Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 708–717
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

New insights on poly(vinyl acetate)-based coated floating tablets: Characterisation of hydration and CO_2 generation by benchtop MRI and its relation to drug release and floating strength

Sandra Strübing, Tâmara Abboud, Renata Vidor Contri, Hendrik Metz, Karsten Mäder *

Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany

Received 17 November 2007; accepted 13 December 2007
Available online 23 December 2007

Abstract

The purpose of this study was to investigate the mechanism of floating and drug release behaviour of poly(vinyl acetate)-based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm^2 were investigated regarding drug release in 0.1 N HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, benchtop MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm^2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics. Poly(vinyl acetate) proved to be an appropriate excipient to ensure safe and reliable drug release. Floating strength measurements offered the possibility to quantify the floating ability of the developed systems and thus to compare different formulations more efficiently. Benchtop MRI studies allowed a deeper insight into drug release and floating mechanisms noninvasively and continuously.

Keywords: Floating tablets; Coated tablets; Poly(vinyl acetate); MRI; Kollidon® SR; Kollicoat® IR; Kollicoat® SR

1. Introduction

The absorption of active pharmaceutical ingredients from oral drug delivery systems is related to gastrointestinal tract transit time. The retention of oral dosage forms in the upper gastrointestinal tract results in a prolonged contact time of drugs with the gastrointestinal tract mucosa. Gastroretentive devices exhibiting controlled drug release are of particular interest for drugs that are absorbed incompletely due to a relatively narrow region for absorption in the gastrointestinal tract, such as cyclosporin, ciprofloxacin and furosemide [1–4]. Drugs that are less soluble or are degraded in a higher pH environment such as verapamil HCl and captopril, respectively, may also benefit from gastric retention [5–7]. Furthermore, the application of gastric retentive devices to drugs acting locally in the stomach (e.g. antibiotics against *Helicobacter pylori* and misoprostol) is of great interest [8,9]. Prolonged gastric residence is expected to lead to an increased contact interval with the main absorption site, the mucosa of the small intestine. Due to an improved bioavailability combined with a reduced frequency of administration and thus improved patient compliance gastric retentive devices may be used as extended release drug delivery systems as well [10]. As for a reliable retention behaviour in the stomach food effects and the complex motility of the stomach are of vital importance only convincing in vivo data can prove the retention efficacy of a developed system.

Gastric retention of solid dosage forms can be achieved using mucoadhesive, swelling, expanding and floating drug delivery systems [11–14]. Poly(vinyl acetate) based matrix

* Corresponding author. Martin-Luther-University Halle-Wittenberg, Institute of Pharmacy, Wolfgang-Langenbeck-Strasse 4, 06120 Halle/Saale, Germany. Tel.: +49 345 5525167; fax: +49 345 5527029.
E-mail address: karsten.maeder@pharmazie.uni-halle.de (K. Mäder).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.12.009

tablets have been recently developed and characterised [15]. They flow due to their intrinsic low density. In our study a floating oral drug delivery system consisting of a sodium bicarbonate containing tablet core covered by a polymeric film coat to obtain a membrane controlled drug delivery device was developed.

The formulation was characterized by a biplanar tablet core with beveled edges consisting of Propranolol HCl as a highly water soluble model drug and sodium bicarbonate as a CO_2 developing agent. Kollidon® SR was chosen as an excipient for direct compression leading to a high tablet hardness at low compression forces while the density of the tablet core was relatively low [16]. It was expected that the good floating properties of Kollidon® SR would be able to compensate the deficient floating properties of Propranolol HCl. The tablet cores were then coated with a coating formulation consisting of Kollicoat® SR as a water insoluble polymer and Kollicoat® IR as a hydrophilic water soluble polymer with two different compositions. As the formation of cracks in polymer films is related to the loss of functionality concerning the floating and the drug retaining abilities, Kollicoat® SR was chosen as the membrane forming excipient due to its exceptional elasticity of the polymer film [17]. The coating level varied from 10 to 20 mg polymer/cm^2. After contact with an acidic medium comparable to the conditions in the stomach the hydrochloric acid was expected to diffuse through the polymer coat and initialize CO_2 development inside the tablet, leading to a reduced density of the tablet and flotation of the system.

