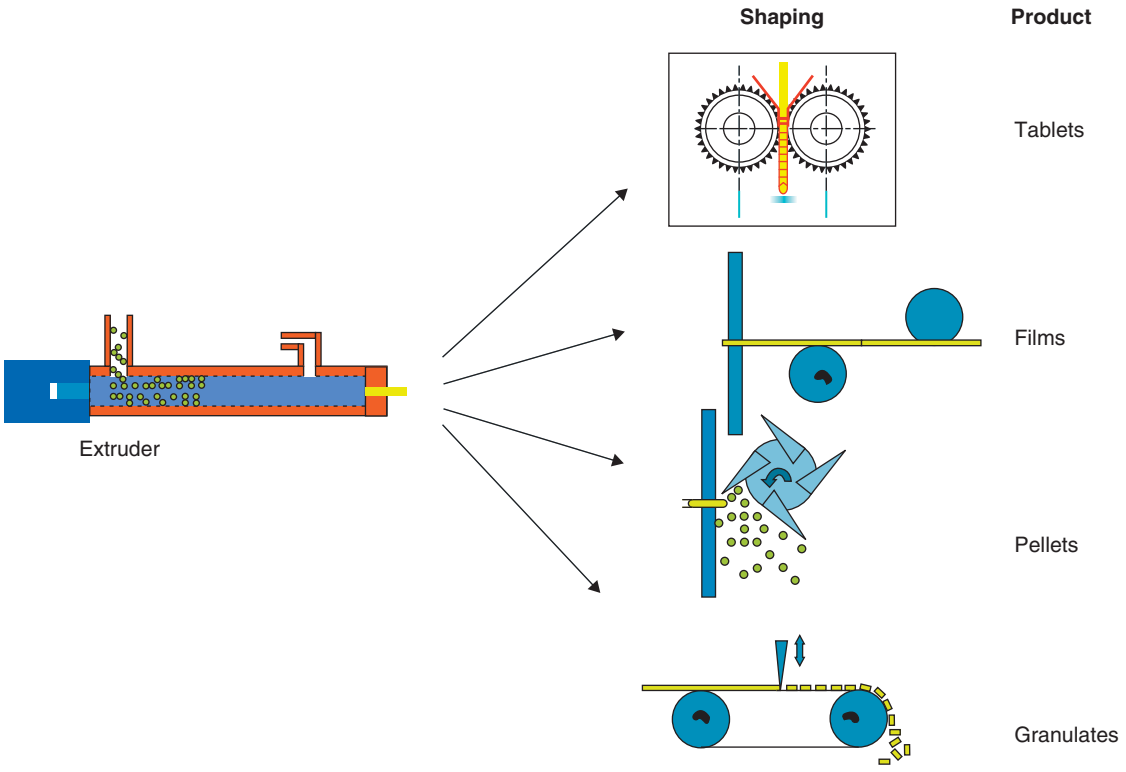

Figure 2. Schematics of various dosage forms produced using hot melt extrusion technology.
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3.1 Screw design and configuration

The efficiency of the melting process is highly dependent on the polymer's properties and the extruder design. In general, polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process. However, very few articles in the literature discuss the effects of screw design and configuration on HME processing. Thompson and Sun demonstrated the screw elements have an influence on the particle size and the particle shape of the products when using a twin-screw extruder [55]. Another example is the kneading paddle elements of the twin-screw extruder. Nakamichi *et al.* demonstrated that they played an important role in changing the crystallinity and dissolution properties of a solid dispersion of kneaded nifedipine–hydroxypropylmethylcellulosephthalate [56].

3.2 Processing parameters

Processing parameters play a key role in determining the properties of the extrudates. Some of the most commonly adjusted parameters include screw speed, processing temperature and feeding rate. The screw speed and feeding rate are also related to shear stress, shear rate and mean residence time, which will affect the dissolution rate and stability of the final products. Certain minimum temperatures are required in the HME process to reduce the torque needed to rotate the screw. Typically, the temperature of the melting zone is set 15 – 60°C above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers [57,58]. The torque is directly proportional to the viscosity of the molten feedstock. The viscosity of the polymer at a fixed shear rate can be expressed by the Arrhenius equation (1) [59]:

$$\eta = K' \times e^{Ea/RT}$$

where: η is the viscosity of the polymer melt; K′ is a constant depending on the structure and the molecular mass (MM) of the polymer; Ea is the activation energy of the polymer for the flow process and is a constant for the same type of polymer; R is the gas constant; and T is the temperature in degrees Kelvin.

Heat conduction from the electrical bands on the barrel contributes to the melting process; however, heat is also generated by shearing of the polymer melt. 'Viscous heat generation' is the process of transforming mechanical energy from shearing into thermal energy. The rate of heat generation per unit volume due to viscous heat dissipation follows Equation (2) [59]

$$E = m \times \gamma^{n+1}$$

in which m is a constant, γ is the shear rate and n is the power law constant.

3.3 Process analytical technology

PAT has gained much attention from the pharmaceutical industry over the last decade. It is utilized to monitor, analyze

and characterize hot melt processing and products in-line. In this way, flow properties, polymer structures, polymer–drug interactions as well as concentrations of drugs and additives can be measured immediately downstream of the extrusion process. Many analytical technologies have been incorporated into this system such as rheometric, optical, ultrasonic, electrical Raman spectroscopy and NIR. Saerens *et al.* utilized Raman spectroscopy as a PAT for the determination of drug concentration in the extrudates as well as the solid-state characterization thereof [60]. Dhumal *et al.* characterized the co-crystal agglomeration of ibuprofen (IBU) and nicotinamide using NIR [61]. Indeed, extruder manufacturers are positively reacting to the pharmaceutical industry's needs in this area.

3.4 Co-extrusion

Co-extrusion is the process of extruding two or more materials through a single die with two or more orifices arranged so that the extrudates merge and weld together into a laminar structure before chilling. Each material is fed to the die from a separate extruder, but the orifices may be arranged so that each extruder supplies two or more layers of the same material. The final product obtained may be in the form of a laminar structure with multiple layers, which may offer several advantages due to material and composition characteristics imparted by the individual extruded polymer layer.

A classic example of co-extrusion technology is the production of an intravaginal (IVR) thermoplastic ring currently on the market: the contraceptive, NuvaRing®. This product contains the drug within a poly (ethylene vinyl acetate), pEVA reservoir, which forms the core while the crystalline pEVA (i.e., lower vinyl acetate fraction) on the exterior serves as a rate-limiting membrane to control drug release [62,63].

Recently, co-extrusion has been reported in combination therapy where more than one drug is administered as a single dosage form to treat various diseases such as HIV or cancer. The combination therapy may result in lower treatment failure rates and slower development of resistance. However, this process could comprise several limitations such as physical/chemical incompatibility among excipients and API's and inconsistent release rates and pharmacokinetic profiles. These systems developed for combination therapy may contain two or more actives present as either separate immediate release/controlled release layers or a combination thereof. In addition, they may also be manufactured as for a combination of highly soluble and poorly soluble actives in two separate layers [64].

The principle of co-extrusion shows promise for many novel dosage forms, including oral, transdermal and implants.

4. Materials used in HME

The materials used in the production of hot melt extruded dosage forms are the same pharmaceutical compounds used in the production of more traditional systems. Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered using HME does not limit all thermolabile compounds. The incorporation of plasticizers may lower the processing temperatures encountered in HME, thus reducing drug and carrier degradation. In addition, the active moiety may function as a plasticizer. Drug release from these systems can be modulated by the incorporation of various functional excipients. The dissolution rate of the active compound can be increased or decreased depending on the properties of the rate-modifying agent. For systems that display oxidative or free radical degradation during processing or storage, the addition of antioxidants, acid acceptors and/or light absorbers may be warranted.

4.1 Carrier materials

In hot melt extruded drug delivery systems, the active compound is embedded in a carrier formulation comprised of one or more meltable substances and other functional excipients. Carriers used in hot melt extruded dosage forms can be grouped into two categories: i) polymeric carriers and ii) non-polymeric carriers. The selection of an appropriate carrier compound is important in the formulation and design of a hot melt extruded dosage form. 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. **Table 2** lists some of the properties of various carrier compounds used in the production of hot melt extruded dosage forms [1].

Although a majority of our discussions within this review focus on polymeric carriers, Reitz and Kleinebudde have demonstrated the utility of 'cold' extrusion for drug delivery using lipids, a few of which are listed in **Table 2**. Recently, a solid lipid extrusion process utilizing a twin-screw extruder was introduced to prepare sustained release dosage forms. Reitz and Kleinebudde successfully extruded theophylline with either of the two lipids, glyceryl palmitostearate (Precirol ATO 5®) or glyceryl trimyristate (Dynasan 114®), in varying ratios and at temperatures below their melting ranges. Formulations containing glyceryl palmitostearate/theophylline (50:50) and glyceryl trimyristate/theophylline (50:50) exhibited sustained release properties. Additionally, influence of extrusion temperature on drug release of extrudates was studied [65]. These authors also demonstrated a two-step solid lipid extrusion process to modify dissolution behavior. In this study, a hydrophobic model drug, chloramphenicol, was initially extruded with either triglyceride tripalmitin or PEG as the first extrusion step, which was further milled and extruded with the other matrix component, interchangeably. Initial extrusion with PEG led to increased dissolution rates, while original extrusion with tripalmitin demonstrated a slower release rate in comparison to extrudates containing the same composition produced by one-step extrusion [66].

Table 2. Carriers used to prepare hot melt extruded dosage forms.

Chemical name	Trade name	T_g (°C)	T_m (°C)
Ammonio methacrylate copolymer	Eudragit® RS/RL	64	–
Poly(dimethylaminoethylmethacrylate-co-methacrylic esters)	Eudragit® E	50	–
Poly(methacrylic acid-co-methyl methacrylate) 1:2	Eudragit® S/L	160	–
Cellulose acetate phthalate	–	165	192
Poly(vinyl pyrrolidone)	Kollidon®	90 to 156	–
Poly(vinyl acetate)	Sentry® plus	35 to 40	–
Hydroxypropyl methylcellulose phthalate	–	137	150
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	101	–
Polyvinyl caprolactam-polyvinyl acetate-PEG graft copolymer	Soluplus®	70	–
Hydroxypropyl methylcellulose	Methocel®, Benecel®	160 to 210	–
Hydroxypropyl methylcellulose acetate succinate	Aqoat-AS®	~ 120	–
Ethyl cellulose	Ethocel® Aqualon® EC	130 to 133°C	–
Hydroxypropyl cellulose	Klucel®	Softens at 130°C	Chars at 260 – 275°C
PEG	Carbowax®	-17°C for MM 6000	37 – 63°C
Polyethylene oxide	PolyyOx® WSR	-57 to -50°C	62 – 67°C
Polymethacrylates	Eudragit® RSPM Eudragit E	52°C, 40°C	–
Carnuba wax	–		81 – 86°C
Glyceryl palmitostearate	Precirol ATO 5®	–	52 – 55°C
Glyceryl trimyristate	Dynasan 114®	–	55 – 58°C
Triglyceride tripalmitin	Dynasan 116®	–	61 – 65°C

Appropriately revised and reproduced from [1].
MM: Molecular mass.

