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REVIEW

Advances in hot-melt extrusion technology toward pharmaceutical objectives

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Abstract Hot Melt Extrusion (HME) technology is a widely used for manufacturing process in the plastic and pharmaceutical industries and is an efficient and simple for the production of a solid dispersion. This technique is an environmental friendly, continuous process that does not use solvents. It is time and cost efficient and can be easily scaled up. In addition, HME may be used in conjunction with other technologies to effectively increase the solubility and dissolution rate of poorly water-soluble drugs. Numerous research papers on the progress of HME technology in the pharmaceutical industry have been written, and products manufactured using HME have been approved by the FDA. However, there are some drawbacks to the products manufactured using through HME. These are related to the high energy input coming from the applied shear forces and high temperature, which could lead to drug or polymer degradation and thus significantly impact the product quality. Despite these disadvantages, HME has been employed in various advanced applications, such as taste masking and targeted drug delivery. This review article focuses on advances in HME technology, which include improvement in the weaknesses of HME, patient-centric formulations, and the outlook for uses such as formulation development.

Keywords Hot melt extrusion (HME) · Overcome weakness · Patient centric formulation · Future-outlook

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Introduction

The low solubility of active pharmaceutical ingredients (APIs) generally leads to low bioavailability. Many techniques have been attempted to improve the solubility of the API, such as structural changes, particle size reduction, pH control, prodrug preparation, and solid dispersion, which molecularly disperses the drug in water-soluble polymers. Among the available techniques to enhance the solubility of poorly water-soluble drugs, solid dispersion is widely used in pharmaceutical fields; Hot Melt Extrusion (HME) is an efficient and simple technique for the production of a solid dispersion (Fule et al. 2014; Jaiswar et al. 2016).

HME technology is a widely used for manufacturing process in the plastic and pharmaceutical industries and has demonstrated many possibilities in a continuous pharmaceutical process. Many researchers have used the HME process for drug delivery systems, including granules (Follonier et al. 1995), sustained release formulations (Crowley et al. 2002, 2004; Zhang 1999; Zhang and McGinity 2000), and pellets (Follonier et al. 1994; Young et al. 2002). HME technology is emerging as an alternative to existing pharmaceutical processes and has been widely used to improve the safety and efficacy of pharmaceutical products.

HME technology offers many advantages. There are no toxicity concerns about residual solvents because there is no requirement for water or organic solvent during processing; the absence of a solvent leads to save time, cost, and makes this system environmentally friendliness (Javeer et al. 2013). It is possible to conduct a continuous process by reducing the process steps in the production of the solid dispersion, and the quality of products can be increased. HME is a well-known highly scalable process. Also, the release behavior of the drug can be easily controlled (Fule et al. 2013). Thus, a number of HME products have entered

the markets and a few of them are decribed in Table 1. However, there are some limitations to the products manufactured using through HME. During the process, a temperature above the glass-transition temperature of the carrier or polymer is required; therefore, HME is performed at a relatively high temperature range of approximately 100–150 °C. When thermosensitive drugs are applied in the HME process, the drug and polymer may be degraded by the high temperature and torque. HME technology is also used to control the release of drugs. To prepare a more retarding dosage form, a higher molecular weight polymer is usually used. However, the higher viscosity can generate a higher torque. Although this will form highly homogeneous extrudates, overtorque may stop the machine or degrade the API and polymer. Therefore, plasticizers are usually included in this process to minimize the thermal degradation of the API or carrier (Maniruzzaman et al. 2012), but may not always be sufficient. These advantages and drawbacks of HME were represented in Fig. 1.

Despite these disadvantages, HME has become a promising technology in the twenty-first century and has been employed in various advanced applications, such as taste masking and targeted drug delivery (Maniruzzaman et al. 2014; Patil et al. 2016). HME has simplified the steps of continuous processes; a wet granulation process is used to prevent hydrolysis of the API. In addition, co-extrusion technology has been used to manufacture fixed-dose combination drugs. High drug loading formulations made with HME have improved the therapeutic response and compliance of patients.

Table 1 Currently marketued HME products with drug, route of administration, polymers, duration of the release and product shape (Reprinted with permission from Stankovic et al. 2015. Copyright© 2015 Elsevier Ltd)

Name/company/drug	Indication, route of administration	Polymer	Duration of the release	Product size and shape
Lacrisert®, Valeant (no drug)	Dry eye syndrome Ocular insertion	HPC	1 day	Rod-shaped implant 1.27 mm × 3.5 mm
Ozurdex®, Allergan (dexamethasone)	Ocular insertion Macular edema; uveitis	PLGA	90 days	Rod-shaped implant 0.46 mm × 6 mm
Zoladex®, AstraZeneca (goserelin acetate)	Prostate cancer Subcutaneous insertion in the anterior abdominal wall below the navel line	PLGA	28 days or 90 days	Rod-shaped implant 1.2 mm × 10–12 mm or 1.5 mm × 16–18 mm
Implanon®, Merck (etonogestrel)	Contraceptive Subcutaneous implantation in the inner side of the upper arm	EVA	3 years	Rod-shaped implant 2 mm × 40 mm
NuvaRing®, Merck (etonogestrel/ethylvinyl estradiol)	Contraceptive Intravaginal ring	EVA	21 days	A ring with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm
Norvir®, Abbott (ritonavir)	Viral infection (HIV) Oral tablet	PEG-glyceride	12 h	Oval tablet
Kaletra®, Abbott (Iopinavir/ritonavir)	Viral infection (HIV) Oral tablet	PVP/PVA	6 h	Oval tablet
Onmel®, Merz (itraconazole)	Onychomycosis Oral tablet	HPMC	1 day	Oval tablet
Gris-PEG®, Pedinol (griseofulvin)	Onychomycosis Oral tablet	PEG	1 day	Oval tablet
Covera-HS®, Pfizer (Verapamil HCl)	Hypertension and angina pectoris Oral tablet	HPC	24 h	Round tablet
Nurofen (Meltlets lemon®) Reckitt Benckiser Healthcare (ibuprofen)	Analgesic Oral tablet	HPMC	4 h	Round tablet
Eucreas®, Novartis (vildagliptin/metformin HCl)	Diabetes type 2 Oral tablet	HPC	12 h	Oval coated tablet
Zithromax®, Pfizer (azithromycin enteric-coated Multiparticulate prepared by HME and melt congealing)	Bacterial infection Oral tablet	Pregelatinizeo Starch	24 h	Oval tablet

