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Review article

Melt extrusion: from process to drug delivery technology

Jörg Breitenbach*

Soliqs, Abbott GmbH and Co. KG, Ludwigshafen, Germany

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Abstract

Starting from the plastic industry, today melt extrusion has found its place in the array of pharmaceutical manufacturing operations. This article reviews the process technology with regard to the set up and specific elements of the extruder as well as its application. Melt extrusion processes are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. As a specific area the manufacture of solid dispersions, in particular, solid molecular dispersions using the melt extrusion process is reviewed. Melt extrusion is considered to be an efficient technology in this field with particular advantages over solvent processes like co-precipitation. Potential drawbacks like the influence of heat stress and shear forces on the drug active have been overcome in a number of examples with drugs of different chemical structure. Examples of suitable excipients and recent findings like self-emulsifying preparations are presented. The article concludes with a number of published examples of melt extrudates applying the principle of solid molecular dispersions. Improved bioavailability was achieved again demonstrating the value of the technology as a drug delivery tool. © 2002 Published by Elsevier Science B.V.

Keywords: Melt extrusion; Solid dispersion; Solid molecular dispersion; Extruder; Bioavailability; Solubility

1. Introduction

Industrial application of the extrusion process dates back to the 1930's [1]. One can therefore consider the extrusion process as being a well elaborated manufacturing technology with a plethora of different technical solutions already available in other fields. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through die under controlled conditions [2]. Extrusion may be operated as a continuous process, which affords a consistent product flow ideally at relatively high throughput rates.

An extruder consists of two distinct parts: a conveying system which transports the material and sometimes imparts a degree of distributive mixing, and a die system which forms the materials into the required shape. Extrusion may be broadly classified into molten systems under temperature control or semisolid viscous systems. In molten extrusion, heat is applied to the material in order to control its viscosity, to enable it to flow through the die. Semisolid systems are multiphase concentrated dispersions containing a high proportion of solid mixed with a liquid phase [3].

Solid molecular dispersions of drugs in a matrix fit the molten systems especially as the fusion method in polymeric matrices has been applied to achieve such specific distributions of drugs. Generally, solid dispersions of drugs with poor solubility revealed remarkably higher bioavailability [4,5]. Less drug material may be applied and potentially a lower degree of variability in bioavailability are obvious advantages [6]. With the recent advent of high throughput screening and the growing specificity for given receptors poorly soluble drugs present a frequent and growing challenge to formulation scientists [7,8].

Solid dispersions of drugs therefore fulfill the prerequisites of drug delivery systems being designed to:

increase the active agent bioavailability,
reduce side effects,
increase the duration of the drug action in the body.

At the same time, extrusion represents an efficient manufacturing technology required to disperse drugs in a melt up to a true molecular solution of the active agent in the matrix. It is a striking example of a technology transfer establishing a new technology life cycle curve.

The most relevant technologies for the manufacture of solid dispersions are hot spin mixing [9], embeddings by means of spray drying [10], co-evaporation, co-precipitation [11], freeze-drying [12] and roll-mixing or co-milling [13,14].

* Soliqs Abbott GmbH and Co. KG Knollstrasse 50, D 67061 Ludwigshafen, Germany. Tel. : + 49-621-589-3555; fax: +49-621-589-3666.
E-mail address: joerg.breitenbach@abbot.com (J. Breitenbach).

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An indication that life cycle management is a key driver for the melt extrusion technology is the remarkable amount of publications in the patent literature.

2. Melt extrusion: the process technology

2.1. General remarks

With regard to pharmaceuticals, most systems extruded today consist of particles dispersed in a matrix. Although consideration is given to the manufacture of pure thermoplastics, the main emphasis is still on paste extrusions [15]. These differ in the fact that a connective matrix is present between solid particles. The relative position of solid and liquid can change during the various stages of the extrusion process, and hence produce effects different from those associated with single-phase systems like a molecular distribution of a drug in a polymeric matrix. In the latter, the matrix acts as a real solvent for the drug. Ideally, such systems are supposed to have a single-phase over a wide range of solubility of the drug in the polymeric matrix.

The various types of extruders have a common feature of forcing the extrudate from a wider cross-section through the restriction of the die. The theoretical approach to understand the system, is therefore, generally associated with dividing the process of flow into four sections:

feeding of the extruder,
conveying of mass and entry into the die,
flow through the die,
exit from the die and down-stream processing.

These four sections drive considerations of different aspects like flow of powder, shear force, residence time and pressure, cooling rate and shaping.

Generally, the extruder consists of at least one rotating screw inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product (see Fig. 4).

Sometimes as much as 80% of the heat required to melt or fuse the material is supplied by the heat generated by friction as the material is sheared between the rotating screws and the wall of the barrel. Additional heat may be supplied by electric or liquid heaters mounted on the barrel. It is important to realize that residence time and pressure in the die area might have a significant impact on the impurity profile of the product [16].

Most commercial extruders have a modular design, providing a choice of screws or interchangeable sections which alter the configuration of the feed, transition, and metering zones. This makes it possible to modify the process to meet particular requirements, for example, from a standard to a high shear extrusion. Modified screw designs allow the extruder to perform a mixing role in addition to extrusion, so that the material can be blended into the extrudate or even dissolved (Fig. 1). The various screw and die designs available and practical considerations of thermoplastic extrusion are reviewed by Whelan and Dunning [17].

The extrusion channel is conventionally divided into three sections: feed zone, transition zone, and metering zone (Fig. 4). The starting material is fed from a hopper directly into the feed section, which has deeper flights or flights of greater pitch (Fig 2). This geometry enables the feed material to fall easily into the screw for conveying along the barrel. Pitch and helix angle determine the throughput at constant rotation speed of the screws. The material is transported as a solid plug to the transition zone where it is mixed, compressed, melted, and plasticized. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth while maintaining a constant thread pitch [18]. Both methods result in increased pressure as the material moves along the barrel. The melt moves by circulation in a helical path by means of transverse flow, drag flow, pressure flow, and leakage; the latter two mechanisms reverse the flow of material along the barrel. The space between screw diameter and width of the barrel is normally in the range of 0.1–0.2 mm.

The material reaches the metering zone in the form of a homogeneous plastic melt suitable for extrusion. For an extrudate of uniform thickness, flow must be consistent and without stagnant zones right up to the die entrance. The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity.

The twin-screw extruder has two agitator assemblies mounted on parallel shafts (Fig. 3). These shafts are driven through a splitter/reducer gearbox and rotate together with the same direction of rotation (co-rotating) or in the opposite sense and are often fully intermeshing. In such case, each agitator element wipes both the surface of the corresponding element on the adjacent shaft, and the internal surfaces of the mixing chamber. The agitators are said to be self-wiping, an arrangement that eliminates stagnation areas within the mixing chamber and ensures a narrow and well-defined residence time distribution. If the agitators are chosen not to intermesh, the arrangement comes close to a single-screw set up. In general, co-rotating shafts have better mixing capabilities as the surfaces of the screws move towards each other. This leads to a sharp change in mass flow between the screw surfaces [19]. As the screws rotate, the flight of one screw element wipes the flank of the adjacent screw, causing material to transfer from one screw to the other. In this manner the material is transported along the extruder barrel.