4.2 Plasticizers

The use of polymeric carriers may require the incorporation of a plasticizer into the formulation in order to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product.

Plasticizers are typically low-molecular-mass compounds capable of softening polymers to make them more flexible. Plasticization of the polymer is generally attributed to the intermolecular secondary valence forces between the plasticizer and the polymer. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains [67]. The choice of a suitable plasticizer will depend on many factors, such as plasticizer–polymer compatibility, plasticizer stability and permanence. Several plasticizers including triacetin [68], citrate esters [24,69], D-α-tocopheryl PEG 1000 succinate (vitamin E TPGS) [70], surfactants [33], methyl paraben [27] and low-molecular-mass PEGs [24,68] have been investigated in hot melt extruded systems. Moreover, injection of pressurized CO_2 during HME demonstrates reduction in processing temperatures of various polymers in producing solid dispersions by melt extrusion techniques, in addition to acting as a foaming agent [21]. Additionally, several drug substances have been reported to function as plasticizers in hot melt extruded dosage forms [24,25,68,69]. Plasticizers may also be incorporated into hot melt extruded dosage forms to improve the physical–mechanical properties of the final dosage form. In transdermal films, the addition of a plasticizer to the polymer matrix can improve the film's flexibility [24,69,70]. Plasticizers may also influence the product's tensile strength and elastic modulus. In addition to the plasticizer's effect on the performance of hot melt extruded polymer systems the thermal history of the material may influence the properties of the final dosage form.

4.3 Release modifying agents/other functional excipients

To improve or modulate drug release from these systems, functional excipients may be added. Depending on the physical and chemical properties of these additional excipients, various release profiles may be achieved. Several investigators [71] studied a variety of compounds in several polymeric systems using diltiazem hydrochloride (DTZ) as a model compound. The additives were incorporated into the formulation in an effort to increase the drug release rate by increasing the porosity of the pellet during dissolution. Viscosity inducing agents were incorporated in the polymer matrix to limit the burst effect often seen with matrix systems. The use of ionic or pH-dependent polymers in the carrier matrix may allow for zero-order drug release or pH-dependent drug delivery.

Swelling agents, such as croscarmellose sodium and sodium starch glycolate, were also investigated as a method to modulate drug release. In contrast, it has been demonstrated that sodium starch glycolate could be used as a super-absorbent

in HPC hot melt extruded films to facilitate moisture or exudate uptake in wound care applications [70].

Recently, Schilling *et al.* [31] explored citric acid monohydrate (CA MH) to enhance the release of DTZ from melt extruded Eudragit® RS PO tablets and to eliminate drug particle size effects. The addition of CA MH to the formulation promoted the thermal processibility and matrix integrity by plasticization of the polymer. The drug release from systems with constant drug:polymer ratio was significantly increased when CA MH was added due to enhanced pore formation. Particle size effects were eliminated when large amounts of CA MH were used due to the loss of drug crystallinity. Moreover, citric acid was used as pH modifier by modulating the micro environmental pH of the hot melt extruded patches containing an ester pro-drug of tetrahydrocannabinol [22].

Injection of pressurized CO_2 during HME led to increased specific surface area and the porosity of the polymers, which resulted in enhanced dissolution of PVP VA-64 [72], Eudragit® E100 alone and itraconazole in ethylcellulose 20 capsule matrices [21]. Besides acting as foaming agent, pressurized CO_2 reduced the processing temperature during melt extrusion, thus acting as a plasticizer.

4.4 Other processing aids

These miscellaneous compounds include embodying agents and antioxidants. Excessive temperatures needed to process un-plasticized or under-plasticized cellulose-based polymers (i.e., hydroxypropylcellulose (HPC) or ethyl cellulose (EC)) may lead to polymer oxidation. One manufacturer of these materials recommends the incorporation of an antioxidant, such as butylated hydroxytoluene or ascorbic acid, into formulations containing low-molecular-mass HPC [73].

Similarly, a combination of an antioxidant, light absorber and acid acceptor is recommended for systems using EC [74]. PEO films have been reported to be protected from free radical and oxidative degradation by the incorporation of an antioxidant [75]. However, careful choice of API based on degradation pathways and stability studies should be considered and monitored when PEO is chosen as a matrix polymer for a delivery system.

5. Applications of HME for drug delivery

5.1 HME in oral drug delivery

Over the past 2 decades, researchers have investigated a myriad of applications of HME techniques in drug delivery and drug targeting, irrespective of dosage form size, shape or design. Numerous bioactives of known therapeutic value and a wide choice of available excipients have been utilized to develop efficient drug delivery systems involving HME for immediate, sustained and/or targeted drug release, which could increase effectives in treating a number of disease conditions.

5.1.1 *Immediate release*

It is essential for many delivery systems to demonstrate fast drug release to provide rapid pharmacological activity. HME techniques have been widely used in several instances to produce granules and/or solid dispersions into formulations with improved dissolution characteristics, especially for drugs with solubility-limited bioavailability.

Researchers have shown the formation of immediate release granules or pellets using both ram [76] and single screw extruders [77]. McGinity and Koleng produced acetaminophen (APAP) hot melt extruded granules with low-molecular-mass PEG, which were later compressed into tablets [78]. Tablets containing melt extruded granules with 15% PEG met the release criteria of 80% APAP in 30 min, per USP 30. Other immediate release preparations such as effervescent granules were also prepared utilizing HME, as discussed in US patents by Robinson *et al.* [50]. The granules with controlled rate of effervescence were produced via melt extrusion of a blend containing an acidic and basic ingredient, including a binder that was capable of forming a eutectic mixture with the acidic agent.

Fu et al. [79] demonstrated an increased dissolution of poorly soluble nimodipine (NM) from directly compressible tablet formulations containing NM solid dispersions using Eudragit® EPO and PVP/vinyl acetate copolymer (Kollidon® VA 64) as a polymeric matrix. In another study, Sun and coworkers utilized Eudragit E100 and Plasdone® S630 to produce NM solid dispersions through HME, which was further finely dispersed into a semi-solid system made of PEG and Plasdone S630, and filled in cellulose-based capsules [80]. Thus, HME technology combined with a semi-solid system was successfully used to develop a stable and pH-independent immediate release formulation with similar bioavailability characteristics as marketed Nimotop®, but with significantly faster apparent rate of absorption (indicated by t_{max}).

Lately, newer applications such as development of fast disintegrating tablets (FDTs) and taste masking of bitter drugs using HME have been explored. Especially, FDTs have gained more importance as alternative delivery systems for fostering patient compliance, as well as contributing to product life cycle management. A recent US patent application by Sherry describes the development of FDTs using HME, which contains an NSAID and APAP [81]. These drugs were dry blended and extruded with low melting sugar alcohols such as xylitol, and the obtained extrudates were milled, mixed with suitable excipients and compressed into tablets. These FDTs were found to be more robust in comparison to the tablets produced by conventional dry blending processes.

Gryczke *et al.* utilized Eudragit EPO with suitable excipients and HME techniques to produce a fast disintegrating taste-masked dosage form with improved palatability or superior patient compliance [35]. In this study, IBU (a bitter active) and Eudragit EPO were co-processed using HME to produce

a solid dispersion and milled to produce granules. These granules were blended with superdisintegrants at varying ratios and directly compressed to produce orally disintegrating tablets, which had physical properties similar to the marketed Nurofen® Meltlet FDTs. The taste intensity evaluation of the extruded formulations in healthy human volunteers revealed an excellent taste masking ability with zero degree of bitterness and smoother mouth feel in comparison to the moderate roughness levels experienced with administration of Nurofen FDTs. In addition, HME tablet formulations with 25% IBU demonstrated similar release rates as Nurofen tablets, but 40% IBU/EPO formulations showed a faster dissolution, which was attributed to a lower talc concentration in the formulation, compared to the 25% IBU/EPO formulation (**Figure 3**). Overall, the HME formulations with similar disintegration properties and crushing strengths as that of the marketed formulation had faster drug release rates and could mask the bitter taste effectively.

Recent studies demonstrated the utility of low-molecular-mass HPC, Klucel™ ELF hydrophilic matrices for the solubilization of poorly soluble drugs. Dissolution profiles of immediate release HME tablets of the poorly soluble drug, KTP, prepared using Klucel ELF as a hydrophilic matrix polymer were compared to commercially available 50 mg capsules of KTP (**Figure 4**) and were found to exhibit similar release profiles [82]. This alternative, simple processing method demonstrated the utility of the HPC polymer system coupled with HME.

A new, innovative polymer, Soluplus®, was specifically developed for products developed using HME. This polymer has both hydrophilic and hydrophobic elements, which, therefore, enhances the ability of forming a solid solution as well as increasing solubilization. Due to these reasons, Soluplus performs very well as a carrier matrix for HME techniques to increase the solubility of poorly soluble drugs and hence improve bioavailability, as well as providing a tool for immediate release dosage forms. Therefore, Soluplus, exhibiting a low glass transition temperature, can be used as a carrier matrix for a wide range of drugs (low melting to high melting drugs), including thermo-sensitive APIs. Repka and co-workers investigated the properties of Soluplus as carrier matrix for increasing the solubility of the poorly soluble drug, nifedipine [83]. Also, the compressibility of Soluplus before and after extrusion was studied. The release profiles of the Soluplus–nifedipine melt extruded tablets were compared to their directly compressed (physical mixture) tablets, as well as to crystalline nifedipine. The HME processed tablets demonstrated a significantly faster release profile than that of the respective physical mixture tablets. In addition, all of the physical mixtures and extruded formulations with a polymer concentration of 33.3% w/w could be easily compressed into tablets. Another study using Soluplus as a solid solution HME carrier matrix for itraconazole showed a significant increase in release and bioavailability compared to either the crystalline drug or the physical mixture of the Soluplus–itraconazole formulation (**Figure 5**) [84]. These data demonstrate the much needed addition of an effective, extrudable polymer in the pharmaceutical formulators' toolbox.