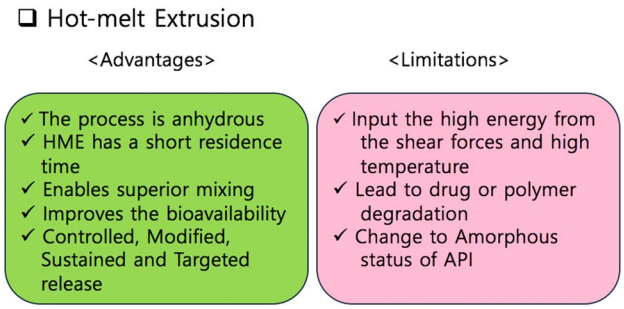

Fig. 1 Advantages and disadvantages of hot melt extrusion technology

Furthermore, the range of potential HME applications can be expanded by its use in conjunction with other technologies such as High-pressure homogenization (HPH), pressurized CO_2 gas, and a 3D printer. This review, which discusses the advances in HME technology including conjunction with other technologies, is categorized into three sections with specific examples: (1) ways to overcome the weaknesses of the HME process; (2) introduction of patient-centric formulations; and (3) an overview of the future of the HME process.

Process improvements to overcome HME weaknesses

Low processing temperature

HME requires a temperature above the glass-transition temperature of the carrier or polymer during the process, which can degrade the drug and polymer and affect the quality of the product. Thus, the drug choice is limited by the requirement of thermal stability at process temperature (Crowley et al. 2007). Although the process time may only last for a few minutes, the thermal stability of the drug is imperative (Saerens et al. 2011).

During relatively high processing temperatures, especially temperatures over the melting point of the API, the drugs change from crystalline to amorphous. Although it has been shown that the amorphous API form displays increased solubility, it is physico-chemically more unstable than the crystalline form (Joe et al. 2010; Kawabata et al. 2010; Shim et al. 2006). Therefore, it would be advantageous to maintain drug stability through the use of the crystalline form.

The content uniformity of very low dose drugs was investigated using the twin-screw HME method at low processing temperatures to minimize the effect of heat on the HME process (Park et al. 2013). Low dose drugs, such as tamsulosin, glimepiride, and limaprost were used as model drugs. Hydrophilic polymers with a low melting point and thermosensitive properties, such as poloxamer 188 and polyethylene glycol 6000, were selected to prepare the extrudates with a low processing temperature and a low drug dose. When the melt extrusion was performed at approximately 50 °C, the model drugs remained in a crystalline solid form and the polymers were completely dissolved. Confocal laser scanning microscopy (CLSM) imaging showed that the drugs were well dispersed in the extrudate and content uniformity was analyzed by HPLC to investigate the validity of HME at a low processing temperature. Compared with the physical mixture, the batch-to-batch variation was lower and the content uniformity was improved. DSC, PXRD, and FT-IR data showed no interaction between the drug and the polymer. This study has demonstrated that with an appropriate choice of polymer, the HME process can be efficient at low temperatures.

Pressurized carbon dioxide

Another weak point of HME is that the increased viscosity of the API or polymer can generate a higher torque. This will produce highly homogeneous extrudates but overtorque can stop the machine or degrade the API and polymer. Therefore, a plasticizer may sometimes be necessary to reduce the processing temperature and torque. Typically, plasticizers are used at approximately 5–30% of the extrudable mass (McGinity and Zhang 2003; McGinity et al. 2001; Mehuys et al. 2004). This increases the total mass of the formulation, which can cause the patient discomfort when ingesting the drug or lose the properties of polymer such as structural control. Therefore, it is important to minimize the use of plasticizer in an HME system in order to avoid significant the mass increasing of the formulation and to maintain the specific functions of thermoplastic polymer or excipients (Verreck et al. 2005). The use of plasticizers affects the physico-mechanical properties and drug release behavior of the hot-melt extrudates; plasticizers increase the elasticity and flexibility of the extrudates (Crowley et al. 2007).

Pressurized carbon dioxide gas can act as a reversible plasticizer and foaming agent (Elkovitch and Tomasko 2000). Carbon dioxide is non-toxic, non-flammable, chemically stable (Medina-Gonzalez et al. 2012; Subramaniam et al. 1997), and is known as a plasticizer that reduces the glass transition temperature of amorphous and semi-crystalline polymers. When carbon dioxide is absorbed between the polymer chains, the free volume is increased and melt viscosity and entanglement between chains is reduced (Chiou et al. 1985). These properties make the combination of pressurized carbon dioxide and HME an interesting prospect (Rizvi et al. 1995).

Ashour et al. (Ashour et al. 2016) investigated the effect of pressurized carbon dioxide on the physico-mechanical properties of ketoprofen (KTP)-incorporated hydroxypropylcellulose produced using HME techniques and assessed the plasticization effect of pressurized carbon dioxide on various polymers. Carbon dioxide was injected into the extruder using a high-pressure regulator connected to the hose. The other end of the hose was connected to a four-way connection with a pressure gauge, bleed valve, and check valve, and was connected to the injection port in the extruder.

