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Review paper

Hot-melt extrusion and prilling as contemporary and promising techniques in the solvent free production of solid oral dosage forms, based on solid dispersions

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Abstract

Hot melt extrusion and prilling are gaining importance as solvent free and continuous techniques in the production of solid oral dosage forms with added value, by incorporating active compound in a molten carrier which is further solidified to form solid dispersion. This article reviews these two techniques in terms of understanding process basics, equipment characteristics, required properties of processed materials and application of the processes for development of solid oral dosage forms. Studies revealed that both hot-melt extrusion and prilling are regarded as simple, robust and continuous methods for processing different types of materials and production of solid dosage forms based on solid matrices. However, understanding of their concepts and requirements together with careful material selection is crucial for stable material processing and obtaining stable products of high-quality. Hot-melt extrusion proved to be a suitable method for production of modified release dosage forms, taste masked dosage forms and dosage forms offering improved drug dissolution rate and solubility. Prilling till now has been successfully applied just in the production of multiple unit drug delivery systems for immediate and sustained drug delivery. Further studies on product development and process understanding are required for full implementation of prilling in the pharmaceutical field.

Keywords: hot-melt extrusion, prilling, solid oral dosage forms, modified release, bioavailability, taste-masking

Introduction

Contemporary pharmacy is facing many challenges, which demand increased investments in new ideas in terms of establishing new drug delivery platforms and implementation of new technologies coping with the principles of quality by design (QbD) and process analytical technology (PAT) (Qui et al., 2009). The oral route of drug administration is still the leading one when medications are prescribed. Even though tablets and capsules and their production have been intensively scientifically evaluated during the past decades their basis is still a very rich field for implementation of new ideas and achieving novel formulation and manufacturing goals. Delivering active compounds in a controlled fashion and/or to a desired place in the GIT, improving the solubility and thus bioavailability of poorly soluble compounds, masking the unpleasant taste of some active principles are objectives which still attract huge attention from both academic and industrial environment (Aulton, 2007; Rnadade et al., 2004). Another aspect gaining importance in the last period is the implementation

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of novel, less complex and less demanding but robust, reproducible and environment friendly production technologies, which fit well in the concept of continuous pharmaceutical manufacturing. Continuous manufacturing involves production in a fully integrated, non-stop, end-to-end continuous fashion from the raw materials to the final dosage form. By employing continuous production (coupled with PAT) and avoiding conventional batch manufacturing many benefits could be gained, such as more quantity flexible process depending merely on time of processing, lesser need to switch to bigger scale equipment, shorter process development, possibility of real-time product release due to coupling with PAT and cost-effectiveness (Center for Healthy Policies, 2015).

Hot-melt extrusion is also recognized as technology which fits well into designing of solid oral dosage forms with added value. By understanding and transferring this process from the plastic industry to the pharmaceutical field hot melt extrusion was successfully applied in the development of solid dosage forms, which offer improved drug dissolution rate and solubility, modified drug release or taste masking. Therefore this technique is increasingly implemented not only in the academic environment but also in the industrial field (Repka et al., 2012). Prilling of molten masses and subsequent sphere formation in cooling tower is a relatively new process, applied in the design of multiple unit drug delivery systems (MDDS) for both immediate and sustained drug release. Prilling may represent a viable alternative to traditional production of pellets through extrusion/spheronisation and also to more contemporary process such as spray congealing. Due to the (semi-) continuous nature of both hot-melt extrusion and prilling they also become natural platforms for full implementation of PAT and Design space concept in the pharmaceutical production (Pivette et al., 2012; Repka et al., 2012).

The aim of this article is to review hot-melt extrusion and prilling as contemporary modalities in the production of solid oral dosage forms. Following pages give an insight in the process basics, equipment features, suitable materials and process applications. The aim is to reveal the multiple possibilities that these techniques offer, together with all the advantages and disadvantages that are introduced with their use.

Hot melt extrusion

Introduction of hot melt extrusion (HME), as industrially applicable technology, dates back to the 1930's and since that time till today it is one of the most prominent fabrication technique, mainly in the plastic and rubbery industry. Extrusion is a method for production of pipes, wires, cables, sheets, plastic bags etc. (Britenbach, 2002). Within the last 20 years HME emerged as alternative pharmaceutical technique to conventional ones (wet and dry granulation, tableting) in the production of solid dosage forms. Scientists and industry recognized the potential of HME and due to this fact it has become significant topic for research activity and patent application. HME represents a process of forcing raw materials through dies into uniform final product, usually by rotation of one or two screw/s (Thiry et al., 2015). As a technique it offers several advantages over conventional ones such as: it is (semi-) continuous, requires less processing steps, provides shorter processing times, eliminates the usage of water and other solvents, minimizes the impact of powder flow ability and compressibility (Repka et al., 2008). However, HME shows also drawbacks such as: heat generation (inadequate for thermally labile compounds), requirements for higher energy input per unit mass, investment in a new dedicated equipment (Maniruzzaman et al., 2012a). HME is applicable to production of solid dosage forms (granules, pellets, mini-matrices, tablets, films) and allows to achieve their special properties (increased drug solubility, extended drug release, masked taste etc.) (Repka et al., 2007; Repka et al., 2008).

Equipment and process basics

The extrusion process is based on four sections (Breitenbach, 2002):

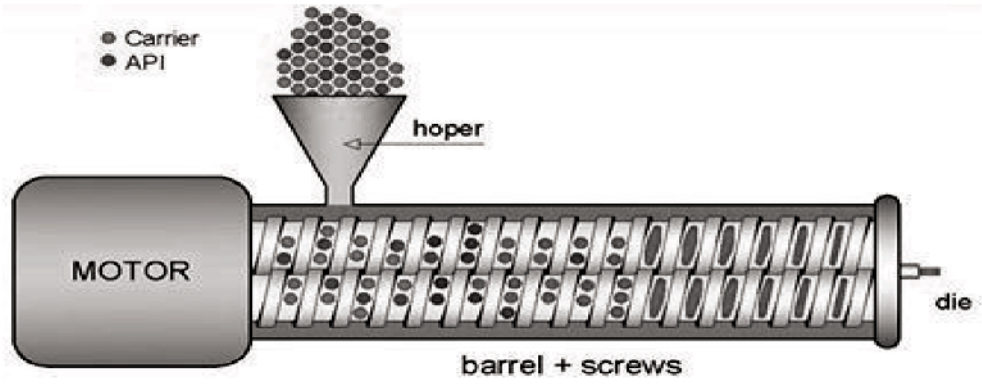

Fig. 1. General concept of pharmaceutical twin-screw extruder (TSE).

- material feeding,
- conveying, mixing, melting, kneading and conveying of the material up to the die,
- pushing of the material through the die extrusion channeland
- extrudate downstream processing.

A hot melt extruder consistsof different parts: feeding system with hopper, extrusion barrel with one or two screws, die and temperature controlling system. Additional segments are the control panel, extruder instrumentation (torque, temperature and pressure sensors) and in-line PAT tools (NIR and Raman probes). All contact parts of the extruder must be non-reactive, non-absorptive and resistant to abrasion. Additionally, pharmaceutically suitable extruders must be designed in such a manner to fulfill the requirements for cleaning and validation (Repka et al., 2012; Crowley et al., 2007). A general overview on extruder assembly is shown in Figure 1.

Feeders, hopper and extrusion barrel

Two types of feeding systems could be included in the extruder assembly: volumetric feeders and gravimetric feeders. Volumetric feeders deliver the solid inside the extruder with constant volume in a unit of time. These feeders are usually equipped with a screw conveying element or an auger which enables material discharge. The accuracy of the volumetric feeding is mainly dependent on material flow and its bulk density and it is determined through a calibration. Variation in the bulk density of the material may lead into inaccurate feeding. Therefore suitable devices providing agitations or vibrations are assembled to the feeder to ensure uniform bulk density of the mixture and eliminate air pockets which could hinders uniform powder delivery in the extruder (Thiry et al., 2015). Gravimetric feeding is based on volumetric feeder equipped with weighting device which provides powder discharge as a constant mass per unit time. This type of feeding system enables constant weighing of the discharged mass and uses that signal to provide uniform material discharge in the extruder through compensation of the variations in bulk density and flow ability of the material. Gravimetric feeders may be designed based on loss-in-weight or gain-in-weight principles. Volumetric feeding systems are less accurate compared to the gravimetric ones but still they are also less expensive (Thiry et al., 2015).

Material is introduced inside the extrusion barrel via hopper. It is required that the angle between the hopper walls and the horizontal plane is higher than the angle of repose of the supplied powder material in terms of preventing powder arch formation at the entrance of the hopper inside the barrel and thus providing reliable powder flow (Crowley et al., 2007). The extrusion barrel is the cylindrical static part of the extrusion equipment wherein the screws are placed and which are rotated with predefined speed using a gearbox. The barrel has usually modular design, where every section could be equipped with electric- or liquid-based heater/cooler and thus provide locally unique temperature setup and control. Barrel sections are further clamped/bolted between themselves and as such represent one closed and interconnected system, which however allows modification of barrel length (L) (Maniruzzaman et al., 2012a; Jani and Patel, 2015).

Screws

The screw is the most important part of each extruder. It provides material transport, melting, mixing, kneading, metering and finally material pumping through the die. Screws are connected to gearbox drive shaft, which is rotating them with a predefined speed. Screw speed selection depends on the desired final outcome of the extrusion process and also on the nature of processed material. Most screws are made from special surface and hardened coated stainless steels which usually offer compromise between chemical inertness and susceptibility to abrasion and thus damage and wear. Screw dimension is determined by the length-to-diameter ratio (L/D) and may vary between the lab and pilot scale equipment where D is in the range from 16 to 27 mm and the production equipment where D is usually in the range of 40-60 mm. Typically extrusion process is mainly governed with screws having L/D values between 20:1 and 40:1 (or even 50:1 on production scale). Screw size together with its geometry and the process parameters are the main factors affecting the residence time of the material which may vary from 5 seconds up to 10 minutes (Patil et al., 2015a; Crowley et al., 2007; Thiry et al., 2015). The screw (Figure 2) can be divided into an interchangeable sequence of roots and flights and it is thedistance and position between themselves and against the barrel wall which is affecting the material processing pattern and the final outcome of HME. Pitch wideness, helix angle and the channel depth are seen as crucial screw design factors determining material treatment through the barrel (Patil et al., 2015a; Crwoley et al., 2007; Breitenbach et al., 2002).