5.1.2 *Sustained release*

Scientists have also demonstrated HME as a viable technique by virtue of flexibility in the selection of suitable polymers and excipients for achieving drug release in a sustained and/or controlled manner. In the late 1980s, several thermoplastic polymers were extruded by Mank *et al.* to demonstrate the possibility of developing sustained release pellets utilizing HME [77]. In the mid-1990s, Follonier *et al.* also successfully produced polymer-based smoother and denser pellets of DTZ with biphasic sustained release patterns using this anhydrous and continuous process of HME [68]. Later, the same research group [71] demonstrated release modulation of DTZ from the extruded pellet-filled hard gelatin capsules by incorporation of hydrophilic polymers (to obtain complete drug release), swelling agents (to reduce the initial burst) and/or addition of functional excipients such as superdisintegrants (to vary the dissolution rate).

In a study by De Brabender *et al.*, bioavailability of melt extruded EC-based mini-matrices of IBU containing HPMC and/or xanthum gum was investigated in healthy human volunteers against the marketed formulation, Ibu-slow® [85]. Although, both of the experimental formulations had a significantly lower C_{max}, time during which the plasma concentration was at least 50% of the C_{max} value was higher than the Ibu-slow, achieving a relative bioavailability of ~ 80%. Similarly, a recent study by Ozgüney *et al.* elucidated the development and characterization of Kollidon® SR mini-matrices containing IBU for extended drug release [86]. The plasticizing effect of the active on the polymeric extrudates was evident from the lowered glass transition temperature and the observed torque values during extrusion with increasing drug load. The drug (up to 35% loading) formed an amorphous solid dispersion, and the higher extrusion temperatures led to increased drug release rate, which is indicative of the drug's plasticizing effect on Kollidon SR.

Almeida *et al.* have utilized different grades of ethylene vinyl acetate (EVA) and produced sustained release matrices of metaprolol tartarate (MPT) via melt extrusion [87]. The polymer extrudability was studied as a function of EVA grade, MPT loading and extrusion temperature. All of these parameters influenced drug release from the matrix dosage form. The scanning electron micrographs (SEM) of pure EVA matrices as well as those with up to 50% MPT exhibited smoother surfaces, without any visible defects. However, the images of EVA40 (with 40% vinyl acetate content) containing 50% MPT, which had an initial framework supported by drug crystals, lost the rigidity of its polymeric structure after 72 h of dissolution. This was explained as a result of drug leaching from its surface (**Figure 6**). These results were also corroborated by X-ray tomography measurements, which

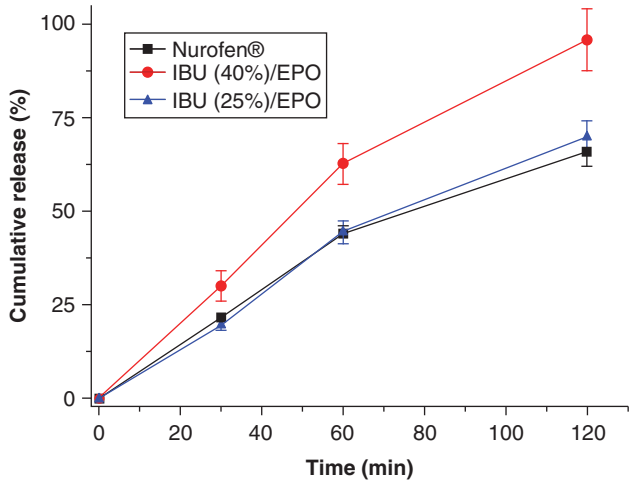

Figure 3. Release profiles of Nurofen® and ODTs with IBU/EPO extruded granules at 25 and 40% drug loading.
Reprinted with kind permission from Elsevier Ltd [35].
IBU: Ibuprofen; ODT: Orally disintegrating tablet.

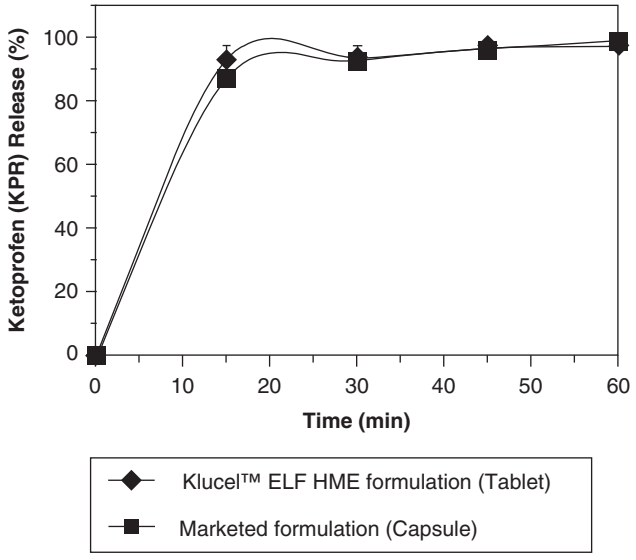

Figure 4. Comparison of release profiles of Ketoprofen–Klucel™ ELF hot melt extruded tablets to marketed capsules.
Dose strength: 50 mg (n = 3) [82].

demonstrated a small decrease in porosity of EVA40 matrices after dissolution. Moreover, these studies exhibited porous EVA matrices after extrusion with larger pores located at the center of the matrix, while a high concentration of smaller pores present just under the matrix surface were possibly due to the pressure exerted on the material during extrusion. The total matrix porosity was also decreased after dissolution for all of the produced matrices with maximum decrease being observed in EVA40 matrices, which was attributed to the elastic rearrangement of the polymer and partial melting of the structure. Among the formulations studied, EVA 15 and EVA 28, with 15 and 28% vinyl acetate content, respectively, released 90% of MPT in 24 h, and were found to be stable during gastrointestinal transit.

Another study performed by Verhoeven *et al.* [88] demonstrates the development of MPT containing EC-based minimatrices for sustained drug delivery utilizing PEG and/or PEO as dissolution promoters. The influence of MM grades and the concentration of PEG/PEO on different parameters such as drug content and drug release were evaluated. Raman spectral analysis revealed that irrespective of polymer concentration and grade, MPT was homogeneously dispersed in the EC-based matrices. Additionally, the drug release was faster with increasing concentration of the dissolution promoters (irrespective of molecular mass), whereas the influence of molecular mass depended on polymer concentration. An *in vivo* evaluation of the experimental formulations containing 5 and 20% PEO 1,000,000, administered orally in dogs, exhibited a limited sustained release effect with a relative bioavailability of 66.2 and 148.2%, respectively.

The novel concentric theophylline co-extrudates containing an inner hydrophilic PEG layer and an outer lipophilic microcrystalline wax layer were prepared in a single step by a modified ram extruder for sustained release [89]. The optimal co-extrudate formulation selected based on *in vitro* dissolution profiles was subjected to an *in vivo* study in healthy human volunteers, which demonstrated sustained release characteristics of the formulation. In addition, a predictive and reliable mathematical model to obtain plasma–drug concentration profiles following an oral administration of the co-extrudates was also developed. These data are indicative of uses of other types of extruders, besides twin screw, to attain an innovative outcome for sustained release formulations.

5.1.3 *Enteric release*

A method to produce enteric matrix tablets as an alternative to an enteric coating process [90] using HME technology was identified by Andrews *et al.* In this research, triethyl citrate (TEC) pre-plasticized Eudragit® L100-55 was used as an enteric polymer and citric acid (at 17%w/w) was used as a solid-state plasticizer with an optional gelling agent to produce enteric matrix tablets of 5-amino salicylic acid (5-ASA), which was used as a model drug. The portion of the extrudates, obtained as cylinders, was cut into tablets and the other part was milled and compressed into tablets, which were further characterized for various physicochemical properties. The drug release from these enteric tablets depended on the concentration of plasticizer, inclusion of citric acid or the gelling agent (PVP K30/Carbopol® 971P) in the formulation, and the pH of the dissolution medium. The tablets obtained by cutting the extrudates demonstrated an excellent resistance in the acidic environment of stomach releasing < 10% of the drug in comparison to the compressed tablets, which demonstrated a significantly higher release rate.

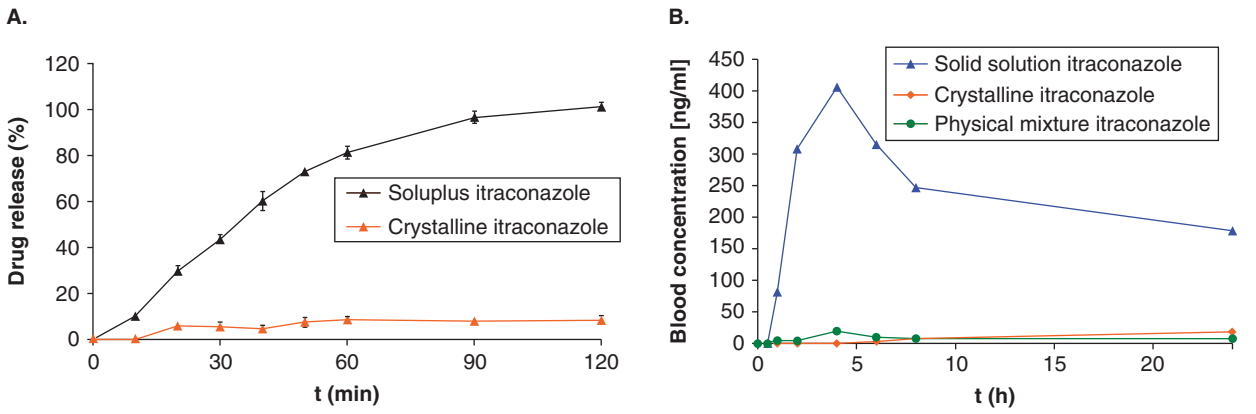

Figure 5. *In vitro* and *in vivo* evaluation of melt extruded ITZ vs crystalline drug. (A) Comparison of dissolution profiles of crystalline ITZ to melt extruded ITZ using Soluplus®; **(B)** Blood concentration of ITZ after administration of solid solution of Soluplus and crystalline ITZ.
Reprinted with kind permission from BASF [84].
ITZ: Itraconazole.