The penetration of hydrochloric acid through the polymer film into the tablet core and subsequent formation of carbon dioxide play a vital role regarding the floating characteristics as well as the hydration of the tablet core being related to the initiation of drug dissolution. Therefore, the monitoring of these processes leads to a deeper understanding of floating and drug release mechanisms. Studies regarding the characterization of swelling and hydration processes of matrix devices have already been performed [18–20]. Although the application of Magnetic Resonance Imaging to monitor drug delivery processes is widely accepted, the method is scarcely used due to high investment and running costs of superconducting MRI machines. NMR benchtop instruments capable of imaging have been developed very recently. Compared to superconducting standard MRI machines they are much more affordable due to lower price and running costs. In this study the benchtop MRI instrument was used to monitor diffusion and swelling processes as well as carbon dioxide development inside the polymer shell.

In terms of floating characteristics of gastric retentive devices not only the onset and duration of flotation plays a major role, but also the ambition of the system to float. Although many studies in the field of gastroretentive drug delivery systems have been performed, the characterisation of the floating strength has been neglected in many studies [21]. As the presence of food in the stomach might increase the viscosity heavily, higher floating forces increase the probability of the tablet to remain afloat, reducing food effects on tablet retention. Therefore the floating strength of the developed systems was monitored using a simplified apparatus according to Timmermans and Moës [22,23].

2. Materials and methods

2.1. Materials

Propranolol HCl, sodium bicarbonate, magnesium stearate, triacetin and talc were obtained by Sigma–Aldrich (Taufkirchen, Germany). Propranolol HCl and sodium bicarbonate were ground thoroughly in a mortar and passed through a 250-μm sieve. Titanium dioxide was received from Kronos Titan GmbH & Co. OHG, Leverkusen, Germany. Kollidon® 30, Kollidon® SR, Kollicoat® SR 30 D and Kollicoat® IR were a kind donation from BASF (Ludwigshafen, Germany) and were used as received.

2.2. Preparation of tablet cores

The powder mixture for the manufacturing of the tablets was prepared according to Table 1 by blending Propranolol HCl, sodium bicarbonate and Kollidon® SR for 10 min in a z-arm mixer (AR 400, Erweka, Germany). After adding magnesium stearate the mixture was blended for another 2 min. Tablets with beveled edges measuring 11 mm in diameter were prepared by direct compression using a single punch tabletting machine (Korsch EK0/DMS, Germany). Compression force was set to 6 kN to receive tablets characterized by a crushing force of 75 ± 4 N. The crushing force was determined using an Erweka TBA 30 crushing force tester (Erweka, Heusenstamm, Germany). Tablets were then stable enough to resist the mechanical forces in the drum coater and showed a low friability of 0.1%.

2.3. Coating of tablet cores

To investigate the influence of Kollicoat® IR content on drug release and floating characteristics coating formulations with different Kollicoat® SR/Kollicoat® IR ratios (SR/IR, 9:1 and SR/IR, 8.5:1.5), related to each other as dry mass, were produced. Coating dispersions were prepared according to the compositions shown in Table 2. Therefore Kollicoat® IR, Kollcoat® SR, 7.0 g triacetin

Table 1
Composition of the tablet cores of the floating devices

Tablet components	Amount (mg)
Propranolol HCl	35.0
Kollidon® SR	249.2
Sodium bicarbonate	62.3
Magnesium stearate	3.5

Table 2
Composition of coating formulations with different Kollicoat® SR/Kollicoat® IR ratios

Kollicoat® SR/Kollicoat® IR ratio	9:1	8.5:1.5
Kollicoat® SR 30 D	496.0	496.0
Kollicoat® IR	16.5	22.3
Triacetin	7.0	7.0
Kollidon® 30	5.0	5.0
Titanium dioxide	5.0	5.0
Talc	35.0	35.0
Distilled water	435.5	429.7

and 300 g distilled water were mixed thoroughly. For the pigment suspension titanium dioxide, talc and Kollidon® SR were dispersed in 135.5 or 129.7 g distilled water, respectively. The pigment suspension was then added to the polymer dispersion and mixed again. Blending was always performed using an Ultra Turrax (T18 basic, Ika, Germany) working at 18,000 rpm for 3 min. The coating process was carried out in a drum coater (Lab-Coater GC 300, Glatt Maschinen-und Apparatebau AG, Pratteln, Switzerland). Coating parameters were adjusted as follows: inlet temperature 50 °C, process air 100 m^3/h, atomizing air pressure 2 bar, 7.5 g/min, pan speed 7 rpm. Tablet samples were taken at 10, 12, 14, 16, 18 and 20 mg polymer/cm^2 coating level.

