European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 302–309

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Drug release from MCC- and carrageenan-based pellets: Experiment and theory

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ARTICLE INFO

Article history:
Received 7 April 2009
Accepted in revised form 15 May 2009
Available online 22 May 2009

Keywords:
Extrusion–spheronisation
Pellets
Microcrystalline cellulose
Carrageenan
Release mechanisms

ABSTRACT

Microcrystalline cellulose (MCC) is a well-established pelletisation aid. However, MCC pellets generally do not disintegrate, resulting in prolonged drug release, especially in the case of drugs with poor/low aqueous solubility. The major objectives of this study were (i) to modify the prolonged matrix-type drug release from MCC pellets by addition of a disintegrant (croscarmellose Na) or pore former (PEG 6000), (ii) to evaluate carrageenan as potential alternative pelletisation aid for manufacturing high-dose immediate release pellets, and (iii) to better understand the underlying drug release mechanisms. Pellets containing 77–90% drug with poor/low aqueous solubility (vatalanib succinate, SAG/ZK, or theophylline) were prepared by extrusion–spheronisation. All batches showed acceptable yields, aspect ratios, tensile strengths, and porosities. Drug release from MCC pellets was predominantly controlled by pure diffusion and limited drug solubility and could be quantitatively described using Fick's law. Importantly, the apparent drug diffusivity could effectively be adjusted by adding small amounts of a disintegrant or pore former, allowing for release periods ranging from a few minutes to several hours. The drug diffusion coefficients varied between 0.36 and 29 $\times$ 10^{-6} cm^2/s. In contrast, carrageenan-based pellets very rapidly disintegrated upon contact with aqueous media and released high doses of drugs with poor/low aqueous solubility within a few minutes.

1. Introduction

Pellets are an attractive dosage form for immediate or controlled drug delivery, as they provide the typical advantages of multiple-unit dosage forms. When compared to single-unit systems, they can improve the bioavailability of compounds, decrease potential local irritations in the gastrointestinal tract, and lower the risk of dose dumping [1]. Furthermore, the amount of administered drug can be easily varied when using pellets, thus leading to considerable dose flexibility during clinical trials.

Pellets are manufactured by techniques such as layering of drugs onto sugar or microcrystalline cellulose (MCC) cores in a fluid bed coater or by direct pelletisation in a high shear mixer or rotary processor [2]. Preparation of pellets by extrusion–spheronisation is another well-established process, which has been described as a potent method to obtain pellets of high density, narrow size distribution, and high drug loading within reasonable processing times [3]. The extrusion–spheronisation process is based on two main steps: (i) During extrusion, a wet mass of drug and extrusion aid is pressed through dies of defined diameters to obtain an extrudate. During the extrusion process, the mass must possess inherent fluidity, permitting flow during the process and self-lubricating properties as it passes through the die. (ii) The extrudate is transferred to a spheroniser and spherical beads are formed by the action of the friction plate in the spheroniser. Here, the extrudate must be brittle enough to be broken down to shorten lengths, but not too friable to avoid complete disintegration [4,5].

To date only few extrusion aids have been identified which meet the requirements of sufficient plasticity upon extrusion and brittleness during spheronisation [6,7]. The most commonly used extrusion aid is microcrystalline cellulose (MCC), which fulfills the described requirements even when used in fractions below 20% of the total pellet mass. However, pellets based on MCC generally do not disintegrate, thus leading to prolonged drug release [8]. In vivo, this might cause decreased bioavailability, especially when formulating compounds with poor/low aqueous solubility. Furthermore, potential adsorption of drugs to MCC or decomposition of drugs in the presence of MCC might represent further drawbacks of this pelletisation aid [9,10].

Pectinic acid was investigated as an alternative extrusion aid by Tho et al. [11–14]. The amount of pectinic acid was varied in a wide range and almost round-shaped pellets were obtained. However, in vitro drug release significantly depended on the pH. *Chitosan* pellets were successfully prepared using the extrusion–spheronisation technology by Steckel and Mindermann-Nogly [15]. No further additive was required when replacing water as granulation aid

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doi:10.1016/j.ejpb.2009.05.007

by diluted acetic acid. However, the suitability of chitosan as solely extrusion aid needs to be confirmed for highly dosed drugs. Furthermore, the use of diluted acetic acid as granulation aid might be critical for drugs prone to degradation at low pH. Charoenthai et al. [16] studied the influence of the formation of a polyelectrolyte complex between (cationic) chitosan and (anionic) sodium alginate on pellets manufactured without MCC. Acetaminophen was used as a model drug, while lactose monohydrate was added as filler. The resulting drug release kinetics depended on the type of release medium. Chatchawalsaisin et al. [17] investigated the properties of pellets containing different model drugs, MCC and *glycerol monostearate*. Manufacturing spherical pellets without MCC was feasible only when using diclofenac. For the other drugs, a combination of MCC and glycerol monostearate was required, emphasizing the unique properties of MCC. Also, *starch* and *starch derivatives* have been suggested as potential substitutes for MCC in pellets prepared by extrusion–spheronisation [18,19]. Systems containing hydrochlorothiazide and piroxicam were characterized in vitro as well as in vivo (dogs) and showed promising results.

Recently, *κ-carrageenan* was proposed as a potential alternative pelletisation aid for MCC during extrusion–spheronisation by Kleinebudde and co-workers [20–25]. Carrageenans are polysaccharides based on the repetition of a disaccharide sequence (galactose and anhydrogalactose). κ-Carrageenan pellets showed acceptable spherical shape and narrow pellet size distributions. In contrast to MCC pellets, systems based on κ-carrageenan showed fast disintegration of the pellet core, allowing for rapid drug release. Interestingly, the effects of adding different types of fillers on the pelletisation process and drug release were negligible. Therefore, the authors concluded that κ-carrageenan could be a promising excipient for extrusion–spheronisation especially in order to overcome matrix-type drug release profiles of MCC pellets. However, limited knowledge is yet available on the underlying drug release mechanisms from this type of delivery systems.