The twin-screw extruder is characterized by the following descriptive features:

Short residence time: The residence time in the twin-screw extruder in a typical extrusion process is of the order of up to 2 min.

Fig. 1. Screw and kneading elements.

Self wiping screw profile: The self wiping screw profile i.e. the flight of one screw wipes the root of the screw on the shaft next to it, ensures near complete emptying of the equipment and minimises product wastage on shutdown.
Minimum inventory: Continuous operation of the equipment coupled with the low volume of the mixing chamber load to reduced inventories of work in progress. This is important when processing valuable or potentially hazardous materials.
Versatility: Operating parameters can be changed easily and continuously to change extrusion rate or mixing action. The segmented screw elements allow agitator designs to be easily optimized to suit a particular application. Die plates can also be easily exchanged to alter the extrudate diameter and hence the spheroid diameter. This allows processing of many different formulations on a single machine, leading to good equipment utilization. Polymers with a wide range of viscoelastic and melt viscosities can be processed and even fine powders can be directly fed into the system (Fig. 3).

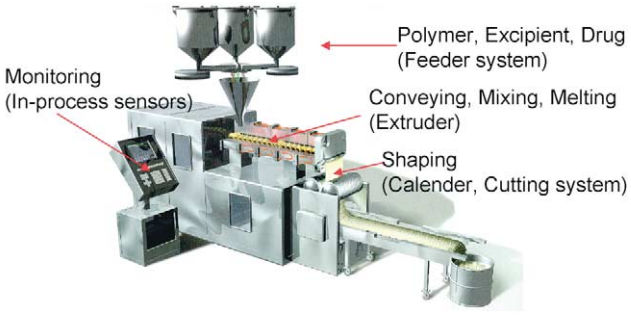

Fig. 3. Schematic presentation of a twin-screw extruder set-up.

Typical twin-screw laboratory scale machines have a diameter of 16–18 mm and a length of four to ten times

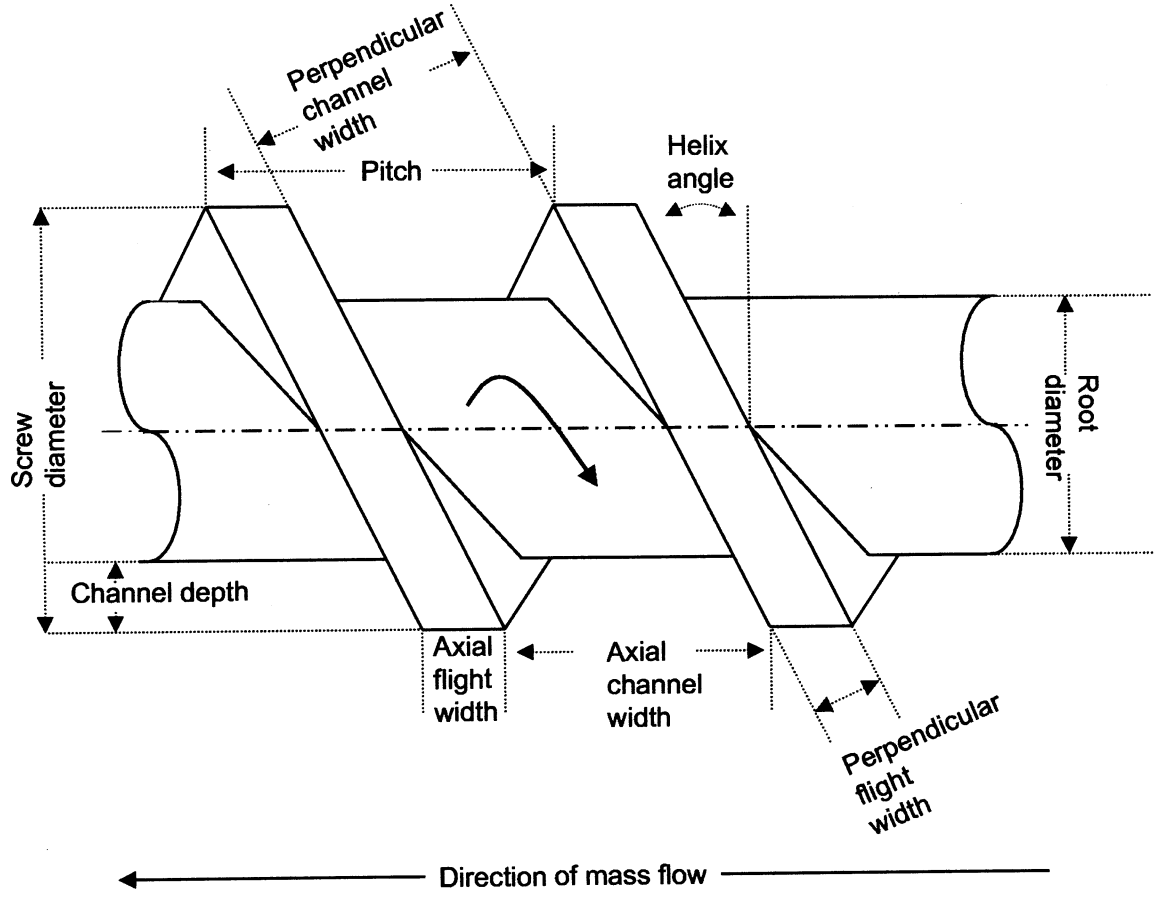

Fig. 2. Extrusion screw geometry.

the diameter. A typical throughput for such type of equipment is 0.5–3 kg/h.

As the residence time in the extruder is rather short and the temperature of all the barrels are independent and can be accurately controlled from low temperatures (30°C) to high temperatures (250°C) degradation by heat can be minimized. In addition oxygen and moisture may be excluded almost completely – an advantage for components sensitive towards oxidation and hydrolysis.

Extrusion processing requires close monitoring and understanding of the various parameters: viscosity, variation of viscosity with shear rate and temperature, elasticity, extensional flow, and slippage of the material over hot metal surfaces. Today extruders allow in process monitoring and control of parameters, such as the temperature in the extruder, head and die as well as pressures in extruder and die (Fig. 4) [20].

