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Novel delivery device for monolithical solid oral dosage forms for personalized medicine

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ABSTRACT

There is an evident need for solid oral dosage forms allowing patients' tailor-made dosing due to variations in metabolization or small therapeutic indexes of drug substances. The objective of this work is the development of a device equipped with a novel solid dosage form, containing carvedilol as model drug, for the delivery of monolithical drug carriers in individual doses.

The device was developed and constructed enabling an exact feed rate and dose adjustment by a cutting mechanism. A twin-screw extruder was used for producing cylindrical solid dosage forms. Divided doses were characterized by mass variation, cutting behavior and drug dissolution in order to investigate their applicability for practical use.

Different formulations could be extruded obtaining straight cylindrical rods, which are divisible in exact slices by using the novel device. Forces below 20 N were needed to divide doses which comply with pharmacopoeial specification "conformity of mass". The developed formulations exhibit a sustained release of carvedilol within a range from 7 up to 16 h.

A novel system consisting of a device and a cylindrical dosage form was developed. Patients' individual doses can be applied as monolithical solid dosage forms for oral use.

1. Introduction

Personalized medicine has become an important research area in recent years. The impact of varying gene expressions and activities, resulting in different metabolizing capacities, has been well investigated. Mainly the research focused on metabolizing enzymes such as CYP2D6 or CYP3A4 and the occurring problems of poor, but also ultra rapid metabolizing (Zhou et al., 2008; Cholerton et al., 1992; Ingelman-Sundberg et al., 2007). The deviating drug metabolization may require precise dose adaption. Furthermore drugs with small therapeutic indices like warfarin must be given in adjusted doses subject to the actual blood clotting time. Further, pediatric and geriatric drug therapy are areas where definite dosing is urgently needed (Standing and Tuleu, 2005; Kearns et al., 2003). To transfer this basic knowledge into daily practical drug therapy, suitable and safe dosage forms are needed, especially for oral drug administration (Ingelman-Sundberg et al., 2007). So far, mainly liquid dosage forms are available allowing an individual dosing for oral application. In this case the metering is made by graduated measuring cups, spoons, droppers or oral syringes. These delivery devices often have the problem of incorrect dosing due to the poorly visible graduation marks (Brown et al., 2004; Sobhani et al., 2008). The safety of dispensing of liquid pharmaceuticals especially for children could be increased by using oral syringes instead of spoons, e.g. in the application of antibiotics (Griessmann et al., 2007). However, due to drug solubility and stability or manufacturing issues numerous substances are inappropriate for liquid oral dosage forms.

The individual therapy with solid oral dosage forms is not yet established because of the insufficiency of the currently available systems. Common tablets can be split into four parts, in the best case. However, there is the problem of incorrect splitting which often leads to deviations in mass and content (Quinzler et al., 2006; Van Santen et al., 2002; Rodenhuis et al., 2004; Teng et al., 2002; McDevitt et al., 1998). Even healthcare professionals failed in splitting tablets (Rosenberg et al., 2002). Moreover, tablet splitting may cause hazardous dust (Wessel et al., 2001). Therefore, a new basic technical concept is needed to enable the variable and safe dosing of solid drugs. Provided concepts in patent or scientific literature belong either to a group of devices, dispensing multiple unit dosage forms or to divisible tablets. The underlying idea of the multiparticulate dosage forms is to select a fixed number of pellets, mini-tablets or other molded bodies (Breitkreutz and Wazlawik, 2005; Knoll, 1999; Schuster, 1988; Bauriegel, 2007; Bredenberg et al., 2003). They can be dosed as multiparticulate form in water or a meal by using a corresponding device or special spoons. How-

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ever, especially the dosing spoons allow only one fixed dose. Except for the dosing spoon for mini-tablets (Knoll, 1999) none of these novel concepts has reached market maturity yet. The Dispetron patent (Ronca, 2007) based on cores which can be impregnated by a defined drug solution, whereby this two-stage procedure can only be made in a pharmacy. Usually divisible tablets with a breaking notch can be split into halves or quarters, whereas one recently developed tablet can be split into eight parts (Kayitare et al., 2009). A special novel concept is to split a matrix tablet in up to five different parts (Dicke, 2008). Beside the different drug loads of the divided compartments the respective occurring surfaces have been resulted in different release profiles. However, even these types of tablets can only be divided into fixed compartments.

In a recent patent application a schematic drawing of a device is provided (Schomakers and Grummel, 2002). Such a system should enable a freely selectable dose for oral use which is ingestible as monolithical dosage form. With a feed rate mechanism a cylindrical dosage form can be fed and the exact dosage appointed. Finally an individual tablet-like slice can be cut off from the dosage form with a conducted blade, meaning that the dose is defined by the height of the cut slice.