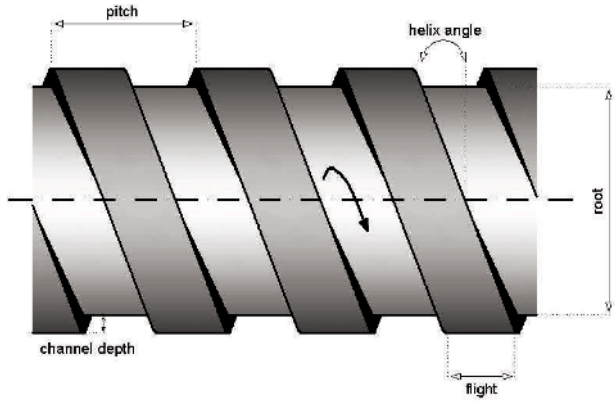

Fig. 2. Geometry of an extruder's screw.

Extrusion screws may be interchangeable for one barrel or may have a modular design which means that different screw elements could be assembled on the splined shaft. This allows the setup of different screw configurations and thus different processing effects can be obtained. Screw elements are differently shaped and thus will provide diverse actions inside the extrusion barrel (Breitenbach, 2002; Crowley et al., 2007). Screw elements could be divided into two types (Kolter et al., 2012):

- **Conveying elements** – their main role is to provide material transport, moderate mixing and pressure buildup along the barrel. According to their design they could be forwarding, neutral and reverse and as such could provide different degree of transport, mixing and shearing.
- **Kneading elements** – their main role is to introduce high shear forces on the material and subsequently to provide plasticizing and mixing effect. According to their design (characteristic angle between discs or elements with open structure) kneading elements could be classified as forwarding, neutral and reversing which subsequently will imply different degrees of shearing, mixing and transporting of processed material.

Due to unique configuration of mixing and kneading elements, having different geometries, screws used for pharmaceutical application enable two types of mixing, **distributive mixing**, providing uniform distribution of solids inside the molten mass, and **dispersive mixing** which provides higher shear forces that enable break down of formed clusters or particles or even material amorphization (Repka et al., 2012; Patil et al., 2015a; Kolter et al., 2012).

Barrel void space and single screw design with predominantly conveying elements are forming three distinctive zones of the extrusion equipment (Breitenbach et al., 2002; Maniruzzaman et al., 2012a; Thiry et al; 2015; Patil et al., 2015a):

- **Feed zone:** Material introduced by the hopper is transferred to the barrel for processing. The channel depth is largest and/or the pitch is wider in this zone, which facilitates the introduction of powder into the screw void space and further transport towards the next zone. Within this zone material is still solid and due to the specific screw configuration only slight pressure is applied which reduces powder porosity by deareation and causes gentle mixing of the powder constituents, but does not lead to melting of material.
- **Transition zone:** Solid material arrives to this zone where it is subjected to melting, more intense mixing and turning into viscous mass. Within this zone channel depth is decreasing and also the screw flights are positioned in denser manner (screw pitch decreases). This leads into increase in the pressure inside the barrel, increased friction between material and the screw/barrel wall, further removal of entrapped air in the mixture, increase in the material temperature and thus material softening and melting. Molten or softened mass further continues its path along the barrel to the last zone mainly by the drag flow, which is reduced by the opposite directed leakage and pressure flows, while material transverse (circulatory) flow mainly contributes to material mixing and increased heat transfer.
- **Metering zone:** The final zone of the barrel is responsible for providing uniform material distribution across the channel, reduces flow pulsations and thus provides uniform flow of the molten mass till the die.

When the material is introduced to the feeding zone of the rotating screws it starts to move along the barrel length. This results in shearing of the material with the equipment surfaces and thus heat energy generation. Friction occurring at the barrel wall promotes longitudinal movement of the material while friction occurring at the screw surface is opposing material motion. Material flow through the barrel should be efficient enough to diminish process variations in terms of material mass flow pulsations at the die exit and ensure final product with uniform and satisfying quality. Smart choice of compound properties and extruder configuration is mandatory for achieving the final goal, i.e. a product with optimal characteristics (Crowley et al., 2007; Patil et al., 2015a; Repka et al., 2012).

According to the number of the screws assembled in the extrusion barrel, pharmaceutical extruders can be divided into three types (Maniruzman et al., 2012a; Repka et al., 2012; Breitenbach et al., 2002;Thiry et al., 2015; Jani and Patel, 2015; Patil et al., 2015a; Crowley et al., 2007; Kolter et al., 2012):

- **Single screw extruders (SSE):** SSE (Fig. 3) is the most simple type of extruder containing only one rotating screw inside the barrel which provides efficient feeding, melting, conveying and extrusion of the material through the die. Sufficient mixing inside these devices is only possible for less demanding applications. SSE is usually performed in flood feed mode, although optionally also in starve feed mode. The screw is rotating within the barrel and a flow channel is formed between its flights and the inner wall of the barrel. Due to frictional forces between the material and the heated barrel surface in the flow channel material transport, melting and pumping is enabled. Main drawbacks of SSE are high heat generation and high pressure generation. As mentioned before the rotation of screw causes high shear stresses and wall-induced friction. This leads into heat generation, which is proportional to the screw rotation speed. Additionally, screw rotation and material melting generate high pressure.
- **Twin screw extruders (TSE):** TSE (Fig. 3) are

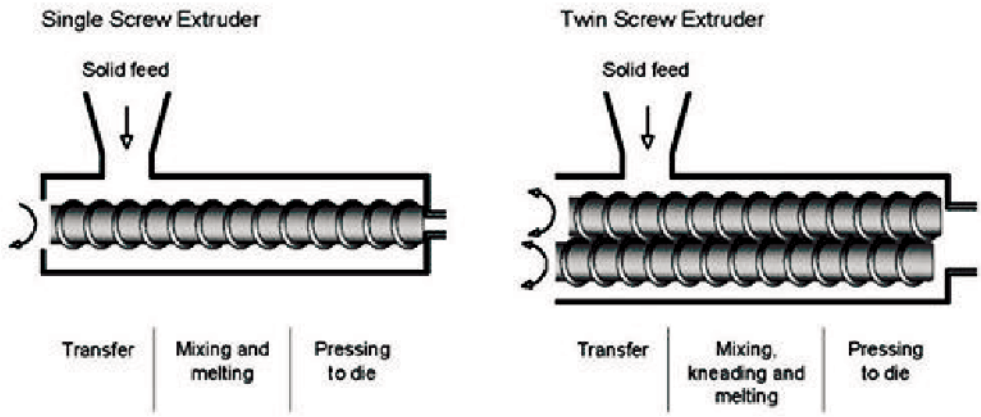

Fig. 3. Cross-section of SSE and TSE.

most common types of extruders used in the pharmaceutical field. They contain two screws placed one to another, usually with intermeshed geometry, which could rotate in the opposite direction (counter-rotation) or in the same direction (co-rotation). Presence of two screws with variable geometry enables achieving different shearing conditions and functionalities within the individual extrusion zones.

- *Counter-rotating screws* are not common in the pharmaceutical practice. They are mainly used when high shearing is required (suitable for material with high viscosities), since they offer squeezing of the material between themselves due to their movement one towards another. These types of extruders suffer from several drawbacks such as: high pressure generation, air entrapment, low maximal rotation speeds, faster surface wear etc.
- TSE consisting of *co-rotating screws* are the primary choice for drug solid dispersion development purposes. Opposite to counter-rotating extruders co-rotating ones offer high screw speeds and thus higher material throughput, good material melting, mixing and transport with lower pressure generation and equipment wear.

Regarding the screw assembly TSE could be additionally divided into non-intermeshing and fully intermeshing. Fully intermeshing co-rotating TSE are of main interest for pharmaceutical application. Their movement and assembly allow so-called ''self-wiping'' functionality, where each screw collects the material from the surface of the other one and also from the surface of the barrel. Intermeshed screw movement allows efficient material mixing, melting and transport; minimized stagnation and thus minimal possibility of overheating; short and well-defined mixture residence times; complete barrel emptying. Non-intermeshing TSE are less popular for development of different types of dosage forms. Their usage is mainly limited on processing of highly viscous materials and in cases when devolatilization is required.

- **Multi-screw extruders:** Extruders with more than two screws positioned in a circumferential or linear manner depending on the final product requirements. Their usage in the pharmaceutical field is still very limited.

Dies and downstream processing

The die is the final part of the extruder assembly. With its design and position at the end of the barrel the die controls the final size and shape of the extrudate. In that manner extrusion dies vary in extrusion channel shape in order to suit the final product requirements. Various end plate dies and downstream equipment are used in order to obtain the following solid forms:

- **Granules** – Hot-melt granulation is conducted on a standard extruder with barrel and screw segments adjusted in such a manner to provide primary mixing followed by melting of the binder and granule formation and finishing by cooling down the material. Contrary to standard hot-melt extrusion, granulated mixture should not be over densified in terms of avoiding poor compressibility and due to this reason die should be excluded from the assembly (Kolter et al., 2012; Patil et al., 2015b; Mu and Thompson, 2012). A milling step may be further required in terms of sizing the granules, however by installation of screws with modified endings (conveying elements) the milling step could be avoided (Van Melkebeke et al., 2006). Granules could be obtained also from films, rods and pellets by applying milling step (Evonik, 2012; Vanarase et al., 2015).