In particular, the molecular weight of polymeric matrices, their respective glass transition temperature and the sensitivity of the matrix or the drug towards heat and shear force create a basic set of data that qualify materials for the extrusion process. Additionally, miscibility can experimentally be determined with differential scanning calorimetry (DSC) and hot stage microscopy (HSM). In order to determine the miscibility of drug and excipient to predict if glass solutions are likely to form when drug and excipient are melt extruded, estimation of drug/excipient miscibility has been investigated. Melt extrusion of miscible components resulted in solid solution formation, whereas extrusion of an 'immiscible' component led to amorphous drug dispersed in crystalline excipient. In conclusion, combining calculation of solubility parameters with thermal analysis of drug/excipient miscibility has been successfully applied to predict formation of glass solutions with melt extrusion [21]. The challenge to determine the solubility of a drug in a polymeric matrix still needs to be addressed more adequately. A screening system based on a dimeric moiety of polyvinylpyrrolidone (PVP) has been presented which is capable of comparing the solubility in the liquid to that in the solid, in this case the polymer [22].

2.2. Industrial applications

2.2.1. General

Extrusion technology is extensively applied in the plastic and rubber industries, where it is one of the most important fabrication processes. Examples of products made from extruded polymers include pipes, hoses, insulated wires and cables, plastic and rubber sheeting, and polystyrene tiles. Plastics that are commonly processed by extrusion include acrylics (polymethacrylates, polyacrylates) and copolymers of acronitrile, cellulosics (cellulose acetate, propionate, and acetate butyrate), polyethylene (low and high density), polypropylene, polystyrene, vinyl plastics, polycarbonates, and nylons.

The process often is referred to as profile or line extrusion in which the shape of the extrudate like a tube is determined by the die. The extruded profile proceeds horizontally to the cutoff equipment, which controls its length. Profiles may be further processed, for example, as in film extrusion, blow molding, or injection molding [23].

In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the finished sheet. This is known as cast film. Plastic packaging film is also formed by blow extrusion, where tubular film is produced by the melt, usually vertically, through an annular-shaped slit die. The extruded tube is inflated by air to form a large cylinder. Blow molding refers to a process where the plastic is heated to a melted or viscous state and a section of molten polymer tubing is extruded usually downward from the die head into an open mold. The mold is closed around it, sealing it at one end. Compressed air is blown into the open end of the tube, expanding the viscous plastic to the walls of the cavity, thus

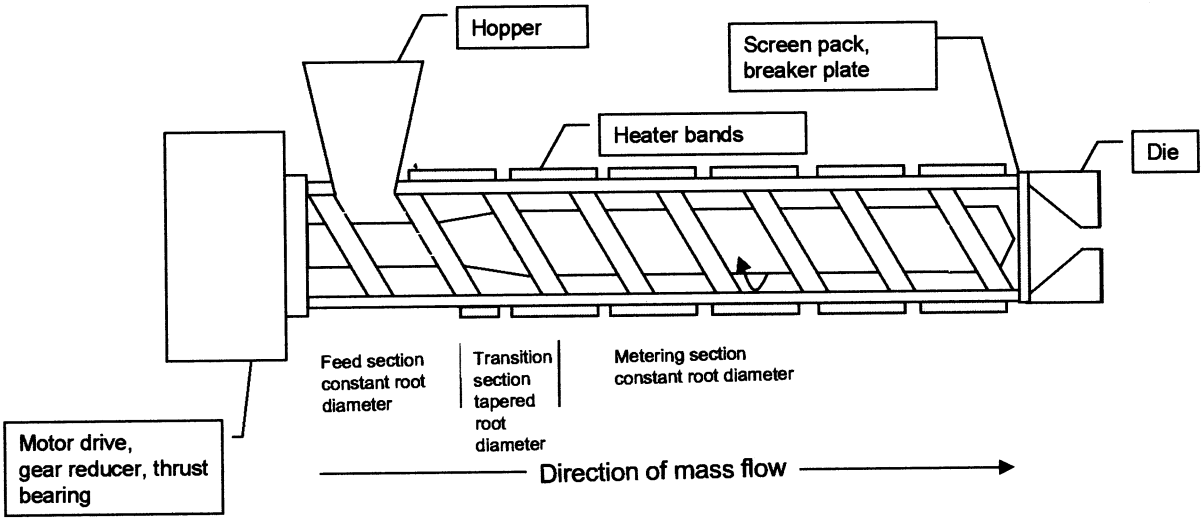

Fig. 4. Component parts of a single-screw extruder.

forming the desired shape of the container. During injection molding the molten plastic is not extruded but rather injected into a cavity mold at high pressure. The material cools in the cavity and solidifies. The mold is then opened and the article is removed.

Injection molding, has been used to manufacture tablets [24] and sustained release preparations [25]. In terms of feasibility, fast drug release, and economics, injection molding was considered suitable for drug solid dispersion or solution manufacture [26]. Injection molding has been exploited for its potential to manufacture sophisticated bilayer tubular systems for customized release profiles [27].

In the food industry extrusion has been utilized since 1930s for pasta production. A widely used versatile technique combines cooking and extrusion in a so-called extrusion cooker [28].

In the animal feed industry, extrusion is most commonly applied as a means of producing pelletized feeds [29]. The manufacture of implants by extrusion or injection molding is another field of application in the veterinary field.

The need to formulate drugs with poor solubility is not only limited to the pharmaceutical field. Fast dispersing PVP melt extrudates of poorly soluble active agents as molecular dispersions are marketed in the crop protection field [30].

2.2.2. Application in the pharmaceutical industry

The most important application of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape, and density, containing one or more drugs [31]. The process involves a preliminary stage in which dry powders, drug, and excipients are mixed by conventional blenders, followed by addition of a liquid phase and further mixing to ensure homogeneous distribution. The wet powder mass is extruded through cylindrical dies or perforated screens with circular holes, of typically 0.5–2.0 mm diameter, to form cylindrical extrudates [32]. In the large-scale manufacture of suppositories and pessaries extrusion rather refers to forcing the material through a capillary die [33,34].

Melt extrusion for the manufacture of pellets [35] had revealed the potential for controlled release of polymer-embedded drugs and limitations. Pioneering work in the field employing the melt extrusion process as a manufacturing tool was performed by Doelker [36]. Typically, a co-rotating twin-screw configuration is used in most of the published studies. The equipment for the manufacture of solid dispersions has been described more precisely by Nakamichi [37,38].

The second core element of the integrated technological system is the device to shape on-line the thermoplastic strand leaving the extruder [39]:

(a) Calendering, in which the molten strand is forced between two calender rollers, thus producing films, flakes or sheets which may already contain single tablet cores.

(b) Pellet-forming, which may, for example, be a rotating knife cutting spaghetti-like extruded strands.

2.2.3. Regulatory aspects

Oral pharmaceutical products from the melt extrusion process have been approved in the USA, European and Asian countries. The process technology lends itself to comprehensive documentation, thus satisfying regulatory authorities. It is a major advantage that extrusion is a mature engineering technology. As a process it provides many parameters, such as feeding rate, segmental temperatures and pressure or applied vacuum, which can be monitored on-line with local meters and sensors. Such data contribute to the comprehensive documentation and the quality of production lots and may finally simplify quality control.