The aim of the present work is the development of an improved system based on the patent application for delivery of solid drug carriers for oral use, which contains patients' individual or application-specific drug content. To complete the system, suitable dosage forms containing the model drug carvedilol, which can be produced by using common industrial manufacturing techniques, had to be developed. The dosage form should be produced in a cylindrical form and obtain the feasibility to be cut into slices. Processes of compaction, molding and extrusion should be investigated and evaluated concerning their feasibility.

2. Materials and methods

2.1. Materials

Hydroxypropyl cellulose (Klucel® HXF-Pharm), ethyl cellulose (EC N22 Pharm) and hydroxyethyl cellulose (Natrosol® 250 HHX Pharm, Hercules, Zwijndrecht, The Netherlands), hydroxyethyl cellulose (Tylose® H 10.000 P2, H 30.000 P2 and H 300 G4, Clariant, Gersthofen, Germany), hypromellose (Metolose 65SH, Harke, Muehlheim, Germany), tragacanth (Cerotrag® 884) and xanthan gum (Ceroga® 602, C.E. Roeper, Hamburg, Germany), k-Carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, USA), arabic gum (Merck, Darmstadt, Germany), potato starch (Emsland Staerke GmbH, Wietzendorf, Germany), α-lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), mannitol (Mannitol 160, Roquette, Lestrem, France), macrogol 600, 1500, 2000 (Polyglycol, Clariant, Gersthofen, Germany), gelatin (Gelita, Eberach, Germany), white bees wax and carnauba wax (Caesar & Lorentz, Hilden, Germany), neutral oil (Miglyol®, Sasol, Witten, Germany), Glycerol 85% (Caesar & Lorentz, Hilden, Germany) were used as received. Carvedilol (Salutas Pharma, Barleben, Germany) was used as model drug.

2.2. Methods

2.2.1. Compaction and molding

For preliminary investigations cylindrical tools were developed consisting of a punch and a die of two different diameters (4.5 and 9.0 mm) each with a length of 10 cm. The dies can be fixed within a guide rail which also serves as bottom of the die. Powder components were blended in a Turbula Mixer (Bachofen, Nidderau, Germany). The liquid binder was subsequently incorporated in the blended mixture using mortar and pestle. The dies were filled with the wetted powder mixture which was afterwards compressed in cylindrical molds of a length of approximately 2 cm.

2.2.2. Extrusion

Extrudates were manufactured using a co-rotating twin-screw extruder Micro 27GL/28D (Leistritz, Nuremberg, Germany) equipped with die plates with 2.7, 3.5 or 4.5 mm die diameters and a die length of 0.5 mm. Powder components were blended for 15 min in a laboratory scale blender (LM 20, Bohle, Ennigerloh, Germany) and afterwards transferred into a gravimetric feeder (K-CL-KT 20, K-Tron Soder, Niederlenz, Switzerland). Glycerol 85% was used as liquid binder supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with flow-through metering device (Corimass MFC-081/K, Krohne, Duisburg, Germany). During extrusion a temperature of 25 °C, a screw rotation speed of 100 rpm, a powder feed rate of 40 g/min and a suitable liquid feed rate were adjusted. A band-conveyer (Brabender, Duisburg, Germany) with a length of 131 cm and an adapted speed was used to obtain straight extrudates. Extrudates were stored without further drying steps at 20 °C and 45% RH.

2.2.3. Cutting experiments

For force–distance measurements the Test Apparatus H10KM (Hess, Sonsbeck, Germany) equipped with a 1000 N load cell was used. To record force–distance-graphs during cutting the slices a cutter device was developed. The cutter is positioned between two jaw systems, whereof one is fixed on the bottom of the apparatus and the other is connected to the load cell directly. The load cell is fixed at a mobile bar. Twenty slices were cut from the cylindrical rod at a speed of 100 mm/min and weight to determine mass variations.

2.2.4. Drug release

Dissolution tests according to USP Method 2 and Ph.Eur. Method 2.9.3 were performed using paddle apparatus Sotax AT 7 (Sotax, Loerrach, Germany). Experiments were conducted in 900 ml 0.1-N hydrochloric acid at a stirring speed of 100 rpm and a temperature of 37 ± 0.5° C. The concentration of released drug was determined in intervals of 10 min using a UV-spectrometer Lambda 40 (PerkinElmer, Rodgau-Juedesheim, Germany) at a wave length of 284 nm in a continuous flow-through 10 mm cuvette. Six replicates were measured per batch.