- **Pellets and mini-matrices** - Circular dies are used for pellets and mini-matrices. Extruded material leaves the barrel in a continuous rod-like strand which is further cut into small cylinders by rotary knifes. The knife could be located on the die-face (Robleg et al., 2011) or could be separate piece of equipment into which extrudates are transported via a conveyor belt (Kipping and Rein, 2016). The knife speed is setting the length of the mini-matrices (Jedinger et al., 2015) and its action provides units with narrow size and weight distribution, which therefore could be successfully used as solid dosage forms (single or multiple unit systems). Collected mini-matrices could be further transferred into a spheronizer and subsequently transformed into pellets (Reitz and Kleinebudde, 2009).
- **Tablets, caplets**– Tablets/caplets could be easily made by cutting the extruded wire with a knife in a manner as described above. Unit size could be easily varied by varying the die diameter (unit diameter) or knife cutting frequency (unit height) (Rein and Kipping, 2016). In-situ formation of tablet capsules by melted material may be achieved by a process named calendering. In calendering melted material is transferred through 2 or more pairs of tempered rolls. These rolls may already have tablet/caplet-shaped cavities wherein material is placed and further solidified into the final dosage form (Kolter et al., 2012; Tho et al., 2010; Vynckier et al., 2015). An additional way of achieving final dosage form (tablet/caplet) is by injection moulding. In injection moulding, previously melted or softened material, obtained by screw rotation, is subsequently pressed via longitudinal screw-piston movement into a cavity - mould with defined size and shape. Inside this cavity the molten material solidifies into the desired form (Clayes et al., 2015).
- **Oral films** – Extruders intended for film production are usually equipped with flat opening dies from where molten mass is squeezed out (Repka et al., 2012). Similar as with calendering the mass is further transferred between two tempered rotating rolls which press edit into film and subsequently cool it down. Features such as roll distance, rotating speed and temperature are of essential importance in terms of obtaining a suitable final product. A cutting device installed at the end of the line is necessary for obtaining films/wafers with the desired size and shape (Jani and Patel, 2015).

Important process parameters and extrusion monitoring/ controlling by process analytical technologies (PAT)

The most important process parameters during hot-melt extrusion are feed rate, screw speed and processing temperature. As a response to these process parameters shear stress (mirrored as a torque on the screw shaft), residence time and residence time distribution will determine the final product outcome (Repka et al., 2012). Extrusion is gaining significant attention as promising technology fitting in the frame of continuous manufacturing. Therefore this technique is extensively studied and implemented in the production within the guidelines of quality by design (QbD) and PAT. PAT is a mechanism of monitoring, analyzing and controlling processes and/or products with purpose of producing them in the optimal way and is actually enabling continuous manufacturing techniques, intended to be used in pharmaceutical manufacturing. Along with process parameters monitoring PAT is also focused on real-time identification and measurement of critical inlet and outlet material attributes with real-time or near real-time result interpretation. Obtained data could further be used for intelligent process control in order to assure critical attributes of the final product (FDA, 2004). Raman spectroscopy and near-infrared (NIR) spectroscopy are common PAT tools utilized in in-line monitoring of HME (Saerens et al., 2014; Islam et al., 2015). By installing Raman and NIR probes at the end of the barrel several parameters such as – average drug/carrier ratio, variability of the drug content, solid-state properties of the materials and drug-carrier interactions could be successfully and rapidly analyzed during the process of extrusion (Saerens et al., 2014). Treffer et al. introduced a photometric stereo image analyzer as a tool for monitoring particle size and shape and size distribution of pellets obtained via hot-melt extrusion (Treffer et al., 2014). Additionally, some non-pharmaceutical case-estudies revealed several other techniques which could be suitable for in-line monitoring of HME. Such techniques include less common spectroscopical ones (UV-VIS, fluorescence, terahertz, dielectric, NMR), ultra sound techniques, in-line rheology measurements, glass windows mounted on the barrel enabling process and material visualization etc. (Saerens et al., 2014).

Materials used in hot melt extrusion

Materials used in pharmaceutical HME must meet the same safety and purity requirements as the ones used in traditional pharmaceutical processes. Therefore most of the studies conducted on HME involve well established and known pharmaceutical compounds. The main prerequisite for materials intended to be processed by HME is thermal stability. Additionally, materials should exhibit plastic behavior with low yield stress upon heating inside the barrel and should solidify/harden rapidly after exiting the extruder (Kolter et al., 2012). Mixtures intended for extrusion may be simple or complex mixtures of active compound and different carriers. Additionally some other miscellaneous compounds may be included into the formulation in terms of improving mixture processabilityduring extrusion or to achieve the desired product outcome. Within this chapter a brief overview on materials used for HME is presented.

- **Active compounds -** As already mentioned the main requirement for an active compound to be taken in account for processing by HME is its thermal stability. Extensive investigation of the compatibility and miscibility of the API with the potential excipients is a viable step towards understanding the type of the product which will be obtained (solid solution or amorphous/crystalline suspension) (Crowley et al., 2007). Additionally, these investigations may reveal some unexpected properties of active compounds such as plasticizing effect (carbamazepine for Soluplus® (Gupta et al., 2014) and chlorpheniramin maleate for HPC (Zhu et al., 2002)) or detrimental effect on the extrusion process (oxprenolol hydrochloride decreased melt viscosity of polymer mixture (Follonier et al., 1995)) and obtained extrudates (fenoprofen Ca inhibits hardening of extrudates with MCC-PEG (Cuff an Rauf, 1998)).
- **Carriers -** HME is a technology based on embedding of API in a defined carrier. Carriers are usually meltable materials which act as thermal binders during processing and later as solubility enhancers or release retardants after exposing the extrudate to the gastro-intestinal (GIT) fluids. Carriers must be selected upon confirmation of its compatibility with the API, low melting/glass transition temperature in terms of protecting the compound from possible thermal degradation as well as physical and chemical stability (Kolter et al., 2012). The properties of the used carrier affect the features of the process and the finished dosage form to a large extent. Understanding material's nature is thus of vital importance when formulating and producing a product via HME. Carriers used in HME can be divided into two main groups: polymeric and non-polymeric.

Polymers used in HME may be from natural and synthetic origin and according to their affinity to water they can be classified as hydrophilic or hydrophobic. Polymers intended to be utilized by humans should be biocompatible and nontoxic. Polymeric carriers have been successfully employed with purpose of solubility enhancement of poorly soluble active compounds (Stankovic et al., 2015). Some of the polymers used as bioavailability enhancers of poorly soluble drugs are povidone, copovidone, PEG, HPC and HPMC (Hulsmann et al., 2001; Feng et al., 2012; Perissutti et al., 2002; Mohammed et al., 2012; Yun et al., 2014). Different hydrophobic and hydrophilic polymers were also investigated as possible release retardant agents when preparing sustained release dosage forms. Hydrophobic polymers tend to deliver the API by diffusion, while hydrophilic ones usually by diffusion and erosion. Ethyl cellulose, HPC, HPMC, PEO, PVA, xanthan, chitosan (Crowley et al., 2004; Loreti et al., 2014, Ma et al., 2012; Maddineni et al., 2015; Ozguney et al., 2009; Fukuda et al., 2006a) are just some of the polymers which have been successfully processed by hot-melt extrusion and were designed as extended release units of different active compounds. pH dependent polymers from the class of poly(meth)acrylates, which are known by the brand name Eudragit®, were pointed as suitable carriers for different dissolution outcomes (Qi et al., 2008; Yang et al., 2008).

Non-polymeric carriers include mainly lipid compounds, sugars and sugar alcohols. Pharmaceutically approved lipids are large group of oils, waxes, glycerides and fatty acids, gaining significant attention as bioavailability enhancers and sustained release agents. Solid lipids are suitable crystalline excipients for thermal processing into extended release dosage forms due to their biocompatibility, low-toxicity, compatibility with many active compounds, moderate melting temperatures and low cost. Due to their extreme hydrophobicity and insignificant degree of swelling and erosion, lipid matrices deliver the active compound mainly by diffusion through the pores of the system. A main drawback of lipids is their polymorphism and physical instability, which appears during the thermal treatment and also with storage (especially at higher temperatures) (Rosiaux et al., 2014; Reitz and Kleinebudde, 2007). Changes in the solid state of the lipid may trigger further changes in the drug delivery pattern. Overcoming the problems associated with changes in the crystallinity of the lipids may be possible by selecting low storage temperatures for the obtained products, enabling rapid product cooling or conducting HME at temperatures lower than the melting point of the lipid (Rosieux et al., 2014; Reitz and Kleinebudde, 2007). This last process is known as solid lipid extrusion and is based on partial melting of the lipid in the barrel and extrusion occurring due to thermo-mechanical treatment of the mixture. Solid lipid extrusion in some cases may retain the primary crystal packaging of the lipid and thus prevent changes in the solid state properties during processing and storage (Gures and Kleinebudde, 2011; Reitz et al., 2008). Lipids explored as carriers for HME include: waxes (cetyl palmitate, (Witzleb et al., 2012)), fatty acids (stearic acid, behenic acid, myristic acid; (Vervaeck et al., 2015a)), triglycerides (trilaurin, tripalmitin, tristearin; (Windbergs et al., 2009a)), mixed glycerides (glyceryl palmitostearate, glyceryl behenate; (Krause et al., 2009)) etc..

Additionally to lipids some other compounds appear as suitable carriers for hot melt extrusion. Starch and sugar (Yeung et al., 2015), mannitol (Thommeset al., 2011) and isomalt (Ndindayino, 2002) were also pointed as carrier candidates for HME.