The microscopic morphology of the extrudates prepared with pressurized carbon dioxide injection was changed to a foam-like structure, which increased surface area and porosity. This morphological change may enhance the milling efficiency of hot-melt extrudates. The extrudates processed with pressurized carbon dioxide injection demonstrated enhanced KTP release compared with the physical mixtures and the extrudates processed without pressurized carbon dioxide injection, which was attributed to the increase in the surface area and porosity. Thus, pressurized carbon dioxide acts as a plasticizer to enhance the processing and drug release behavior.

pH modifiers

pH modifiers are promising agents that can increase drug solubility through the modification of microenvironment pH (pH_M) in pH-dependent APIs. This is a promising technique for the solubilization of poorly soluble drugs when the drug is a weak acid or base and the solubility is affected by pH (Yang et al. 2014). The pH_M is defined as a thin layer that aids water adsorption and the formation of a saturated solution, which surrounds the drug particle surface (Yang et al. 2014). This method can be used to adjust the pH_M of the formulation using an alkalizer or acidifier (Dvořáčková et al. 2013); consequently, the stability and solubility of the drug can be improved (Siepe et al. 2006; Tran et al. 2010).

Alshehri et al. (Alshehri et al. 2016) investigated the combined effect of magnesium oxide (MgO) as an alkalizer and polyethylene glycol (PEG) as a plasticizer and wetting agent in the presence of Kollidon® polymer carriers on the release profile of mefenamic acid (MA), which was prepared via an HME technique. All formulations were successfully extruded under the employed parameters. DSC revealed that the MA was completely miscible in up to 20%w/w drug load extrudate. PXRD confirmed that the drug was in an amorphous form after extrusion. Different grades of Kollidon had an effect on the solubility of MA by transforming the drug crystals into an amorphous configuration to form a solid dispersion system. MgO and PEG increased the alkalinity of the microenvironment to pH 9 and increased the hydrophilicity and dispersibility of the extrudates to enhance MA solubility and release, respectively. The in vitro release study demonstrated immediate release over 2 h with more than 80% of the drug released within 45 min in matrices containing MgO and PEG in combination with polyvinylpyrrolidone compared with the binary mixture, physical mixture, and pure drug. This study demonstrated that adding an alkalizer to the formulation has a marked positive effect than without pH_M modifier on its dissolution rate by increasing the pH_M to almost 9 and alkalizing the surrounding area.

Patient-centric formulations via HME

Co-extrusion

A fixed-dose combination refers to a drug that has been prepared in a single formulation of two or more ingredients with different pharmacological actions. Fixed-dose combinations are extensively used worldwide, and offer advantages in the improvement of therapeutic effects, safety, and patient compliance. Furthermore, the cost is lower than the separate administration of single drugs. Fixed-dose combination is a promising technology that confers clinical and commercial benefits on a variety of drugs (Moon and Oh 2016). It is also suitable for formulations that contain high doses of drugs and can be used in the manufacture of fixed-dose combinations (Tiwari et al. 2016). As shown in Fig. 2, co-extrusion is a process involving the simultaneous supply of two or more materials through the same die and progress in the HME, which produces a multi-layer extrudate. This is an advanced continuous production technology that offers many advantages over traditional pharmaceutical process technology (Vynckier et al. 2014).

The pharmaceutical industry is interested in this advanced technology, which has many advantages over existing technology. The major advantages are the reduction in the number of process steps and continuous

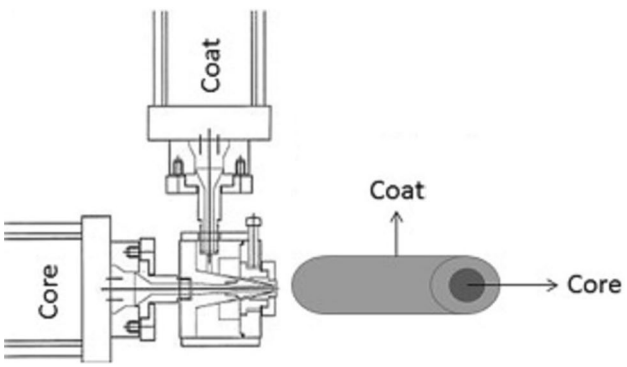

Fig. 2 Schematic diagram of co-extrusion (Reprinted with permission from Vynckier et al. 2015. Copyright© 2015 Elsevier Ltd)

processing. Furthermore, the process does not use organic solvents or water and has the potential to improve drug solubility and control drug release (Breitenbach and Magerlein 2003; Follonier et al. 1994; Sprockel et al. 1997; Verhoeven et al. 2008). Finally, this technology can be used to produce multilayer products, especially fixed dose combination continuously, therefore, this can reduce production costs (Giles et al. 2005).

Dierickx et al. (2012) prepared multi-layer formulations using hot-melt co-extrusion, in which the core induced sustained drug release and the outer layer immediately released the drug. At the core of the multi-layer formulations was the combination of metoprolol tartrate and polycaprolactone, and polyethylene oxide/polyethylene glycol in the outer section promoted the immediate release of hydrochlorothiazide. Fixed-dose combination tablets prepared by co-extrusion using polycaprolactone and polyethylene oxide showed good in vitro performance. The solid comprised metoprolol tartrate in a crystalline form, but hydrochlorothiazide was dispersed in the co-extrudates. In vivo tests were also performed to compare the reference formulation with the test formulation, but no statistically significant differences were observed.