3. The drug delivery technology

3.1. Introduction

Melt extrusion may be applied to disperse drugs in a given matrix down to the molecular level, e.g. to form a true solution. It is the convenience of the technology that gives new hope to the glass or solid solution approach as a delivery system for poorly soluble drugs. The use of melts in order to obtain solid molecular dispersions, e.g. glass or solid solutions, is well known to the expert and the essential advantage of a melt process in this domain is its solvent-free formation of such dispersions [40]. Since with solvent processes there are various problems relating to their use (environmental pollution, explosion-proofing and residual organic solvent) and measures to counteract these problems are desirable [41].

The melt extrusion process is capable of handling active agents of different particle sizes as well as amorphous solids or other polymorphic forms leading to the same product. Basically, solid dispersion systems can be divided into six different categories (Fig. 5) [42].

Sekiguchi and Obi were first to report the melting or fusion method [43]. In 1974 solid dispersions of drugs were described as: "… a relatively new field of pharmaceutical technique and its principles play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs" [44].

When we look at the market of pharmaceutical products today solid dispersion systems, in particular, solid molecular dispersions are still found to be neglected. Only a few ever made it to the market including a griseofulvin–polyethyleneglycol-dispersion (Gris-PEG® marketed by Wander), Cesamet® a nabilone-PVP (polyvinyl pyrrolidone) preparation (marketed by Lilly) [45] as well as a formulation of troglitazone (Rezulin®) marketed by Parke-Davis which had to be withdrawn from market for toxicology related issues of the drug. Several implants containing

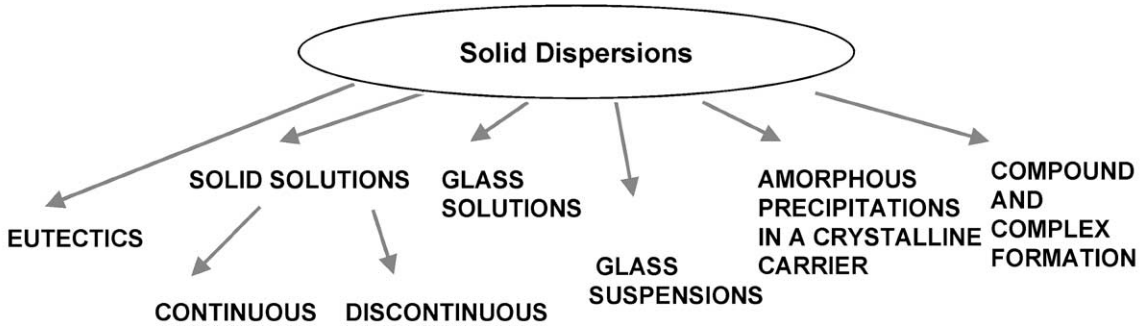

Fig. 5. Categories of solid dispersions.

LHRH agonists for parenteral use have become commercially available, such as goserelin (Zoladex®) or buserelin (Depot–Profact®) embeddings in poly(lactide-co-glycolide) (PLGA) [46].

The troglitazone formulation in PVP was actually manufactured by melt extrusion [47]. Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinylacetate (EVA) co-polymers. Based on this technology, two controlled release systems Implanon® and NuvaRing®; have been developed [48].

Problems limiting the commercial application of solid dispersions involve mainly the method of preparation, reproducibility of physicochemical properties, formulation into dosage forms, the scale up of manufacturing processes, and the physical and chemical stability of drug and vehicle [49].

A matter of uncertainty rarely addressed is the analytical differentiation of amorphous embeddings in crystalline carriers compared to a true solid solution, where the drug is molecularly dispersed in the carrier. The same holds true for the amorphous embedding in a glassy carrier compared to a glass solution. The term solid molecular dispersion differentiates from amorphous embeddings [50]. Solid molecular dispersion summarizes solid and glass solution irrespective of the nature, e.g. the molecular weight, of the solvent or solute.

Two major factors that stabilize solid molecular dispersions are intermolecular interactions [51–53] between the drug and the carrier and the viscosity of the carrier [54]. Glass transition temperature has long been seen as the predominant factor governing the physical stability of solid dispersions. However, this concept only holds for true solid molecular dispersions above their saturation limit. Within solid amorphous dispersions, the mobility of the active molecule is already given in the amorphous phase of the active itself possibly leading to recrystallization processes [55]. In the meantime investigations have shown that direct linear correlations between glass transition temperature and recrystallization tendency are rarely given. The solubilizing and stabilizing effects of the carrier systems' intermolecular interactions are often of far greater importance for physicochemical stability [56–59].

The mechanisms of drug release from solid dispersions in water-soluble polymers has been reviewed recently [60]. Because of surface activity of carriers used, complete dissolution of drug from melt extruded solid dispersions can be obtained without the need for further pulverization, sieving and mixing with excipients [61]. The effect of the molecular weight of the matrix polymers on the dissolution profile has been described with special respect to solid dispersions and solid molecular dispersions [62].

These findings contribute to the field of melt extrusion as the molecular weight and other characteristics of a polymeric carrier such as crystallinity and hydrogen bonding, vice versa pre-determine the manufacturing conditions in the extrusion process.

3.2. Application of melt extrusion as drug delivery technology

The breakthrough was achieved by the availability of a great variety of pharmaceutically approved carrier systems [63]. Such carrier systems include PVP [64] or its co-polymers [65], poly(ethylene-co-vinylacetate) [66], polyethylene glycol (PEG) [67], cellulose-ethers [68], and acrylates [69]. The properties of polyethylene oxide (PEO) as a drug carrier in melt extrusion with the aim to obtain chlorpheniramine maleate matrix tablets was examined by McGinity [70]. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic poly(esters) like poly(lactide) (PLA), poly(glycolide) (PGA), and the copolymer of lactide and glycolide, poly(lactide-co-glycolide) (PLGA) have been used in extrusion. Starch and starch derivatives have been applied along with [71] low molecular weight excipients like sugars and sugar alcohols and waxes [72]. The basic prerequisite for the use in melt extrusion is the thermoplasticity of the polymers or that of the respective formulations.

Long residence time and high glass transition temperature (T_g) resulting in high process temperatures have often been described as potential drawbacks of the melt extrusion process. The comparison of the influence of two different implant manufacturing techniques, extrusion and injection molding, on the in vitro degradation of the polymeric matrix

of polylactic acid (PLA) was studied. Both kinds of implants were loaded with a somatostatin analogue. It was shown that both molecular weight and polydispersity decreased after extrusion or injection molding. This decrease was more pronounced with the latter technique possibly due to an increased residence time [73]. Repka et al showed that a thermally labile drug, hydrocortisone, could be successfully incorporated into hydroxypropylcellulose (HPC) films produced by melt extrusion [74].