- **Miscellaneous compounds -** This category concerns compounds which may be included in the formulation in terms of facilitating its process ability and achieving the desired product performance.
  - ***Release modifiers*** are often included in the formulation in order to achieve the desired release pattern from the extruded product. Hydrophilic polymers such as HPMC, HEC and super dis-

integrant such as crospovidon in low amounts tended to swell and disturb the lipid matrices leading to better wettability and faster release of a model drug diprophylline by diffusion and erosion (Gures and Kleinebudde, 2011). Incorporation of PEG with different molecular weight inside extrudates based on the lipid carrier tripalmitin and the model drug theophylline increased unit wett ability, induced faster pore formation and thus faster leaching of the active compound (Windbergs et al., 2009b). Inclusion of water soluble pore formers such as lactose and mannitol in polymeric and lipid matrices respectively increased the system's hydrophilicity and yielded faster drug release due to dissolving and leaching of the pore former creating a system with higher porosity (Zhang et al., 2000; Gures and Kleinebude, 2011). Inclusion of pH dependent polymers such as Eudragit® L100 and Eudragit® S enabled triggering sigmoidal indomethacin delivery from extruded matrices based on Eudragit® RD, due to increased solubility of the first two polymers at higher pH values (Zhu et al., 2006). Inclusion of organic acids or bases in extended release extruded products containing weakly basic/acidic compounds may be a suitable approach for achieving the desired drug delivery rate by modulation of the microenvironmental pH (Badway and Hussain, 2007). Inclusion of citric acid as plasticizer in extrudates based on 5-ASA and Eudragit® S 100 induced slower drug release by lowering the microenvrionmental pH and thus decreasing the polymer's solubility (Bruce et al., 2005).

- ***Plasticizers*** are compounds with low molecular weight which interact with polymers and subsequently decrease the glass transition temperatures and melt viscosities of the latter ones. This enables performing HME at lower temperatures, which subsequently decreases the possibility of thermal degradation of the API and/or the polymer. Plasticizers additionally increase polymer flexibility and finally improve the physico-mechanical properties of the final product. Lipid carriers do not require addition of plasticizers due to their lower melting temperatures and low melt viscosities. Many compounds have been successfully used as plasticizers, among them citrate esters such as triethyl citrate (Maru et al., 2011), glycols (polyethyleneglycol (Maru et al., 2011), propylene glycol (Rahman et al)), phthalate esters (dibuthylphthalate, diethyl phthalate (Rahman et al., 2012)), triacetin (Follonier et al., 1995). The choice of a plasticizer may significantly influence drug delivery, with water-soluble compounds (triethyl citrate) providing faster release rate due to increased water penetration, while water-insoluble plasticizers (dibuthylsebacateand diethyl phthalate) may increase system hydrophobicity and decrease drug delivery rate as shown for extrudates based on ethyl cellulose and xantangum (Verhoeven et al., 2008)
- ***Other process aiding compounds*** may include various compounds which may provide better processing of melted mixtures and product stability. Antioxidants such as Vitamin E and its derivates may be used in terms of preventing oxidation of used carrier (Crowley et al., 2002). Colloidal silica dioxide may be used as flow aid when mixtures with poor flow properties are aimed to be extruded, while waxy materials such as glyceryl monostearate may be used as thermal lubricants during extrusion (Crowley et al., 2007).

Fields of application of hot melt extrusion in oral solid dosage form development

Solid dispersions for solubility and bioavailability enhancement

Many of the new drug molecules discovered by combinatorial chemistry and high throughput screening are belonging to the BCS class II and BCS class IV and thus are considered as poorly soluble. The bioavailability of an active compound after oral administration depends, apart from its permeability, mainly on its solubility. It is required that molecules are in the dissolved state in order to be absorbed in the gastro-intestinal tract (Khadka et al., 2014). Low solubility of active compounds represents one of the major challenges in formulation development and thus gains attention of many pharmaceutical scientists. Improving drug solubility may be done by several approaches including: size reduction (Loh et al., 2015), formation of inclusion complexes (Miletic et al., 2013), salt formation (Melo et al., 2016), formulation of self (micro/nano) emulsifying systems (Čerpnjak et al., 2015), solid dispersions (Wlodarski et al., 2015). The term solid dispersion in general refers to dispersion of a solid drug in a solid carrier. Solid dispersions include several types of systems such as eutectic mixtures, solid (molecular) solutions, and solid suspensions. In cases when solubility is limiting factor it is desired that drug is dispersed inside a carrier in its molecular form or as amorphous phase. By constant screw rotation, providing efficient distributive and dispersive mixing of the components inside the barrel, hot-melt extrusion appears as very potent technique for (molecular) dispersing of poorly soluble APIs in different carriers, which subsequently leads to increased solubility of the used active compounds (Shah et al., 2013). Several examples of application of HME in improving drug solubility will be discussed in this chapter.

Jujin et al. used HME to increase the solubility of ni-

modipin by formulating it with Kollidon VA64 (copovidone) in stable amorphous solid dispersion which was further compressed into tablets. Results pointed that extrusion temperature and drug loading play a crucial role in increasing the solubility of the drug. Lower extrusion temperatures (130 °C) and high drug loading (20%) led to slower drug release due to the fact that drug was mainly present in its crystalline form. Increasing the extrusion temperature (150 °C) and reducing the drug loading (15%) improved the dissolution of the drug since at these parameters it was completely transformed in its amorphous form. Drug release was insignificantly affected by the medium's pH. Interestingly decreasing the particle size of granules obtained from extrudates from 40 mesh to 80 mesh led into slower drug release after tablet disintegration due to agglomeration of the smaller particles on the dissolution medium's surface, which decreased its contact surface and thus wettability. In-vivo studies showed a higher oral bioavailability of nimodipin after formulating it as a solid dispersion (Jijun et al., 2010).

De Jaeghere et al. increased the solubility of poorly soluble drugs hydrochlorothiazide and celecoxib by molecularly dissolving them in partially hydrolyzed polyvinyl alcohol (PVOH) by hot-melt extrusion. Solubility was dependent upon the degree of hydroxylation of the polymer, with types having a high degree of hydroxylation (>70%) providing faster drug release independent on medium's pH and ionic strength compared to types having a lowerdegree of hydroxylation. Additionally, increasing the drug content from 5% to 15% enhanced drug leaching from the matrix due to higher water sorption, higher osmotic pressure and more polymer swelling. Inclusion of sorbitol (up to 40%) in a binary mixture with the pure polymer prepared by HME and re-extrusion of the milled mixture, containing celecoxib, enabled extruding at lower temperatures due to the plasticizing effect of the polyol. Solid dispersions containing celecoxib, PVOH and sorbitol provided better in-vitro dissolution and similar in-vivo characteristics compared to commercially available product (De Jaeghere et al., 2015).

Thommeset al. produced stable solid crystal suspension of weakly soluble drug griseofulvin (10% or 50%) and mannitol (90% or 50%) by hot-melt extrusion. Solid-state studies (x-ray, DSC) revealed that the API remained in its crystal form after cooling and crystallization of the carrier. However, this type of solid suspension provided significant increase of drug release compared to the pure drug and a physical mixture. This increase of the dissolution rate of griseofulvin was correlated with the reduction of its particle size due to high shearing during extrusion and also due to the intimate contact of the drug with the hydrophilic mannitol, which subsequently increases drug wettability and thus dissolution. Additionally formulating solid crystal suspensions avoids the tendencies of recrystallization seen with time in some solid solutions and amorphous suspensions, which may alter drug dissolution. By varying drug loading and screw speed tailoring of drug particle size could be achieved. This principle of crystal solid suspension was also successfully employed on two other drugs, spironolactone and phenytoin (Thomes et al., 2011).

Extended drug release

Extended release dosage forms are gaining huge attention from both pharmaceutical scholars and industry as therapeutically advantageous systems over conventional immediate release units. By delivering the active principle in a continuous fashion through longer time periods, extended release systems provide longer effective therapeutic plasma concentration levels which are less prone to fluctuation and thus side effect appearance is decreased. Additionally extended release systems provide reduced dosing frequency which increases patient's compliance (Kim et al., 2015). Extended release systems are mainly formulated as matrix or reservoir systems and also as single or multiple-unit systems (Qui et al., 2009; Aleksovski et al., 2015a; Marucci et al., 2013). The API in matrix systems is homogenously dispersed within a carrier which controls the drug release. The active compound in reservoir systems is situated inside a core which is surrounded by a membrane layer controlling the drug release. Matrix systems are generally less complicated from a manufacturingpoint of view and additionally have less risk of dose dumping compared to reservoir systems (Nokhodchi et al., 2012). Hot-melt extrusion has been extensively studied as a method suitable for the production of both single and multiple unit matrix extended release systems by combining different active compounds with different release retarding carriers. HME allows formation of solid dispersions with active compounds embedded in (partially)melted release retardant carriers which after solidification control the API's release. A brief review on the achievements of HME in the field of extended release is presented in the following paragraphs.

Loreti et al. (2014), successfully applied HME for production of extended release matrices based on HPC and two model drugs theophylline and ketoprofen. Obtained matrices were compared to matrices based on the same formula but prepared by direct compression (DC). HME showed superior over DC in terms of obtaining final product since DC formulations provided very poor powder flow properties. Both DC and HME techniques provided extended drug release overlonger time periods with HME inducing slightly faster delivery rate due to partial (theophylline) or complete (ketoprofen) solubilisation inside the molten polymer during HME (Loreti et al., 2014). Ma et al. (2012) developed extruded matrices for sustained delivery of theophylline (30%) embedded in a crystalline form inside an HPMC matrix. Results showedthat low molecular weight HPMCs (E6 and K100 LV) did not provide sustained release while polymers with higher molecular weight (K4M, K15M, K100M) delivered the active compound in prolonged fashion (12 hours) by anomalous trans-

port with diffusion being dominant over erosion. Increasing the molecular weight and viscosity of the polymer from 4M up to 100M did not provide significantly different theophylline release due to overcoming the polymer critical entanglement value (M_e). Further inclusion of propylene glycol (28%) in the mixtures, aimed to be processed by HME, caused reduction in HPMC's glass transition temperature and improved the extrusion process of all evaluated mixtures (Ma et al., 2012).