The major objectives of the present study were (i) to modify drug release from MCC pellets by the addition of a disintegrant (croscarmellose Na) or pore former (PEG 6000), (ii) to evaluate carrageenan as potential alternative extrusion aid for manufacturing highly dosed immediate release pellets, and (iii) to explain the observed phenomena based on the physicochemical properties of the core pellets and underlying drug release mechanisms. Pellets were prepared by extrusion–spheronisation containing at least 77% drug (vatalanib succinate, SAG/ZK, and theophylline).

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: vatalanib succinate ((4-Chlorophenyl)[4-(4-pyridylmethyl)phthalazin-1-yl]ammonium hydrogen succinate) and SAG/ZK (3-(5-Chloro-2-{2-[(2R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy} phenyl)uronium hydrogen sulfate) (Bayer Schering Pharma, Berlin, Germany); theophylline (BASF, Ludwigshafen, Germany); acetonitrile, ammonium dihydrogen phosphate, hydrochloric acid, phosphoric acid, potassium dihydrogen phosphate, and sodium hydroxide (Merck, Darmstadt, Germany); κ-carrageenan (Gelcarin GP 911 NF), croscarmellose Na (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH 101) (FMC, Cork, Ireland); ferric oxide pigment, talcum, and titanium dioxide (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany); hydroxypropyl methylcellulose (HPMC; Methocel E5, Colorcon, Nordmann Rassmann, Hamburg, Germany); and triethylammonium acetate buffer (Fluka Chemie, Buchs, Switzerland). All chemicals were reagent grade or higher.

2.2. Preparation of pellets

Pellets were prepared by extrusion–spheronisation. Dry powder blending of the drug and microcrystalline cellulose or carrageenan was performed in a Turbula® mixer (W.A. Bachhofen AG, Basel, Switzerland) at 22 rpm for 10 min. Thereafter, remaining excipients were added to the blend and mixed for another 10 min (for compositions of the formulations see Table 1, dry powder blending was performed on a 2000 g scale). For the discontinuous extrusion–spheronisation process, the dry powder blend was divided into smaller fractions. Wet granulates were prepared in a Nica™ high shear mixer (ML 6, Lejus, Mölndal, Sweden) by adding an appropriate amount of purified water. The wet mass (300 g) was then extruded through a ring die with 1 mm holes by using a Nica™ extruder (Lejus, Mölndal, Sweden) at a feeding speed of 75 rpm. Finally, the extrudate was processed in a Nica™ spheroniser (SP 300, Lejus, Mölndal, Sweden) fitted with a cross hatched friction plate rotating at 400 rpm for 2–8 min. After spheronisation, the pellets were dried in a fluid bed coater (GPCG-1, Glatt, Binzen, Germany). Pellets in a size range of 800–1250 μm were used throughout the study.

2.3. Coating of pellets

For the optional coating process, fractions of 500 g of pellets were coated with hydroxypropyl methylcellulose (HPMC, Methocel E5) in a fluid bed coater (GPCG-1) using bottom spray and a Wurster insert until a theoretical coating level of 10% or 20% (w/w, based on core pellets) was reached. Talcum (0.3%) was added as anti-tacking agent, titanium dioxide (1.0%), and ferric oxide pigment (0.004%) were used as coloring agents (w/w, based on the pellet cores). The coating conditions were as follows: inlet temperature = 60 °C, nozzle diameter = 0.8 mm, spray pressure = 0.8 bar, and spray rate = 7.2 g/min. After coating, the pellets were dried at 60 °C for 20 min.

2.4. Drug release studies

In vitro drug release was determined using the USP XXIX rotating basket method at 100 rpm or paddle method at 50 rpm (1000 ml dissolution medium, 37 °C, $n = 6$). Theophylline release was measured in water (solubility of theophylline in water = 73.2 mg/ml). To provide sink conditions, vatalanib succinate and SAG/ZK were released in 0.05 M phosphate buffer pH 3.0 (solubility = 7.9 mg/ml and 3.0 mg/ml, respectively). Using a Distek Premiere 5100 Dissolution System (Distek Inc., North Brunswick, USA), 10 ml samples were withdrawn (not replaced) at predetermined time intervals, filtered, and assayed. The amount of released SAG/ZK was measured using a Waters HPLC system (2695D Separation Module, Transfer Module, 2487 Dual Absorbance Detector, Waters Corp., Milford, USA). Samples (20 μL volume) were injected into a Symmetry C 18 column (3.5 μm, 4.6 mm × 150 mm, Waters, Milford, USA). A mixture of 55 ml 0.05 M triethylammoniumacetate buffer and 45 ml acetonitrile was used as mobile phase (flow rate = 1.0 ml/min, UV detection drug at 244 nm). The amount of released vatalanib succinate and theophylline was measured UV-spectrophotometrically at 316 nm and 272 nm, respectively.

2.5. Solubility measurements

Excess amounts of vatalanib succinate, SAG/ZK, or theophylline were exposed to water or phosphate buffer of pH 3.0 at 20 °C ($n = 3$). The pH of the medium was measured and – if required – adjusted by the addition of NaOH or HCl. The drug content in the supernatant was determined using HPLC or UV-spectrophotometer

Table 1
Compositions of the investigated pellets (all quantities are given in %).