2.4. Determination of the floating strength

To monitor in vitro the total vertical force F working on an immersed object an experimental setup using an apparatus simplified according to Timmermans and Moës was used [22,23]. As the force F determines the resultant weight of the floating tablet, it may be used to quantify and thus to further characterize floating behaviour. The magnitude and direction of force F and thus the resultant weight of the floating object is determined by the vectorial sum of the gravity (F_{grav}) and buoyancy (F_{buoy}) forces acting on the tablet,

$$\begin{aligned} F &= F_{buoy} - F_{grav} \\ &= d_f gV - d_s gV = (d_f - d_s)gV \\ &= (d_f - m/V)gV \end{aligned} \quad (1)$$

where F is the total vertical force, g is the acceleration of gravity, d_f is the density of the fluid, d_s is the density of the tablet, m is the tablet mass and V is the tablet volume.

The instrument used to determine the floating strength of the tablet samples measured the force equivalent to F required to maintain the tablet totally submerged into the dissolution medium [23]. A sample holder was connected to a metal base placed on an analytical balance via a metal pole. For the performance of floating strength experiments the tablets were placed in a beaker with 0.1 N HCl of 37 °C, so that the sample holding device was covered with dissolution medium. After the positioning of the tablet in the dissolution medium and subsequent taring of the analytical balance the sample was shifted under the sample holder. The floating strength was then determined as the weight diminution on the analytical balance over time. Floating experiments were performed in triplicate.

Furthermore, the floating lag time (FLT) was measured in conjunction with the dissolution experiments. FLT is defined as the time taken by the tablet to reach the top from the bottom of the vessel. In addition the floating duration (FD) within a time interval of 24 h, defined as the time period for which the tablet constantly floats on the surface of the medium, was measured. Floating lag time and floating duration were determined in triplicate in conjunction with the dissolution experiments.

2.5. Determination of dissolved drug amount

Propranolol HCl dissolution studies were carried out with an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) in 900 ml of 0.1 N HCl of 37 °C at 50 rpm. Released Propranolol HCl amounts were determined by measuring the UV absorption at 290 nm and calculated using calibration curves of the drug. Dissolution experiments were carried out over 24 h and performed in triplicate.

After extrapolating the linear part of the dissolution curve to the abscissa it was possible to calculate the lag times at the initial phase of the drug dissolution profiles. Errors were a function of the correlation coefficient of the best fit straight line and reached maximum values of 1.7%.

2.6. Benchtop ^1H NMR Imaging experiments

^{1}H NMR imaging experiments were performed on a benchtop MRI spectrometer working at a frequency of 20 MHz and having a static magnetic field of strength (B_0) of 0.5 T (Oxford Instruments, UK). Tablets were placed in a USP paddle dissolution apparatus with 900 ml of 0.1 N HCl of 37 °C, stirred at 50 rpm and removed for MRI measurements after predefined time intervals. The sample holder was filled with 2 ml 0.1 N HCl and glass beads on the bottom to allow three-dimensional water penetration even in case of sinking tablets. A slice of 10-mm thickness was selected. A standard spin–echo sequence was used with an echo time (TE) of 9.8 s and a repetition time (TR) of 300 ms leading to an acquisition time of about 10 min for each image. Sixteen scans were accumulated to obtain 128 × 128 pixel images with a field of view of 4 cm, which led to an in-plane resolution of 312.5 μm. The MRI images were taken after 10 min, 1 h and then in 1-hour intervals up to 8 h. The last image was taken after 24 h of hydration and swelling in 0.1 N HCl. MRI experiments were performed in triplicate for each tablet composition.

2.7. Impinging light micrographs

To confirm the results obtained by benchtop MRI, impinging light micrographs of axial cut floating tablets

after different time intervals of contact with 0.1 N HCl were taken.

3. Results

3.1. Determination of floating behaviour

All examined tablet samples were initially sinking. After a lag time the tablets began to move to the surface of the medium and remained afloat until the end of the monitored 24 h time interval. The lag times before floating were related to coating level and increased for tablets with higher coating levels, whereas the increase for tablets with coat SR/IR, 8.5:1.5 was linear and for tablets with coat SR/IR, 9:1 almost exponential (Fig. 1). An increased Kollicoat® SR/Kollicoat® IR ratio led for all tablet samples to higher lag times compared to tablets with coat SR/IR, 8.5:1.5. The shortest lag time was observed for floating devices with an SR/IR, 8.5:1.5 coat of 10 mg polymer/cm^2 and was found to be 12 ± 1 min.