Ozguney et al. designed extended release mini-matrices based on hydrophobic Kollidon SR (polyvinyl acetate/polyvinyl pyrolidone 80%/20%) and ibuprofen or theophylline as model drugs. Ibuprofen was present in the extrudates in dissolved form and additionally acted as plasticizer. In contrast, theophylline was suspended in the polymer matrix. Increasing the amount of the drug (25-50%) inside the formulation led into faster drug leaching due to the increased hydrophilicity of the system and the higher porosity that is established during dissolution of the drug. Increasing the extrusion temperature from 80 to 90 °C reduced drug release in case of theophylline due to a higher matrix density. In case of ibuprofen, increasing the extrusion temperature yielded a faster drug release due to more pronounced water uptake by the system. Replacing a part of Kollidon SR with low molecular weight HPC (30%) provided faster drug release due to HPC dissolution and leaching, resulting in amore porous matrix (Ozguney et al., 2009). De Brabander et al. (2005) used hydrophobic ethylcellulose - EC (40%) as a base of producing sustained release mini-matrices containing ibuprofen (60%) as model drug. Primary formulation showed very low drug release (not more than 20%) within 24 hours. Replacing part of the EC with HPMC (10-30%) enhanced drug release, with formulations containing highest amount of HPMC providing the fastest drug delivery due to the pronounced hydrophilicity of the matrices. Increasing the HPMC viscosity grade increased ibuprofen release due to the higher swelling ability of these polymers which opened the matrix structure. Using xantan gum instead of HPMC, at amounts of 20%, provided zero-order like drug release kinetics with less expressed burst release, probably due to the faster liquid uptake and swelling of xantan gum. Additionally, decreasing the drug loading from 60% to 30% also provided less burst release. Drug release from mini-matrices was mainly by diffusion but the swelling of the hydrophilic polymers should be also taken in account. Evaluated matrices were stable at room conditions but showed faster drug delivery after storage at accelerated condition, probably due to matrix softening (De Brabander et al., 2003).

Windbergs et al. (2009b) developed sustained release mini-extrudates based on tripalmitin as release retardant with(out) PEG and theophylline as model drug by solid-lipid extrusion. Solid state studies revealed retaining of the crystalline nature of all compounds after the extrusion process. Inclusion of PEG in the lipid matrix (1:9) increased drug delivery due to a higher hydrophilicity and increased *in-situ* forming porosity of the system. Matrices containing PEG with lowest molecular weight (10000) tended to release the drug in fastest manner compared to matrices containing PEG with higher molecular weight (20000-7000000) due to smallest contact angle and thus better wettability by the dissolution medium. Replacing tripalmitin with glycerides with longer fatty acid chain (tristearin) reduced the drug release rate, while glycerides with shorter fatty acid chains (trilaurin) provided faster drug release. A longer fatty acid chain increased the contact angle of the matrix, negatively affecting drug release (Windbergs et al., 2009b). Vithani et al. successfully employed HME for production of extended release tablets of diclofenac sodium and glyceryl behenate. Additives were included eitherby mixing them with the melted granules of drug and glyceryl behenate (obtained by milling extrudates) or were included in the mixture prior to HME. Processing binary mixtures of drug and lipid did not give significant difference in the crystalline solid state properties of the components. Inclusion of sorbitol (27%), dibasic Ca phosphate anhydrous (14%) and magnesium aluminium silicate (3%) in premixes prior to extrusion transformed the drug into molecularly dispersed or amorphous state, mainly due to its mixing with sorbitol. Hot (above melting T) and cold extrusion (below melting T) of binary mixtures provided sustained drug release within 6 hours without significant difference between the delivery patterns obtained from the different techniques. Tablets composed of completely melted premixes (processed above melting T) gave slower drug delivery compared to the tablets where additives were added without thermal treatment. Slower drug release in premixed tablets was due to the lower tablet wet ability as additives were embedded inside the lipid matrix. On the other hand, in partially melted tablets additives were leaching faster from the matrix, leading to more expressed tablet porosity and thus erosion and drug delivery. Increasing the drug concentration inside the premixed matrices (30%-50%) tends to enhance drug release due to the more hydrophilic character of the system (Vithani et al., 2013).

Targeted oral dosage forms

Conventional oral drug delivery is not the ideal platform for every drug candidate and every health condition. Many molecules show local action in a specific part of the gastrointestinal tract (GIT), narrow absorption window within the GIT, pH dependent solubility, instability in different GIT media, side effect appearance when absorbed in some segment of the GIT etc. These issues led scientist into developing oral dosage forms, which will target aspecific GIT segment and will deliver the active compound in fast or prolonged fashion. Hot-melt extrusion emerges also as viable alternative in the development of targeted oral dosage forms and its potential in this field will be further discussed in this chapter.

- Gastro-retentive floating dosage forms

Gastro-retentive dosage forms are designed in such a manner to remain present in the stomach for longer time periods and thus deliver the active compound in prolonged fashion. These types of dosage forms are suitable for drugs acting locally in the stomach, drugs that have narrow absorption window in the upper GIT, drugs which are instableor poorly soluble in slightly acidic/basic environment. Several platforms were developed for providing gastric retention with floating dosage forms emerging as most promising devices in this field (Aleksovski, 2012). Floating dosage forms are systems capable of remaining buoyant over the gastric content for prolonged time periods without being affected by the gastric emptying pattern. Flotation is achieved due to the lower density of these systems compared to the gastric content. Low density of floating forms may be inherent (non-effervescent systems) or obtained by gas formation (effervescent systems) (Aleksovski, 2012; Aleksovski et al., 2013). HME has also been investigated to design floating dosage forms.

Fukuda et al. successfully developed stable floating systems based on Eudragit RS PO as insoluble polymeric carrier and acetohydroxamic acid or chlorpheniramine maleate as model drug. Incorporation of sodium bicarbonate (5-10%) increased unit porosity and reduced density and thus enabled *in-vitro* buoyancy through 24 hours in acidic media while delivering the APIs in controlled fashion. Increasing drug levels and replacing part of the polymer with Eudragit E PO (soluble in acidic media) led to faster drug release. However, combining Eudragit RS PO and Eudragit E PO increased the unit density and thus disabled its flotation. Increasing the size of the unit from 1 to 6 mm decreased drug delivery rate due to decreased surface to volume ratio, but on the other hand did not influence flotation of the systems. Hot-melt extrusion proved as superior technique over direct compression in both achieving buyouncy and extended drug release in acidic media (Fukuda et al., 2006b). Vo et al. utilized hot-melt extrusion and the liquid-vapor phase transition phenomena in order to prepare floating pellets based on theophylline as model drug, Eudragit RS PO and HPMC K15M as matrix formers and ethanol as foaming agent. Pellets with porous structure and high specific surface area were obtained. The structure of the pellets allowed immediate flotation in0.1 N HClduring12-24 hour periods and also theophylline delivery in prolonged fashion (Vo et al., 2015). Malode et al.(2015), designed multiple-unit floating delivery system containing metoprolol succinate as model drug incombination withthree different polymers (Eudragit RS PO, polyethylene oxide – PEO WSR 303 and HPMC K100M) and sodium bicarbonate as *in situ* gas generator. Units based solelyon Eudragit RS PO did not float, even though sodium bicarbonate was present. Incorporation of PEO inside the system induced floatation within 3 minutes and overall buoyancy over3 hours. Introducing HPMC in the system in amounts of 15% maintained the short floating lag time but also significantly increased the total floating time up to 12h while delivering the API in continuous manner by zero order kinetics. The optimal formulation was unaffected by storage conditions with regard to floating properties and drug delivery (Malode et al., 2015).

- Delayed/enteric drug release

Many active compounds used in current pharmaceutical practice show instability in the acidic environment of the stomach and thus their release in this part of the GIT will trigger an unsuitable therapeutic outcome. Additionally, some compounds act as irritants to the stomach and it is desired to minimize the presence in this region to avoid side effects (Hussan et al., 2012). Enteric/delayed drug delivery is a viable solution for targeting drug delivery in the small intestine with minimal amount of drug being released in the stomach. This approach will subsequently overcome the problems associated with presence of some drugs in the stomach. An enteric platform is usually based on pH sensitive polymers which are insoluble at low pH (1-5.5), but start to dissolve at a pH above 5.5 by salt formation (Albanez et al., 2013). The enteric/delayed release is well-known practice in the pharmaceutical industry, where polymers are applied in form of thin films over different types of cores such as tablets, capsules or most often MDDS (Pan et al., 2015; Huyghebaert et al., 2004; Dukić-Ott et al., 2008). However, film-coating is time consuming process with several process steps required to obtain the final product. Additionally coating process often requires usage of organic solvents which makes it environmentally unfriendly. Several studies revealed HME as a simpler, less time consuming and environmental friendly technique, suitable for production of delayed release matrices.

Yang et al. developed enteric and sustained release dosage forms of stomach-irritatingketoprofen based on Eudragit L-100 (preplasticized with triethylcitrate) produced by hot-melt extrusion with(out) subsequent milling and compression. Hot-melt extrusion provided an amorphous form or a molecular dispersion of the API inside the enteric polymer. Results showed that extrusion with(out) compression provided minimal drug release in 0.1 M HCl for the first 2 hours and sustained drug release up to 100% in phosphate buffer pH 6.8 over the next 8 hours. Drug release was governed by surface erosion of the extrudates and by combination of diffusion and erosion in case of tablets, compressed from milled extrudates. Increasing the amount of polymer resulted in a more pronounced sustained drug delivery (Yang et al., 2008). Andrews et al. used HME to produce delayed and sustained release matrices (tablets) of 5-ASA, which was suspended in its crystalline form inside pH-sensitive polymer Eudragit L100-55, plasticized with TEC and citric acid. The plasticizer combination (20%: 20%) enabled better process ability of the mixture, acid-resistance and subsequent controlled drug release. Incorporation of hydrophilic polymers in amounts of 20% (PVP K30 and Carbopol 971P) increased API leaching in 0.1 M HCl, but further retarded its delivery in phosphate buffer

by gel layer formation. Milling and subsequent compression of the extrudates gave units with a lower density, compared to untreated extrudates, which failed to provide acid resistance (Andrews et al., 2008). Schiling et al. (2010) developed matrix pellets for delayed and subsequent extended release of theophylline produced by hot-melt extrusion. Eudragit® S 100 emerged as optimal polymer among the Eudragits® grades, while HPMC-acetate succinate provided acid-resistance and acceptable processing temperatures. Inclusion of a plasticizer in concentrations of 30% tended to reduce the polymer's glass transition temperature and melt viscosity, facilitating extrusion process. Incorporation of water soluble plasticizers (citric acid monohydrate and PEG 8000) induced faster, even burst drug release. In contrast, when less soluble plasticizers (triethyl citrate and methylparaben) were used, they did not significantly affect acidresistance and provided extended drug release over4 hours in phosphate buffer pH 7.4. These insoluble plasticizers additionally yielded units with a low porosity in which drug was homogenously suspended in its native, crystalline form (Schilling et al., 2010).