3D Printing

Ink-jet printing is suited to the deposition of drug solutions onto flat substrates such as oral wafers (Buanz et al. 2011). The technology has been used to make personalized-dose medicines by printing dots of solution onto a substrate (Scoutaris et al. 2011, 2012) and it is also possible to make 3D particles by printing droplets into liquid nitrogen and subsequently freeze-drying (Mueannoom et al. 2012; Sharma et al. 2013). The concept of 3D printing was introduced in the 1970s. However; since 2010, potential medical applications have been explored, including tissues from the heart, bladder, and vaginal cells (Ventola 2014). Recently, the pharmaceutical industry has interested in the manufacture of pharmaceuticals using 3D printing technology. This technology is attracting attention for patient-centered treatments, which provide the patient with customized medication. In conjunction with HME, 3D printing technology offers advantages in the manufacture of tablets containing high doses of drugs. This can improve patient compliance by a reduction in the dose quantity and size of dosage form (Tiwari et al. 2016).

3D printing technology requires thermoplastic polymers. Some of the most commonly used polymers in 3D printing technology are acrylonitrile butadiene styrene (ABS), polylactic acid (PLA) and polyvinyl alcohol (PVA). ABS is a polymer composed of styrene, acrylonitrile, and polybutadiene and the advantages of ABS include ease of use in filament form, durability, heat resistance, cost-effectiveness, and flexibility. However, one drawback is that it is not degraded in the body (Rosenzweig et al. 2015). Therefore, ABS is becoming less popular among 3D printing users who prefer environmentally friendly materials. PLA is a polymer based on renewable materials, such as corn starch, sugar cane, and potato starch, and is a thermoplastic resin that decomposes in the body (Giordano et al. 1997). PLA is environmentally friendly and available in a variety of colors, which makes it a suitable polymer for 3D printing. It is also used as a resin and filament. PVA is commonly used as a thickener, glue, or packaging film. It is biocompatible, degradable, water soluble, and it is also used as a binder (Wu et al. 2011).

Pietrzak et al. (Pietrzak et al. 2015) developed a formulation that provided a flexible dose for immediate-and sustained-release formulations. As shown in Fig. 3, it was made by the combination of a digitally controlled 3D printer and HME. Theophylline, methacrylic polymers, and cellulose-based polymers were used to make the tablets. DSC and PXRD data showed that the drug maintained crystalline form. The drug release behavior was associated with drug content: low-dose drugs showed faster drug release than high-dose drugs. This study has shown that the tablets made through coupling 3D printing with HME can adjust the drug content and drug release profile.

HME technology a view to the future

Nanotechnology with hot-melt extrusion

The emergence of nanotechnology has influenced the current approaches in the drug administration field. Nanotechnology, by virtue of its nanoscale formulations, improves the efficacy of patient recovery, which has led to increased interest in several pharmaceutical fields (Kumar 2010).

Drug formulations with poor water solubility exhibit low dissolution rates and prevent rapid and complete absorption in the gastrointestinal tract (Hanafy et al. 2007). To overcome these problems, nanoparticles with reduced particle size have been developed (Chandra Sekhara Rao et al. 2004) In these nanosize formulations, solid lipid nanoparticles (SLNs) are a well-known drug-delivery system. SLNs increase the drug dissolution rate and bioavailability. The main problem facing these nanotechnologies is the need for several steps, which normally increase cost and product variability compared to a continuous process. Therefore, when delivering nano-based drugs for products, it is essential to develop technologies that can overcome the limitations of existing nanotechnology formulations (Patil et al. 2014).

High-pressure homogenization (HPH) has been introduced as a reliable technique in SLN manufacturing, and