The increase in floating strength of the monitored tablet samples was strong within the first phase of the floating process and slowed down to reach a maximum value after about 9–15 h (Figs. 2 and 3). Maximum floating strength values were higher and were reached earlier for tablets with SR/IR, 8.5:1.5 coat as well as for floating devices with a thinner polymer film layer. Additionally, these samples exhibited a faster increase in floating strength at the beginning. A subsequent plateau phase was more pronounced for SR/IR, 9:1 tablet samples. Tablets with coat SR/IR, 8.5:1.5 and a coating level of 20 mg polymer/cm^2 exhibited within the monitored time interval of 24 h only an increase in floating strength. After the plateau phase the floating strength values decreased, whereas the decay was slower than the increase in floating strength in the beginning of the floating process.

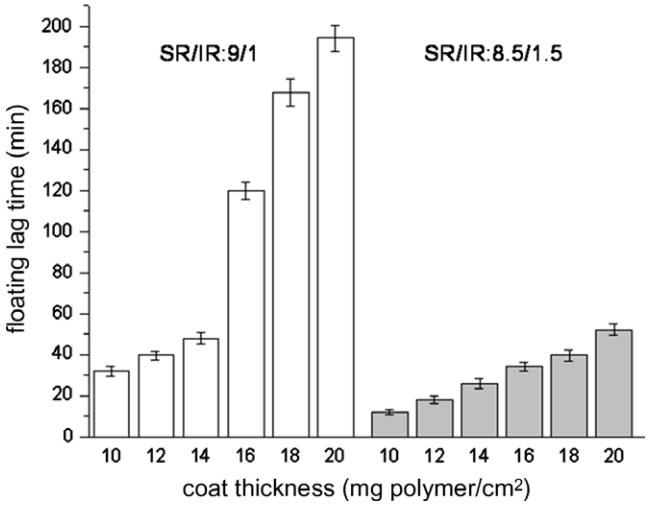

Fig. 1. Floating lag times of the floating tablets in relation to coat thickness and coat composition.

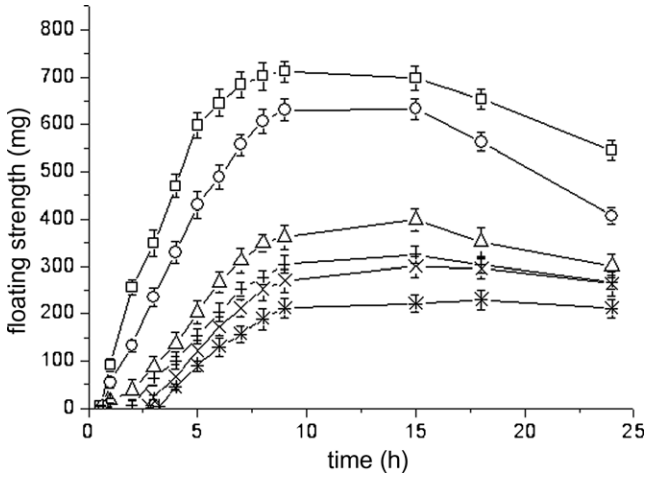

Fig. 2. Floating characteristics of tablets with SR/IR, 9:1 coat and coating level 10 (□), 12 (○), 14 (Δ), 16 (+), 18 (×) and 20 (∗) mg polymer/cm^2 in 0.1 N HCl.

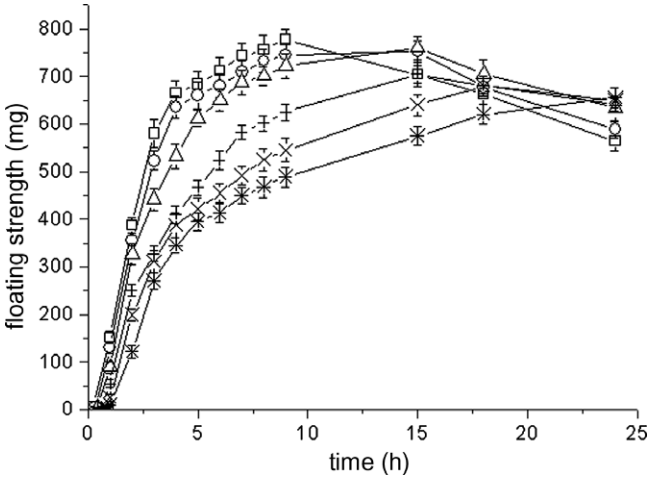

Fig. 3. Floating characteristics of tablets with SR/IR, 8.5:1.5 coat and coating level 10 (□), 12 (○), 14 (Δ), 16 (+), 18 (×) and 20 (∗) mg polymer/cm^2 in 0.1 N HCl.