Formulation no.	Vatalanib succinate	Theophylline	SAG/ ZK	MCC	Carrageenan	Croscarmellose Na	PEG 6000	Lactose	Mannitol	Dicalcium phosphate	Water*
1	90.0	–	–	10.0	–	–	–	–	–	–	35.0
2	90.0	–	–	9.0	–	1.0	–	–	–	–	40.0
3	90.0	–	–	7.5	–	2.5	–	–	–	–	45.7
4	90.0	–	–	5.0	–	5.0	–	–	–	–	60.0
5	90.0	–	–	7.5	–	–	2.5	–	–	–	30.0
6	90.0	–	–	5.0	–	–	5.0	–	–	–	15.0
7	80.0	–	–	–	20.0	–	–	–	–	–	75.0
8	77.0	–	–	–	20.0	–	–	3.0	–	–	73.0
9	77.0	–	–	–	20.0	–	–	–	3.0	–	74.0
10	77.0	–	–	–	20.0	–	–	–	–	3.0	77.0
11	–	80.0	–	–	20.0	–	–	–	–	–	65.0
12	–	90.0	–	10.0	–	–	–	–	–	–	23.0
13	–	–	80.0	–	20.0	–	–	–	–	–	70.0
14	–	–	90.0	10.0	–	–	–	–	–	–	27.0

* Processing aid removed upon drying. The 100% reference value is the total dry mass of the pellets.

as described earlier. The drug solubility was the equilibrium concentration in the supernatant.

2.6. Pellet disintegration

Pellet disintegration was monitored using a tablet disintegration tester (ZT 3, Erweka GmbH, Heusenstamm, Germany). One hundred milligrams of pellets were filled into tubes (diameter = 10 mm; length = 17 mm) that were closed with sieves with a mesh size of 710 μm. The disintegration time was determined at a dipping speed of 30 dips/min in water at 37 °C ($n = 6$).

2.7. Tensile strength

Prior to the measurements, the pellets were stored at 25 °C and 60% RH until constant weight was reached. The mechanical properties of the pellets were determined using a texture analyzer (TAXT plus, Stable Micro Systems, Godalming, England). Individual pellets were placed between the flat plate and upper punch of the texture analyzer and the puncture probe was driven downward at a crosshead speed of 0.1 mm/s. The force to fracture the pellets (F) was converted into tensile strength according to the following equation:

$$\sigma = \frac{1.6 \cdot F}{\pi \cdot d^2} \quad (1)$$

where σ is the tensile strength and d *is* the diameter of each pellet in crushing direction. At least 30 pellets per batch were investigated to determine the tensile strength.

2.8. Water sorption

The sorption/desorption isotherms of MCC and carrageenan were determined using a Gemini sorption test system (Gemini 2360, Micrometrics, Mönchengladbach, Germany). Samples of approximately 2 g were exposed to 60% relative humidity at 25 °C. The weight of the samples was measured until equilibration was reached ($n = 3$).

2.9. Porosity measurements

The gas pycnometric density (ρ_g) of the pellets was determined using a helium pycnometer (Ultrapyk 1000 T, Quantachrome, Odelzhausen, Germany). The apparent density of the pellets (ρ_a) was measured with a mercury porosimeter (Pascal 140, Fisons, Valencia, USA). For apparent density measurements, the samples were first degassed and then intruded by mercury. Gas pycnometric and apparent density measurements were conducted in triplicate and the porosity (ε) of the pellets was calculated as follows:

$$\varepsilon = \left(1 - \frac{\rho_a}{\rho_g}\right) \quad (2)$$

2.10. Optical analysis

Image analysis was conducted using an optical microscope (BX 50, Olympus, Hamburg, Germany) combined with a video camera (HV-T20, Hitachi Kokusai Electric Europe GmbH, Erkrath, Germany). For pellet size and shape measurements, approximately 500 pellets of each sample were placed on a glass slide, which was scanned and imaged with the video camera (1 pixel = 13.3 μm). The digital image processing was performed using the software Analysis five (Olympus Soft Imaging Solutions GmbH, Münster, Germany). The ratio of the maximum Feret diameter to the Feret diameter perpendicular to the maximum Feret diameter was used to calculate the aspect ratio.

2.11. SEM photographs

Pellets were coated for 60 s under an argon atmosphere with gold–palladium (MED 020, Bal-tec AG, Liechtenstein) and then observed with a scanning electron microscope (DSM 982, Zeiss, Oberkochen, Germany).

2.12. Laser diffraction measurements

The particle size distributions of the drug powders were determined by laser diffraction measurements (volume distribution, Coulter LS 13320, Coulter Corporation, Hialeah, USA).

3. Results and discussion

One of the major aims of this study was to develop and manufacture pellets by extrusion–spheronisation, which contain at least 77% (w/w, based on total pellet mass) drug with low/poor aqueous solubility and exhibit immediate release (>75% drug released within 30 min). Hence, these pellets aim at avoiding the slow matrix-type drug release of conventional MCC pellets manufactured by extrusion–spheronisation. In contrast to tablets, pellets provide the advantages of multiple-unit dosage forms such as increased dosing flexibility. Therefore, they are an interesting option during clinical trials, requiring flexible drug dosing within large ranges.

Vatalanib succinate was used throughout this study as a poorly water-soluble model drug. For the most promising formulations, results were confirmed with poorly water-soluble SAG/ZK and slightly water-soluble theophylline.

3.1. Shape, yield, and required water content

Pellets with up to 90% (w/w, based on the total dry pellet mass) drug were successfully prepared by extrusion–spheronisation. The yield of all batches (defined as particles in the size range of 800–1250 μm) was ⩾90% and the aspect ratios of the pellets varied between 1.09 and 1.16, indicating spherical geometry (an aspect ratio of 1.00 indicates ideal spherical geometry, in general values of up to 1.20 are considered as acceptable). SEM pictures of selected formulations (nos. 1, 6, and 7 in Table 1) also clearly indicate the spherical shape of the pellets, irrespective of the type of matrix former (MCC versus carrageenan) or presence of PEG as a pore former (Fig. 1). Furthermore, very similar pellet properties were observed with respect to the aspect ratio and yield when repeating pelletisation (formulation nos. 1, 6, and 7 in Table 1) at given formulation and process parameters.

