1. Introduction

1.1. Opportunities and Challenges of Individual Dosing

Individual dosing of medicines is a key topic in paediatrics and geriatrics (Breitkreutz and Boos, 2007; Standing and Tuleu, 2005; Stegemann et al., 2010) as well as in personalised medicine (Florence and Lee, 2011; Ingelman-Sundberg et al., 2007).

The demand for flexible dosing has been investigated and most recently accessible systems and development approaches have been categorised according to their dose flexibility and expenditure (Wening and Breitkreutz, 2011). Recently, delivery devices for the administration of paediatric formulations have been reviewed and have been discussed by the European Paediatric Formulation Initiative (Walsh et al., 2011).

The repertory for individual oral dosing so far includes liquid drug formulations like suspensions or solutions as well as solid multiparticulate dosage forms like granules, pellets or (mini-)tablets. Measuring can be achieved via partition of monolithical forms or accumulation of multiple drug carriers (Wening and Breitkreutz, 2011).

Due to stability concerns or drug solubility, liquid oral dosage forms are frequently limited (Breitkreutz et al., 1999). Dosing devices like spoons, cups, or syringes for liquid drug formulations often fail in measuring appropriate doses (Griessmann et al., 2005; Sobhani et al., 2008; Tanner et al., 2014).

In contrast, solid monolithic dosage forms may provide a stable and easy dosing approach (EMA/CHPM, 2013) and the acceptance of uncoated mini-tablets as oral solid single dosage forms, for instance, was shown to be superior to syrup (Klingmann et al., 2013; Spomer et al., 2012). However, the number of dose-strengths needed to treat patients appropriately is increased by applying solid single dosage forms (Salunke et al., 2011).

One common strategy of dose adaption for peroral applications is the splitting of tablets. By means of divisible tablets a limited number of fixed parts may be administered (Kayitare et al., 2009). But this approach may involve difficulty of breaking, imprecise dosing, loss of drug-loaded mass, and potentially lead to the formation of potent dust (van Santen et al., 2002).

Due to these still existing challenges in individual dosing, innovative drug formulation concepts and novel devices or dispensing systems are needed. For the compliance of patients, acceptance as well as safe and easy handling of such devices, both from the patients' and caregivers' perspectives, were demanded (Salunke et al., 2011). Moreover, principal requirements in the field of pharmaceutics like dosage conformity and specified drug release properties, which have to be independent of the delivered individual dose, have to be taken in mind.

The superior target to overcome challenges of individual dosing would be the provision of one dosage form and one corresponding device which meet the requirements of all patient groups.

1.2. The Solid Dosage Pen

A novel dosing device, a "dosing stick for rod-shaped tablets", was patented in 2002 for the individual dosing of medicines for oral administration (Schoemakers and Grummel, 2002). Based on this idea, a prototype of the device has been constructed and evaluated (Wening and Breitkreutz, 2010; Wening et al., 2012). This device - called the Solid Dosage Pen (SDP) - consists of an adjusting screw for dose definition, a feeder- and a cutting mechanism, a sample outlet and a sealing cap (Figure 1).

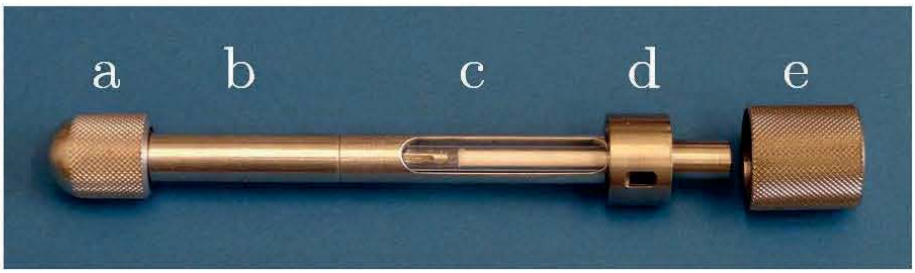

Figure 1: Solid Dosage Pen, adjusting screw for dose definition (a), feeder mechanism (b), drug-loaded rod (c), cutting mechanism and sample outlet (d) and sealing cap (e)

A drug-loaded rod, which may be manufactured via extrusion technologies, is placed into the shaft of the device and made individual dosing by cutting slices of pre-defined heights possible. Finally, these individually dosed tablet-like slices can directly be administered. Due to the possibility to refill the delivery device for reuse, costs of the system could be reduced to an acceptable value. Therefore, the SDP may combine low expenditure with high dose flexibility according to the classification of Wening et al. (2011).