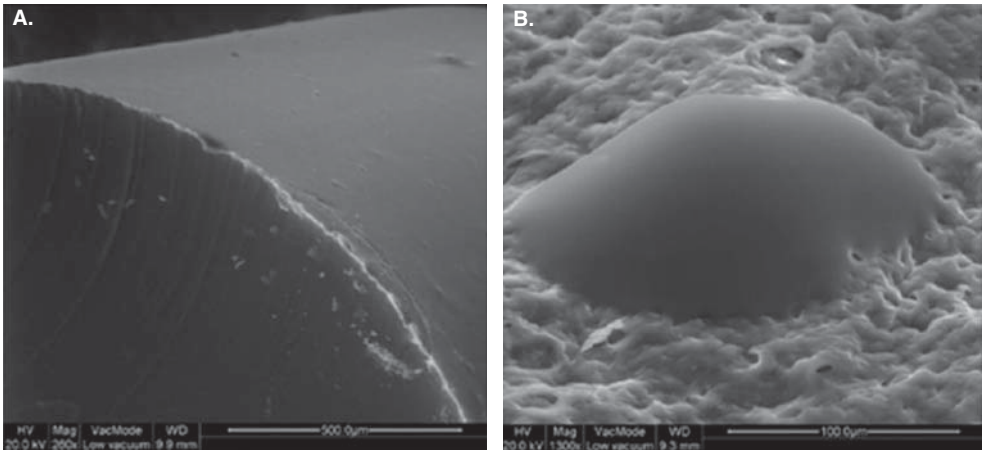

Figure 6. Surface structure of (A) pure EVA after hot melt extrusion at 90°C; **(B)** Surface structure of EVA40 matrix with 50% MPT loading after 72 h dissolution.
Reprinted with kind permission from Elsevier Ltd [87].
EVA: Ethylene vinyl acetate; MPT: Metaprolol tartarate.

Addition of gelling agent to the formulation could lower the erosion, but not retain the enteric properties of the tablets, due to formation of the porous channels within the matrix.

Similarly, Schilling *et al.* developed enteric matrix pellets utilizing HME techniques in a single step [15]. The researchers evaluated different plasticizers as processing aids and different Eudragit® grades L100-55, L100 and S100, and hydroxyl propyl methylcellulose acetate succinate (Aqoat) grades LF and HF as possible carrier matrices with enteric properties. The strand diameter as an indicator for polymer swelling and the yield were evaluated by extruding formulations with varying drug loads of 10 – 40% through a 500 µm diameter die. As demonstrated in **Figure 7**, an increase in the drug load resulted in decreased extrudate diameter, thereby indicating reduced polymer swelling. The drug was in its crystalline phase during extrusion due to a higher melting point and the higher drug concentrations led to increased resistance and torque levels resulting in lower process yields. The lower yield values were attributed to smaller batch size and insufficient plasticization of the material leading to high resistance and back flow.

Of the five plasticizers tested, PEG 8000 and citric acid utilized in the study could not retain the enteric properties due to their hydrophilic nature resulting in drug leaching from

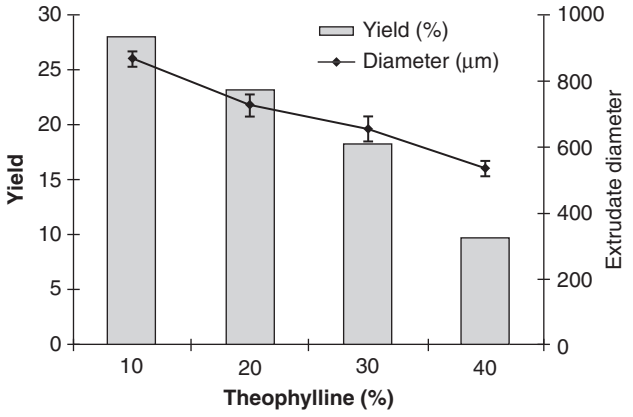

Figure 7. Influence of the theophylline content on the extrudate diameter and the process yield for the extrusion of Eudragit® S100 matrix pellets.
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the formed pores. In addition, acetyltributyl citrate and citric acid containing formulations, in spite of promoting partial drug solubilization in the polymer matrix, required higher extrusion temperatures and demonstrated drug re-crystallization. However, TEC and methyl paraben were identified as efficient plasticizers that had a significant impact on the microstructures of the extruded pellets revealed by SEM and PXRD studies. These plasticizers in the formulation produced dense pellets with drug being homogeneously distributed in its original polymorphic form. The extruded pellets containing theophylline as a model drug were successfully obtained using Eudragit S100, which released < 10% of the active in the acidic medium. The plasticized enteric matrix pellets containing 30% API and Eudragit S100 demonstrated superior gastric protection of the drug and acceptable extrudability.

Recently, a potential advantage of HME in processing the polymer-coated soft drug granules was demonstrated by Schilling and McGinity [91]. This study highlighted the novel application of HME for the preparation of monolithic matrices containing enteric-coated particles for delayed drug release. Theophylline was used as a model drug in the current study, where the drug loaded microcrystalline spheres or the spheronized pellets obtained from the wet extrusion with different mechanical strengths were coated with an enteric polymer, Eudragit® L30D-55, and characterized for various physical, chemical and mechanical properties. Later, the coated drug particles were extruded with six different hydrophilic matrices under evaluation using an extruder. The release studies revealed that the delayed release properties of the incorporated drug particles were independent of their tensile strength; however, the type of the polymeric matrix utilized affected it. A good correlation was observed between the miscibility of carrier, the coating polymers and the drug release in acidic media. The higher the miscibility between the polymers, the greater was the film permeability leading to increased drug release and loss of its enteric properties. Of all of the matrices investigated, polaxamer 407 could incorporate about 40% of enteric-coated pellets and meet the USP dissolution requirements for delayed release dosage forms, exhibiting the least miscibility with Eudragit L30D-55.

5.1.4 *Targeted release*

Delivery of the drug to a specific target site to elicit its action continues to gain significant interest, which has several advantages, such as minimizing the bioactive's side effects and minimizing drug dose. Over the past few years, researchers' have been focusing on unique HME techniques to achieve targeted drug delivery. Miller *et al.* have improved the oral absorption of itraconazole by the targeted intestinal delivery of the supersaturated drug utilizing HME [92]. Amorphous solid dispersions of itraconazole were prepared using HME with Eudragit L100-55 as a carrier matrix, and Carbopol® 974P, at 20 and 40% of polymer weight, as a stabilizing agent. Incorporation of Carbopol® assisted in the prolonged release of supersaturated levels of the drug from the drug–polymer matrix *in vitro*. Similarly, evaluation of pharmacokinetic parameters followed by oral administration in Sprague-Dawley rats revealed that Carbopol considerably decreased the intestinal absorption variability seen with the Eudragit L100-55 system. In addition, a fivefold improvement in targeted intestinal absorption was reported with the dispersions containing 20% Carbopol in comparison to the authors' previously reported supersaturated drug dispersion compositions, which limited absorption mainly from the stomach.

Insights into HME techniques have also uncovered newer applications of colon targeting. An Eudragit-based HME delivery system containing a photo-sensitizer was developed as a novel treatment option for curing several serious infections of clinical significance caused by multidrug-resistant organisms such as *Enterococcus faecalis* and *Bacteroides fragilis* [93]. In another study, Bruce *et al.* demonstrated the possibility of developing Eudragit S100-based hot melt extruded tablets containing 5-ASA for colonic delivery [94]. TEC and citric acid were evaluated as liquid and solid plasticizers, respectively. As per study results, the concentration of TEC efficiently lowered the polymer's glass transition temperature and extrusion temperature and influenced drug release. Interestingly, a chemical interaction (formation of an amide bond associated with a dehydration reaction) was observed between the functional groups of 5-ASA and citric acid during the melt extrusion process that resulted in lower drug recovery from this HME tablet formulation. However, no interaction was observed between the drug and the carrier matrix.

5.2 Trans-drug delivery systems

HME has shown substantial viability for the production of films and patches to be used in transdermal and transmucosal drug delivery (TMD) systems, as well as transungual applications. Although melt extrusion techniques are increasingly being used the most common method for producing these products is the solvent cast technique. This method utilizes

either aqueous or organic solvents, both of which have considerable limitations beyond their long processing periods [69]. Aqueous solutions are not feasible for the increasing number of BCS class II and class IV drug molecules, or molecules that are susceptible to hydrolysis. On the other hand, the use of organic solvents leads to other concerns such as trace solvents within the finished drug product, environmental contamination and increased expense. Additionally, acrylic films produced by the casting method have been shown to lose plasticity over time as the polymer chains move toward a state of equilibrium [69]. By contrast, HME is solvent free, offers short and continuous processing and is a practical approach to processing both freely and poorly soluble drug molecules by virtue of a wide variety of available polymers.

5.2.1 *Transdermal drug delivery*

A patent filed by Breitenbach *et al.* utilizes HME technology for the production of patches intended for the transdermal delivery of (R)-3,3-diphenylpropylamin-monoesters for the treatment of urinary incontinence [69,95]. Transdermal application is a particularly attractive approach for this compound as it helps avoid the peak plasma concentrations associated with oral dosing and undesirable muscarinic side effects in addition to being equally, if not more, suitable for the target population, that is, the increasing geriatric population. However, one version of this procedure utilizes organic solvents such as dichloromethane, which is a known carcinogen and, as stated previously, the removal of trace solvents is difficult at best. In the hot melt procedure, the molten polymers (acrylate, silicone and styrene based) are mixed with the active ingredient without the use of any solvents, and the melts are spread out over foil as a hot melt casting approach. Interestingly, the active ingredients listed fesoterodine in particular, which proved to be stable at processing temperatures up to 200°C. This material seems to be a prime candidate for the HME process, wherein the benefits of extrusion outweigh the disadvantages of solvent-based casting methods.

Crowley *et al.* utilized HME technology to produce films composed of PEO and two model drugs: guafinesin (GFN) and KTP [25]. Differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and x-ray diffractometry (XRD) were used to examine the thermal stability, surface morphology and crystallinity of the films, respectively. Both of the model drugs were found to be stable during extrusion in addition to functioning as plasticizers, which was indicated by a marked reduction in melt viscosity and decreased drive load. SEM and XRD measurements demonstrated the occurrence of GFN crystallization on the surface the films at all concentrations; however, crystallization of KTP did not occur until drug loading reached 15%. The films loaded with 15% KTP demonstrated a more than twofold increase in percent elongation in contrast to the re-crystallized GFN containing films, which exhibited discontinuity in the polymeric network.