The amount of water required for the extrusion process strongly depended on the type of matrix former (MCC versus carrageenan), presence of a disintegrant (croscarmellose Na), type of drug (vatalanib succinate, SAG/ZK, or theophylline), and presence of a pore former (PEG 6000) (formulation nos. 1–14 in Table 1). The relative amount varied between 15% and 77% (w/w, based on the total dry pellet mass). In general, carrageenan-based formulations required higher water amounts compared to MCC formulations. This can be explained by the higher water binding capacity of carrageenan as observed in sorption experiments: The water content of carrageenan and MCC powders stored at 60% relative humidity was found to be equal to 24% and 9%, respectively. These findings are in good agreement with data reported in the literature [21]. Croscarmellose Na swells upon contact with water and, thus, also requires higher amounts of water for pelletisation. Insoluble fillers and poorly water-soluble drugs are mainly suspended during the extrusion/spheronisation process and, hence, require additional amounts of water. The ranking order of the drug solubility in water [theophylline (73 mg/ml) > SAG/ZK (5.9 mg/ml) > vatalanib succinate (0.35 mg/ml)] is in good agreement with the ranking order of the water amounts required for pelletisation (theophylline < SAG/ZK < vatalanib succinate). In contrast, water-soluble components are to a much higher extent dissolved during extrusion. Consequently, less water is required for the pelletisation process in the case of PEG 6000 (Table 1).

3.2. In vitro drug release

First of all, the effects of the type of dissolution apparatus (paddle versus basket), amount of pellets per vessel and volume of the release medium (phosphate buffer pH 3.0) on the resulting drug release kinetics were studied with one model formulation (formulation no. 4 in Table 1). Pellets consisting of 90% vatalanib succinate, 5% MCC, and 5% croscarmellose Na were exposed to phosphate buffer of pH 3. Fig. 2 shows the following: (i) The use of 500 ml or 1000 ml release medium did not significantly affect drug release (open squares versus filled triangles). (ii) Increasing the amount of pellets from 186 mg to 372 mg led to a decrease in the drug release rate (filled versus open triangles). (iii) The type of dissolution tester strongly affected drug release: Vatalanib succinate release was much faster in the paddle apparatus (filled squares). Importantly, the pellets remained intact in both types of setups. Thus, pellet disintegration due to higher shear forces cannot explain this phenomenon. Most likely, the differences in the hydrodynamic conditions within the release medium near to the pellets' surface

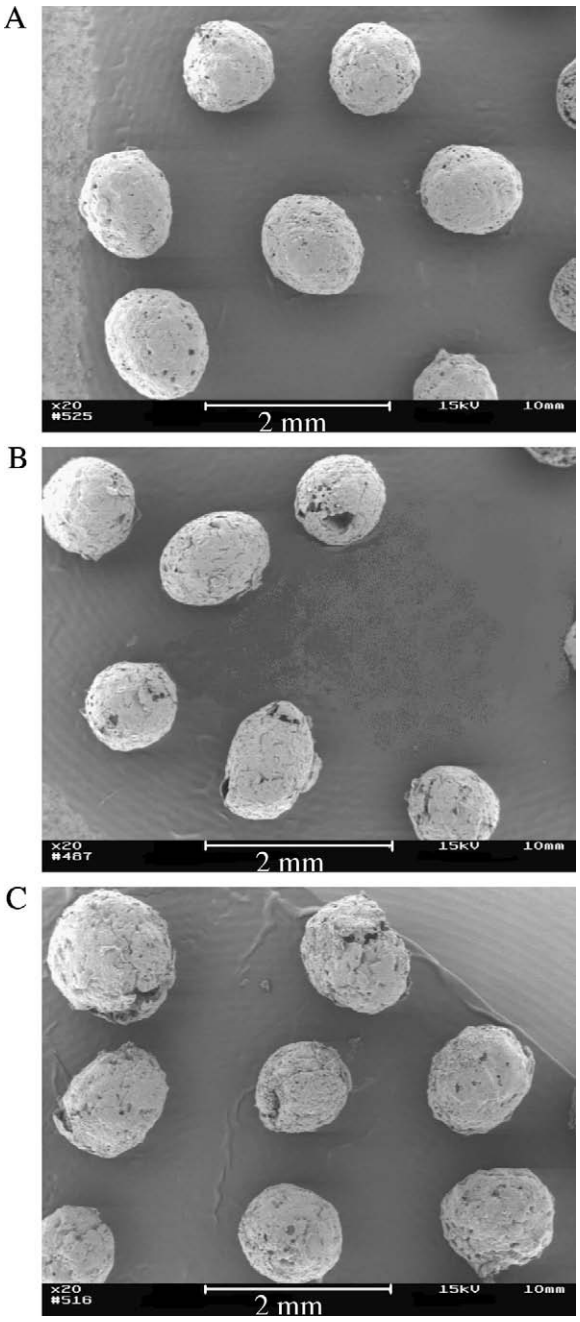

Fig. 1. Scanning electron micrographs of pellets based on (A) MCC, (B) MCC and PEG 6000, and (C) carrageenan (formulation nos. 1, 6, and 7 in Table 1).

are responsible for this effect. When using the paddle apparatus, the bulk fluid is more rigorously agitated and convectional mass transport much more important, in particular in the pellets' vicinity. In contrast, the degree of bulk fluid agitation within the baskets is much lower, resulting in reduced convectional drug transport. As the drug is poorly soluble in water, such differences in the degree of bulk fluid agitation are likely to significantly alter the resulting dissolution rate. With decreasing intensity of agitation, the thickness of unstirred liquid boundary layers increases, resulting in decreased drug concentration gradients, being the driving forces for drug dissolution [26]. Thus, drug release is faster in the more rigorously stirred bulk fluid in the paddle apparatus. The observed decrease in the relative drug release rate when increasing the pellet amount in the basket apparatus can also be attributed to the