- Colon targeting dosage forms

Targeting drug compound release in the colon after peroral application is a suitable route in the treatment of local diseases affecting this part of the GIT, such as irritable bowel syndrome, Crohn's disease and colorectal cancers. Additionally, the colon environment is a promising GIT section for systemic delivery of different peptide and protein compounds. Studies offer different approaches for targeting the colon, which are mainly based on predicting colon pH, gastric transit time and use of compounds, which are digested by the colonic microflora (Amidon et al., 2015; Palugan et al., 2015). Hot-melt extrusion has also proved its potential as a technique capable of producing colon targeted oral dosage forms.

Bruce et al. used hot-melt extrusion to develop colon targeted tablets of 5-amino salicylic acid (5-ASA) and Eudragit® S100 polymer, which dissolves at pH 7. Units tended to provide minimaldrug release in 0.1 M HC land anextended release (by diffusion and erosion) in phosphate buffer pH 7.4. Incorporation of triethyl citrate (TEC) as plasticizer decreased the glass transition temperature of the polymer and thus facilitated the extrusion process. Increasing the amount of TEC increased system's hydrophilicity and induced faster drug release. Introduction of glyceryl monostearate as lubricant and citric acid as additional plasticizer decreased drug delivery rate due to a higher hydrophobicity and lower microenvironmental pH, respectively. Additionally, citric acid interacted with 5-ASA. Increasing the 5-ASA content from 25% up to 50% resulted in a delay ofthe drug release due to the lowering of microenvironmental pH, induced by the acidic nature of the drug (Bruce et al., 2005). Cassidy et al. (2011) developed extruded matrix systems based on Eudragit® S100 and TEC (60:40) for continuous delivery of different photosensitizers in the colonic region. Eudragit® S100 provided acid resistance and thus minimal to insignificant drug release in 0.1 N HCl. By increasing the pH of the medium at 7.4 the polymer started to dissolve and drug was delivered over6 hours in continuous fashion viaboth diffusion and surface erosion. The produced matrices showed acceptable mechanical properties and thus further development of these types of dosage forms could be considered as promising (Cassidy et al., 2011).

Taste masking and patient friendly dosage forms

Recently the pharmaceutical community has become more aware of the need to deliver more patient friendly dosage forms. One of the aspects of this concern is providing medicines which will improve the patient compliance during and after the treatment (Aleksovski et al., 2015b). Children, elderly and patients with impaired swallowing are emerging as specific groups, demonstrating difficulties in swallowing of conventional medicines (standard tablets and capsules) and susceptibility towards the unpleasant taste of the drug(especially children). These facts may lead to poor adherence of these patients towards conventional medicines, hence reduce the success ofthe final therapeutic outcome (Okuda et al., 2012; Slavkova and Breitkreutz 2015). One of the main tasks, when developing patient friendly dosage forms, is to efficiently mask the unpleasant taste of active compounds and to increase the palatability of the formulation. There are several techniques employed to mask the taste of active compounds ranging from simple ones such as using of sweeteners and flavors to more complex ones such as microencapsulation, lyophylisation, complexation, particle coating, use of taste suppressors etc. (Gittings et al., 2014; Khan et al., 2015).

Hot-melt extrusion has been successfully applied in terms of masking the unpleasant taste of active compounds. Namely embedding the API into a suitable carrier by formation of solid dispersions may provide a physical barrier between the drug and the taste receptors located on the tongue. Maniruzzaman et al. successfully masked the unpleasant taste of paracetamol by hot-melt extrusion with two different polymers, pH sensitive metacrylic Eudragit® EPO and copovidone. Results have shown the ease in obtaining extrudates, where paracetamol was partially (Eudragit EPO) or completely solubilized (copovidone) in the polymer carrier. Evaluation of sensory response by electronic tongue and by healthy volunteers revealed the success in masking the unpleasant taste of the drug, when lower drug amounts were incorporated. Taste masking was most efficient in case of extrudates based on copovidone and 30% API. This finding coupled with the fast drug release in gastric medium outlines the potential of this system of being patient friendly and effective (Maniruzzaman et al., 2012b). Alsherhi et al. provided masking of the bitter taste of mefenamic acid by hot-melt extruding it with Eudragit® EPO. The extrudates increased the API's solubility in media with acidic pH, when it was present in concentra-

tion up to 25% in the mixture, due to the amorphous state of the drug. Extrudates containing 20% and 25% were milled and compressed into orodispersible tablets, which provided fast disintegration times, potential taste masking, improved API solubility and overall stability (Alshehri et al., 2015). Gryczke et al. (2011) developed orodispersible tablets based on solid solutions of ibuprofen in pH sensitive metacrylic polymer (Eudragit® EPO). Ibuprofen was successfully molecularly dispersed in the polymer by hot melt extrusion, and extrudates were further milled into granules which were compressed in tablets with different amounts of fillers and disintegrants. The whole platform was tested *in-vitro* and *in-vivo* and provided fast mouth disintegration with an acceptable texture sensation, suppressed bitter taste (due to the polymer's insolubility at saliva's pH) of the drug and fast drug delivery (Gryczke et al., 2011). Pimparde et al. (2015) successfully used hot-melt extrusion for taste masking of caffeine citrate by incorporating it in a matrix composed of ethylcellulose and different pore formers and further tableting into orodispersible tablets. The screw design, employed in the research, retained the APIs crystallinity in the carrier, while the formulation design enabled a limited API release in artificial salivary fluid and sufficient drug delivery undergastric conditions. These features decreased the bitter sensation detected *in-vitro* by electronic tongue and *in-vivo* by healthy volunteers (Pimparde et al., 2015). Witzleb et al. (2011) efficiently masked the bitter taste of praziquantel by extruding it together with glyceryl tristearate and PEG below the lipid's melting point. The taste masking potential of the matrices was tested via application to healthy cats, indicating that drug and PEG concentration together with different extrudate's cross sections do not lead to different taste perception (Witzleb et al., 2011).

Prilling

Prilling as a technique is well known in the agrochemical industry where it has been extensively used in the production of urea and other fertilizers. Prilling involves conversion of a liquid melt into droplets through a nozzle. Droplets are further solidified into spherical particles by means of hardening at temperatures below the melting point of the material in a high cooling tower. Recently, prilling has gained attention as a promising technology in the production of matrix spheres with narrow particle size distribution aimed to be formulated into multiple unit drug delivery systems (MDDS) (Sequier et al., 2014). Several benefits are linked to this technology and its use in the pharmaceutical field; prilling is a promising technology for continuous manufacturing of large quantities of uniform spherical particles with very good flow properties. The obtained spheres can be successfully filled into capsules or sachets, providing the benefits of MDDS. As a technique where primary materials are directly transformed into the final dosage form, prilling offers simplicity based on a single processing step using equipment with a simple design. Since prilling is based on melting of the material and subsequent solidification in a tempered tower without the use of organic solvents this manufacturing method is categorized as environmentalfriendly (Vervaeck et al., 2013).

Despite its advantages prilling also poses several disadvantages, which should be taken in account when considering this process during product development. To obtain larger particles with uniform and regular spherical size high prilling towers are required. As large production facilities are needed to accommodate the equipment an increase of the manufacturing cost is inevitable (Wu et al., 2007). Due to the high temperatures generation during prilling this technique is regarded as unsuitable for processing of thermolabile compounds.

The potentials of prilling as pharmaceutically suitable technique will be presented in the following pages.

Equipment and process basics

Prilling as a process is based on three different steps (Pivette et al., 2012):

- material melting and mixing in a vessel,
- droplet generation via a nozzle,
- droplet solidification in a prilling tower and product collection.

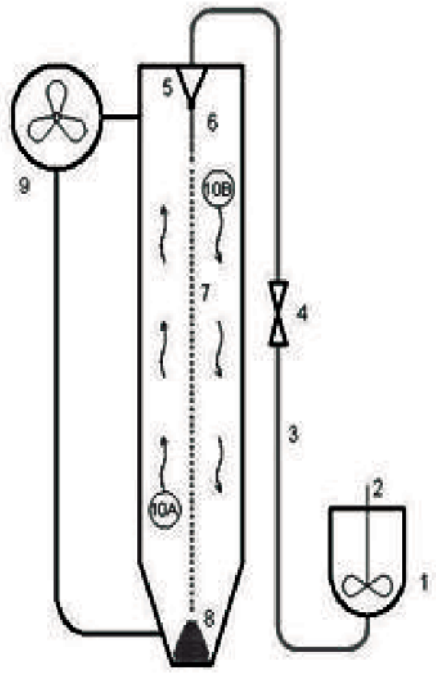

Fig. 4. Schematic overview of a prilling device: (1) pressurized melting vessel; (2) mixing device; (3) thermostated transport channel – tube; (4) filter; (5) tempered nozzle; (6) prilling tower; (7) droplets; (8) product container; (9) cooler; (10A) counter-current cooling gas; (10B) co-current cooling gas.

Similar to HME prilling equipment used for the production of human pharmaceutical formulations should be made of non-reactive material, easily cleaned and validated. A schematic image of a prilling machine is given in Figure 4.

Melting vessel

The vessel represents a pressurized tank equipped with heating/cooling system. Inside the vessel the matrix forming material are melted at suitable temperature. Afterwards the active compound which is embedded inside the matrix is added while continuously stirring with a mixing device. When the drug is completely dispersed inside the molten carrier the mixture is forced towards the nozzle by applying pressure inside the vessel. Transport from the vessel towards the nozzle may be conducted via thermostated silicon tubes if the melting vessel is a separate part of the prilling assembly. When the barrel and the nozzle are designed as single pot equipment, the material transport is conducted through channels built in inside the equipment. The applied pressure may vary regarding the properties of the melted mixture. Melts with high viscosity require higher pressure and could cause processing difficulties due to blocking of the channels. The size of the melting vessel size will vary depending on the batch size.