Dissolution results were fitted according to the square root of time and to the exponential equation of Korsmeyer and Peppas (Eq. (1)). M_t/M_α, is the drug released at time t, k denotes a constant incorporating the properties of the macromolecular polymeric system and the drug. n is a kinetic constant which is used to characterize the release mechanism. According to Korsmeyer and Peppas, the exponents for cylindrical matrices are $n = 0.45$ for Case I or Fickian diffusion, $n = 0.89$ for Case II transport and $0.45 < n < 0.89$ for anomalous behavior or non-Fickian transport (Korsmeyer and Peppas, 1981).

$$\frac{M_t}{M_\alpha} = kt^n \quad (1)$$

3. Results

3.1. Device

One developed prototype of the device has a length of 16.5 cm and a diameter of 1.2 cm in the middle part. It consists of 25 metal components (Fig. 1). The drug loaded rod is located in the center of the device within an exchangeable plastic tube as packaging material. This is a major difference to the technique from the device disclosed in the patent application (Schomakers and Grummel, 2002), where a direct contact between the drug loaded

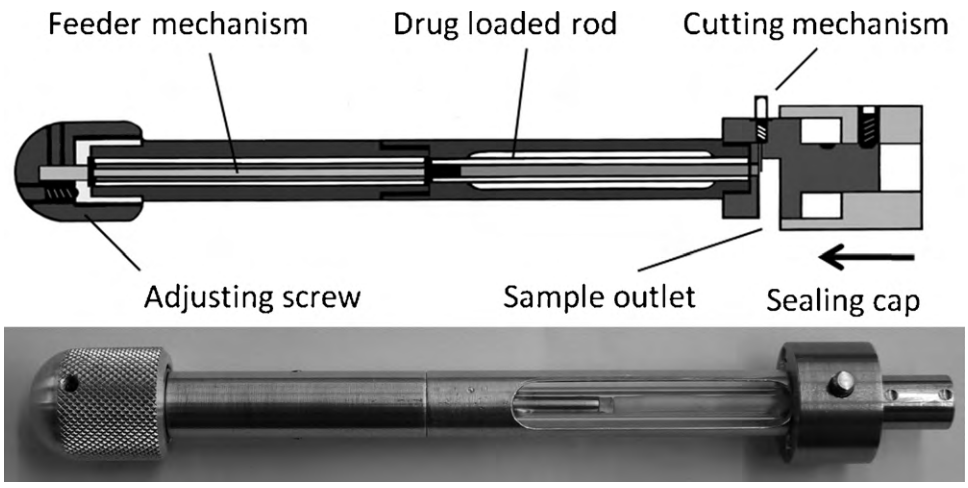

Fig. 1. Top: schematic drawing of the developed device in cross section equipped with a cutting module. The drug loaded rod is moved by the feeding mechanism. The cutting mechanism cuts the rod and determines the dose which leaves the device via outlet gap. To protect the drug loaded rod the device can be closed by a sealing cap, inactivating the cutting mechanism. Bottom: the prototype of the device equipped with the cutting module (total length 16.5 cm) containing a cylindrical drug loaded rod.

rod and the device exists. The tube for the prototype is made from acrylic glass. It is intended to use common packaging materials like polyethylene or polycarbonate for the tube in further investigations. Additionally, plastic components will be used for the construction of the device instead of metal components. An adjusting screw is used to move a piston to push the rod forward depicted in the schematic drawing (Fig. 1). The piston is conducted by a M2 fine thread and ensures an exact feed rate of the rod. The feed rate is accurately defined by the slope of the thread and must be converted concerning the rotation of the wheel. A full rotation of the screw reveals a feed rate of 0.4 mm. To control the feed rate the wheel arrests by a spring mechanism after each rotation. For the cutting process a module with a diameter of 2.4 cm were developed located at the edge of the device (Fig. 2). A button outside of the module connected with a cutting blade can be pushed down to cut off a slice from the rod. The cutter enables a cut in a square angle. The slice can leave the device by a single-sided bore (Fig. 2). To protect the drug substance from ambient air during the period of use the module can be covered by a closing cap. The button is pushed down by the cap, ensuring that the cutters protect the drug loaded rod against mechanical or chemical stress.

Fig. 2. Cutting module viewed from the inner side, showing blade and outlet gap for cut doses.

3.2. Compaction and molding

Preliminary experiments were conducted to evaluate compacting and molding processes. The hardness and brittleness of compacted solid formulations led to the problem of unequal divided slices after cutting, which also occurs when splitting common tablets (Quinzler et al., 2006; Van Santen et al., 2002; Rodenhuis et al., 2004; Teng et al., 2002; McDevitt et al., 1998; Rosenberg et al., 2002). Major problems of molded dosage forms are that common pharmaceutical excipients like PEGs are inappropriate for oral use at the required concentrations, as well as the brittleness of these formulations. Therefore the work was continued with wet extrusion process using acceptable polymers. However when using the twin-screw extruder at least 600 g powder mixture were needed to obtain a constant and successful process. Therefore the extruder is less suitable for screening experiments, especially when using costly substances. To avoid a high waste of material and to enable the screening of a high number of different formulations, the developed molding tool, described in the experimental part, was used for preliminary investigations with an entire batch size of 10 g/batch. Hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl celluloses, hypromellose, tragacanth, xanthan gum, k-carrageenan, arabic gum, potato starch, α-lactose monohydrate, mannitol, polyethylene glycols, gelatin, white bees and carnauba wax, neutral oil, water, glycerol 85% were investigated in different compositions for the screening experiments using carvedilol as model drug, which are herein not being specified in detail. The obtained molds were assessed concerning their visual appearance focusing on homogeneity and surface properties and analyzed concerning their feasibility to cut them into slices. Furthermore their dissolution behavior was determined. Promising pre-formulations were used for an extrusion process.