1.3. Manufacturing of Rods for the SDP

Melt extrusion represents a promising drug delivery technology as matrix formulations in which the drug is homogeneously embedded may be produced (Breitenbach, 2002; Crowley et al., 2007; Repka et al., 2007). Moreover, melt extrusion has proved to be a suitable technology to produce drug-loaded rods as dosage forms for the SDP (Wening and Breitkreutz, 2010; Wening et al., 2012).

Extrusion processes include amongst others ram-extrusion and screw-extrusion:

For ram-extrusion, materials are introduced into a heated cylinder and after an initiation period to soften the materials, a ram (or a piston) presses the soft materials through the die and transforms them into the desired shape (Crowley et al., 2007).

Rod-shaped dosage forms manufactured via ram-extrusion have already been described in literature (Grassi et al., 2003; Perissutti et al., 2002; Pinto and Silverio, 2001; Quintavalle

et al., 2007). For example, a cylindrical sustained-release dosage form with 3 mm diameter and 5 mm length was developed by means of a ram-extrusion process by Grassi et al. (2003) and ram-extrusion was proposed as manufacturing technique for a potential rapid release dosage form by Perissutti et al. (2002).

Due to the discontinuous process, ram-extruders may be operated with small quantities of material and thus have outstanding properties for early development. Nevertheless, some drawbacks, like the poor temperature uniformity within the extrudate or lower homogeneity, as compared to extrudates processed by screw extrusion, have to be faced (Crowley et al., 2007).

For pharmaceutical applications, twin-screw extruders are widely utilised as they include distributive and dispersive mixing as main advantages over ram-extrusion (Crowley et al., 2007). Mixing, melting, and shaping are continuously performed as a one-step process. So far, the drug-loaded rods for the SDP have been manufactured on a twin-screw extruder via wet-extrusion or melt-extrusion (Wening and Breitkreutz, 2010; Wening et al., 2012).

Hot-melt co-extrusion has recently been proposed for various peroral, subcutaneous as well as intra-vaginal pharmaceutical applications (Fischer, 2008; Groenewegen, 1999; Iosio et al., 2008). Via co-extrusion, more than one layer, for instance a core and a concentric coat (Dierickx et al., 2013; Dierickx et al., 2012; Quintavalle et al., 2008; Vynckier et al., 2014a) or a multi laminar structure (Müllers et al., 2013; Oliveira et al., 2014), can be manufactured. Bi-layered pellets have been prepared by a co-extrusion and spheronisation process (Iosio et al., 2008; Pinto et al., 2001). In 2003 a "polymer release system" based on a polymer (mixture) - typically including polyethylene oxide (PEO) - and a water-insoluble coating, which tailors the dissolution behaviour of an included active pharmaceutical ingredient (API), was patented (Fischer et al., 2003). In a first review, the requirements, challenges, and opportunities of the co-extrusion technique have been highlighted and an overview of the co-extrusion equipment and downstream processing is given (Vynckier et al., 2014b).

Quintavalle et al. (2007 and 2008) manufactured cylindrical co-extrudates with controlled drug release via melt-extrusion. They utilised a laboratory scale vertical ram-extruder with a specially modified head. It was demonstrated that the drug release properties can be tailored through a suitable selection of the dimensions of the cylinder and the formulation of the core and the coat layer.

Lately, co-extrusion with two twin-screw extruders connected by a co-extrusion die was proposed to manufacture fixed dose combination mini-matrices (2 mm in length and 3 mm in diameter) for oral application (Dierickx et al., 2012; Vynckier et al., 2014a).

More recently, dual drug release formulations were successfully produced via co-extrusion (Dierickx et al., 2013). The term "dual release" has been introduced in literature and means in this context the superposition of two release kinetics resulting in a biphasic dissolution profile. Two different polymer combinations were utilised to obtain multilayer

mini-matrices. The drug release could be tailored by varying the drug-loading within the core and the coat.