The production of a hot melt co-extruded multilayered laminate was discussed in a patent filed by Crowley [96]. By utilizing a co-extrusion technique, wherein multiple feed streams are brought into contact with each other prior to exiting an extrusion die, the inventors were able to produce a transdermal laminate in which both the reservoir and backing layer were produced by a single HME process. Here the reservoir layer containing the active ingredient is composed of a hydrophilic bioadhesive thermoplastic, while the backing layer has a predominately hydrophobic composition. It is noted in the patent application that the individual layers must have at least one polymer in common, which facilitates adhesion between the layers without the use of an adhesive and that the melt flow indices of the hydrophobic and hydrophilic components should be within 50% of each other. In addition, the laminate should have a consistent transverse cross-section. Additionally, the backing layer can be tailored to have therapeutic properties by including the active ingredient as per the requirements of the laminate, while the reservoir itself can be designed to exhibit controlled release properties. The inventors also noted that when the laminate is separated into unit doses of roughly equal size, and meeting the mentioned criteria, they demonstrate excellent content uniformity. Thus, this patent application demonstrates the increasing versatility and applicability of HME technology for transdermal drug delivery.

5.2.2 *Transmucosal drug delivery*

TMD is particularly suitable for drugs that are highly vulnerable to first pass metabolism. TMD, however, is also advantageous for poorly soluble drugs and for localized treatment of conditions in which oral dosage forms are ineffective or otherwise undesirable. Repka and co-workers, among others, have embarked on a great deal of research wherein HME was examined as a viable means of producing patches for buccal drug delivery [22,32,39,97,98].

Films and patches intended for buccal or other TMD need to be thin and flexible while also demonstrating desirable release profiles. Additionally, these films must have sufficient bioadhesion characteristics in order to withstand the mechanical stresses at the site of application. In one study, Repka *et al.* successfully extruded two thin films composed of the polymers HPC and HPMC [97]. In both films, lidocaine was used as the model drug, which underwent no significant degradation. Thermal analysis by DSC indicated that lidocaine was in the amorphous state in both films. This was confirmed by wide-angle X-ray diffractometry. The film containing only the HPC polymer was compared to the film containing an 80:20 mixture of HPC:HPMC. While both formulations exhibited sustained release characteristics, their dissolution profiles implied that HPMC in the HPC:HPMC mixture reduced drug release in addition to increasing the films' bioadhesion properties. The films also demonstrated an initial burst effect, which would be particularly beneficial when a rapid onset of action is desired. The authors concluded that the films produced by HME in this study would be useful for both dental procedures and other topical applications where local analgesia was desired.

In a series of studies, Repka *et al.* examined the practicality of incorporating the poorly water soluble and thermolabile drug Δ^9-tetrahydrocannabinol (THC) into hot melt films for potential transmucosal delivery [98,99]. In addition to the limitations already mentioned, THC experiences considerable first pass metabolism, which makes it a prime candidate for TMD. In these studies, the films were assessed for mechanical and release properties in addition to stability and mechanisms of degradation. When examining the bioadhesive properties of THC carrying HPC films it was determined that the increasing bioadhesivity was a function of THC content, which suggests that THC itself has bioadhesive properties and naturally lends itself to TMD. When incorporated into PEO carriers it was determined that PEO was more effective than HPC at controlling weight loss of the mixture when held at the elevated temperatures of 160 and 200°C. Of the processing aids tested, THC demonstrated the least compatibility with vitamin E succinate (VES). In additional studies by Repka and co-workers, a prodrug of THC, Δ^9-tetrahydrocannabinol hemiglutarate (THC-HG), was also studied [22,32]. THC-HG demonstrated a noteworthy decrease in degradation when in the presence of all plasticizers tested. However, in this case VES was the most effective plasticizer (**Figure 8**). Additionally, the prodrug was further stabilized by the addition of citric acid, which decreased the micro-environmental pH to a region of maximum stability for THC-HG.

Repka and McGinity prepared films composed of HPC and PEO with and without vitamin E TPGS in order to test its effects on the physical-mechanical properties of the film [70]. Vitamin E TPGS was of particular interest due to its amphiphilic nature. The incremental addition of vitamin E TPGS (1, 3 and 5%) into films composed of either a 50:50 or 80:20 ratio of HPC:PEO linearly decreased the glass transition temperature, which qualifies it as a plasticizer. The authors observed that the incorporation of vitamin E TPGS further assisted the processing of the films by decreasing barrel pressure and torque on the extruder.

In a similar set of studies, Prodduturi *et al.* investigated the effects of a polymer's molecular mass on the physico-mechanical properties and stability of thin extruded films composed of PEO (MM 200,000 and 300,000 Daltons) [97] and HPC (MM 140,000; 370,000; 850,000 Daltons) [39]. In both studies clotrimazole (CT) was used as a model drug. Additionally, the films were used to characterize the physical and chemical stability of the poorly water-soluble model drug post-extrusion. The films exhibited favorable bioadhesive and mechanical properties in addition to demonstrating zero order kinetics and considerable content uniformity. However, recrystallization of the model drug in the PEO films was confirmed by XRD after 3 months of stability testing (25°C/60% RH). The HPC/PEO films displayed considerable stability when stored at 25°C/60% RH for 3 months, but recrystallization of CT was observed when the films were stored at accelerated conditions over the same time period when PEO exceeded 50% within the polymer blended films. In the case of both polymers, molecular mass affected dissolution rate considerably leaving the possibility of tailored release profiles. It was concluded that PEO and HPC matrices are potentially suitable carriers of CT and that the production of these films by HME can produce thin films with excellent content uniformity.

In a very recent study, Palem *et al.* explored the viability of utilizing HME technology for the production and characterization of immediate release mucoadhesive buccal films containing the motion sickness drug domperidone (DOM) [100]. The formulations explored in this study contained PEO N10 alone or in mixtures with HPMC E5 LV and/or Eudragit® RL100 and PEG 3350 as a plasticizer. The extruded films were assessed for a variety of significant characteristics including drug content, drug–excipient interaction, mechanical properties, *in vitro* bioadhesion and *in vitro* drug release. The optimized formulation (DOM2) was selected for bioavailability studies. In addition to demonstrating excellent content uniformity and no drug–excipient interactions, DOM2 showed < 5% drug loss over the 6 month accelerated stability (40°C and 75% RH) testing conditions. A peak detachment force of 1.55 N was also noted in addition to leaving no sign of irritation at site of application. Furthermore, DOM2 exhibited a 1.5-fold increase in bioavailability relative to that of currently marketed instant release tablets. This ultimately indicates that less of the drug is needed to achieve the desired therapeutic effect when in this melt extruded dosage form, which should reduce the incidence of side effects associated with the drug. The authors concluded that the utilization of HME technology for the production of buccal films containing DOM is a very advantageous approach.

A patent filed by Richard Fuisz explores the use of HME technology for the production of a smokeless tobacco product [101]. The administration of nicotine through a transmucosal film is of particular interest as it provides an alternative to other forms of tobacco use, which are generally considered less safe. The author claims that nicotine can be made highly bioavailable when tobacco in the form of snuff is extruded with HPC in an amount of > 20%wt of the entire formulation. This approach ultimately results in the user ingesting less tobacco overall, which may be associated with a decrease in health risks. The dissolution profile can be further adjusted through the addition of other insoluble polymers. This film also demonstrates a certain degree of versatility in that it can be used as a buccal patch, held to the palate or used sublingually. In another patent application by the same inventor, it is indicated that the approach previously mentioned can be used to produce extrudates of bioactive agents in which at least one thermoplastic polymer is in an amount of > 20%wt of the entire formulation [102]. In this instance, the product is not limited to the oral mucosa and can also be used on the nasal, rectal and vaginal mucosa as well.

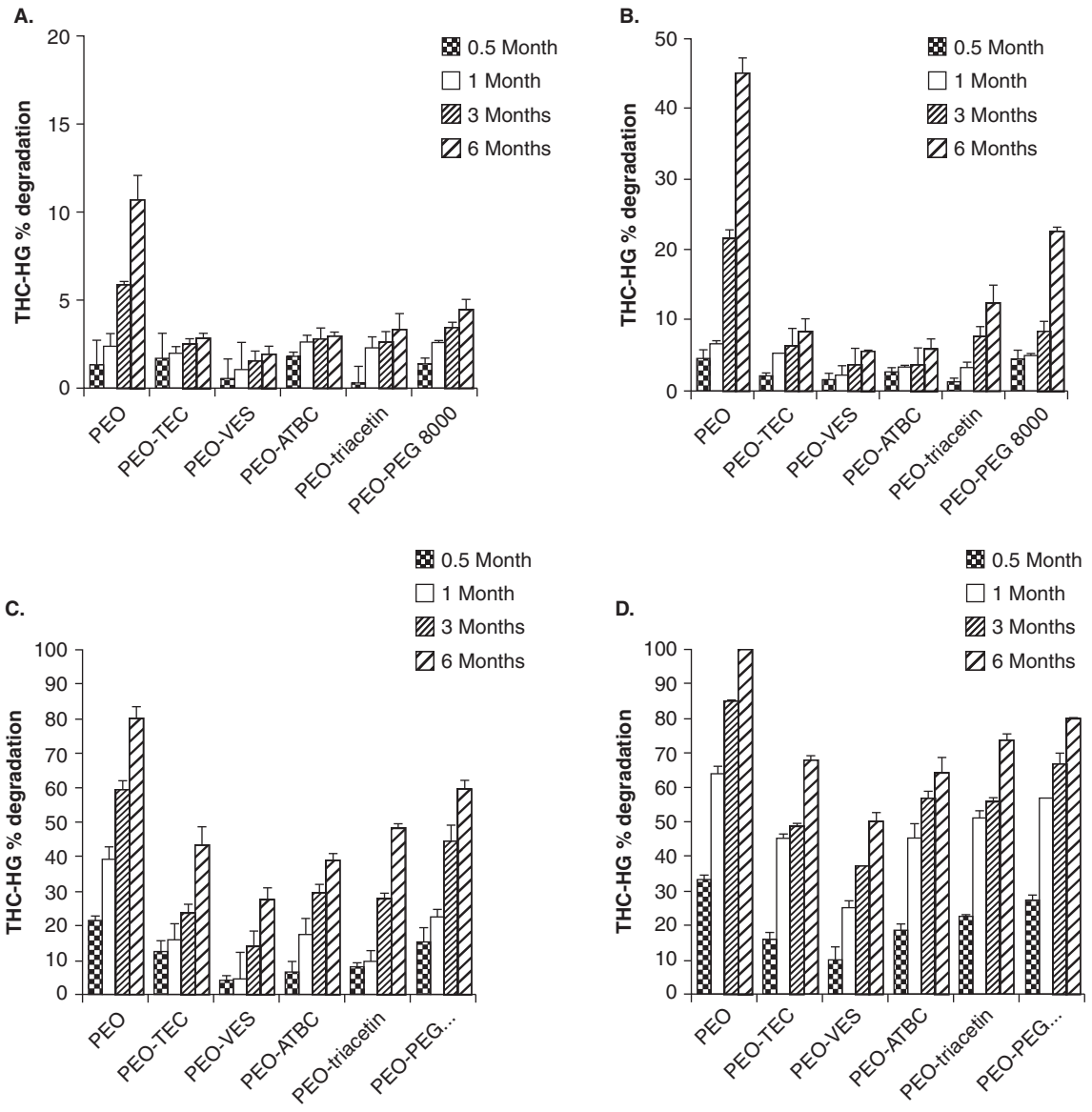

Figure 8. Effect of plasticizers on the chemical stability of THC-HG in PEO polymeric matrices (n = 3) stored at four different temperatures: (A) -18°C, **(B)** 4°C, **(C)** 25°C and **(D)** 40°C. The films were fabricated at 110°C for 7 min.