3.2. Propranolol HCl release studies

The developed floating drug delivery systems were able to efficiently control Propranolol HCl release over a time period of 24 h (Figs. 4 and 5). Lag times prior to drug release were related to the thickness of the polymer film, as tablets with a higher coating level showed decreased Propranolol HCl release rates (Table 3). Comparing both coating formulations, an increased Kollicoat® IR content in the polymer film tended to decrease the lag times. Both heightened segments within the Figs. 4 and 5 are giving a more detailed description of the initial drug release characteristics. It is obvious that the lag times do not represent time intervals without any drug release but with at least marginal Propranolol HCl liberation. Drug release rates remained low for a short period of time and increased afterwards.

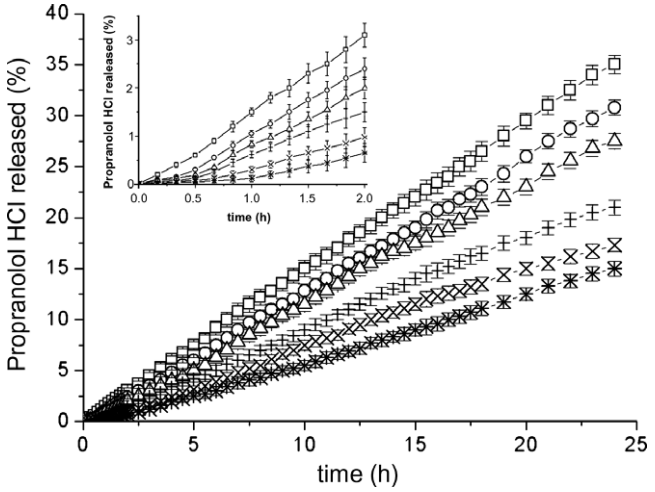

Fig. 4. Release of Propranolol HCl from tablets with SR/IR, 9:1 coat and coating level 10 (□), 12 (○), 14 (Δ), 16 (+), 18 (×) and 20 (∗) mg polymer/cm^2 in 0.1 N HCl. Small figure represents a magnification of the first 2 h.

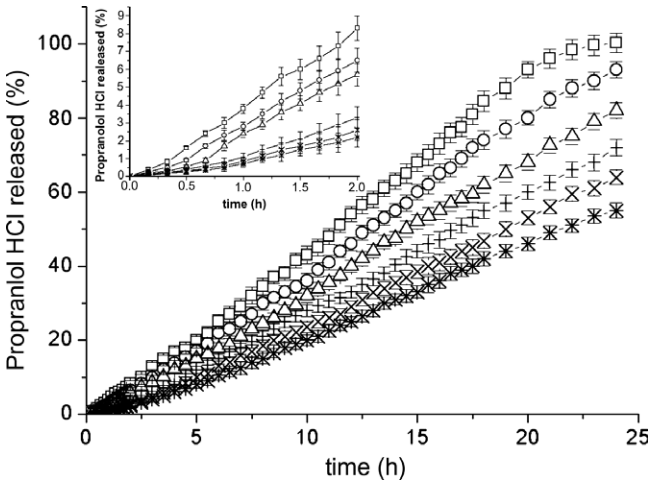

Fig. 5. Release of Propranolol HCl from tablets with SR/IR, 8.5:1.5 coat and coating level 10 (□), 12 (○), 14 (Δ), 16 (+), 18 (×) and 20 (∗) mg polymer/cm^2 in 0.1 N HCl. Small figure represents a magnification of the first 2 h.

The drug release profiles exhibited linear zero order release kinetics with different total amounts of liberated drug within 24 h. Propranolol HCl release rates increased with a higher Kollicoat® IR concentration in the coating formulation. A complete drug delivery within the monitored time interval was only registered for tablet samples with coat SR/IR, 8.5:1.5 of 10 mg polymer/cm^2. In contrast maximum drug release values for tablets with coating formulation SR/IR, 9:1 reached only about 15–35%.