Apart from distinct dosage forms or tailored release profiles melt extrusion offers the chance to circumvent the problem of polymorphic forms with different solubilities, the possibility to start from different particle sizes and a possible reduction of tablet size. Examples have shown that more favorable polymorphic forms may be stabilized on incorporation into PVP [75,76]. Melt extrusion with pharmaceutical actives having a low melting point has also been described. Under such conditions the extrusion process may serve as an agglomeration step [77]. An example for a change in morphology, continuously introduced in the melt extrusion process, applied to alter the release characteristics has been presented by Gurny et al. [78]. In order to influence the release of an extrudate a 200 μm thick layer on the extrudate surface was introduced while extruding.

In addition, implants [79,80], stents [81], oral dosage forms [82], bioadhesive ophthalmic inserts [83], topical films [84], and effervescent tablets [85] have been developed using the melt extrusion process.

3.3. Solid dispersions with melt extrusion technology

Melt extrusion is a significant step forward to cover the technology related issues and makes the solid molecular dispersion approach a viable option. The viability of melt extrusion technology for the production of thin, flexible, acrylic films for topical drug delivery has been investigated by Aitken-Nichol et al. ([86]). Lidocaine HCl was able to plasticize the acrylic polymer and the drug was completely dispersed at the molecular level in the extruded films. Solubilized drug molecules were shown to plasticize the polymer by increasing the average polymer chain spacing [86].

A contraceptive vaginal ring containing etonogestrel and ethinyl estradiol has been prepared by melt extrusion. Coaxial fibers have been produced with varying steroid concentrations in the polymer and the release has been studied. The powder mixtures were blended in a twin-screw extruder. The polymer melted and the steroids completely dissolved in the polymer. After leaving the extruder, the strands were cooled to room temperature and granulated using a strand granulator. For the preparation of the coaxial fibers, a co-extrusion installation was used. The installation consisted of two single-screw extruders that are connected to a spinning block. The two extruders were used to melt the core and membrane polymer at temperatures above 110°C. The molten polymers were delivered to two gear pumps, which assure an accurate flow of both polymers to the spinneret. Subsequently, the membrane and core polymers were combined in a spinneret, thereby forming the coaxial fiber [87].

A floating sustained release dosage form composed of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate was prepared using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of the die outlet, and by controlling the barrel temperature, a puffed dosage form with very small and uniform pores were obtained. It was shown that the puffed dosage form, consisting of enteric polymer prepared using the twin-screw extruder, was very useful as a floating dosage form that was retained for a long period in the stomach [88].

Sustained release formulations of isosorbide nitrates with polyvinylacetate have been developed using melt extrusion as manufacturing process. The in vitro release profiles indicate that even at low amounts (w/w) of the polymer the sustaining action of the polymer is sufficient to delay the release [89]. Formulations and dosage forms for poorly soluble drugs applying melt extrusion technology have been evaluated in a number of cases.

Underlining the economic importance of the melt extrusion process Ghebre-Sellassie[90] examined the use of different polymers revealing that hydroxypropyl cellulose may be a better water-soluble polymer compared to PVP for poorly soluble drugs. X-ray powder diffraction studies suggested that the drug substance mostly existed in the crystalline state truly representing a crystalline solid dispersion. Extrusion as a way of manufacture is mentioned and a variety of examples using melt processes are given[90].

A number of glass solutions of poorly soluble drugs have been developed using the melt extrusion process with a drug load ranging from 30 to 60% with real time stability up to 9 years. During this time period no crystallization could be detected by means of X-ray powder diffraction or differential scanning calorimetry [91]. It seems obvious, that stability of solid molecular dispersions is achieved when the solubility of a given drug in the carrier is not exceeded. By definition such systems are thermodynamically stable as their stability is related to the solubility of the active and not to the viscosity of the matrix as in supersaturated systems which are kinetically stabilized.

Glass solutions of a lipophilic drug substance by melt extrusion technology which on dissolution forms nanoparticles and thereby increases the dissolution kinetics have been presented recently [92]. PVP or a vinylpyrrolidone–vinylacetate copolymer have been studied together with different surfactants.

17-Estradiol hemihydrate as a poorly water-soluble drug was improved with respect to its solubility and dissolution rate by melt extrusion. Different compositions of excipients such as PEG 6000, PVP or a vinylpyrrolidone–vinylacetate-copolymer were used as polymers and Sucroester®WE15 or Gelucire® 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate when compared

to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17-Estradiol, 50% PVP and 40% Gelucire™ 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets [93].

Amorphous polysaccharide matrices determining the release rate of melt extruded dispersions have been examined by Rein et al. [94]. Carbohydrate based glassy matrices which are stable in the glassy state at ambient temperatures may be prepared by the use of aqueous plasticizers with melt extrusion. Such glassy matrices are useful for the encapsulation of drugs and flavoring agents [95].

Foster et al. melt extruded indomethacin, lacidipine and tolbutamide with PVP. Indomethacin samples remained amorphous on storage as demonstrated by X-ray powder diffraction (XRPD) and temperature modulated differential scanning calorimetry (TMDSC). For lacidipine and tolbutamide low crystallinity levels were detected which, at estimated 7% crystallinity, decreased the dissolution rate significantly. The presence of significant hydrogen bonding (as indicated by the deviation of the experimental from the theoretical glass T_g values) may decrease uptake of moisture and restrict plasticization of the matrix. However, lacidipine recrystallized even when T_g was well above the storage temperature [96].

Along with literature describing the in vitro performance of solid dispersions a number of melt extruded solid dispersions have been examined in humans.

The antiretroviral agent loviride has been melt extruded to a solid molecular dispersion in HPMC and showed remarkably lower food-effect compared to capsules [97].

Further, the extrusion process has been applied in order to combine a sparingly water-soluble drug compound, a cyclodextrin, and a physiologically tolerable water-soluble organic polymer [98].

Antifungal compositions of itraconazole were prepared as solid dispersions from the melt extrusion process. In a limited number of volunteers the melt extruded tablet gave an area under the curve (AUC) of itraconazole in the fasted state that was 2.3 times the area under the curve of the marketed reference capsule [99].

Melt extruded dispersions of ibuprofen were compared to the lysinate salt of ibuprofen in healthy volunteers. Bioequivalence was demonstrated with the relevant parameters AUC and C_{max}. Also, the t_{max} as a measure for onset proved to be equivalent with 0.5 h for test and reference [100].