In conclusion, co-extrusion offers various opportunities for the development of solid peroral dosage forms. Nevertheless, this technique includes some challenges, like finding functional polymer combinations for the desired dissolution characteristics, having a similar extrusion temperature and melt viscosity for the extrusion process, and achieving sufficient adhesion between the layers (Dierickx et al., 2013; Dierickx et al., 2012; Vynckier et al., 2014a; Vynckier et al., 2014b). Until now, co-extrusion technologies have not been used for the purpose to produce drug-loaded rods for the SDP and so far, a combination of immediate and sustained release characteristics of a drug in one formulation for the SDP has not been realised.

The SDP has been introduced for individual dosing of monolithic, tablet-like drug carriers sliced from a drug-loaded rod. The formulations provided both immediate and sustained release characteristics (Wening and Breitkreutz, 2010; Wening et al., 2012). But as a drawback, the extent of the drug release prolongation for sustained release formulations depended on the dose of the monolithic sliced drug carriers due to square root kinetics or non-Fickian diffusion mechanism of the prolongation (Wening, 2011). Multiparticulate solid dosage forms like coated pellets (Kayumba et al., 2007) permit dose-independent dissolution characteristics, but often lack the ease of administration (Wening and Breitkreutz, 2011).

Lately, peroral drug delivery systems for administration of multiparticulates have been proposed: Sustained release coated pellets have been embedded into tablet-shaped matrices made from macrogol (polyethylene glycol, PEG) with different molecular weights (Schmidt and Bodmeier, 2001). Moreover, Schilling and McGinity (2010) prepared monolithic matrices containing enteric-coated micropellets. Multiparticulates of different mechanical strength (granules, pellets and drug-layered spheres) were embedded into six hydrophilic polymers (PEGs, PEOs and poloxamers) by single-screw hot-melt extrusion. As oral drug delivery systems, flat-faced tablets were cut from the extruded strand (diameter 6 mm). Matrices containing up to 40 % particles met the requirements for delayed-release dosage forms of the United States Pharmacopoeia (USP) and stability over storage was proven due to the low tendency of the carrier to migrate into the enteric film.

1.4. Carbamazepine as Model Drug

In this work, carbamazepine (CBZ) was utilised as model drug. CBZ is administered as an anticonvulsive drug in a wide range of doses for the medical treatment of children, adults, as well as elderly people suffering from seizures and other epileptic episodes (Kearns et al., 2003; Rowan et al., 2005).

The molecule stabilises the inactivated state of voltage-gated sodium channels leaving the affected cells less excitable (Ragsdale et al., 1991; Willow et al., 1985). The drug has also been shown to modulate γ-amino butyric acid (GABA)-receptors (Granger et al., 1995).

Both the incidence and prevalence of epilepsy are particularly high among children and elderly people. Figure 2 illustrates the incidence of unprovoked seizures in industrialised countries according to Cloyd et al. (2006). Besides, the age-specific incidence of status epilepticus shows a bimodal distribution, with the highest rates in infants and the elderly (Cloyd et al., 2006).

The World Health Organization (WHO) listed CBZ on the "Model List of Essential medicines" (18th edition, April 2013, final amendments October 2013) attesting its global relevance in treatment.

The therapeutic dose for adults was described to be 5 - 8 mg/kg twice a day (Kearns et al., 2003). As the clearance of CBZ from plasma was discovered to be higher in children than in adults, Kearns et al. suggested higher weight-adjusted doses for infants and children (3 - 10 mg/kg body weight three times a day). Exemplarily, for a 6-year-old child weighing 20 kg, this regimen results in single doses of 60 - 200 mg. At present, there are immediate release tablets of 200 mg CBZ and sustained release tablets of 150, 200, 300, 400, and 600 mg CBZ available as well as a liquid formulation in form of a suspension (5 ml = 100 mg CBZ).

The therapeutic range of CBZ is described to be between 4 and 12 mg/L in plasma (Eadie, 1998). Above 12 mg/L ataxia and diplopia may already appear. For patients with a multiple anticonvulsive therapy adverse effects have been described to exist for even lower plasma concentrations. Moreover, considerable inter-patient variability in the relationship between seizure control and effective drug concentration were reported. Therefore, for optimal seizure control, a dosing regimen giving the best response and the fewest adverse reactions for each individual patient has to be found (Carlsson et al., 2005).