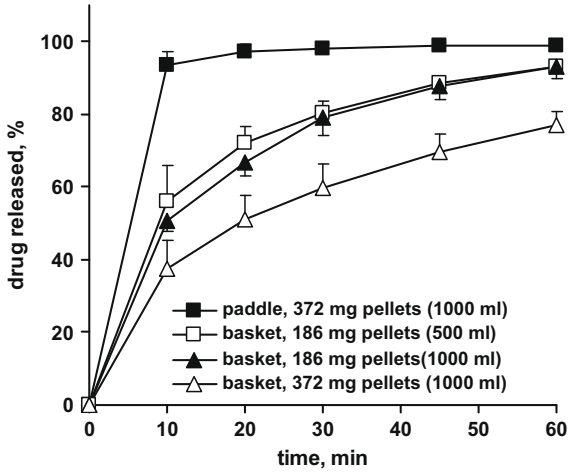

Fig. 2. Effects of the type of dissolution apparatus (paddle versus basket), amount of pellets per vessel and volume of the release medium (phosphate buffer pH 3.0) on the resulting vatalanib succinate release kinetics from pellets based on MCC and croscarmellose Na (formulation no. 4 in Table 1).

relatively low degree of bulk fluid agitation in the basket and to the limited drug solubility. When doubling the number of pellets per basket, the increase in the absolute release rate is limited due to the hindrance of drug release by already released drug (which is not rapidly transported far away from the pellets' surface). At the same time, the 100% reference value is doubled. As 372 mg pellets represent a typical dosing, all further experiments were performed with this pellet amount. Also, as the paddle apparatus can be expected to better simulate the hydrodynamic conditions in the contents of the GIT, drug release was measured with this type of experimental setup in all further experiments.

Importantly, drug release was slow when using only MCC as pelletisation aid (open triangles in Fig. 3). To better understand the underlying drug release mechanisms, a mathematical model based on Fick's law was used to quantitatively describe the observed vatalanib succinate release patterns. The theory considers that

- The drug is homogenously distributed throughout the pellets before exposure to the release media.

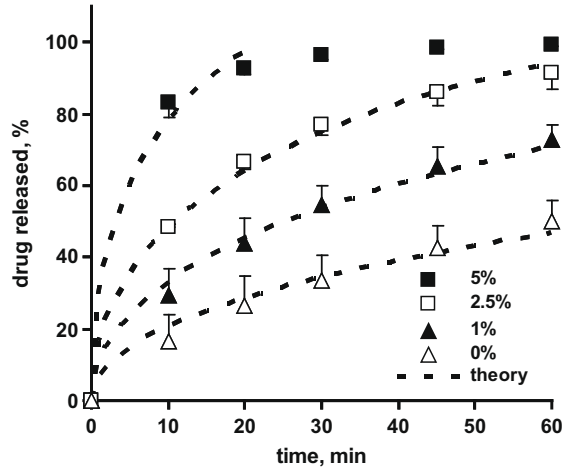

Fig. 3. Effects of the addition of different amounts of croscarmellose Na on the release of vatalanib succinate from MCC pellets (formulation nos. 1–4 in Table 1). Symbols represent experimental results and dotted lines indicate theoretical values (Eq. (3)).

- The initial drug concentration in the dosage form is well above drug solubility.
- The pellets are spherical in shape.
- The pellets remain intact during drug release within the observation period.
- Perfect sink conditions are maintained throughout the experiments.
- Drug release is controlled by diffusion with constant diffusivities and the limited drug solubility.

Taking these initial and boundary conditions into account, the following equation can be derived [27]:

$$M_t = 4 \cdot \pi \cdot r^2 \cdot \left[\sqrt{2 \cdot (c_0 - c_s) \cdot c_s \cdot D \cdot t} + \frac{4 \cdot c_s \cdot D \cdot t}{9 \cdot r} \cdot \left(\frac{c_s}{2 \cdot c_0 - c_s} - 3 \right) \right] \quad (3)$$

where M_t is the cumulative absolute amount of drug released at time t; r represents the radius of the pellet; c_0 and c_s are the initial drug concentration and the solubility of the drug within the system, respectively; and D denotes the constant diffusion coefficient of the drug. Note that this equation is valid only as long as non-dissolved drug excess exists.

As it can be seen in Fig. 3, fitting Eq. (3) to the experimentally determined release rate of vatalanib succinate from the MCC-based pellets resulted in good agreement between theory (dotted curve) (r = 0.051 cm, c_0 = 900 mg/cm^3, c_s = 7.9 mg/cm^3) and experiment (open triangles). Thus, drug diffusion in combination with limited drug solubility is likely to be the dominant mass transport mechanism in this type of drug delivery systems. Based on this fitting, an apparent diffusivity of 1.3×10^{-6} cm^2/s could be determined for vatalanib succinate in these MCC pellets.

Importantly, the resulting drug release rate could effectively be increased by addition of only a few percentages of the disintegrant croscarmellose Na (Fig. 3). Interestingly, fitting Eq. (3) to these sets of experimental values resulted in good agreement between theory and experiment in all cases (dotted curves and symbols in Fig. 3). Thus, the dominant drug release mechanism remains unaffected. Based on these calculations, the following apparent diffusion coefficients of vatalanib succinate in MCC pellets containing 1%, 2.5%, and 5% croscarmellose could be determined as 3.6, 8.4, and 29×10^{-6} cm^2/s, respectively.