3.3. Benchtop ^{1}H NMR imaging experiments

Benchtop ^{1}H NMR Imaging was used to monitor tablet and film coat hydration and swelling characteristics of selected tablet samples. Figures represent axial side images of tablet samples characterized by a coating level of 10 mg and 14 mg polymer/cm^2 and coating formulation SR/IR, 9:1 and SR/IR, 8.5:1.5, respectively (Figs. 6–9). Dark areas in the ^{1}H NMR images refer to low spin densities or short T_1 relaxation times, which are related to dry parts of the tablet or carbon dioxide development inside the tablet core. Brighter areas of the tablets compared to the 0.1-N HCl surrounding the device may lead to the conclusion that the spin density in this area is higher than in the dissolution medium, but this contrast was obtained by measuring with a repetition time which was shorter than the T_1 of the free water in the medium but much longer than the T_1 of water in the matrix tablets. As the magnetization of the free water in the medium, in contrast to the water in the tablet, was not able to return to equilibrium, the signal intensity for water inside the tablet increased although its spin density was lower. Thus it was possible to follow hydration characteristics and carbon dioxide formation of the developed systems more easily.

Table 3
Calculated lag times prior to drug release

Tablet samples	Lag times prior to drug release (min)
SR/IR, 9:1 (mg polymer/cm^2)	
10	0
12	17
14	24
16	28
18	34
20	49
SR/IR, 8.5:1.5 (mg polymer/cm^2)	
10	0
12	15
14	21
16	28
18	30
20	31

Fig. 10 gives a schematic sequence of different main phases regarding swelling and carbon dioxide development taking place inside the tablet, which can be monitored using the benchtop MRI instrument. Swelling processes started with an initially hydrated polymer film and a dry unswollen tablet core, whereas in this phase the device was not yet afloat. Carbon dioxide development started on the top side of the tablet directly on the surface of the tablet core leading to an expansion of the film coat. Thus, a dome shaped, floating tablet could be observed. Additionally, the swelling of outer parts of the tablet core occurred, whereas the inner part was still dry and unhydrated. Continuing diffusion of hydrochloric acid inside the tablet led to a biconvex and swollen tablet with gas development on the top side as well as on the bottom side of the tablet core. The carbon dioxide inside the floating device expanded the tablet coat intensively, leading to the formation of a balloon shaped floating tablet. The swelling layer of the tablet core had increased, whereas a part of the inner core was still unhydrated. Ongoing diffusion processes increased the development of carbon dioxide and thus the volume of the floating device. A completely

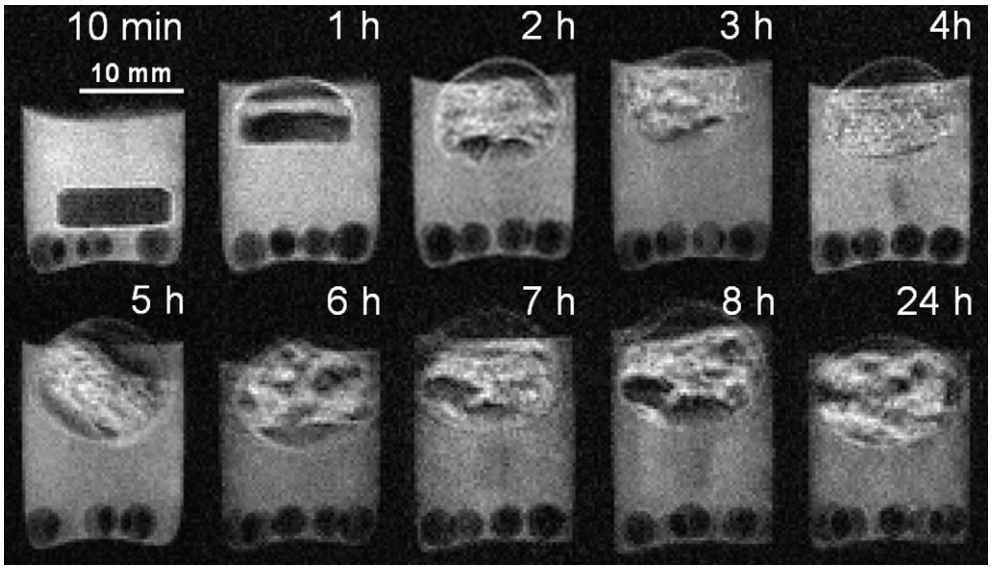

Fig. 6. Benchtop magnetic resonance images of tablet samples with 10 mg polymer/cm^2 SR/IR, 9:1 coat.