According to the commentary on the European Pharmacopoeia further dose adaption is necessary for the start and for the set-off of the therapy with CBZ due to the adaption of the potency and the adverse effects of the drug. Therapeutic drug monitoring is advised for the start of the therapy and after dose adaptions within the treatment.

The CBZ metabolism was described to happen predominantly hepatic and to depend largely on CYP 3A4 (Kerr et al., 1994). Furthermore, CBZ induces CYP 3A4 itself, increasing the elimination of CBZ, which plays a role for multiple applications in the course of the therapy.

To conclude, individual dosing of CBZ would be desirable due to (A) the age-dependent incidence and prevalence of epilepsy, (B) a dose regimen depending on the clearance capacity and the body weight of the patient, (C) considerable inter-patient variability for effective seizure control, and (D) need of dose adaption during the treatment.

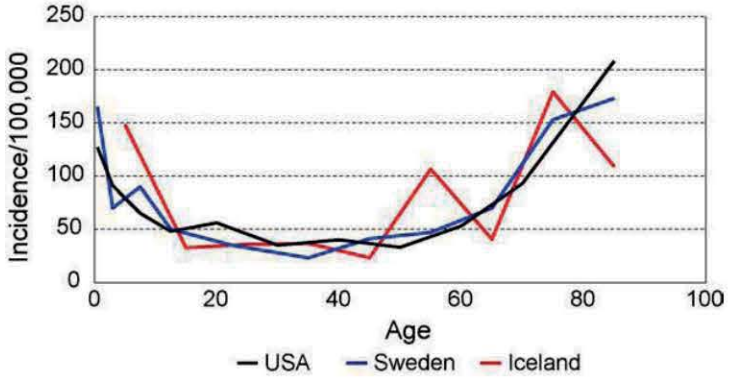

Figure 2: Incidence of unprovoked seizures per 100,000 inhabitants in industrialised countries according to Cloyd et al., 2006

The CBZ molecule (Figure 3) is a small molecule (236.3 g/mol) and has lipophilic properties, represented by a logarithmic octanol/water partition coefficient (log P) of 1.51 (Scheytt et al., 2005).

CBZ exists in at least four anhydrous polymorphic modifications (Grzesiak et al., 2003). Polymorphic modifications are different crystalline forms of the same pure substance. These different crystalline forms result of different arrangements and/or different conformations of the molecules and have different chemical and physical properties, like melting temperatures, dissolution rates or bioavailability (Brittain, 1999). For CBZ, modification III is required by the European Pharmacopoeia (Ph. Eur.) for medicinal products. Nevertheless, in the past, commercial medicinal products did not only contain CBZ III, but also other modifications and mixtures of modifications (Auer et al., 2003) and notable differences in the bioavailability were observed regarding generic CBZ formulations (Meyer et al., 1992).

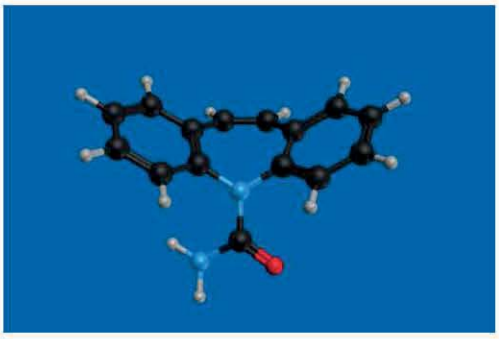

Figure 3: CBZ molecule in minimised geometry, Merck molecular force field, colour decoding of the atoms: carbon in black, hydrogen in light grey, nitrogen in blue, and oxygen in red (Molecular Operating Environment, Chemical Computing Group)

Within pharmaceutical production processes polymorphic transitions may occur due to the employment of pressure, heat, or humidity in hot-melt extrusion or granulation, for example (Zhang et al., 2004). Whereas no polymorphic transitions of CBZ have been detected during grinding and compression (Grzesiak et al., 2003; Lefebvre et al., 1986), it

has been stated that the polymorphic transition of CBZ was influenced by the melting temperature in a HME-process and the molecular weight of utilised PEGs (Pajander et al., 2012). Moreover, a polymorphic transition of CBZ III to CBZ I was found to occur when solid dispersions with PEGs were prepared by the solvent method (Nair et al., 2002).