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PEO: Polyethyleneoxide; THC-HG: Δ9-Tetrahydrocannabinol hemiglutarate.

5.2.3 Transungual drug delivery

Insufficient bioadhesion to the finger and toenails has been a major issue in the development of transungual drug delivery systems. Lacquers were developed to address this issue; however, lack of robustness necessary to withstand the mechanical stresses present at the site of application as well as sustained drug release have proved problematic. In an attempt to further address the issues associated with transungual drug delivery, Repka *et al.* utilized HME technology for the development of films composed of 20% w/w ketoconazole with PEO as the polymeric carrier [103]. The films demonstrated enhanced bioadhesion and permeability of the API when applied in the presence of an 'etchant,' and demonstrated excellent content uniformity. Moreover, DSC revealed that the API was molecularly dispersed within the extruded films, which increases bioavailability. The authors concluded that these films coupled with an etching agent may provide an advantageous approach to the treatment of onychomycosis.

In a similar study, HME technology was used for the production of HPC films of multiple MM (80 – 850 kDa) containing itraconazole and α-tocopherol for the transungual treatment of onychomycosis [46]. DSC measurements of the

extruded films indicated that the active ingredients were present in the amorphous state. Interestingly, the results of this study indicated that there existed an inverse relationship between the molecular mass of HPC in the films and the release kinetics of itraconazole. Therefore, altering the molecular mass of HPC enables tailoring the film's release properties possible. Repka recently was granted a US patent pertaining to the above discussion on transungual drug delivery [104]. Therefore, production of films via HME could serve as an appealing dosage form for transungual therapies.

5.3 Implants

Ghalanbor *et al.* prepared model protein (lysozyme)-loaded poly (D,L lactide-co-glycolide) (PLGA) implants with special emphasis on protein stability, burst release and release completeness using HME [17]. The authors studied the feasibility of HME for processing of proteins and examined with regard to the main challenges in the field, that is, protein instability during manufacture and release, as well as the release incompleteness. Stability of lysozyme was confirmed using DSC, FTIR, HPLC and biological activity. Lysozyme, recovered from implants, retained its biological activity during the HME process and during *in vitro* release of the enzyme for 60 – 80 days. Nearly complete recovery of active lysozyme as a model protein illustrated that the melt extrusion process did not alter protein integrity. In contrast, poly (lactic acid) implants containing vapreotide, a somatostatin analog prepared by HME, revealed degradation of the peptide during processing which led to the formation of an impurity, lactoyl lactyl–vapreotide conjugate [105]. The authors observed that the presence of residual lactide in the polylactic acid significantly influenced the formation of the peptide impurity, illustrating that carrier purity influences the quality of the dosage form.

Additionally, PLGA (50:50 molar ratio of lactic:glycolic acid) copolymer was used to prepare biodegradable implants of melanotan-I (MT-I), a super potent tridecapeptide capable of stimulating melanotropic activity, by an HME method [106]. The *in vitro* release of MT-I governed by pore-diffusion and polymer erosion exhibited a tri-phasic profile with an initial rapid release (< 5% of the drug load) followed by a secondary phase of slow release. It was also observed that a tertiary phase of rapid release commenced after about 3 weeks due to erosion of the polymer. The polymer erosion and degradation were considered as the factors influencing the drug release and controlled by the physical properties of the polymer, such as molecular mass and viscosity. The *in vivo* studies with guinea-pigs demonstrated a prolonged peptide release into the systemic circulation for at least 36 days, which illustrated the potential of the implanted delivery system to increase the therapeutic efficacy of MT-I.

Thermoplastic elastomers, pEVA and segmented polyurethane (PU), an important material class from which FDA approved IVR devices, have been constructed. IVR devices from this class are manufactured by injection molding or continuous HME [2,3]. In extrusion, the polymer rod is cut to length and end-joined together using butt welding, over molding, solvent welding or biomedical grade epoxies to form the final ring [107]. The only IVR thermoplastic ring currently on the market – the contraceptive NuvaRing – is made from pEVA, a copolymer of vinyl acetate and ethylene that varies from 10 to 40% vinyl acetate content. NuvaRing is a thermoplastic reservoir IVR fabricated from two different grades of pEVA [62,63]. As the mole fraction of vinyl acetate increases, the polymer crystallinity was reduced, Young's modulus decreased and the drug permeability within the matrix increased. Because of these properties, it is possible to produce, via co-extrusion, a reservoir device comprising a softer higher vinyl acetate mole fraction pEVA in the interior that promotes drug permeation and contributes the majority of the ring's mechanical properties. A crystalline pEVA (i.e. lower vinyl acetate fraction) on the exterior serves as a rate-limiting membrane to control drug release. The contraceptive vaginal ring consisted of two steroids (etonogestrel and ethinyl estradiol) present in the molecularly dissolved state in a coaxial fiber consisting of two types of PEVA copolymers. The coaxial fiber comprised a core polymer (EVA 28; 28% vinyl acetate; high solubility and permeability of steroids) with the two steroids incorporated and enveloped within a thin polymer membrane (EVA 9; 9% vinyl acetate; lower solubility and permeability of the steroids). This study demonstrated the application of HME in manufacturing structurally and functionally more intricate dosage forms such as the vaginal ring, incorporated with more than one bioactive.

Sustained release, dual segmented PU IVR rings were fabricated for two antiretroviral drugs with disparate hydrophilicity, dapivirine and tenofovir to prevent the sexual transmission of HIV (**Figure 9**) [108]. Drugs were individually formulated using appropriate polymers with matching hydrophilicity using solvent casting followed by HME. The resulting drug loaded rods were butt-welded to form dual segment IVRs that were mechanically comparable to the widely acceptable NuvaRing IVR. In addition, the formulated ring exhibited sustained release of medicament for a period of 30 days while it was found to be chemically and physically stable at accelerated stability conditions for a period of 90 days.

6. Conclusions and scope

Innovation in formulation, polymer manufacturing science and equipment processing and technology has revolutionized the advancement of HME techniques. Industrial acceptability and adaptability continues to influence the development of improved and scalable equipment, serving batch sizes as small as 5 g to 1000 kg/h. This review describes recent developments in immediate release formulations including solubilization by transforming drugs into their amorphous state using a solid solution/solid dispersion approach assisted by novel polymer matrices such as Soluplus and low-molecular-mass HPC, taste masking of bitter drugs using pH-dependent polymers, as

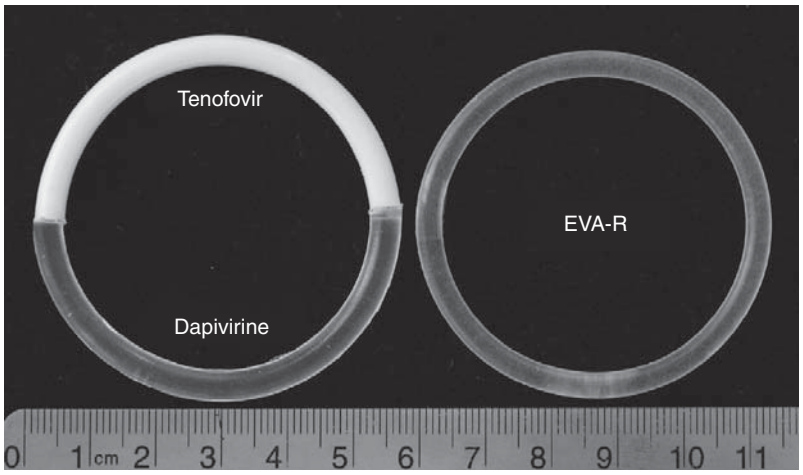

Figure 9. Left: segmented ring consisting of tenofovir in WS-PU (Tecophilic® HP-60D-20) (top section) and dapivirine in NWS-PU (Tecoflex® 85A) (bottom section). Right: EVA-R Nuvaring®.
Reprinted with kind permission from Elsevier Ltd [107].

well as effervescent dosage forms. Moreover, exploitation of polymer properties encourages their use in varied modified and targeted release delivery systems. HME, being a solvent-free process for the production of films, enables future opportunities to develop immediate and prolonged release patches and multilayer systems to modulate drug release for oral and transdermal applications. The breadth of research and publications in the field of HME demonstrates this technology's versatility and applicability for transformation of pharmaceutical industry development and manufacturing.

7. Expert opinion

Enhancing solubility and bioavailability of poorly soluble drugs – an ever increasing topic for seminars, workshops, meetings and internal industry discussions – coupled with this same forum trend for melt extrusion validates the present and future of this enabling technology. It is apparent to us that literally every multi-national pharma has at least touched HME; however, an ever-increasing number are embracing it as a solution to the solubility issues of the majority of NCEs. Is melt extrusion the only answer to these types of issues? Obviously, it is not. Other technologies, such as spray drying, have shown to be applicable in some cases. No technique can solve all of the problems that our industry faces. However, innovations in formulation, exploiting new polymers and properties of existing polymers and lipids, as well as equipment modifications and scalability have thrust HME into the forefront to change the paradigm of pharmaceutical manufacturing.

Other advantages of melt extrusion, such as a solvent-free and continuous process, are making even more sense to pharma executives. Successful products have been marketed using this technology and many others are in the pipeline. The FDA is cognizant of this technology's unique adaptability to PAT and QbD. Process engineers are working together with formulation scientists to enhance this already proven technology. Contract manufacturers with melt extrusion capability are increasing in number across the US and the world. These examples, and many others, are evidence that HME will be commonplace within the pharmaceutical industry in the not too distant future.