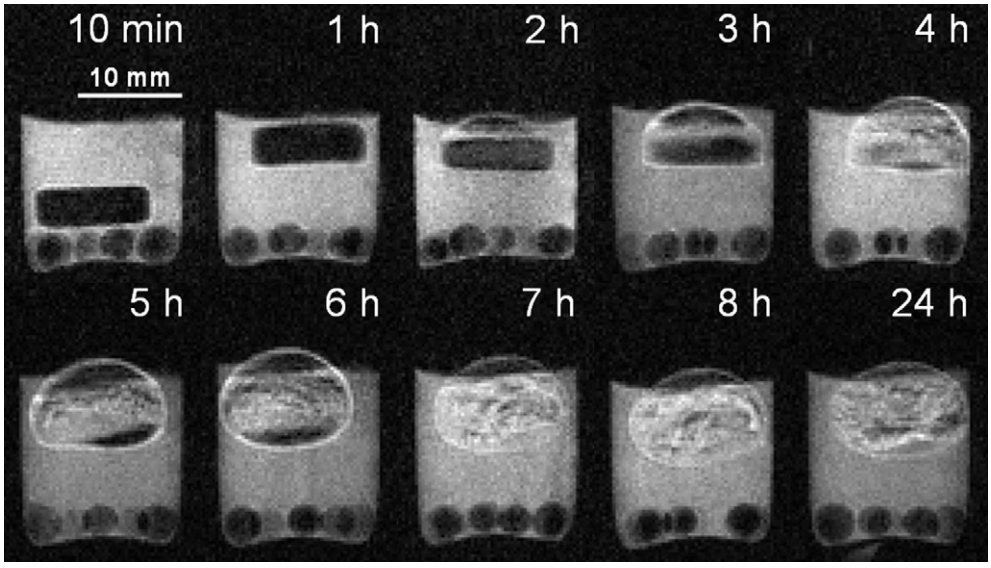

Fig. 7. Benchtop magnetic resonance images of tablet samples with 14 mg polymer/cm^2 SR/IR, 9:1 coat.

hydrated tablet core with beginning CO_2 development inside the tablet core was observed. The former shape of the core was still visible though now intensively swollen. The final phase was represented by a tablet, which was often slightly reduced in size exhibiting a disintegrated core entrapping several smaller gas bubbles.

The process of the above-described phases of swelling and gas development is accelerated for samples with a lower Kollicoat® SR/Kollicoat® IR ratio and a lower coating level. Therefore, magnetic resonance images of tablets with coat SR/IR, 8.5:1.5 exhibited a faster initial increase in tablet size compared to samples with a higher Kollicoat® SR/Kollicoat® IR rate. After 1 h of contact time with hydrochloric acid magnetic resonance images of SR/IR, 8.5:1.5 tablets showed biconvex, swollen tablets with a dry core, whereas this phase was attained by SR/IR, 9:1 samples not until 2 h (10 mg polymer/cm^2 coat) and 6 h (14 mg polymer/cm^2 coat), respectively. Due to an intense carbon dioxide formation inside the tablet samples with an SR/IR, 8.5:1.5 coat, causing a fast expansion of the device, a phase with a dome shaped tablet cannot be observed. Furthermore, an increased Kollicoat® IR rate led to an earlier disintegration of the tablet core. Differences in swelling and CO_2 development characteristics were more pronounced for SR/IR, 9:1 samples with different coating levels than for SR/IR, 8.5:1.5 tablets with varying film thicknesses. For SR/IR:9/1 tablets, the tablet core of samples with 14 mg polymer/cm^2 started to disintegrate only marginally after 7 h, while tablets with a decreased polymer film exhibited a strong core disintegration after