4. Conclusions and outlook

Melt extrusion technology today represents an efficient pathway for the manufacture of drug delivery systems. Resulting products are mainly found amongst semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms covering oral, parenteral and topical applications. In addition, the physical state of the drug in the melt extruded formulations reaches from simple crystalline embeddings, mainly in the field of sustained release applications, to amorphous or molecularly dissolved stages. Compared to solvent processes aiming at solid molecular dispersions melt extrusion offers a promising alternative. The possible use of a broad selection of excipients from high molecular weight polymers to low molecular weight additives like sugar alcohols, waxes or surfactants opens a field of numerous combinations for formulation research.

Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. This is where process engineering comes into play. The design of screw assemblies and extruder dies are two major areas, which have significant impact on the degradation of drugs and excipients. As the residence time is rather short compared to conventional processes like sterilization, even drugs known to be sensitive to elevated temperatures have been processed successfully. In addition the exposure to oxygen in the extrusion channel is limited.

Work in the field is increasing and the literature published reveals interesting new aspects like in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion.

Unlike other delivery systems, most of which consist of a random dispersion of a drug in a matrix, extrusion technology may be used to place exact amounts of active drug in well-defined layers of micrometer range thickness. In addition, the processing of the polymer determines not only the design of the device but it influences its morphology, namely its microporous structure, polymeric chain orientation and crystallinity to a high degree.

Further, it remains to be seen whether the intense interaction in the melt can be used to form complexes with rather sensitive molecules like peptides and proteins in order to stabilize such structures.

References

[1] Ch. Rauwendaal, Polymer Extrusion, Hanser Publishers, München, Wien, New York, NY, 1986 pp. 20–55.
[2] A. Echte, Handbuch der Technischen Polymerchemie, VCH Verlagsgemeinschaft, Weinheim, 1993 pp. 74–83.
[3] Z. Tadmor, I. Klein, Engineering Principles of Plasticating Extrusion, Van Noostrand Reinhold, New York, NY, 1970 pp. 152–158.
[4] C. Leuner, J. Dressman, Improving drug solubility for oval delivery using solid dispersions, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[5] J.L. Ford, The current status of solid dispersions, Pharm. Acta Helv. 61 (1986) 69–88.
[6] M.K. Vadnere, Coprecipitates and melts, in: J. Swarbrick, J.C. Boylan (Eds.), Encylopedia of Pharmaceutical Technology, Marcel Dekker, New York, NY, 1990, pp. 337–352.
[7] S. Yee, In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small intestinal) absorption in man – fact or myth, Pharm. Res. 14 (1997) 763–766.
[8] H. van De Waterbeemd, D.A. Smith, K. Beaumont, D.K. Walker,

Property-based design: optimization of drug absorption and pharmacokinetics, J. Med. Chem. 44 (2001) 1313–1333.
[9] M. Dittgen, S. Fricke, H. Gerecke, H. Osterwald, Hot spin mixing: a new technology to manufacture solid dispersions, Pharmazie 50 (1995) 225–226.
[10] J.-Y. Jung, S.-D. Yoo, S.-H. Lee, K.-H. Kim, D.-S. Yoon, K.-H. Lee, Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique, Int. J. Pharm. 187 (1999) 209–218.
[11] H. Sekikawa, T. Arita, M. Nakano, Dissolution behaviors and gastrointestinal absorption of phenytoin in phenytoin-polyvinylpyrrolidine coprecipitate. Chem. Pharm. Bull. 26 (1978) 118–126.
[12] H. Sekikawa, W. Fukyda, M. Takada, K. Ohtani, T. Arita, M. Nakano, Dissolution behavior and gastrointestinal absorption of dicumarol from solid dispersion systems of dicumarol-polyvinylpyrrolidine and dicumarol-beta-cyclodextrin. Chem. Pharm. Bull. 31 (1983) 1350–1356.
[13] Y. Nozawa, T. Mizumoto, F. Higshide, Roll-mixing of formulations, Pharm. Acta Helv. 60 (1985) 175–177.
[14] Y. Nozawa, T. Mizumoto, F. Higashide, Improving dissolution rate of practically insoluble drug kitasamycin by forcibly roll mixing with additives, Pharm. Ind. 8 (1986) 967–969.
[15] S.L. Rough, J. Bridgwater, D.I. Wilson, Effects of liquid phase migration on extrusion of microcrystalline cellulose pastes, Int. J. Pharm. 204 (2000) 117–126.
[16] J.P. Puaux, G. Bozga, A. Ainser, Residence time distribution in a corotating twin-screw extruder, Chem. Eng. Sci. 55 (2000) 1641–1651.
[17] T. Whelan, D. Dunning (Eds.), The Dynisco Extrusion Processors Handbook 1st ed., London School of Polymer Technology, Polytechnic of North London, London, 1988.
[18] P.S. Johnson, Developments in Extrusion Science and Technology, Polysar technical publication No. 72, Polysay Limited, South Sarnia, Ontario, 1982.
[19] M.H. Pahl, Dynamische Mischer für hochviskose Flüssigkeiten, Mischen von Kunststoffen, VDI-Verlag, Düsseldorf, 1983 p. 186.