Nozzle

After being melted and mixed the material is transported to the nozzle which enables droplet generation. In the agrochemical industry the prilling processes for urea and other fertilizers use rotary nozzles which consist of rotating bucket with perforated walls. The melted material is transferred into this rotating bucket and pushed through the perforations by the centrifugal force, forming liquid jets which are - due to hydrodynamic instability - broken into droplets and subsequently solidified inside the prilling tower. During this process the jet breakage is not controlled and thus a product with very broad particle size distribution is obtained. This approach is not acceptable for pharmaceutical purposes and therefore a more sophisticated nozzle for pharmaceutical dosage form development is required (Partridge et al., 2005).

Vibrational nozzles are the most used devices for droplet formation during prilling. When this kind of nozzle is used, the molten liquid jet is broken in a row of uniform droplets, which are subsequently solidified by falling through the prilling tower. Vibration nozzles are equipped with a vibrational unit which provide mechanical vibrations at defined frequency and with defined amplitude. These vibrations apply force on the liquid jet and subsequently break it down to cylindrical units. Due to the surface tension of liquids these cylinders prefer to occupy a smaller volume and they change from rod-like to sphere-like droplets. The melt viscosity, jet flow speed, nozzle diameter and frequency and amplitude of the vibrations determine the size of the droplets when prilling is conducted by vibration nozzle. The method of droplet formation by jet breakage using vibrating nozzle differentiates prilling from spray chilling (congealing) where nozzles are used to atomize the molten mass (Whelehan and Marison, 2011; Sequier et al., 2014; Pivette et al., 2009).

A new prilling device has been designed by Peira based on a different nozzle design and the mode of droplet generation (Figure 5). The PrillDrop® device is gener-

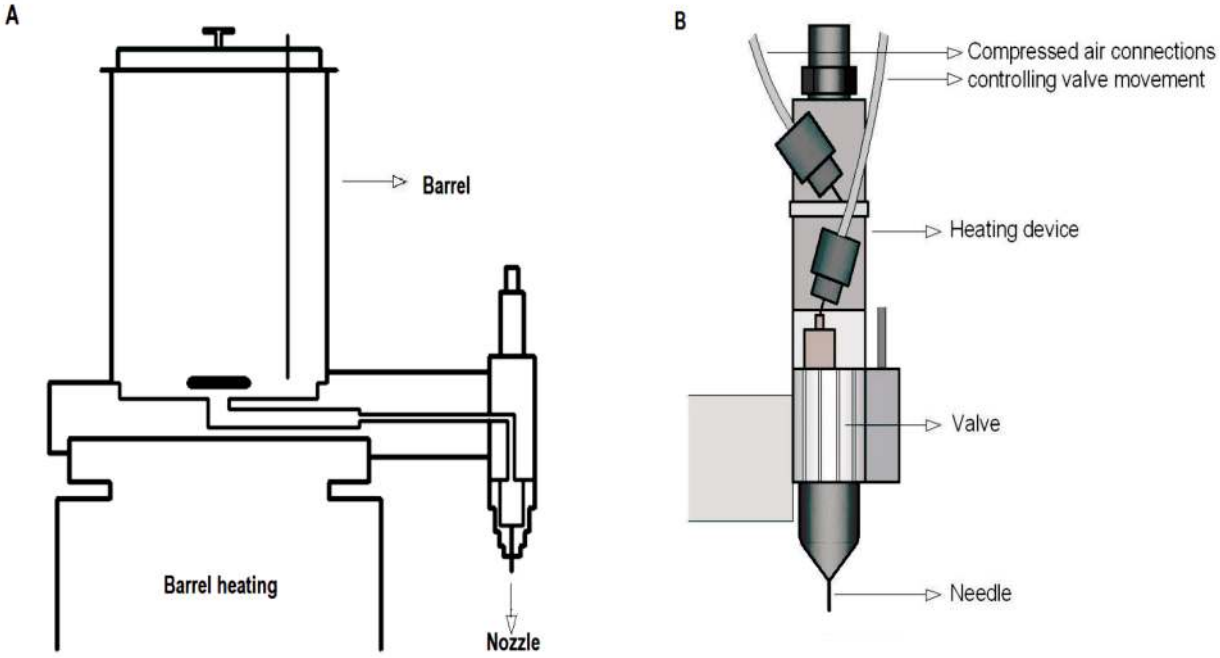

Fig. 5. Schematic overview of (A) PrillDrop® device and (B) PrillDrop® nozzle.

ating the droplets by dripping of the melted materials from the nozzle. In this device material is transferred from pressurized heated vessel to a pneumatic thermostated nozzle. This nozzle is equipped with a valve and a capillary (inner diameter of 0.33 mm) and is coupled with a heating device. This design enables adjustment of droplet generation in function of the properties of the processed materials. When the device is in its working mode the nozzle valve is periodically switching from a closed state to an open state for a specific time periods. Valve movement is enabled by compressed air supplied to the nozzle via pressurized tubing. In the open state (i.e. droplet formation time) a predefined amount of molten material is pushed towards the tip of the needle where a droplet is formed. When the gravitational force exceeds the surface tension of the melt, the droplet is released from the needle. The volume of the obtained prill depends on the rheological and surface properties of the molten mass, pre-nozzle pressure, needle diameter and frequency of open/close change cycles of the valve. The droplets are further cooled down in a prilling tower. The process output could be controlled by varying the droplet time formation and also by the applied pressure. A higher pressure may increase the amount of formed drops. However, when exceeding a certain pressure, the dripping may be impaired and regular and uniform droplets will not be obtained. The drop diameter is mainly defined by the diameter of the capillary needle (Whelehan and Marison, 2011; Vervaeck et al., 2015a; Vervaeck, 2015b; Peira, 2015).

Prilling tower

The last part of the prilling process is the solidification of the generated droplets in a prilling tower. Prilling towers refer to high columns offering an environment with temperatures below the solidification point of the molten carrier. Solidification inside the tower may be governed by circulating cooled air or a generator can be installed to provide forced co-current or counter-current flow of a cooled gas (air, N_2 etc.) through the column, in order to improve the heat transfer during solidification process (Rahmanian et al., 2015; Vervaeck, 2015b). During their fall through the prilling tower due to gravitational force, the droplets solidify from the surface towards the core. The solidification of the droplets is governed by three steps. Firstly the drops are losing their heat in the airstream and are cooling down to the melting point. In the second stage a solid layer appears (material freezing with possible crystallization) on the surface of the droplet and is spreading towards the core of the unit. In this stage a solid and a liquid phase are coexisting inside the droplet. Heat transfer within droplets slows down as it now only allows for heat conduction across the formed solid surface layer of ever increasing thickness. The final third step includes final cooling and complete solidification of the droplet (Mehrez et al., 2012). Depending on the density of the molten and solid mass, particles with different properties may be obtained. If the density of the molten material is similar to the density of the solid material, a dense core will be obtained. However, incase of a large difference between the density of the solid and the liquid phase, a core with a central void may be formed (Wu et al., 2007). To prepare prills with optimal characteristics regarding shape and structure, droplets must completely solidify inside the prilling tower. Therefore, prilling towers, which provide sufficient falling time and a droplet-to-cooling gas volume ratio of 0.1% are required to achieve this goal. The height of the prilling tower is proportional to the desired prill size. Larger droplets have a higher terminal fall velocity and a larger resistance towards heat transfer, which requires longer periods for solidification and thus higher towers (sometimes height is even unrealistic) (Wu et al., 2007). It is of essential importance to know the material properties such as density, viscosity, surface tension, thermal conductivity and combine them with mathematical modeling of tower height and also with variations of the solidification conditions (temperature, gas flow) to predict the solidification efficacy and the final outcome of the prilling process (Sequier et al., 2014). Inadequate cooling of the prills may lead to caking at the bottom of the tower, sticking to the wall and particle deformation. In recent studies, scientific groups have explored prilling towers designed with an upper column part and lower fluid bed part. Introduction of fluid bed inside the prilling tower may prolong the residence of the drops inside the column that will result in more effective solidification. This tower modification may reduce the height of the column and improve the overall efficacy of the prilling process. However, the primary solidification of the droplet must occur in an optimal manner before the prills enter the fluidized bed region in order to prevent particle damage, coalescence and deformation caused by the turbulent air movement (Wu et al., 2007; Vervaeck, 2015b).

After being solidified prills are collected and can be further processed via capsule or sachet filling.

Materials used in prilling and application of the technique in development of solid oral dosage forms

Prilling of molten masses is a relatively new technology to produce solid oral dosage forms and not many scientific projects have been published on this topic. Therefore the number of examples regarding thematerials and applications of multiple unit drug delivery systems based on prills is limited.

Concerning the materials used during prilling it is of essential importance to take the thermal character of this technique into account, therefore thermo stable active compounds and carriers are required for successful development of stable spheres. It is also important to investigate the compatibility and miscibility of the drug and the carrier as well as the viscosity and surface tension of the molten material. Processing highly viscous materials and immiscible compounds may impair the flow of the material from the pressurized vessel to the nozzle and may also

block the nozzle or disturb the droplet formation. Pharmaceutically approved lipids are the mostly studied materials for production of spheres by prilling. Pharmaceutically approved lipids are considered as highly suitable compounds for processing via prilling due to their low melting points, low melt viscosity, compatibility with other compounds and biocompatibility. Additionally, due to the hydrophobic nature of the majority of lipid compounds, their use as carriers for extending drug release is an interesting platform for development of novel solid oral dosage forms (Rosiaux et al., 2014). Fatty acids and their mixtures (stearic, behenic, myrsitic), mixed glycerids (glyceryl behenate, glyceryl palmitostearate) and hydrogenated castor oil are lipid compounds that have already been studied for prilling applications (Pivette et al., 2009; Sequier et al., 2014; Pivette et al., 2012; Vervaeck et al., 2013). The low viscosity of lipid melts is on one of the benefits when prilling is performed due to the ease of material flow and droplet generation. However, this low viscosity of molten lipids can be a drawback during droplet solidification in a tower equipped with fluid bed system. Due to insufficient solidification of the droplet in towers with moderate height and turbulent motion of the cooling gas in fluid bed section, a portion of the liquid mass of the droplet may be expelled from it and a cup-like particle may be formed. Addition of low-molecular weight polymers such as PEG 20000 may increase the melt viscosity to a value where droplets are not prone to deformation, while retaining suitable rheological properties of the molten mass to allow continuous droplet formation (Vervaeck et al., 2014; Vervaeck, 2015b). Incorporation of the active compound may also hinder the formation of uniform spherical particles as stated by Vervaeck (Vervaeck, 2015b).