CBZ III has a pH-independent aqueous solubility of 379 mg/L at 25 °C (Murphy et al., 2002), which is rated by Ph. Eur. as a very slightly soluble substance. Furthermore, in aqueous medium it transforms into CBZ dihydrate (CBZ DH) with an even lower solubility of 125 mg/L at 25 °C (Murphy et al., 2002) and 311 mg/L at 37 °C (Kobayashi et al., 2000). The therapeutic dose of 200 - 400 mg for adults may not be solved in the adult's stomachs liquid volume of 250 ml. Due to this solubility issue and the high permeability for membranes of the gastrointestinal tract, CBZ has been classified within the Biopharmaceutics Classification System (BCS) as class II drug (Lindenberg et al., 2004). As CBZ is a BCS class II drug and a high correlation between *in-vivo* parameters *and in-vitro* dissolution results was found (Meyer et al., 1992), the pharmaceutical formulation may be decisive for the bioavailability of the drug.

Already since 1985, physical mixtures and solid dispersions of CBZ and various excipients like sugars, sugar alcohols, PEGs, saturated polyglycolised glycerides, or polyvinyl pyrrolidone (PVP) have been investigated regarding the CBZ release rate (Attia and Habib, 1985; Doshi et al., 1997; El-Zein et al., 1998; Langer, 2003; Law et al., 2004; Perissutti et al., 2002; Perissutti et al., 2000; Zerrouk et al., 2001).

1.5. Excipients for the Formulation Development

In order to choose suitable excipients for the formulation development of CBZ-loaded rods for the SDP several aspects have to be taken into account:

For melt-extrusion as production technique, the selection of appropriate excipients is crucial, as glassy polymers, which are commonly used for melt-extrusion (Crowley et al., 2007; Repka et al., 2007), may produce sharp and brittle edges of the tablet-like slices. To allow for a safe swallowing, especially for children and the elderly, these sharp edges must be avoided. Regarding the cutting mechanism of the device, very soft or sticky formulations may show deformation or adhesion to the cutting blade and are therefore inappropriate for cutting via the SDP.

Furthermore, different dissolution profiles may be obtained depending on the excipients used for the rods: With hydrophilic binders immediate release behaviour may be achieved. In contrast, sustained release characteristics may be realised by employing a matrix-system with hydrophobic binders.

For the extrusion of cylindrical dosage forms hydrophilic binders like PEGs have already been investigated (Grassi et al., 2003; Perissutti et al., 2002; Schilling and McGinity, 2010). Due to their capability to improve the wettability and solubility of poorly soluble drugs, PEGs have been extensively utilised as drug carrier (Attia and Habib, 1985; Doshi

et al., 1997; Law et al., 2004; Moneghini et al., 2001) and drug release modifier (Güres and Kleinebudde, 2011; Windbergs et al., 2009).

Furthermore, melt-extrudates made from PEO with different molecular weights as well as Poloxamer (POL) have been successfully developed (Dierickx et al., 2013; Schilling and McGinity, 2010; Thommes et al., 2011). Wening et al. (2012) manufactured melt-extruded rods based on POL with immediate release characteristics for individual oral therapy by the SDP. Moreover, some workgroups involved hydrophilic fillers like lactose (Grassi et al., 2003; Perissutti et al., 2002) or mannitol (Thommes et al., 2011; Wening et al., 2012) for the production of rod-shaped dosage forms to optimise the viscosity of the melt and to modify the drug release characteristics.