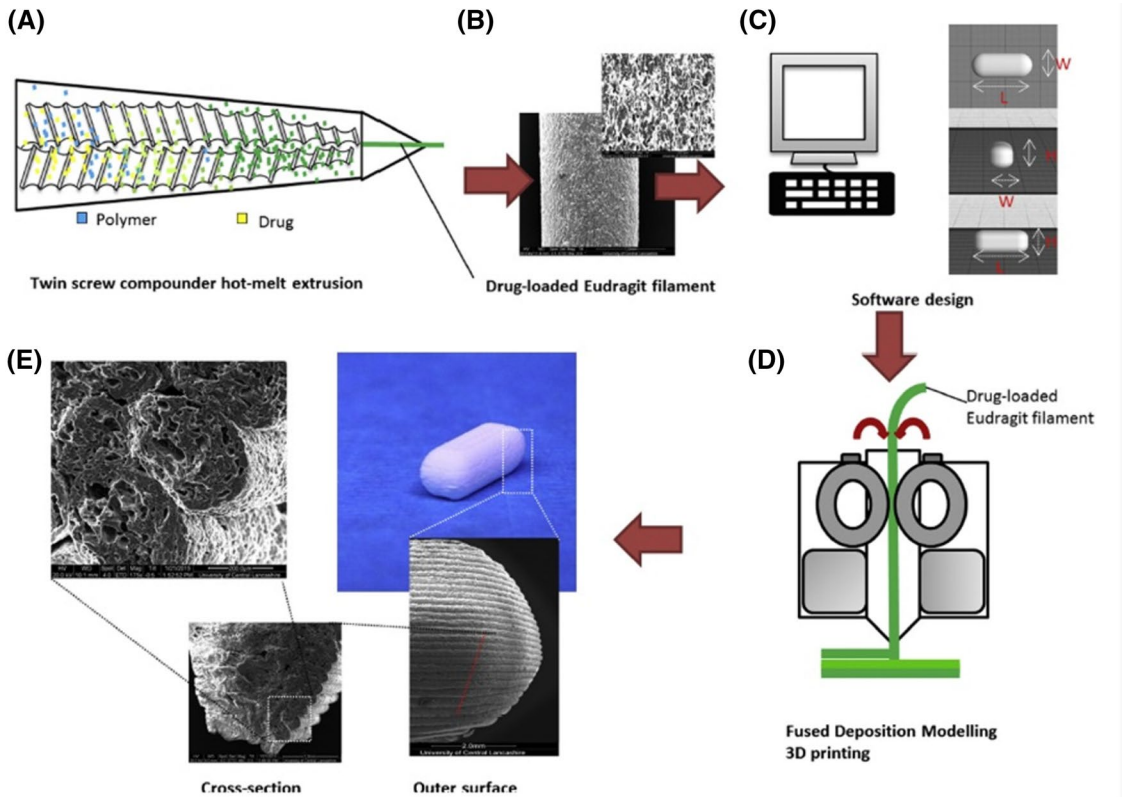

Fig. 3 Tablet creation process combining 3D printing technology with hot-melt extrusion. **a** Physical mixture containing drug and polymer produced filaments through a hot-melt extrusion process; **b, c** Formulation design using computer software; **d** Filament is used as a material in 3D printers; **e** Tablets with a layer thickness of 200 μm were produced, as shown in the SEM images (Reprinted with permission from Pietrzak et al. 2015. Copyright© 2015 Elsevier Ltd)

can be incorporated with HME, as shown in Fig. 4. In the manufacture of SLNs, a multistage process is required with preparatory steps to combine the lipids and drug. In the pharmaceutical industry, continuous processes are more economical than batch processes, as production efficiency can be increased by a reduction in the required space, labor, cost, and resources. Thus, continuous processes are preferred over batch processes. The batch process requires complex and diverse procedures to prevent transformation of the final product. Emulsification is an essential step in the production of SLNs. Particle size reduction using HPH is a continuous process, whereas the emulsification step is a batch process. Therefore, in order to construct a continuous SLN production line, the development of a continuous emulsion manufacturing process is essential (Patil et al. 2015).

Patil et al. (Patil et al. 2015) developed a continuous process for SLN production using HME coupled with HPH for particle size reduction using the poorly water-soluble drug fenofibrate (FBT) as a model drug. In the in vitro drug release study, approximately 94% of the SLN-FBT formulation was released over 5 h compared with 62% of the marketed micronized FBT formulation released over 5 h and 41% of pure FBT released over 5 h. These results showed that SLN-FBT had a higher dissolution rate than the conventional formulation. The increased dissolution rate was attributed to the decrease in the size of the drug particle and increase in the surface area. In this study, it was proven that HME technology could be applied to prepare nanosized drugs in a continuous process.

Wet granulation

Granulation, the process of increasing particle size, has been applied in many pharmaceutical fields and is well-studied. The granulation process using a twin screw granulator can be operated continuously and is a very effective and attractive technique for granulation (Dhenge et al. 2010).

In recent years, interest has increased in the use of twin screw granulation (TSG) for continuous wet granulation within the pharmaceutical industry because it reduces processing time, improves ingredient mixing, and allows for flexible equipment design (Thompson and Sun 2010; Vervaet and Remon 2005). Also, TSG has been shown as an effective alternative method to

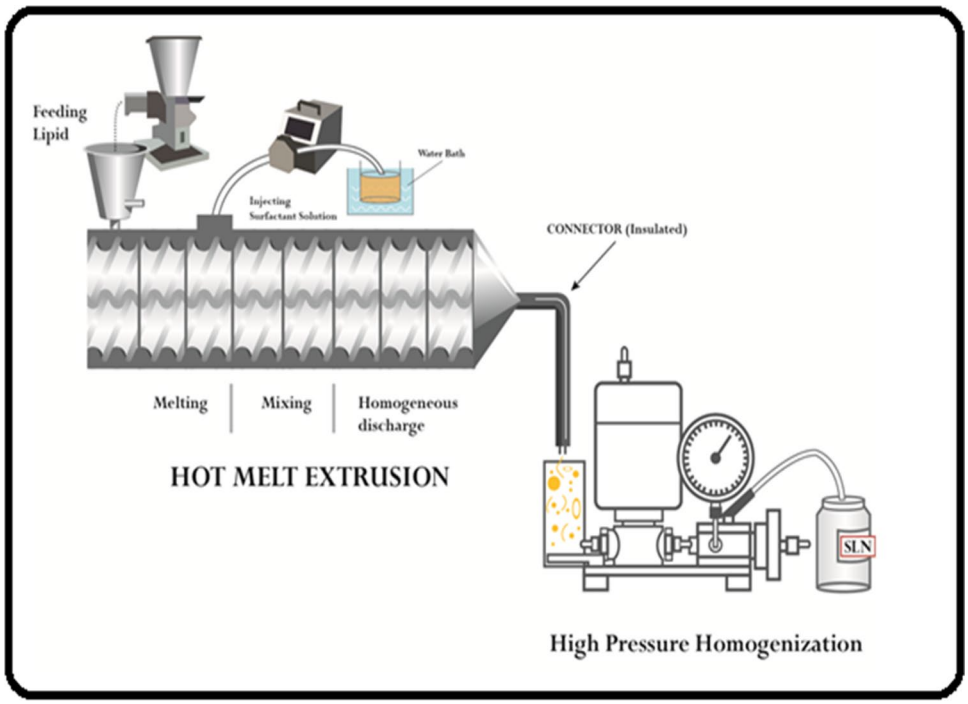

Fig. 4 Manufacturing process of SLNs by the combination of hot-melt extrusion and high pressure homogenization (Reprinted with permission from Patil et al. 2015. Copyright© 2015 The Springer Ltd)

high shear and fluid bed granulations for pharmaceutical formulations that are difficult to process (Lodaya et al. 2003). With continuous process equipment and twin screw granulation, manufacturing quantities can be increased by an increase in the operating time of the machine (Dhenge et al. 2010). Therefore, the same equipment can be used for process optimization and scale-up. This improves the reproducibility of the process and the equipment efficiency and minimizes the problems of scaling up (Vervaet and Remon 2005). Consequently, the potential applications for HME are expanded by the involvement of TSG technology.