In a second approach, the water-soluble pore former PEG was incorporated into MCC-based vatalanib succinate pellets to overcome the slow drug release from "pure" MCC pellets (formulation nos. 1, 4–6 in Table 1). As it can be seen in Fig. 4, this approach was successful and drug release could be significantly accelerated by the addition of 2.5% and 5% PEG. Interestingly, the resulting vatalanib succinate release rate from pellets containing 5% PEG or 5% croscarmellose was very similar (closed and open squares in Fig. 4). Again, the presented mathematical model (Eq. (3)) could successfully be used to quantify drug release from the different types of systems (dotted curves and symbols in Fig. 4). Based on these calculations, the following apparent vatalanib succinate diffusivities could be determined: 5.4×10^{-6} cm^2/s (2.5% PEG) and 27×10^{-6} cm^2/s (5% PEG).

It has been reported that disadvantages of MCC pellets such as prolonged matrix-type drug release could also be overcome when using carrageenan as pelletisation aid [20–25]. Therefore, in a third approach, MCC was replaced by carrageenan. To obtain spherical carrageenan pellets (aspect ratios below 1.20), the amount of vatalanib succinate was slightly decreased to 80% (w/w, based on total dry pellet mass). Drug release from carrageenan pellets was significantly faster compared to drug release from MCC pellets (Fig. 5, formulation nos. 1 and 7 in Table 1). The release rate was in the

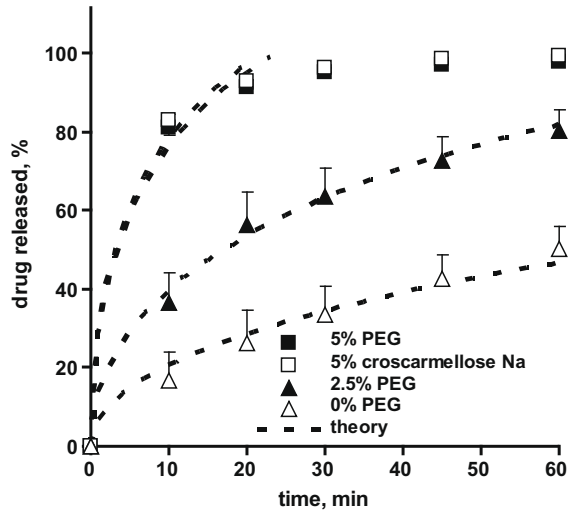

Fig. 4. Effects of the addition of different amounts of PEG on the release of vatalanib succinate from MCC pellets and comparison with pellets based on MCC containing 5% croscarmellose Na (formulation nos. 1, 4–6 in Table 1). Symbols represent experimental results and dotted lines indicate theoretical values (Eq. (3)).

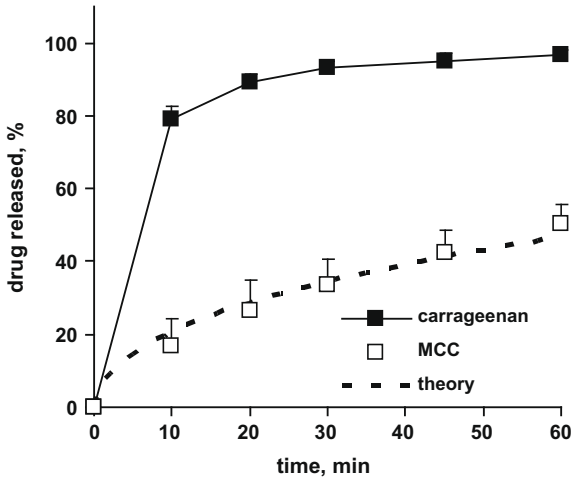

Fig. 5. Release of vatalanib succinate from pellets based on carrageenan in comparison with pellets based on MCC (formulation nos. 1 and 7 in Table 1). Symbols represent experimental results and the dotted curve indicates theoretical values (Eq. (3)).

same order of magnitude as the one from MCC pellets containing 5% disintegrant or pore former (upper curves in Fig. 4). To better understand the observed differences in the release rates of pellets based on carrageenan and MCC, the gas pycnometric and apparent density of the pellets was measured using a helium and mercury pycnometer, respectively. The porosity of the carrageenan and MCC pellets (calculated according to Eq. (2)) was equal to 27.8% and 14.4%, respectively. Hence, the increased drug release rate observed with carrageenan-based pellets can at least partially be attributed to the higher porosity of the systems, allowing for faster water influx. Furthermore, pellet disintegration was observed to be complete within 6 min only during the drug release measurements in the case of carrageenan-based pellets. In contrast, MCC-based systems remained intact during the observation period. As pellet disintegration fundamentally alters the conditions for drug transport and as this process is difficult to be quantitatively described in a mechanistic realistic way, no effort was made in this study to mathematical model drug release from carrageenan-based pellets.

It has to be pointed out that the mechanical stability of pellets is crucial for further processing, e.g. coating and/or tableting. Therefore, the tensile strength of the investigated pellets was determined. The following values were obtained with systems based on MCC, MCC/croscarmellose Na, MCC/PEG, and carrageenan (formulation nos. 1, 4, 6, and 7 in Table 1): 2.8 (±0.3), 2.7 (±0.4), 2.5 (±0.2), and 1.5 (±0.3) MPa (arithmetic mean ± standard deviation), respectively. These differences can at least partially be attributed to the observed differences in the systems' porosities: The porosity of MCC pellets were in the range of 9.1–17.5%, whereas carrageenan pellets were much more porous (ε = 27.8%). These findings are in good agreement with data reported in the literature [21]. Generally, tensile strength values above 1 MPa are likely to be sufficient for further processing.

To allow for easy adjustment of slightly varying water contents of different drug batches in the development phase, small amounts of fillers might be added to compensate for differences in the mass of the powder blends. In order to evaluate the effects of the presence of these fillers on drug release from carrageenan-based pellets, 3% lactose, mannitol, or dicalcium phosphate was incorporated (replacing 3% MCC) (formulation nos. 8–10 in Table 1). As is can be seen in Fig. 6, only minor differences in the in vitro release profiles were observed when using these fillers. The slightly slower drug release from pellets containing dicalcium phosphate can be attributed to the fact that this filler is water-insoluble and, thus, hinders drug release. It has to be pointed out that at higher filler contents, significant effects of the type of filler on drug release can be observed [21]. In principle, all investigated fillers were suitable for manufacturing of vatalanib succinate/carrageenan pellets.