As outlined in this article, melt extrusion techniques are amenable for a myriad of different dosage forms and devices, only limited by struggling with the innovative process. Why are there not more HME produced products on the market? In our opinion, the answer lies primarily in that inherent resistance (or fear) to change. Yes, the economy over the last several years has played a role in many products to be sidelined in every industry. However, perhaps we should reflect on the words of Sir Winston Churchill: 'A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.'

Regardless, many pharmaceutical companies are forging ahead, optimizing the technology and introducing HME produced products. In 2010, a heat stable Norvir® (Abbott Laboratories, Abbott Park, IL, USA) tablet (ritonavir) was approved by the FDA. The product does not require refrigeration and is manufactured using proprietary Meltrex® technology. This product was preceded by Kaletra®, also a melt extruded tablet produced by Abbott, which has significant advantages over the older soft gelatin capsules in terms of dosing frequency and stability. Other melt extruded products include NuvaRing, Implanon® (Organon, a subsidiary of Merck & Co., USA) and Isoptin SR (Abbott Laboratories, USA). However, there are a number of HME produced pharmaceutical products and medical devices in the pipeline. Indeed, melt extrusion technology is marching forward as Amgen and other companies target various markets. Cross-pollination utilizing HME among the pharmaceutical industry, medical device and biotechnology companies is evidence that melt extrusion technology has arrived.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm 2007;33(9):909-26

•• **A detailed review on instrumentation, developmental aspects and characterization techniques of HME dosage forms.**

2. Repka MA, Battu SK, Upadhye SB, et al. Pharmaceutical applications of hot-melt extrusion: Part II. Drug Dev Ind Pharm 2007;33(10):1043-57

•• **A detailed review on various application of HME solubilization, taste masking, sustained release, transmucosal, transdermal patch, implants of HME dosage forms.**

3. Repka MA, Majumdar S, Battu SK, et al. Applications of hot-melt extrusion for drug delivery. Expert Opin Drug Deliv 2008;5(12):1357-76

4. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002;54(2):107-17

• **An interesting review on applications of HME in the field of pharmaceutics.**

5. Kerns EH. High throughput physicochemical profiling for drug discovery. J Pharm Sci 2001;90(11):1838-58

6. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 1999;88(10):1058-66

7. Forster A, Hempenstall J, Rades T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J Pharm Pharmacol 2001;53(3):303-15

8. Ndindayino F, Vervaet C, Van den Mooter G, et al. Bioavailability of hydrochlorothiazide from isomalt-based moulded tablets. Int J Pharm 2002;246(1-2):199-202

9. Breitenbach J, Magerlein M. editors. Melt extruded molecular dispersions. Informa Healthcare; 2003

10. Miller DA, McConville JT, Yang W, et al. Hot-melt extrusion for enhanced delivery of drug particles. J Pharm Sci 2007;96(2):361-76

• **The first known published report on application of hot melt extrusion in conjunction with nanoparticle engineering.**

11. Sauer D, Zheng W, Coots LB, et al. Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit L 100-55. Eur J Pharm Biopharm 2007;67(2):464-75

12. Fukuda M, Miller DA, Peppas NA, et al. Influence of sulfobutyl ether beta-cyclodextrin (Captisol) on the dissolution properties of a poorly soluble drug from extrudates prepared by hot-melt extrusion. Int J Pharm 2008;350(1-2):188-96

13. Upadhye SB, Kulkarni SJ, Majumdar S, et al. Preparation and characterization of inclusion complexes of a hemisuccinate ester prodrug of delta9-tetrahydrocannabinol with modified beta-cyclodextrins. AAPS PharmSciTech 2010;11(2):509-17

14. Prodduturi S, Urman KL, Otaigbe JU, et al. Stabilization of hot-melt extrusion formulations containing solid solutions using polymer blends. AAPS PharmSciTech 2007;8(2):Article 50

15. Schilling SU, Shah NH, Waseem Malick A, et al. Properties of melt extruded enteric matrix pellets. Eur J Pharm Biopharm 2010;74(2):352-61

16. Ozguney I, Shuwisitkul D, Bodmeier R. Development and characterization of extended release Kollidon® SR mini-matrices prepared by hot-melt extrusion. Eur J Pharm Biopharm 2009;73(1):140-5

17. Ghalanbor Z, Korber M, Bodmeier R. Improved lysozyme stability and release properties of poly(lactide-co-glycolide) implants prepared by hot-melt extrusion. Pharm Res 2010;27(2):371-9

18. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm 2001;52(2):181-90

19. Ndindayino F, Vervaet C, Van den Mooter G, et al. Direct compression and moulding properties of co-extruded isomalt/drug mixtures. Int J Pharm 2002;235(1-2):159-68

20. Bialleck S, Rein H. Preparation of starch-based pellets by hot-melt extrusion. Eur J Pharm Biopharm 2011;79(2):440-8

21. Verreck G, Decorte A, Li H, et al. The effect of pressurized carbon dioxide as a plasticizer and foaming agent on the hot melt extrusion process and extrudate properties of pharmaceutical polymers. J Supercrit Fluid 2006;38(3):383-91

22. Thumma S, ElSohly MA, Zhang SQ, et al. Influence of plasticizers on the stability and release of a prodrug of Delta(9)-tetrahydrocannabinol incorporated in poly (ethylene oxide) matrices. Eur J Pharm Biopharm 2008;70(2):605-14

23. Schilling SU, Shah NH, Malick AW, et al. Citric acid as a solid-state plasticizer for Eudragit RS PO. J Pharm Pharmacol 2007;59(11):1493-500

• **Identification of a new application for an existing pharmaceutical excipient for the purposes of HME.**

24. Repka MA, Gerding TG, Repka SL, et al. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. Drug Dev Ind Pharm 1999;25(5):625-33

25. Crowley MM, Fredersdorf A, Schroeder B, et al. The influence of guaifenesin and ketoprofen on the properties of hot-melt extruded polyethylene oxide films. Eur J Pharm Sci 2004;22(5):409-18

• **An interesting discussion on recrystallization of drug during**

stability and its effect on mechanical properties of HME dosage forms.

26. Crowley MM, Zhang F, Koleng JJ, et al. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials 2002;23(21):4241-8
27. Wu C, McGinity JW. Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit RS PO hot-melt extrudates. Eur J Pharm Biopharm 2003;56(1):95-100
28. Schilling SU, Lirola HL, Shah NH, et al. Influence of plasticizer type and level on the properties of Eudragit S100 matrix pellets prepared by hot-melt extrusion. J Microencapsul 2010;27(6):521-32
29. De Brabander C, Vervaet C, Fiermans L, et al. Matrix mini-tablets based on starch/microcrystalline wax mixtures. Int J Pharm 2000;199(2):195-203
30. Verhoeven E, Vervaet C, Remon JP. Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hot-melt extrusion: in vitro and in vivo evaluation. Eur J Pharm Biopharm 2006;63(3):320-30
31. Schilling SU, Bruce CD, Shah NH, et al. Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets. Int J Pharm 2008;361(1-2):158-68
32. Thumma S, Majumdar S, ElSohly MA, et al. Chemical stability and bioadhesive properties of an ester prodrug of Delta 9-tetrahydrocannabinol in poly(ethylene oxide) matrices: effect of formulation additives. Int J Pharm 2008;362(1-2):126-32
33. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: stability testing of selected solid dispersions. Pharm Res 2006;23(8):1928-36
34. Zhou F, Vervaet C, Remon JP. Matrix pellets based on the combination of waxes, starches and maltodextrins. Int J Pharm 1996;133(1-2):155-60
35. Gryczke A, Schminke S, Maniruzzaman M, et al. Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion. Colloids Surf B Biointerfaces 2011;86(2):275-84
36. Repka MA, McGinity JW. Influence of chlorpheniramine maleate on topical hydroxypropylcellulose films produced by hot-melt extrusion. Pharm Dev Technol 2001;6(3):297-304
37. Mididoddi PK, Prodduturi S, Repka MA. Influence of tartaric acid on the bioadhesion and mechanical properties of hot-melt extruded hydroxypropyl cellulose films for the human nail. Drug Dev Ind Pharm 2006;32(9):1059-66
38. Mididoddi PK, Repka MA. Characterization of hot-melt extruded drug delivery systems for onychomycosis. Eur J Pharm Biopharm 2007;66(1):95-105
39. Prodduturi S, Manek RV, Kolling WM, et al. Water vapor sorption of hot-melt extruded hydroxypropyl cellulose films: effect on physico-mechanical properties, release characteristics, and stability. J Pharm Sci 2004;93(12):3047-56
40. Bruce C, Fegely KA, Rajabi-Siahboomi AR, et al. Crystal growth formation in melt extrudates. Int J Pharm 2007;341(1-2):162-72
41. Sri Venkata S, Tumuluri SP, Michael M, et al. The use of near-infrared spectroscopy for the quantitation of a drug in hot-melt extruded films. Drug Dev Ind Pharm 2004;30(5):505-11
42. Ingo Alig DF, Lellinger D, Steinhoff B. Combination of NIR, raman, ultrasonic and dielectric spectroscopy for in-line monitoring of the extrusion process. Macromol Symp 2005;230(1):51-8
43. Mollan M. Historical Overview. Marcel Dekker, Inc; New York, Ny: 2003
44. Ferns A. Twin-screw machines for polymer compounding operations. Plast Polym 1974;42(8):149-57
45. Breitenbach J, Grabowski S, Rosenbberg J. Extrusion von polymer-wirkstoff-gemischen zur herstellung von Arzneiformen. Spektrum der Wissenschaft 1995;11:18-19
46. Trey SM, Wicks DA, Mididoddi PK, et al. Delivery of itraconazole from extruded HPC films. Drug Dev Ind Pharm 2007;33(7):727-35
47. Young CR, Koleng JJ, McGinity JW. Production of spherical pellets by a hot-melt extrusion and spheronization process. Int J Pharm 2002;242(1-2):87-92
48. Fukuda M, Peppas NA, McGinity JW. Floating hot-melt extruded tablets for gastroretentive controlled drug release system. J Control Release 2006;115(2):121-9
49. Quinten T, Gonnissen Y, Adriaens E, et al. Development of injection moulded matrix tablets based on mixtures of ethylcellulose and low-substituted hydroxypropylcellulose. Eur J Pharm Sci 2009;37(3-4):207-16
50. Robinson JR, Mcginity JW, Ethypharm SA. inventors Effervescent granules and methods for their preparation. US6071539. 2000
51. Dreiblatt A. editor. Process design. Marcel Dekker, Inc; New York: 2003
52. Doetsch W. editor. Material handling and feeder technology. Marcel Dekker, Inc.; New York: 2003
53. Liu L, Wang P, Xanthos M, et al. Review Paper: Processing aspects of Hot Melt Extrusion in Pharmaceutical Applications. ANTEC; Chicago: 2009. p. 2370-5
54. Arnum Atfmb PV. Exploring excipient functionality. Pharm Technol 2011;35:6-11
55. Thompson MR, Sun J. Wet granulation in a twin-screw extruder: implications of screw design. J Pharm Sci 2010;99(4):2090-103
56. Nakamichi K, Nakano T, Yasuura H, et al. The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder. Int J Pharm 2002;241(2):203-11
57. Mccrum NG, Buckley CP. editors. Principles of polymer engineering. Oxford University Press; Oxford: 1997
58. Rauwendaal C. editor. Polymer extrusion. 3rd edition. Hanser Publisher; Munich: 1994
59. Repka MA, McGinity JW, Zhang F, et al. editors. Hot-melt extrusion technology. 2nd edition. Marcel Dekker, Inc.; New York: 2002
60. Saerens L, Dierickx L, Lenain B, et al. Raman spectroscopy for the in-line polymer-drug quantification and solid state characterization during a pharmaceutical hot-melt extrusion process. Eur J Pharm Biopharm 2011;77(1):158-63