Hagrasy et al. (El Hagrasy et al. 2013) used three grades of lactose with unique particle size attributes. The granule formation and growth behavior of the different grades of lactose was investigated by varying the liquid to solid (L/S) ratio between 0.15 and 0.45 with 0.05 intervals. The twin screw granulator demonstrated an overall robustness towards remarkable changes in the formulation characteristics, as the three formulation grades displayed similar growth behavior at different L/S ratios. At low liquid levels, broad size distributions were observed, but the narrow distribution obtained with high liquid content was well in excess of the usable size range required for the downstream processing of granules in the pharmaceutical industry. These studies proved that the size distribution of drug particles could be successfully controlled with the wet granulation method using TSG.

Continuous process

A major limitation of batch manufacturing of tablets is that materials with sufficient fluidity must be supplied. Recently, the use of continuous process in solid-dosage manufacturing has grown. A continuous process has the advantage of being able to proceed more quickly and easily than the batch process. Scale-up can also be performed more easily, because it can be obtained by longer operation instead of larger equipment (Markarian 2014). HME was originally a continuous process, and when HME is incorporated with downstream auxiliary equipment, including a tableting machine, pelletizer, film maker, or spheronizer, this system can maintain a continuous process from powder-in to the finished pharmaceutical dosage forms. As discussed in the previous section, HME can be used in a continuous wet granulation process with TSG. Wet granulation is a method used to improve the fluidity and homogeneity of materials by the conversion of free particles into agglomerates. The continuous wet granulation method using TSG was applied to the ConsiGma™ system (Vercruysse et al. 2012). This continuous granulation technology consists of three modules: a fluid bed dryer module, a high shear granulation module, and an evaluation module. The ConsiGma™ system has been tested for various drug products and can be used for both production and research and development (Desai et al. 2015). However, TSG requires a stabilization period before reaching a steady state, which can be

determined by measuring torque, temperature, and granule quality (Kumar et al. 2013). The stabilization period may be a weakness, because the desired granulation yield cannot be immediately obtained (Vercruysse et al. 2013).

Jaiswar et al. (Jaiswar et al. 2015) used HME technology to produce a sustained-release tablet and study the optimization process with continuous production. Rifampicin, a first-line treatment of tuberculosis, was used as the model drug, and hydroxypropylcellulose (HPC) was used to delay the release of the polymer. The prepared tablets were analyzed using SEM, DSC, and FTIR. DSC and FTIR analysis showed no chemical interaction between the polymer and drug, but SEM revealed that micropores were present in the dispersed drug particles. The release behavior of the drug was determined by this internal pore. It was confirmed that the sustained-release matrix of rifampicin prepared using HPC M and HPC LM grades was optimized. In this study, tablets were successfully prepared by HME using a release-retarding polymer via a continuous process.

Conclusion

HME technology has been used for formulation development owing to its many advantages. HME technology is a continuous process, with no solvent requirements, and is an environmentally friendly. It also easy to scale up, and can reduce time and costs of productions. This review article focuses on advanced HME technologies. First, these advanced technologies can overcome the weaknesses of HME by reducing the high processing temperature and torque and increasing the dissolution rate and the solubility of the drug; this extends the range of potential HME applications. Second, we discussed patient-centric formulations that utilized HME coupled with co-extrusion and 3D printing. Finally, expansions of HME, such as nanoscale drug formulation, wet granulation with twin screw, and continuous process, were examined. HME offers significant possibilities to companies producing large quantities of incrementally modified drug and generic drugs. HME has become a promising technology for the formulation development and can be applied to a wide range of pharmaceutical fields.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Alshehri SM, Tiwari RV, Alsulays BB, Ashour EA, Alshetaili AS, Almutairy B, Park J-B, Morott J, Sandhu B, Majumdar S (2016) Investigation of the combined effect of MgO and PEG on the release profile of mefenamic acid prepared via hot-melt extrusion techniques. Pharmaceutical Dev Technol 1–14 (**online**)

Ashour A, Kulkarni E, Almutairy V, Park J-B, Shah SP, Majumdar S, Lian Z, Pinto E, Bi V, Durig T (2016) Influence of pressurized carbon dioxide on ketoprofen-incorporated hot-melt extruded low molecular weight hydroxypropylcellulose. Drug Dev Ind Pharm 42:123–130

Breitenbach J, Magerlein M (2003) Melt-extruded molecular dispersions. Drugs Pharm Sci 133:245–260.

Buanz AB, Saunders MH, Basit AW, Gaisford S (2011) Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. Pharm Res 28:2386–2392

Chandra Sekhara Rao G, Satish Kumar M, Mathivanan N, Bhanoji Rao M (2004) Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems. Die Pharmazie 59:5–9

Chiou J, Barlow JW, Paul D (1985) Plasticization of glassy polymers by CO_2. J Appl Polym Sci 30:2633–2642

Crowley MM, Zhang F, Koleng JJ, McGinity JW (2002) Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials 23:4241–4248

Crowley MM, Fredersdorf A, Schroeder B, Kucera S, Prodduturi S, Repka MA, McGinity JW (2004) The influence of guaifenesin and ketoprofen on the properties of hot-melt extruded polyethylene oxide films. Eur J Pharm Sci 22:409–418

Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, McGinity JW, Martin C (2007) Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm 33:909–926