Furthermore, potential effects of differences in the initial particle size of the drug on the resulting release kinetics from carrageenan-based pellets were studied (formulation no. 7 in Table 1). The D 50 values (indicating that 50% of the particles were below the mentioned size) of the investigated vatalanib succinate batches varied between 50 and 125 μm. As it can be seen in Fig. 7, the drug release rate increased with decreasing drug particle size. This can be explained based on the Noyes–Whitney equation [26] stating that the dissolution rate of a solid particle in its own solution is proportional to the available surface area. With decreasing particle size, the relative surface area of the system increases.

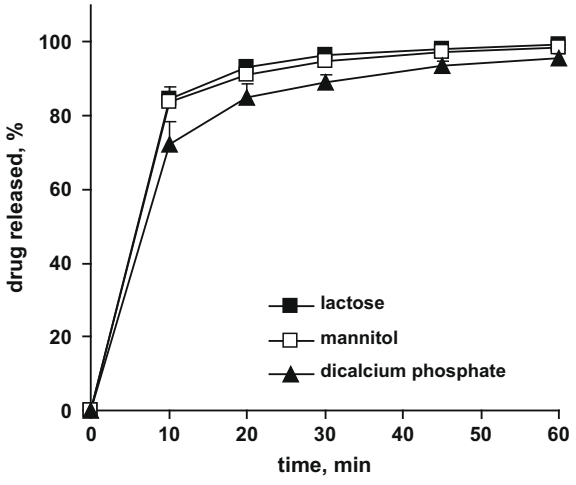

Fig. 6. Effects of the addition of small amounts of different excipients on the release of vatalanib succinate from pellets based on carrageenan (formulation nos. 8–10 in Table 1).

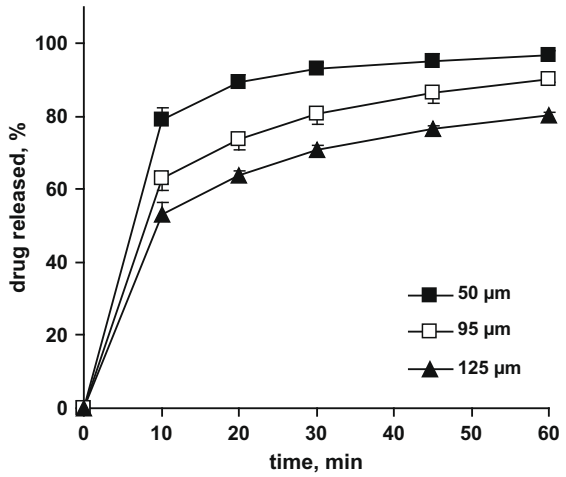

Fig. 7. Influence of the drug particle size (D 50 values indicating that 50% of the particles are below the mentioned size) on the release of vatalanib succinate from pellets based on carrageenan (formulation no. 7 in Table 1).

Furthermore, the effects of an additional (rapidly dissolving) film coating for esthetic reasons and/or taste masking on drug release from carrageenan-based pellets were studied. Pellets containing 80% vatalanib succinate and 20% carrageenan (formulation no. 7 in Table 1) were coated with a low-molecular-weight hydroxypropyl methylcellulose (HPMC, Methocel E 5). A uniform pellet coating was achieved by spraying 10–20% (w/w, based on total core pellet mass) polymer onto the carrageenan pellets. As it can be seen in Fig. 8, the addition of a 10% or 20% HPMC coating only moderately reduced the resulting drug release rate: For instance, after 20 min 89%, 84%, and 78% vatalanib succinate were released from pellets coated with 0%, 10%, and 20% HPMC, respectively. These differences in the drug release rates can be explained by the additional dissolution step of the polymer coating. Thus, these results clearly demonstrate that further processing of carrageenan pellets is feasible.

A very important practical aspect is long term stability of the dosage forms, under ambient and under stress conditions. Carrageenan and MCC/croscarmellose Na pellets (formulation nos. 4 and 7 in Table 1) were stored openly at 25 °C/60% relative humidity (RH), 30 °C/70% RH, and 40 °C/75% RH for 6 months according to the ICH guidelines. As it can be seen in Fig. 9A, vatalanib succinate release from carrageenan-based pellets remained unaltered, irrespective of the type of storage conditions. In contrast, drug release rates from MCC/croscarmellose Na-based pellets significantly slowed down during long-term storage (Fig. 9B). With increasing storage temperature and relative humidity, the decrease in the release rate became more and more pronounced. For example, after 20 min, 93% versus 61% drug release was observed from pellets before and after 6 months storage at 40 °C/75% RH. The exact reasons for this phenomenon are yet unclear, but structural changes within the croscarmellose Na upon water uptake, especially at elevated relative humidity might be involved: The disintegration power of pre-wetted croscarmellose Na can be expected to be reduced.