61. Dhumal RS, Kelly AL, York P, et al. Cocrystalization and simultaneous agglomeration using hot melt extrusion. Pharm Res 2010;27(12):2725-33

62. van Laarhoven JA, Kruft MA, Vromans H. Effect of supersaturation and crystallization phenomena on the release properties of a controlled release device based on EVA copolymer. J Control Release 2002;82(2-3):309-17

63. van Laarhoven JA, Kruft MA, Vromans H. In vitro release properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring. Int J Pharm 2002;232(1-2):163-73

64. Dierickx L, Saerens L, Almeida A, et al. Co-extrusion as manufacturing technique for fixed-dose combination mini-tablets [abstract ID: W5073]. American Association of Pharmaceutical Scientists Annual Meeting; Washington Convention Center, Washington, DC; 2011

65. Reitz C, Kleinebudde P. Solid lipid extrusion of sustained release dosage forms. Eur J Pharm Biopharm 2007;67(2):440-8

66. Windbergs M, Gueres S, Strachan CJ, et al. Two-step solid lipid extrusion as a process to modify dissolution behavior. AAPS PharmSciTech 2010;11(1):2-8

67. Aharoni SM. Increased glass transition temperature in motionally constrained semicrystalline polymers. Polym Adv Technol 1998;9(3):169-201

68. Follonier N, Doelker E, Cole ET. Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs. Drug Dev Ind Pharm 1994;20(8):1323-39

69. Aitken-Nichol C, Zhang F, McGinity JW. Hot melt extrusion of acrylic films. Pharm Res 1996;13(5):804-8

70. Repka MA, McGinity JW. Influence of vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion. Int J Pharm 2000;202(1-2):63-70

71. Follonier N, Doelker E, Cole ET. Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. J Control Release 1995;36(3):243-50

72. Verreck G, Decorte A, Heymansa K, et al. The effect of pressurized carbon dioxide as a temporary plasticize and foaming agnet on the hot stage extruion process and extrudate properties of solid dispersion of itraconzaole with PVP-VA 64. Eur J Pharm Sci 2005;26(3-4):349-58

73. Physical and Chemical Properties, Klucel®, Hydroxypropylcellulose. Hercules, Inc., Aqualon Division; Wilmington, DE: 1997. p. 2-6

74. Physical and Chemical Properties, Aqualon® Ethylcellulose. Technical Bulletin. Hercules, Inc; Wilmington: 1996. p. 250-2

75. Bailey FE, Koleske JV. Poly(ethylene oxide). Academic Press; New York: 1976

76. Perissutti B, Newton JM, Fea P. Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form. Eur J Pharm Biopharm 2002;53(1):125-32

77. Mank R, Kala H, Richter M. Preparation of extrusion pellets containing drugs on the base of thermoplastics. 2. Investigations on the improvement of the drug release on the base of thermoplastics. Pharmazie 1990;45(8):592-3

78. McGinity JW, Koleng JJ. Preparation and Evaluation of Rapid-Release Granules using a Novel Hot-Melt Extrusion Technique. Pharmaceutical Technology Conference: Pharmaceutical technology; 1997. p. 153-4

79. Fu J, Xu L, Wang X, et al. Nimodipine (NM) tablets with high dissolution containing NM solid dispersions prepared by hot-melt extrusion. Drug Dev Ind Pharm 2011;37(8):934-44

80. Sun Y, Rui Y, Wenliang Z, et al. Nimodipine semi-solid capsules containing solid dispersion for improving dissolution. Int J Pharm 2008;359(1-2):144-9

81. Sherry R. inventor. Reckitt Benckiser Healthcare (UK) Limited assignee. Granules comprising paracetamol, a NSAID and a sugar alcohol made by melt extrusion patent. EP1799195; 2007

82. Mohammed N, Majumdar S, Repka MA, et al. Tablets manufactured via HME as a processing technique for solubility enhancement: Stability assessment and in vitro release comparison to a marketed fromulation [abstract ID: #T3277]. American Association of Pharmaceutical Scientists Annual Meeting and Exposition; Washington Convention Center, Washington, DC, USA; 2011

83. Maddineni S, Langley N, Repka MA, et al. Formulation, evalutation and comparison of nifedipine hot-melt extruded tablets [abstract ID: #R6052]. American Association of Pharmaceutical Scientists Annual Meeting; New Orleans, LA; 2010

84. Ali S, Langley N, Djuric D, et al. Eye on excipients: Soluplus, a novel graft copolymer. Tablets & Capsules; 2010

85. De Brabander C, Vervaet C, Van Bortel L. Bioavailability of ibuprofen from hot-melt extruded mini-matrices. Int J Pharm 2004;271(1-2):77-84

86. Ozguney I, Shuwisitkul D, Bodmeier R. Development and characterization of extended release Kollidon SR mini-matrices prepared by hot-melt extrusion. Eur J Pharm Biopharm 2009;73(1):140-5

87. Almeida A, Possemiers S, Boone MN, et al. Ethylene vinyl acetate as matrix for oral sustained release dosage forms produced via hot-melt extrusion. Eur J Pharm Biopharm 2011;77(2):297-305

88. Verhoeven E, De Beer T, Schacht E, et al. Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot-melt extrusion: in vitro and in vivo evaluations. Eur J Pharm Biopharm 2009;72(2):463-70

89. Quintavalle U, Voinovich D, Bea P. Preparation of sustained release co-extrudates by hot-melt extrusion and mathematical modelling of in vitro/in vivo drug release profiles. Eur J Pharm Sci 2008;33(3):282-93

- **Described a mathematical model for predicting a drug plasma concentration profile from *in vitro* data.**

90. Andrews GP, Jones DS, Diak OA, et al. The manufacture and characterisation of hot-melt extruded enteric tablets. Eur J Pharm Biopharm 2008;69(1):264-73

91. Schilling SU, McGinity JW. Novel application of hot-melt extrusion for the preparation of monolithic matrices containing enteric-coated particles. Int J Pharm 2010;400(1-2):24-31

92. Miller DA, DiNunzio JC, Yang W, et al. Targeted Intestinal Delivery of Supersaturated Itraconazole for Improved Oral Absorption. Pharm Res 2008;25(6):1450-9

93. Cassidy CM, Tunney MM, Caldwell DL, et al. Development of novel oral formulations prepared via hot melt extrusion for targeted delivery of photosensitizer to the colon. Photochem Photobiol 2011;87(4):867-76

94. Bruce LD, Shah NH, Malick AW, et al. Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid. Eur J Pharm Biopharm 2005;59(1):85-97

95. Breitenbach A, Meese C, Wolff H-M, et al. inventors. Transdermal delivery of (R)-3,3-diphenylpropylamin-monoestern patent.. US20090274761; 2009

96. Crowley M. inventor. Process for the preparation of a hot-melt extruded laminate patent.. US0136555; 2009

97. Prodduturi S, Manek RV, Kolling WM, et al. Solid-state stability and characterization of hot-melt extruded poly(ethylene oxide) films. J Pharm Sci 2005;94(10):2232-45

98. Munjal M, Stodghill SP, Elsohly MA, et al. Polymeric systems for amorphous Delta 9-tetrahydrocannabinol produced by a hot-melt method. Part I: chemical and thermal stability during processing. J Pharm Sci 2006;95(8):1841-53

99. Munjal M, Elsohly MA, Repka MA. Polymeric systems for amorphous Delta9-tetrahydrocannabinol produced by a hot-melt method. Part II: Effect of oxidation mechanisms and chemical interactions on stability. J Pharm Sci 2006;95(11):2473-85

100. Palem C, Battu S, Maddineni S, et al. Oral transmucosal delivery of domperidone from immediate release films produced via hot-melt extrusion technology. Pharm Dev Technol 2011; In press

101. Fuisz RC. inventor. Smokeless Tobacco Product patent. US0242978; 2010

102. Fuisz RC. inventor. Extrudable and Extruded Compositions for Delivery of Bioactive Agents, Method of Making Same and Method of Using Same patent. US0098192; 2009

103. Repka MA, Mididoddi PK, Stodghill SP. Influence of human nail etching for the assessment of topical onychomycosis therapies. Int J Pharm 2004;282(1-2):95-106

104. Repka MA, inventor University of Mississippi (University, MS), assignee. Delivery of medicaments to the nail United States patent 7,959,904. 2011

105. Rothen-Weinhold A, Oudry N, Schwach-Abdellaoui K, et al. Formation of peptide impurities in polyester matrices during implant manufacturing. Eur J Pharm Biopharm 2000;49(3):253-7

106. Bhardwaj R, Blanchard J. In vitro evaluation of Poly(d,l-lactide-co-glycolide) polymer-based implants containing the alpha-melanocyte stimulating hormone analog, Melanotan-I. J Control Release 1997;45:49-55

107. Grewell D, Benatar A. Welding of Plastics: Fundamentals and New Developments. Intern Polymer Process 2007;1:43-60

108. Johnson TJ, Gupta KM, Fabian J, et al. Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents dapivirine and tenofovir. Eur J Pharm Sci 2010;39(4):203-12

- **Demonstrated the application of HME in developing a structurally and functionally complicated dosage form.**

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