Desai PM, Vaerenbergh GV, Holman J, Liew CV, Heng PWS (2015) Continuous manufacturing: the future in pharmaceutical solid dosage form manufacturing. Pharm Bioprocess 3:357–360

Dhenge RM, Fyles RS, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD (2010) Twin screw wet granulation: granule properties. Chem Eng J 164:322–329

Dierickx L, Saerens L, Almeida A, De Beer T, Remon JP, Vervaet, C (2012) Co-extrusion as manufacturing technique for fixed-dose combination mini-matrices. Eur J Pharm Biopharm 81:683–689

Dvořáčková K, Doležel P, Mašková E, Muselík J, Kejdušová M, Vetchý D (2013) The effect of acid pH modifiers on the release characteristics of weakly basic drug from hydrophlilic–lipophilic matrices. AAPS PharmSciTech 14:1341–1348

El Hagrasy A, Hennenkamp J, Burke M, Cartwright J, Litster J (2013) Twin screw wet granulation: influence of formulation parameters on granule properties and growth behavior. Powder Technol 238:108–115

Elkovitch MD, Tomasko DL (2000) Effect of supercritical carbon dioxide on morphology development during polymer blending. Polym Eng Sci 40:1850–1861

Follonier N, Doelker E, Cole ET (1994) 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 20:1323–1339

Follonier N, Doelker E, Cole ET (1995) Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. J Controlled Release 36:243–250

Fule R, Meer T, Sav A, Amin P (2013) Solubility and dissolution rate enhancement of lumefantrine using hot melt extrusion technology with physicochemical characterisation. J Pharm Investig 43:305–321

Fule R, Meer T, Amin P, Dhamecha D, Ghadlinge S (2014) Preparation and characterisation of lornoxicam solid dispersion systems using hot melt extrusion technique. J Pharm Investig 44:41–59

Giles H, Wagner J, Mount E (2005) Extrusion: the definitive processing guide and handbook. Norwich: William Andrew. Inc

Giordano RA, Wu BM, Borland SW, Cima LG, Sachs EM, Cima MJ (1997) Mechanical properties of dense polylactic acid structures fabricated by three dimensional printing. J Biomater Sci Polym Ed 8:63–75

Hanafy A, Spahn-Langguth H, Vergnault G, Grenier P, Grozdanis MT, Lenhardt T, Langguth P (2007) Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Adv Drug Deliv Rev 59:419–426

Jaiswar DR, Pawar JN, Amin PD (2015) Hot melt extrusion: continuous process of preparation of sustained released matrix tablet by using hydroxypropylcellulose. Am J PharmTech Res 6:295–312

Jaiswar DR, Jha D, Amin PD (2016) Preparation and characterizations of stable amorphous solid solution of azithromycin by hot melt extrusion. J Pharm Investig 46:655–668

Javeer SD, Patole R, Amin P (2013) Enhanced solubility and dissolution of simvastatin by HPMC-based solid dispersions prepared by hot melt extrusion and spray-drying method. J Pharm Investig 43:471–480

Joe JH, Lee WM, Park Y-J, Joe KH, Oh DH, Seo YG, Woo JS, Yong CS, Choi H-G (2010) Effect of the solid-dispersion method on the solubility and crystalline property of tacrolimus. Int J Pharm 395:161–166

Kawabata Y, Yamamoto K, Debari K, Onoue S, Yamada S (2010) Novel crystalline solid dispersion of tranilast with high photostability and improved oral bioavailability. Eur J Pharm Sci 39:256–262

Kumar CS (2010) Nanotechnology tools in pharmaceutical R&D. Mater Today 12:24–30

Kumar A, Gernaey KV, De Beer T, Nopens I (2013) Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production–a critical review. Eur J Pharm Biopharm 85:814–832

Lodaya M, Mollan M, Ghebre-Sellassie I (2003) Twin-screw wet granulation. Drug Pharm Sci 133:323–344

Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D (2012) A review of hot-melt extrusion: process technology to pharmaceutical products. ISRN Pharm 2012:1–10

Maniruzzaman M, Boateng JS, Chowdhry BZ, Snowden MJ, Douroumis D (2014) A review on the taste masking of bitter APIs: hot-melt extrusion (HME) evaluation. Drug Dev Ind Pharm 40:145–156

Markarian J (2014) Optimizing solid dosage manufacturing. Pharm Technol 38:24

McGinity JW, Zhang F (2003) Melt-extruded controlled-release dosage forms. Drugs Pharm Sci 133:183–208

McGinity JW, Zhang F, Koleng J, Repka M (2001) Hot-melt extrusion as a pharmaceutical process. Am Pharm Rev 4:25–37

Medina-Gonzalez Y, Camy S, Condoret J-S (2012) Cellulosic materials as biopolymers and supercritical CO_2 as a green process: chemistry and applications. Int J Sustainable Eng 5:47–65

Mehuys E, Vervaet C, Remon JP (2004) Hot-melt extruded ethylcellulose cylinders containing a HPMC–Gelucire® core for sustained drug delivery. J Controll Release 94:273–280

Moon C, Oh E (2016) Rationale and strategies for formulation development of oral fixed dose combination drug products. J Pharm Investig 46:615–631

Mueannoom W, Srisongphan A, Taylor KM, Hauschild S, Gaisford S (2012) Thermal ink-jet spray freeze-drying for preparation of excipient-free salbutamol sulphate for inhalation. Eur J Pharm Biopharm 80:149–155

Park J-B, Kang C-Y, Kang W-S, Choi H-G, Han H-K, Lee B-J (2013) New investigation of distribution imaging and content uniformity of very low dose drugs using hot-melt extrusion method. Int J Pharm 458:245–253

Patil H, Kulkarni V, Majumdar S, Repka MA (2014) Continuous manufacturing of solid lipid nanoparticles by hot melt extrusion. Int J Pharm 471:153–156

Patil H, Feng X, Ye X, Majumdar S, Repka MA (2015) Continuous production of fenofibrate solid lipid nanoparticles by hot-melt extrusion technology: a systematic study based on a quality by design approach. AAPS J 17:194–205

Patil H, Tiwari RV, Repka MA (2016) Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS PharmSciTech 17:20–42

Pietrzak K, Isreb A, Alhnan MA (2015) A flexible-dose dispenser for immediate and extended release 3D printed tablets. Eur J Pharm Biopharm 96:380–387

Rizvi S, Mulvaney S, Sokhey A (1995) The combined application of supercritical fluid and extrusion technology. Trends Food Sci Technol 6, 232–240.