[20] R.D. Shah, M. Kabadi, D.G. Pope, L.L. Augsburger, Physicomechanical characterization of the extrusion-spheronization process, Pharm. Res. 11 (1994) 355–360.
[21] A. Forster, J. Hempenstall, I. Tucker, T. Rades, Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis, Int. J. Pharm. 226 (2001) 147–161.
[22] J. Neumann, J. Breitenbach, W. Schrof, Confocal Raman spectroscopy: analytical approach to solid dispersions and mapping of drugs, Pharm. Res. 16 (1999) 1109–1113.
[23] H. Schott, Polymer science, in: A. Martin, J. Swarbrick, A. Cammarata (Eds.), Physical Pharmacy – Physical Chemical Principles in the Pharmaceutical Sciences, 3rd ed., Lea and Febiger, Philadelphia, PA, 1983, pp. 131–152 chap. 22.
[24] G. Cuff, F. Raouf, A preliminary evaluation of injection molding as a technology to produce tablets, Pharm. Technol. 6 (1998) 96–106.
[25] R. Hüttenrauch, Spritzgießverfahren zur Herstellung peroraler Retardpräparate, Pharmazie 29 (1974) 297–302.
[26] S. Wacker, M. Soliva, P. Speiser, Injection molding as a suitable process for manufacturing solid drug dispersion or solutions, J. Pharm. Sci. 60 (1971) 1281–1300.
[27] D. Bar-Shalom, Controlled release composition, Eur. Patent, 0,406,315, 1988.
[28] A. Senouci, A. Smith, P. Richmond, Extrusion cooking, Chem. Eng. 417 (1985) 30–33.
[29] E. Sebestyen, Flour and animal feed milling, 10 (1974) 24–25.
[30] D.J. Wedlock, G. DeLind van Wijngaarden, Fast dispersing solid PVP-containing crop protection formulation and process therefore, US Patent, 5,665,369, 1992.
[31] C. Vervaet, L. Baert, J.P. Remon, Extrusion–spheronisation – a literature review, Int. J. Pharm. 116 (1995) 131–146.
[32] K.H. Bauer, K.-H. Frömmimg, C. Führer, Pharmazeutische Technologie, 4, Aufl. Georg Thieme Verlag, Stuttgart, 1993 pp. 292–297.
[33] J. Anschel, H.A. Lieberman, Suppositories, in: L. Lachman, H.A. Lieberman, J.L. Kanig (Eds.), The Theory and Practice of Industrial Pharmacy, 2nd ed., Lea and Febiger, Philadelphia, 1976, pp. 234–245 (chap. 8).
[34] J.W. Hadgraft, Rectal administration, in: E.A. Rawlins (Ed.), Bentley's Textbook of Pharmaceutics, 8th ed., Baillière Tindall, London, 1977, p. 134 Chapter 25.
[35] N. Follonier, E. Doelker, E.T. Cole, Evaluation of hot-melt-extrusion as 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 (1994) 1323–1339.
[36] M. Doelker, M. Adel El-Egakey, M. Soliva, P. Speiser, Hot extruded dosage forms, Pharm.Acta Helv. 46 (1971) 31–52.
[37] K. Nakamichi, H. Yasuura, I. Shougo, Method of manufacturing solid dispersion, Eur. Patent 0,580,860, 1991.
[38] K. Nakamichi, H. Yasuura, H. Kukui, M. Oka, S. Izumi, T. Andou, N. Shimizu, K. Ushimaru, New preparation method of solid dispersion by twin srew extruder, Pharm. Tech. Jpn. 12 (1996) 715–729.
[39] J. Breitenbach, Feste Lösungen durch Schmelzextrusion – ein integriertes Herstellkonzept, Pharm. unserer Zeit 29 (2000) 1–5.
[40] C. Lefebvre, M. Brazier, H. Robert, A.M. Guyot-Hermann, Solid dispersions why and how? Industrial aspect, STP Pharma 4 (1985) 300–322.
[41] K. Nakamichi, H. Yasuura, H. Fukui, M. Oka, S. Izumi, T. Andou, N. Shimizu, K. Ushimaru, A process for the manufacture of nifedipine hydroxypropyl-methylcellulose phthalate solid dispersions by means of a twin-screw extruder and appraisal thereof, Yakuzaigaku 56 (1996) 15–22.
[42] W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 60 (1971) 1281–1302.
[43] K. Sekiguchi, N. Obi, Studies on absorption of entectic mixtures, Chem. Pharm. Bull. 9 (1961) 866–872.
[44] B.R. Hajratwala, Dissolution of solid dispersion systems, Aust. J. Pharm. Sci. 4 (1974) 101–109.
[45] D.W. Bloch, P.P. Speiser, Solid dispersions – fundamentals and examples, Pharm. Acta Helv. 62 (1987) 23–27.
[46] T. Kissel, Y. Li, F. Unger, ABA-triblock copolymers from biodegradable polyester A-blocks and hydrophilic poly(ethylene oxide) B-blocks as a candidate for in situ forming hydrogel delivery systems for proteins, Adv. Drug Del. Rev. 54 (2002) 99–134.
[47] J. Hempenstall, Latest developments in tablet and capsule formulation, European Continuing Education College, Master Classes in Solid Dosage Forms, London, 1997, pp. 1–14
[48] J.A.H. van Laarhoven, H. Vromans, Influence of supersaturation on the release properties of a controlled release device based on EVA co-polymers, Abstract Book, 7th European Symposium on Controlled Drug Delivery, Noordwijk aan Zee, Netherlands, 2002 pp. 133–135.
[49] A.T. Serajuddin, Solid dispersion of poorly water-soluble drugs: early promises problems subsequent and recent breakthroughs, J. Pharm. Sci. 88 (1999) 1058–1066.
[50] T. Matsumoto, G. Zografi, Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization, Pharm. Res. 16 (1999) 1722–1728.
[51] C. Doherty, P.J. York, Evidence for solid- and liquid-state interactions in a furosemide–polyvinylpyrrolidone solid dispersion, Pharm. Sci. 76 (1987) 731–737.
[52] L.S. Taylor, G. Zografi, Spectroscopy characterization of interactions between PVP and indomethacin in amorphous molecular dispersions, Pharm. Res. 14 (1997) 1691–1698.
[53] T. Matsumoto, G. Zografi, Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization, Pharm. Res. 16 (1999) 1722–1728.