3.3. Extrusion

First step of extrusion experiments was a suitability test of the membrane pump with flow-through metering device to feed glycerol 85% constantly and exactly through the nozzle. Based on preliminary investigations formulations consisting of a polymer or a combination of two polymers, potato starch as filler and glycerol 85% as liquid binder were developed. An overview of the compositions of extrudates, each with a diameter of 3.5 mm, except for formulation Hpchec which has a diameter of 2.7 mm, is given in

Table 1
Composition of the investigated formulations (%).

	Formulation name						
	Tra	Trahpc	Xan	Xanhpc	Trahpc20	Xanhpc10	Hpchec
	3.5[a]	3.5[a]	3.5[a]	3.5[a]	3.5[a]	3.5[a]	2.7[a]
Carvedilol	5	5	5	5	20	10	5
Tragacanth	40	20	–	–	15	–	–
Xanthan gum	–	–	40	20	–	20	–
HPC	–	20	–	20	15	20	20
HEC	–	–	–	–	–	–	20
Potato starch	20	20	20	20	15	15	20
Glycerol 85%	35	35	35	35	35	35	35

[a] Diameter [mm].

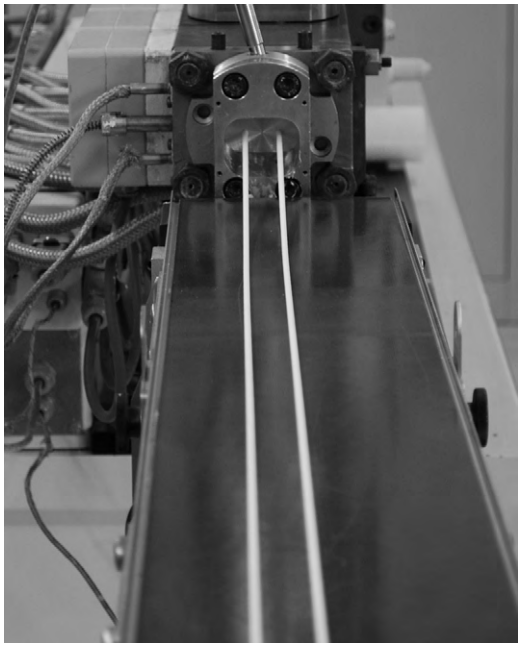

Fig. 3. Continuous extrusion of formulation Xanhpc through a die (3.5 mm diameter) equipped by a band-conveyer showing the straight and smooth form of the extrudates.

Table 1. All formulations contain the active ingredient, preferably with the desired dose of 5%, thickening agents of 40% in total-except formulation Trahpc20 with the highest drug load-, 15–20% potato starch and 35% glycerol 85%. During extrusion the content of glycerol 85% could be adjusted lower than in the preliminary compaction experiments. In total seven different formulations could be extruded. For all formulations with 5% drug load an amount of 20% of potato starch was required to achieve solid, smooth and homogeneous, but not sticky extrudates. Formulations Trahpc and Xanhpc were extruded with diameters of 2.7, 3.5 and 4.5 mm, Xan, Trahpc20 and Xanhpc10 in 2.7 and 3.5 mm, Tra in 3.5 mm and Hpchec in 2.7 mm. All extrudates exhibited a smooth surface and were capable to be transported by the band-conveyer immediately after they left the die of the extruder (Fig. 3). This ensured a straight and smooth shape of the extrudates as well as a continuous process. The samples were cut into rods of 10 cm length for storing. Species with three different diameters for formulation Xanhpc are displayed in Fig. 4. The formulations can be classified into three groups concerning the used polymers: either cellulose ethers, native biopolymers or the combination of both. Beside cellulose ethers and the xanthan gum, which has already been used for oral sustained release formulations (Talukdar et al., 1998), tragacanth was investigated in a wet extrusion process to achieve sustained release formulations.