Rosenzweig DH, Carelli E, Steffen T, Jarzem P, Haglund L (2015) 3D-printed ABS and PLA scaffolds for cartilage and nucleus pulposus tissue regeneration. Int J Mol Sci 16:15118–15135

Saerens L, Dierickx L, Lenain B, Vervaet C, Remon JP, De Beer, T (2011) Raman spectroscopy for the in-line polymer–drug quantification and solid state characterization during a pharmaceutical hot-melt extrusion process. Eur J Pharm Biopharm 77:158–163

Scoutaris N, Alexander MR, Gellert PR, Roberts CJ (2011) Inkjet printing as a novel medicine formulation technique. J Controll Release 156:179–185

Scoutaris N, Hook AL, Gellert PR, Roberts CJ, Alexander MR, Scurr DJ (2012) ToF-SIMS analysis of chemical heterogenities in inkjet micro-array printed drug/polymer formulations. J Mater Sci 23:385–391

Sharma G, Mueannoom W, Buanz AB, Taylor KM, Gaisford S (2013) In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying. Int J Pharm 447:165–170

Shim S-Y, Ji C-W, Sah H, Park E-S, Lee B-J (2006) Characterization of itraconazole semisolid dosage forms prepared by hot melt technique. Arch Pharm Res 29:1055–1060

Siepe S, Herrmann W, Borchert H-H, Lueckel B, Kramer A, Ries A, Gurny R (2006) Microenvironmental pH and microviscosity inside pH-controlled matrix tablets: an EPR imaging study. J Controll Release 112:72–78

Sprockel OL, Sen M, Shivanand P, Prapaitrakul W (1997) A melt-extrusion process for manufacturing matrix drug delivery systems. Int J Pharm 155:191–199

Subramaniam B, Rajewski RA, Snavely K (1997) Pharmaceutical processing with supercritical carbon dioxide. J Pharm Sci 86:885–890

Thompson M, Sun J (2010) Wet granulation in a twin-screw extruder: implications of screw design. J Pharm Sci 99:2090–2103

Tiwari RV, Patil H, Repka MA (2016) Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert Opin Drug Deliv 13:451–464

Tran TT-D, Tran PH-L, Choi H-G, Han H-K, Lee B-J (2010) The roles of acidifiers in solid dispersions and physical mixtures. Int J Pharm 384:60–66

Ventola CL (2014) Medical applications for 3D printing: current and projected uses. Pharm Ther 39:704

Vercruysse J, Díaz DC, Peeters E, Fonteyne M, Delaet U, Van Assche I, De Beer T, Remon JP, Vervaet, C (2012) Continuous twin screw granulation: influence of process variables on granule and tablet quality. Eur J Pharm Biopharm 82:205–211

Vercruysse J, Delaet U, Van Assche I, Cappuyns P, Arata F, Caporicci G, De Beer T, Remon JP, Vervaet, C (2013) Stability and

repeatability of a continuous twin screw granulation and drying system. Eur J Pharm Biopharm 85:1031–1038

Verhoeven E, De Beer T, Van den Mooter G, Remon JP, Vervaet, C (2008) Influence of formulation and process parameters on the release characteristics of ethylcellulose sustained-release minimatrices produced by hot-melt extrusion. Eur J Pharm Biopharm 69:312–319

Verreck G, Decorte A, Heymans K, Adriaensen J, Cleeren D, Jacobs A, Liu D, Tomasko D, Arien A, Peeters J (2005) The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. Eur J Pharm Sci 26:349–358

Vervaet C, Remon JP (2005) Continuous granulation in the pharmaceutical industry. Chem Eng Sci 60:3949–3957

Vynckier AK, Dierickx L, Voorspoels J, Gonnissen Y, Remon JP, Vervaet C (2014) Hot-melt co-extrusion: requirements, challenges and opportunities for pharmaceutical applications. J Pharm Pharmacol 66:167–179

Wu C, Luo Y, Cuniberti G, Xiao Y, Gelinsky M (2011) Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability. Acta Biomater 7:2644–2650

Yang M, He S, Fan Y, Wang Y, Ge Z, Shan L, Gong W, Huang X, Tong Y, Gao C (2014) Microenvironmental pH-modified solid dispersions to enhance the dissolution and bioavailability of poorly water-soluble weakly basic GT0918, a developing anti-prostate cancer drug: preparation, characterization and evaluation in vivo. Int J Pharm 475:97–109

Young CR, Koleng JJ, McGinity JW (2002) Production of spherical pellets by a hot-melt extrusion and spheronization process. Int J Pharm 242:87–92

Zhang F (1999) Hot-melt extrusion as a novel technology to prepare sustained-release dosage forms. University of Texas, Austin

Zhang F, McGinity JW (2000) Properties of hot-melt extruded theophylline tablets containing poly (vinyl acetate). Drug Dev Ind Pharm 26:931–942