To evaluate the suitability of carrageenan-based pellets prepared by extrusion–spheronisation for other types of highly dosed drugs, vatalanib succinate was replaced by theophylline and SAG/ZK (formulation nos. 11 and 13 in Table 1). Again, spherical pellets with aspect ratios of 1.10–1.15 were obtained at a drug/carrageenan blend ratio of 8:2. Irrespective of the type of drug, rapid and complete drug release was observed for these formulations (Fig. 10, upper curves). In contrast, much slower drug release rates were obtained when using MCC as pelletisation aid (formulation nos. 12 and 14 in Table 1) (Fig. 10, bottom curves). Again, good agreement between the presented mathematical model (Eq. (3))

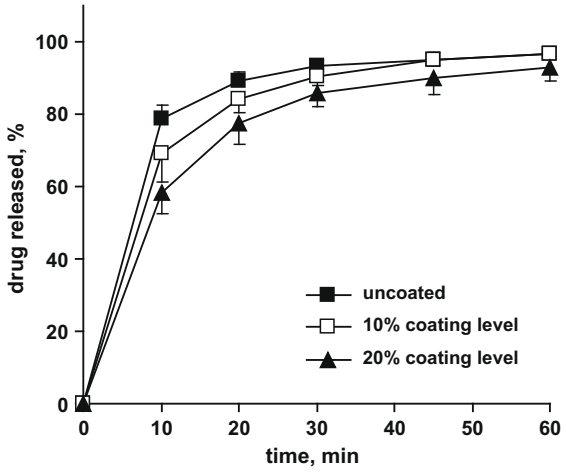

Fig. 8. Effects of an additional, fast dissolving pellet coating (hydroxypropyl methylcellulose) on the release of vatalanib succinate from pellets based on carrageenan (formulation no. 7 in Table 1).

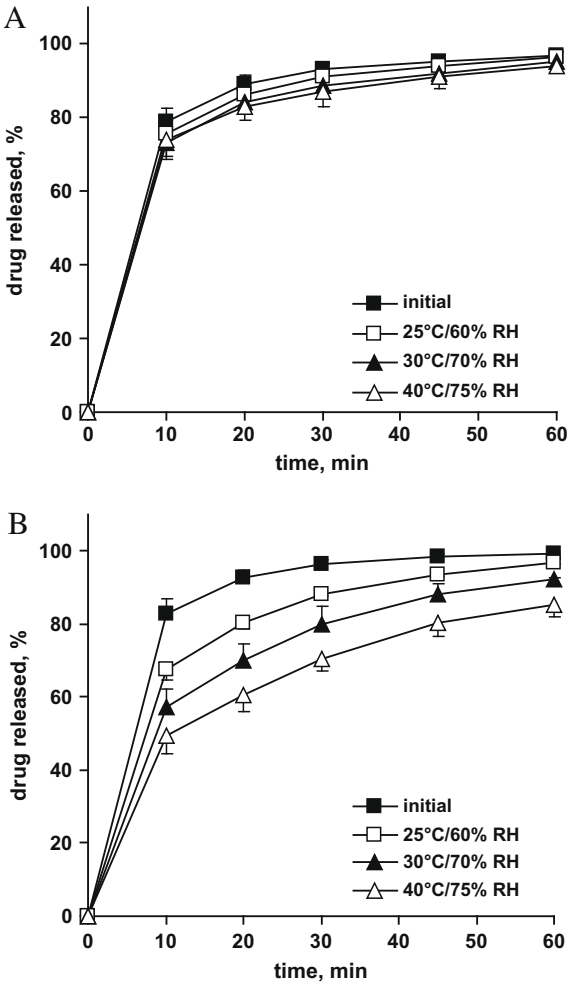

Fig. 9. Vatalanib succinate release from pellets based on (A) carrageenan and (B) MCC and 5% croscarmellose Na before and after 6 months open storage under different conditions (indicated in the diagrams) (formulation nos. 4 and 7 in Table 1).

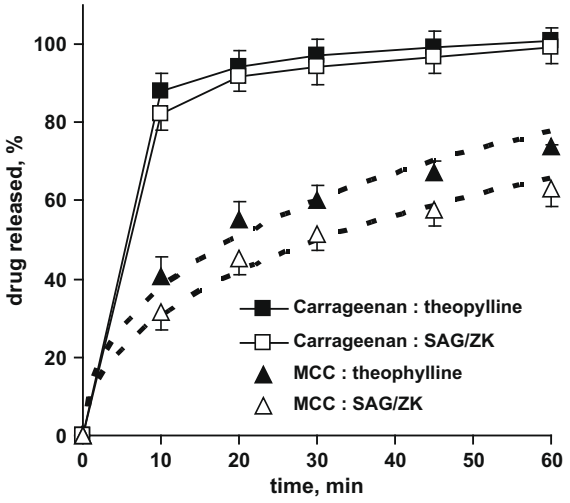

Fig. 10. Effects of the type of drug (theophylline versus SAG/ZK) on the release rate from pellets based on carrageen or MCC (formulation nos. 11–14 in Table 1). Symbols represent experimental results, dotted curves indicate theoretical values (Eq. (3)).

and the experimentally measured theophylline and SAG/ZK release kinetics were observed for MCC-based pellets (dotted curves and triangles in Fig. 10), indicating that drug diffusion in combination with limited drug solubility controls the release from this type of dosage forms. The apparent drug diffusivities in these pellets were determined to be equal to 5.7×10^{-7} cm^2/s (theophylline) and 3.6×10^{-7} cm^2/s (SAG/ZK), respectively. These findings can again be attributed to the different disintegration behaviors and porosities of the systems: ε(SAG/ZK:carrageenan and theophylline:carrageenan pellets) = 26.2% and 28.4% versus ε(SAG/ZK:MCC or theophylline:MCC pellets) = 13.9% and 12.7%.

4. Conclusions

Pellets containing up to 90% drug were successfully prepared by extrusion–spheronisation when using MCC or carrageenan as matrix former. Drug release from MCC pellets is slow and predominantly controlled by pure diffusion in combination with limited drug solubility. Importantly, drug mobility can significantly be increased by the addition of only small amounts of a disintegrant (croscarmellose Na) or pore former (PEG). In contrast to MCC-based pellets, carrageenan-based pellets are much more porous and rapidly disintegrate upon contact with aqueous media, resulting in rapid release, even in the case of highly dosed drugs with low/poor aqueous solubility.

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