3.4. Cutting experiments

Due to the smooth texture and the cylindrical shape of the extrudates common hardness tester could not be used for characterization, because of no detectable crushing point. Therefore a novel tool was developed to cut off slices from the extrudates and to determine the forces during cutting (Fig. 5). The tool consists of three parts (Fig. 5). The upper part holds a blade and two bolts for conducting in the lower part, which owns holes of different diameters for the outlet of the samples. A table is used to fix the extrudates in a square angle and the specified height. Cut slices of three different diameters obtained from formulation Xanhpc are exemplarily shown with a thickness of 2 mm in Fig. 4. Force distance tracks were recorded for each cut. In Fig. 6 they are shown for formulation Xanhpc20. The peaks of the force–distance tracks were used to determine the maximum force. The occur-

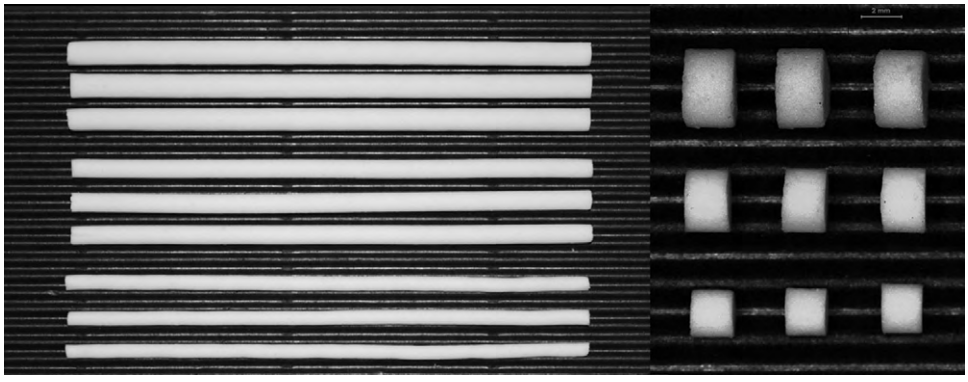

Fig. 4. Left: extrudates of formulation Xanhpc in three different diameters (2.7, 3.5 and 4.5 mm) with a length of 10 cm. Right: slices cut from formulation Xanhpc with diameter of 2.7, 3.5 and 4.5 mm, respectively and 2 mm height.

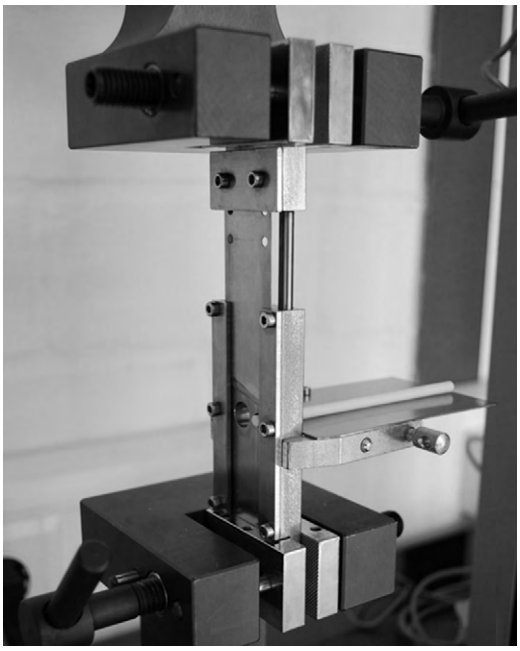

Fig. 5. Equipment for recording force–distance tracks when cutting slices from the extrudates. A conducted mobile blade of the Universal-Test-Apparatus H10KM cuts off slices from the fixed drug loaded rod.

ring maximum forces during the cuts were throughout below 20 N for the formulations with a rod diameter of 3.5 mm. The lowest forces were measured for Trahpc20 with 6.6 ± 0.3 N and the highest forces for formulation Xan with 17.5 ± 0.4 N. By the newly developed tool, extrudates could be cut into small slices having a reproducible weight. Masses of 20 tested slices of each formulation are within the 90–110% range around average (Fig. 7) according to Ph.Eur. monograph 2.9.5. "Uniformity of mass of single-dose preparations."

3.5. Drug release

The dissolution profiles exhibit sustained release properties (Fig. 8a–c). At least 400 min up to more than 16 h were required to release the full amount of the model drug carvedilol. The coefficients of determination and the exponents according to the Korsmeyer/Peppas and the Higuchi equation are shown in Table 2 for drug release up to 60%. Formulations Trahpc, Xanhpc and Hpchec showed almost the same dissolution behavior (Fig. 8b). Differences could be observed by using only one biopolymer. In these cases the release decreasing capacity of xan-

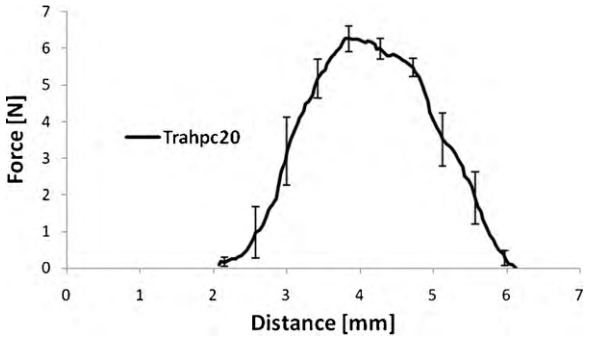

Fig. 6. Force–distance track of the cutting process (Trahpc20, diameter 3.5 mm, $n = 10$, mean ± SD). Peaks of these tracks were used to determine the maximum force needed to cut off slices from the drug loaded rod (Table 2).