Prilling based on melting, droplet generation and subsequent solidification into spheres was until now explored as a technique for production of multiple unit sustained release dosage forms. In the next examples the potential of this manufacturing method in the pharmaceutical field is outlined. Pivette et al. employed prilling as a technique to produce spheres containing an antiepileptic compound as a model drug (33%) and glyceryl behenate and paraffin wax mixture 1:1 as matrix former. Prilling was performed through vibrational nozzles and droplets were successfully cooled in a prilling tower. Uniform prills with a mean particle diameter of 400 μm and a narrow size distribution were obtained, which enabled 24 hour extended release of the model drug. Studies revealed that matrix remained intact during the dissolution and that drug delivery was governed by protrusion of the media through the API crystal network (percolation threshold) and subsequent drug diffusion through the formed channels (Pivette et al., 2012). Vervaeck et al. explored prilling as a manner of producing spherical particles based on metoprolol tartrate and fatty acids (behenic or stearic acid). Uniform spherical particles (2.4 mm) with a mainly amorphous drug homogenously dispersed through the carrier were obtained by application of the Prilldrop® device. Increasing the drug amount (from 10 to 40%) increased the viscosity of the melts and required higher pressure for material transport and also provided faster drug release due the higher hydrophilicity and fraction of soluble matter. Prills based on both fatty acids provided sustained drug release mainly by diffusion. Particles formulated with behenic acid resulted in as lower pattern compared to the ones containing stearic acid due to the longer acid chain and higher hydrophobicity of behenic acid. Dissolution results indicated that drug release from behenic acid matrices was susceptible to pH and ionic strength. Phosphate buffer salts ionized the carbonyl groups of the fatty acid, making the matrix less hydrophobic. Increasing the ionic strength of the phosphate buffer reduced the drug delivery rate due to interaction of the negatively charged carboxylic groups of the fatty acid and the positively charged ions of the buffer. Drug release increased after storage at 40 °C due to a transition of metoprolol tartrate from its amorphous to a crystalline form. In-vivo studies on dogs revealed similar bioavailability after oral administration of prills based on 30% drug and 70% behenic acid and a commercially available metoprolol tartrate extended release tablet (Vervaeck et al., 2013). Vervaeck et al. further investigated prilling as technique for obtaining fixed dose combination of extended release metoprolol tartrate (MPT) and immediate release hydrochlorothiazide (HCT). This study showed that the incorporation of 1-10% PEG 10000 in a mixture containing MPT and behenic acid affected the sustained release properties of the matrices, whereby the dissolution rate increased using a higher PEG content. Prolonged drug delivery did not depend on molecular weight of PEG when 10% of polymer was used, while drug delivery increased using higher molecular weight PEG due to the inhomogeneous distribution of PEG at polymer levels of 5%. Incorporating HCT (10%) in prills containing 70% PEG (type 4000 or 6000) and 20% fatty acid (behenic or stearic) gave immediate drug release within 1 hour. Incorporating 20% of fatty acids in the PEG formulation was found as a good way to decrease the viscosity and improve the material flow of the HCT/PEG mixture. MPT and HCT were both incorporated into prills in an amorphous form. Storage of immediate release prills increased the PEG crystallinity, while storage of extended release prills induced transformation of MPT from the amorphous to a crystalline form. However, these changes did not affect drug release outcome. In-vivo studies showed a similar bioavailability of HCT from immediate release pellets with a reference product. However, the extended release prills enhanced the bioavailability of MPT compared to a reference product, mainly due to higher susceptibility of extended release prills towards the hydrodynamic stress induced in the GIT (Vervaeck et al., 2014). Aleksovski et al. (2016) developed extended release multiple-unit drug delivery systems based on metoprol tartrate (20%-40%) as highly soluble model drug and either glyceryl behenate or glyceryl palmitostearate as ma-

trix former (80%-60%). Mini-matrices were produced by three different techniques: prilling, HME and compression of mini-tablets (from milled extrudates). Results pointed out that HME and compression of granules arerobust and reproducible techniques when producing matrices in all drug-glyceride ratios. Prilling was applicable only when a lower concentration of drug (20%) was included in the formulation. Increasing the drug content up to 30% or 40% resulted in a higher melt viscosity which tended to block the nozzles mounted in the prilling device. Increasing the drug content from 20 to 40% in case of extrudates and mini-tablets resulted in a faster release rate due to a higher hydrophilicity of the system and more leaching of the API from the matrix via diffusion. Matrices containing 20% API load were chosen for further evaluation due to their slow but complete drug delivery within 24 hours. Increasing the matrix size from 1.4 mm to 2 mm in case of prills and from 3 mm to 5 mm height in case of extrudates provoked a slower drug delivery due to the increase in diffusion pathway and reduction of contact surface area. Storage of glyceryl behenate and glyceryl palmitostearate matrices at 40 °C induced significant changes in the drug delivery process which could be linked to the changes in the solid state properties of the glyceride. Such changes in release pattern and solid state were also observed for matrices based on glyceryl palmitosterate after storage at room conditions. This glyceride compared to glyceryl behenate was more affected to changes of the pH of the dissolution medium and to the presence of biorelevant compounds in the medium. Glyceryl palmitostearate is more prone to be affected by pH and biorelevant compounds (mainly vialipolysis) due to its higher acid value and shorter fatty acid chains, respectively, compared to glyceryl behenate. In case of glyceryl behenate only the prilled samples showed a faster drug release in biorelevant medium. This suggested that smaller glyceride particles with larger surface area and central void are more affected by the endogenous compounds causing lipid digestion. As for the influence of processing technique on drug release, processing glyceryl palmitostearate by the three techniques gave different drug profiles, whereas the release from all glyceryl behenate matrices was characterized by a square root of time release profile, independent of the manufacturing technique used to prepare these prills. (Aleksovski et al., 2016).

Conclusion

Implementation of novel innovative technologies in the pharmaceutical field is essential in order to obtain medicines with added value and also in terms of coping with the trends of continuous manufacturing based on PAT and Design space. Scientists have recognized the potential of hot-melt extrusion and prilling as promising processes for production of different types of solid oral dosage forms.

By careful selection of suitable active compounds and excipients with different properties and by profound understanding of the equipment and process features hot melt extrusion was successfully employed as a manufacturing method of single and multiple-unit drug delivery systems which may offer modified release, increased bioavailability and taste masking. Further detailed studies are still required in terms of understanding thermal behavior and solid state transitions of extruded materials, influence of process parameters, as well as determining the properties and stability of obtained products. By implementation of the new knowledge gained for hot-melt extrusion, this technique will obtain an even stronger scientific background and thus its potential could be easily recognized by the pharmaceutical industry.

Prilling of molten masses into uniform spherical particle is suitable, robust and simple alternative for production of multiple-unit drug delivery systems. However, its application in the pharmaceutical sector is still in its infancy. Only a limited number of studies deal with prilling and its application for the production of immediate and extended release systems. Contrary to hot-melt extrusion further basic studies on equipment, process and material requirements are essential to ensure a better implementation of this process for the design and development of solid oral dosage forms.

From all the reviewed materials a conclusion could be drawn that both hot-melt extrusion and prilling are viable approaches for dealing with the current challenges of the pharmaceutical industry. Therefore these techniques represent a rich field for further scientific studies which will strengthen the position of HME as contemporary manufacturing technique and outline prilling as a serious candidate for the new manufacturing concept introduced in the contemporary pharmaceutical production.

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Резиме

Екструзија со топење и стврднување на капки растопен материјал како современи и ветувачки техники во производството на цврти орални дозирани форми базирани на цврти дисперзии без употреба на растворувачи

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Клучни зборови: ескрузија со топење, прилинг, сврсти орални дозирани форми, модифицирано ослободување, биорасположливост, опрема, прикривање на вкус.

Екструзијата со топење и стврднувањето на капки растопен материјал (прилинг) добиваат на значење како континуирани постапки кои немаат потреба од растворувачи и можат да се користат во производството на цврти орални дозирани форми со додадена вредност. Овие техники се базираат на вградување на активна компонента во растопен носач и последователно стврднување на таквата смеса при што настанува цврста дисперзија. Овој труд дава преглед врз овие две техники од аспект на разбирање на нивните основи, карактеристиките на расположливата опрема, својствата на материјалите кои можат да бидат употребувани како и нивната примена при развојот на цврсти орални дозирани форми. Различни научни истражувања укажуваат дека екструзијата со топење и прилингот се едноставни, робустни и континуирани процеси во производството цврсти матрикси кои може понатаму да се користат како дозирани форми. Разбирање на технолошкиот концепт заедно со мудар избор на соодветни материјали се круцијални чекори во стабилна изведба на овие техники и добивање на квалитетен краен производ. Екструзијата со топење е докажана како соодветн процес за производство на дозирани форми со модифицирано ослободување, дозирани форми кои овозможуваат прикривање на непријатниот вкус на различни компоненти, како и дозирани форми кои нудат подобрена растворливост на активни компоненти со слаба растворливост. Прилинг техниката досега е употребувана само за производство на повеќе-единечни дозирани форми со непосредно и пролонгирано ослободување. Идни истражувања наменети за разбирање и понатамошен развој на оваа техника а со тоа и на цврсти дозирани форми се неопходни со цел целосна имплементација на прилингот во фармацевтската сфера.