The use of hydrophobic binders like stearic acid (SA) has already been described for extruded sustained release dosage forms (Grassi et al., 2003). Beneath SA also poly(ε-caprolactone), abbreviated as PCL, could serve as a low melting binder. PCL as semi-crystalline, biocompatible, and biodegradable polymer has been approved by the United States Food and Drug Administration (FDA) as biomedical material. It has been applied for the development of porous scaffolds for tissue engineering (Washburn et al., 2002), implants (Cheng et al., 2010) as well as peroral medicinal products (Dierickx et al., 2013; Dierickx et al., 2012; Douglas et al., 2010; Lyons et al., 2008). Highly hydrophobic PCL has often been blended with hydrophilic PEG (Cheng et al., 2010; Douglas et al., 2010) or PEO (Dierickx et al., 2013; Dierickx et al., 2012; Lyons et al., 2008) to tailor drug dissolution.

In order to study the *in-vitro* drug release from defined extrudates surfaces, Reitz and Kleinebudde (2008) dipped extrudate pieces into a molten lipid preventing the dissolution from those parts. Thus, lipid or wax coatings may be applied to tailor drug dissolution via a distinct surface. Low melting binders like SA, carnauba wax, or (white) bees wax, for instance, have already been described in literature for spray-congealing techniques or melt coatings: SA and carnauba wax have been utilised to produce delayed release microcapsules for the paediatric population (Balducci et al., 2011) and bees wax has been described both for the purpose of taste-masking (Patil et al., 2011) as well as for the production of controlled release dosage forms (Kennedy and Niebergall, 1998; Racz et al., 1997).

For the coating of multiparticulates, which may be incorporated into monolithic dosage forms, polymers like hypromellose (hydroxypropyl methylcellulose, HPMC) or polyvinyl alcohol-polyethylene glycol graft polymer (PVA-PEG, Kollicoat® IR) are known for drug-layering (Bühler, 2007; Schilling and McGinity, 2010; Suhrenbrock et al., 2011). For the sustained release coating of pellets, ammonio methacrylate copolymer (Eudragit® RL/RS) or polyvinyl acetate (PVAc, Kollicoat® SR 30 D) have been utilised (Dashevsky et al., 2004; Sawicki and Lunio, 2005; Schmidt and Bodmeier, 2001). To tailor drug dissolution of PVAc-coated pellets PVA-PEG as a pore-forming agent has been included into the coating (Ensslin et al., 2008; Strübing et al., 2007).

2. Aims and Outline

This work focuses on the development, the manufacturing, and the characterisation of peroral dosage forms intended for implementation by the SDP.

For this purpose, CBZ is chosen as model drug, as it would be reasonable for individual dosing. To open the concept of the SDP to drug substances with higher doses, like the model drug CBZ, rods with a larger diameter shall be manufactured. The existing prototype of the SDP will have to be adapted to be compatible with the new dimensions of the dosage forms. The applicability of the concept of the SDP for these rods - with probably different mechanical properties - shall be examined.

The first aim is to elaborate a small-scale production technique to conduct an excipient screening for the formulation development of melt-extruded rods.

Then, the rods shall be produced via melt-extrusion. Apart from the classic twin-screw melt-extrusion, new and more sophisticated techniques shall be examined for their usability: First, co-extrusion via two twin-screw extruders may produce co-extrudates combining a core- and a coat-layer. Second, ram-extrusion may allow for the embedding of multiparticulates into a matrix. Regarding the sustained release formulations, the dose-, geometry-, and size-dependent dissolution characteristics of the cut slices may be minimised or even overcome by these techniques. Additionally, further drug release profiles like biphasic drug release or zero order kinetics may be accessible.

Another objective is the extensive examination of the dissolution characteristics of the model drug CBZ with regard to the different utilised matrices, the CBZ-loading and other excipients, like pore formers or solubilizers, for example.

Furthermore, this work shall systematically evaluate the mechanical properties of CBZ-loaded rods by finding and assessing appropriate methods to this purpose. Moreover, it shall be clarified, in which way dosing by the SDP and the mass uniformity of sliced doses are influenced by the mechanical properties of the drug-loaded rods. It shall be elucidated whether the mechanical properties may be modulated by suitable excipients and whether the formulations together with the device will be suitable for patient-centred treatment.

As CBZ exists in at least four modifications and pharmaceutical production processes may induce polymorphic transitions, a thorough understanding and surveillance of the solid state properties of CBZ within the formulations has to be built up. Furthermore, it is intended to study whether storage affects the mechanical properties and the dissolution behaviour of the CBZ-loaded rods.