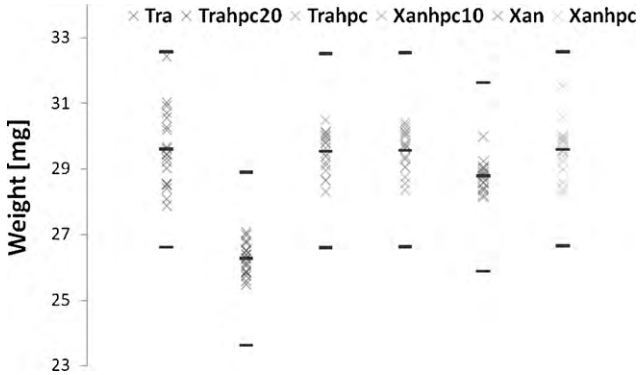

Fig. 7. Masses of 20 slices cut from different formulations using the developed cutting equipment ($n = 20$, mean ± 10%). All weight samples are within the 10% interval of the mean.

Table 2
Coefficients of determination and exponents according to Korsmeyer–Peppas and Higuchi for drug release up to 60%, determined by dissolution profiles. Compositions of formulations are shown in Table 1.

Formulation	Korsm.-pep., R^2	Korsm.-pep., n	$\sqrt{t(R^2)}$
Xanhpc 3.5 mm	0.999	0.54	0.999
Trahpc 3.5 mm	0.999	0.59	0.996
Xan 3.5 mm	0.999	0.54	0.999
Tra 3.5 mm	0.999	0.64	0.989
Xanhpc10 3.5 mm	0.995	0.50	0.920
Trahpc20 3.5 mm	0.999	0.59	0.994
Hpchec 2.7 mm	0.999	0.48	0.999

than gum was distinctly higher in comparison with tragacanth (Fig. 8a) especially in the formulations with higher drug loads (Fig. 8c).

3.6. Use of the finished device

The device was equipped with extrudates with a diameter of 2.7 mm and a length of 60 mm. 20 doses, with a length of 2 mm per dose, were adjusted using the feed rate mechanism and cut by the device. The monolithical dosage forms obtained were weighed. Mass conformity according to Ph.Eur. monograph 2.9.27 "Uniformity of mass of delivered doses from multidose containers" could be shown for formulations Xanhpc, Xanhcp10, Trahpc20 and Trahpc (Fig. 9).

4. Discussion

4.1. Model drug

Carvedilol, a practically insoluble drug with a half-life period of 6–7 h, was chosen as model drug for three different reasons. It is metabolized by CYP2D6 and known for side effects due to gene variations (Giessmann et al., 2004), thus there is an evident reason to provide individual doses for patients with this gene defect. The second reason is that the common dose for adults in the therapy of hypertension is only up to 10 mg twice a day. These low doses can be compared to drugs with small therapeutic indices like warfarin. The individual therapy with a drug with the potential risk of overdosing is well established in the therapy of diabetes by using insulin pens. This implies that high potent drugs like warfarin could be used in individual dosage forms as well, after measuring the clotting time, e.g. A formulation for a once daily therapy is not available yet. The third reason is that carvedilol is used for the whole range of population from small children up to elderly, whereby the dosage cannot only be calculated thoroughly from the