[54] J. Breitenbach, Two concepts, one technology: controlled release and solid dispersion with Meltrex™, in: I. Ghebre-Selassie (Ed.), Modified Release Drug Delivery Technology, Marcel Dekker, New York, NY, 2002 (in press).
[55] B.C. Hancok, S.L. Shamblin, G. Zografi, Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures, Pharm. Res. 12 (1995) 799–806.
[56] E. Fukuoka, Glassy state of pharmaceuticals, Chem. Pharm. Bull. 37 (1989) 1047–1050.
[57] M.C. Etter, Hydrogen bond directed CO-crystallization and molecular recognition properties of diarylureas, J. Am. Chem. Soc. 112 (1990) 8415–8426.
[58] T. Hamaura, J.M. Newton, Interaction between water and poly(vinylpyrrolidone) containing polyethylene glycol, J. Pharm. Sci. 88 (1999) 1228–1233.
[59] L.S. Taylor, G. Zografi, Sugar–polymer hydrogen bond interactions in lyophilized amorphous mixtures, J. Pharm. Sci. 87 (1998) 1615–1621.
[60] D.Q.M. Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, Int. J. Pharm. 231 (2002) 131–144.
[61] G. Berndl, J. Breitenbach, J. Neumann, U. Reinhold, J. Rosenberg, C. Vollgraf, J. Zeidler, Polymer/drug-melt extrusion: control of drug release and morphology in pharmaceutical formulations, American Association of Pharmaceutical Scientists, Annual Meeting Abstracts, San Francisco, 1998, p. 296
[62] H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi, Application of the solid dispersion method to the controlled release of medicine, Chem. Pharm. Bull. 41 (1993) 933–936.
[63] H. Yuasa, T. Ozeki, Y. Kanaya, K. Oishi, Application of the solid dispersion method to the controlled release of medicine, Chem. Pharm. Bull. 41 (1993) 933–936.
[64] V. Tantishaiyakul, N. Kaewnopparat, S. Ingkatawornwong, Properties of solid dispersions of piroxicam in polyvinylpyrrolidone, Int. J. Pharm. 181 (1999) 143–151.
[65] G. Zingone, M. Moneghini, P. Rupena, D. Vojnovic, Characterization and dissolution study of solid dispersions of theophylline and indomethacin with PVP/VA copolymers, STP Pharm. Sci. 2 (1992) 186–192.
[66] N. Follonier, E. Doelker, E.T. Cole, Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials, J. Controlled Release 36 (1995) 243–250.
[67] B. Perissutti, J. Newton, M. John, F. Podczeck, F. Rubessa, Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form, Eur. J. Pharm. Biopharm. 53 (2002) 125–132.
[68] K. Yano, A. Kajiyama, M. Hamada, K. Yamamoto, Constitution of colloidal particles formed from a solid dispersion system, Chem. Pharm. Bull. 45 (1997) 1339–1344.
[69] A. Abd, A. El-Bary, A.S. Geneidi, S.Y. Amin, A.A. El-Ainan, Preparation and pharmacokinetic evaluation of carbamazepine controlled release solid dispersion granules, J. Drug Res. Egypt 22 (1998) 15–31.
[70] F. Zhang, J.W. McGinity, Properties of sustained-release tablets prepared by hot-melt extrusion, Pharm. Dev. Technol. 4 (1999) 241–250.
[71] D. Henrist, J.P. Remon, Influence of the process parameters on the characteristics of starch based hot stage extrudates, Int. J. Pharm. 189 (1999) 7–17.
[72] F. Ndindayino, C. Vervaet, G. Van den Mooter, J.P. Remon, Direct compression and moulding properties of co-extruded isomalt/drug mixtures, Int. J. Pharm. 235 (2002) 159–168.
[73] A. Rothen-Weinhold, K. Besseghir, E. Vuaridel, E. Sublet, N. Oudry, F. Kubel, R. Gurny, Injection-molding versus extrusion as manufacturing technique for the preparation of biodegradable implants, Eur. J. Pharm. Biopharm. 48 (1999) 113–121.
[74] M.A. Repka, T.G. Gerding, S.L. Repka, J.W. McGinity, Influence of plasticizers and drugs on the physical–mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion, Drug Dev. Ind. Pharm. 25 (1999) 625–633.
[75] T. Ozeki, H. Yuasa, Y. Kanaya, Application of the solid dispersion method to the controlled release medicine, Int. J. Pharm. 155 (1997) 209–217.
[76] A.L. Thakkar, C.A. Hirsch, J.G. Page, Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone a cannabinoid derivative, J. Pharm. Pharmacol. 29 (1977) 784–795.
[77] I. Huerner, P. Danz, W. Reinhard, J. Maasz, G. Frank, Thermal granulating process, Eur. Patent, 0,686,392, 1994.
[78] A.G. Sarraf, F. Barja, L. Quali, E.G. Sarraf, R. Gurny, E. Doelker, Effect of polymerorientation induced by melt extrusion on drug release, Proceedings of 28th international symposium on controlled release bioactive materials, San Diego, 2001, p. 1041
[79] C. Witt, K. Mäder, T. Kissel, The degradation swelling and erosion properties of biodegradable implants prepared by extrusion or compression moulding of poly(lactide-co-glycolide) and ABA triblock copolymers, Biomaterials 21 (2000) 931–938.
[80] A. Göpferich, Implants with phased release of medicaments, Eur. Patent, 0,868,171, 1996.
[81] R.P. Eury, Method of incorporating drugs into a polymer component of stents, Eur. Patent, 0,734,721, 1995.
[82] F. Ndindayino, D. Henrist, F. Kiekens, G. Van den Mooter, C. Vervaet, J.P. Remon, Direct compression properties of melt-extruded isomalt, Int. J. Pharm. 235 (2002) 149–157.
[83] V. Baeyens, V. Kalsatos, B. Boisrame, M. Fathi, R. Gurny, Evaluation of soluble bioadhesive ophthalmic drug inserts (BODI) for prolonged release of gentamicin: lachrymal pharmacokinetics and ocular tolerance, J. Ocul. Pharmacol. Ther. 14 (1998) 263–272.
[84] M.A. Repka, J.W. McGinity, Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion, J. Controlled Release 70 (2001) 341–351.
[85] J.R. Robinson, J.W. McGinity, Effervescent granules and methods for their preparation, U.S. Patent, 6,071,539, 1997.
[86] C. Aitken-Nichol, F. Zhan, J.W. McGinity, Hot melt extrusion of acrylic films, Pharm. Res. 13 (1996) 804–808.
[87] J.A.H. van Laarhoven, M.A.B. Kruft, H. Vromans, In vitro release properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring, Int. J. Pharm. 232 (2002) 163–173.
[88] K. Nakamichi, H. Yasuura, H. Fukui, M. Oka, S. Izumi, Evaluation of a floating dosage form of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate prepared using a twin-screw extruder, Int. J. Pharm. 218 (2001) 103–112.
[89] U. Münch, H. J. Mika, B. Eschermann, R. Schmidt, B. Sczepanik, Orally administred solvent free pharmaceutical preparation with delayed active substance release and a method of preparing the preparation, Eur. Patent, 0,552,227, 1990.
[90] I. Ghebre-Selassie, Solid pharmaceutical dosage forms in form of a particulate dispersion, Eur. Patent, 1,011,640, 1997.
[91] H.H. Grünhagen, Polymer/drug-melt extrusion: therapeutic and technological appeal, Pharm. Tech. Eur. 8 (1996) 22–28.
[92] J. Rosenberg, M. Degenhardt, J. Breitenbach, M. Mägerlein, G. Berndl, T. Hantke, Amorphous Embedding of a Lipophilic Drug Substance by Meltrex®-technology. Astract book 7th European Symposium on Controlled Drug Delivery, Noordwijk aan Zee, Netherlands, 2002 pp. 184–188.
[93] S. Hülsmann, T. Backensfeld, S. Keitel, R. Bodmeier, Melt extrusion-an alternative method for enhancing the dissolution rate of 17-estradiol hemihydrate, Eur. J. Pharm. Biopharm. 49 (2000) 237–242.
[94] J. Zeidler, J. Neumann, B. Liepold, J. Rosenberg, G. Berndl, C. Vollgraf, J. Breitenbach, Fast acting analgesic, US Patent, 6,322,816, 1997.
[95] M. Porzio, L. Popplewell, Encapsulation compositions, US Patent 5,603,971, 1993.

[96] A. Forster, J. Hempenstall, T. Rades, Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, J. Pharm. Pharmacol. 53 (2001) 303–315.
[97] L. Baert, C. Elvire, G. Verreck, Antiretroviral compositions with improved bioavailability, Eur. Patent, 0,872,233, 1997.
[98] R. Vandecruys, P. Gerebern, Pharmaceutical compositions comprising cyclodextrins, Eur. Patent, 0,998,304, 1997.
[99] L. Baert, C. Elvire, G. Verreck, D. Thone, Antifungal compositions with improved bioavailability, Eur. Patent 0,904,060, 1996.
[100] J. Zeidler, J. Neumann, B. Liepold, J. Rosenberg, G. Berndl, C. Vollgraf, US Patent 6,322,816, 1997.