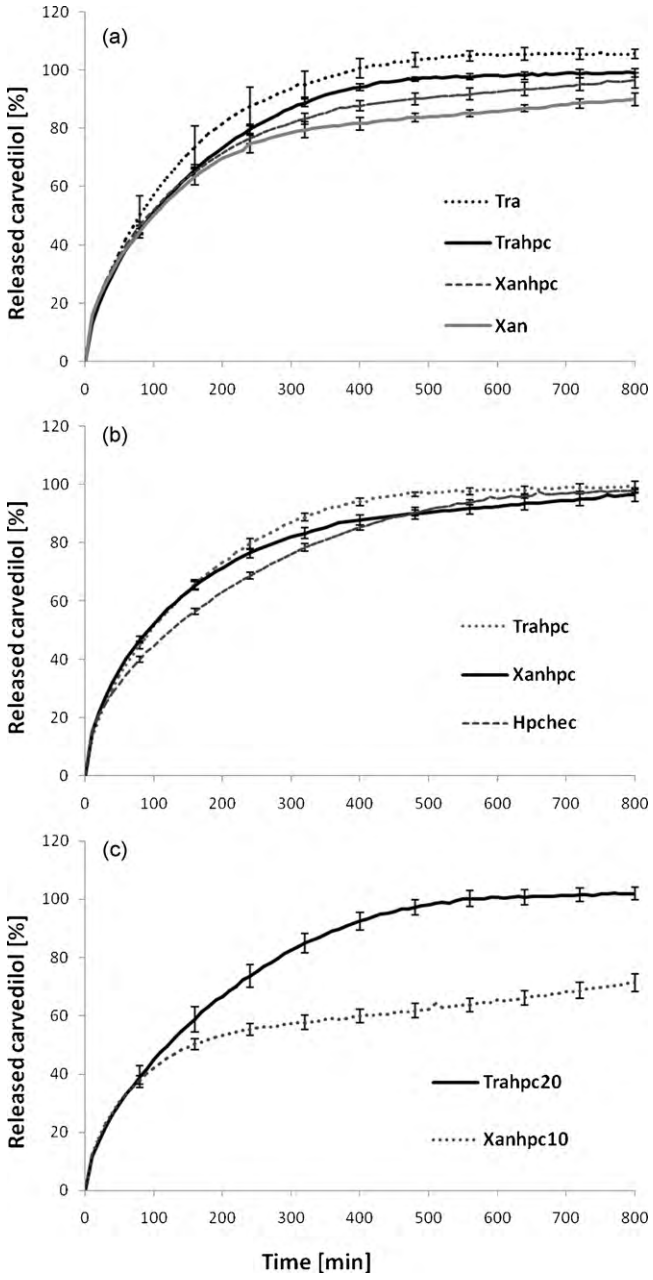

Fig. 8. Dissolution profiles of slices (paddle apparatus, six replicates, mean ± SD). (a) 8 slices, height 2 mm, diameter 3.5 mm of formulations Tra, Xan, Trahpc and Xanhpc. (b) 10 slices, height 2 mm, diameter 2.7 mm of formulations Trahpc, Xanhpc and Hpchec. (c) 6 slices, height 2 mm, diameter 3.5 mm of formulations Trahpc20 and Xanhpc10.

common therapy of adults (Albers et al., 2008). The lowest available single dose preparation contains a drug load of 3.125 mg which is still too high for pediatric use. Therefore, dosage forms containing carvedilol with lower contents, especially in phases of dose titration, are needed.

4.2. Device

The developed device varies in different aspects from the schematic drawing of the patent application (Schomakers and Grummel, 2002). The opportunity to exchange the dosage form, including its primary packaging container, has two major advantages. It leads to a reusable device. Furthermore, it is feasible to use only one device for different rod diameters and drug loads,

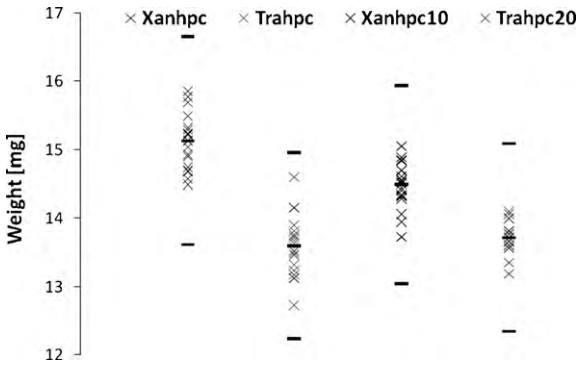

Fig. 9. Realistic use of the device: 20 doses with a diameter of 2.7 mm and 2 mm thickness were cut by the novel device and precisely weight ($n = 20$, mean ± 10%). All weight samples are within the 10% interval of the mean according to pharmacopoeial specifications.

if for example higher drug content is needed. Moreover, the contact between the drug dosage form and the device can be avoided. Strict material controls must be implemented only for one primary packaging material. The variability of materials for constructing the device can be increased. The primary packaging material in form of a tube can be closed by aluminum blister foil on both sides for moisture protection. After filling and before sealing a small piston with a notch can be integrated at one end of the tube. The threaded piston of the device can grip into this notch to ensure a correct guidance of the rod. A conducted one-sided cutting mechanism, sharp and small as a razor-blade, was integrated allowing a more precise cut than the double-sided cutter. When using a double-sided cutter, slices showing burrs were obtained. Such problems could occur even more often when using blades in form of an aperture as also proposed in patent application. Another advantage of the newly developed device is the protection of the extrudate over storage. Ambient air contact is prohibited by the closure system integrated in the cap of the device and the piston integrated in the primary packaging material. Additionally, the newly developed cutter has the feasibility to arrest after the cut to secure the dosage form, especially from mechanical influences.

4.3. Extrusion

Extrusion as a “single-step granulation and tabletting process” has already been published (Keleb et al., 2001). They have been cut wetted extrudates, containing lactose and PVP in water as binder, directly after extrusion into tablets and subsequently dried. A dried formulation would not be able to cut into slices, as previously mentioned. The aim of this work was to maintain a texture which is sliceable over the whole storage period. This could be achieved by using polymers and glycerol 85% as liquid binder. The cylindrical form of the extrudates possesses different features. In contrast to all other previously proposed solid dosage forms for personalized medicine, a freely selectable dosage can be chosen, whereas pellets, mini-tablets or divisible tablets allow only a stepwise dosing. Due to their texture, the moulds are exactly sliceable. The round and smooth shape of the cut slices allows an easy swallowing. The slices with the smaller diameter of 2.7 mm are comparable to mini-tablets and therefore useful in the pediatric therapy. They can be given into a meal or even be swallowed by younger children, recently shown for 3-mm-diameter mini-tablets in the therapy of preschool-aged children (Thomson et al., 2009). To treat different age groups up to adults, the extrusion was implemented with diameters of 3.5 and 4.5 mm as well, enabling higher drug loads.

4.4. Cutting experiments

A critical aspect when using the novel device are the forces needed to cut slices from the drug loaded rod. It could be demonstrated by force–distance measurements that forces below 20 N are needed when cutting the extrudates. This is less than for commonly used devices such as powder inhalers or insulin pens (Kircher, 2007). For cutting most of the extrudates, only forces of 10–15 N are needed, which means that elderly or people disabled by their disease like Morbus Parkinson may use the device, too.

4.5. Drug release

The release of carvedilol from the developed formulations may last more than 16 h and they can therefore be used for a once daily therapy by contrast to commonly available tablets. Especially in the therapy of children the compliance may be increased (Weber, 2007; Henderson et al., 2006). When fitting the drug release to the square root of time, the coefficients of determination indicates a good description. In the evaluation by Korsmeyer and Peppas, which includes the geometric and structural characteristics of polymeric cylindrical matrices, drug release according to square root of time could not be confirmed. For this case the constant k should be at 0.45. As shown in Table 2, all formulations exhibit a constant of 0.48–0.64, therefore mechanisms of erosion and swelling seem to be the main processes during drug dissolution. This characteristic has been shown for xanthan gum matrix formulations previously (Talukdar et al., 1996; Santos et al., 2004), and could be confirmed in our study for tragacanth and the mixtures of tragacanth and HPC. The dissolutions tests were conducted with slices of 3.5 mm in diameter and a thickness of 2 mm. Different diameters and thicknesses may lead to changes in dissolution profiles, however the differences are quite low in the case of carvedilol due to the low solubility of the model drug. Dissolution profiles might be more influenced by slices' thicknesses in the case of soluble drugs, which are currently under investigation. The cheaper price in comparison to the biopolymers xanthan gum and tragacanth reveals the advantages of cellulose ethers. Concerning the properties in dissolution behavior, no major benefits or differences between the formulations could be observed.

4.6. Use of the finished device

The combination of device and dosage form was the final step of this work. The compliance with mass variation tests and the conformity in the dissolution profiles proved the suitability of the developed system for an individualized therapy. A finer grading of the device could realize a larger number of dose steps as the prototype. Such a device, in combination with an appropriate dosage form, would require novel authorization procedures in drug regulatory agencies for solid drug dosage forms. A solid formulation had to be authorized for one drug substance in the full dosage range, in contrast to authorizations for each dosage unit, e.g. capsules or tablets. Only insulin formulations and a few biotechnological parenteral formulations for pen application are authorized by this means. Another issue of the new device are the cost which might be limit the market success. An advantage of the novel system could be an extra benefit when authorization for children and adults is simultaneously planned. Dose adaption for younger children which are able to swallow small slices or take it with their meal could be realized. The novel system can deliver the dose accurately and rapidly. Long-term stability studies are ongoing. In further studies, the applicability of the system will be investigated for other drugs with deviating physicochemical characteristics and for formulations with different properties.

5. Conclusion

A novel device containing a novel dosage form could be developed. Sustained release dosage forms were manufactured by using a twin-screw extruder. Tablet-like slices could be delivered from the cylindrical dosage forms, containing an individual dose of carvedilol by using the developed device. On the contrary to all available solid dosage forms and published approaches for devices, a freely chosen dose can be selected and provided as monolithical oral solid dosage form. Different diameters of the dosage forms as well as different drug loads up to 20% allow the therapy of both adults and younger children. The drug release from the dosage forms shows sustained release characteristics. The new drug delivery system may serve as a technology platform for different drugs in personalized medicine.

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