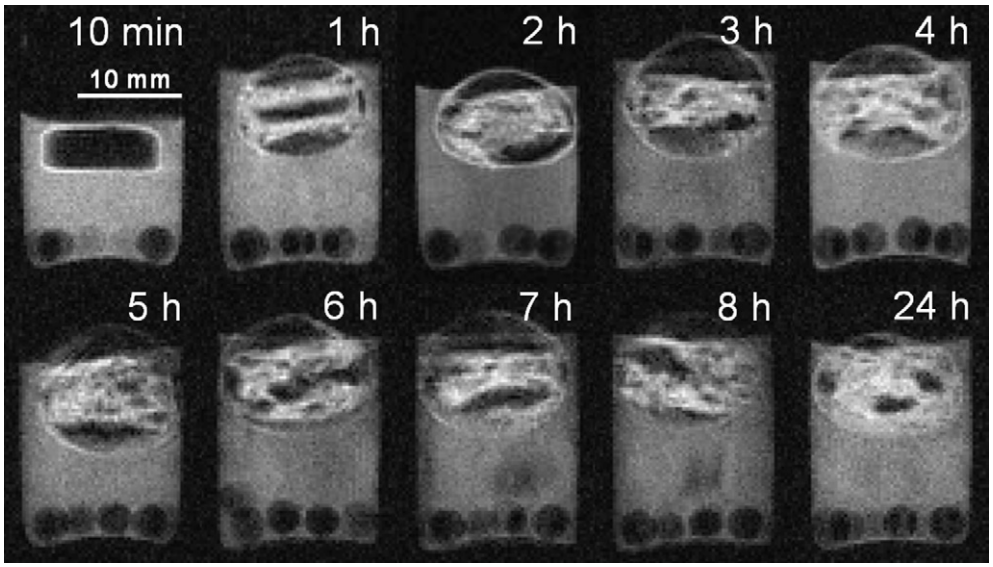

Fig. 8. Benchtop magnetic resonance images of tablet samples with 10 mg polymer/cm^2 SR/IR, 8.5:1.5 coat.

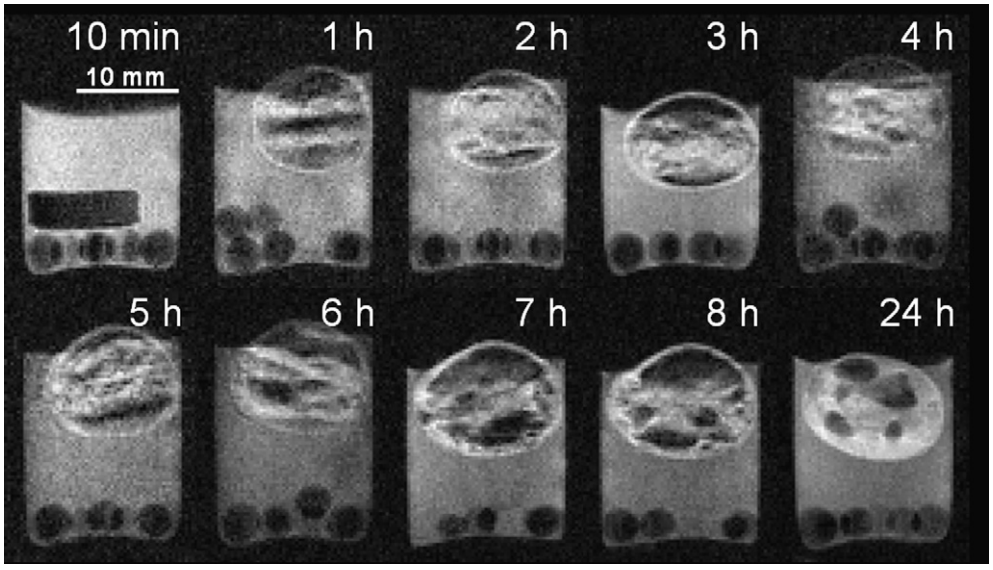

Fig. 9. Benchtop magnetic resonance images of tablet samples with 14 mg polymer/cm^2 SR/IR, 8.5:1.5 coat.

the 6 h. In contrast to this both MRI monitored SR/IR, 8.5:1.5 samples exhibit quite similar swelling and gas formation behaviour.

4. Discussion

Positioning of the samples in 0.1 N HCl led to immediate water and thus hydrochloric acid penetration through the polymer coat. After contact with the sodium bicarbonate of the tablet core carbon dioxide development was initiated leading to an expansion and a reduced density of the system. After varying lag times for the different tablet samples the devices began to float (Fig. 1). Floating characteristics were related to coating level and composition of the polymer film. Increased Kollicoat® IR amounts and lower coating levels led to shortened lag times, a stronger increase in floating strength and higher maximum floating values. These characteristics may be explained by different mechanisms. Since water penetration through the polymer film is related to coating thickness, hydrochloric acid diffusion and thus gas development within the floating devices will act similarly [24]. Another aspect includes the leaching of water soluble compounds out of the polymer shell. The leaching characteristics of water soluble film components such as Kollicoat® IR, povidone and triacetin have been described in previous studies [25]. An increased amount of the water soluble Kollicoat® IR leads to a faster dissolution of other leachable components and a higher porosity of the polymer film coat. As the total amount of the remaining polymer Kollicoat® SR is reduced in samples

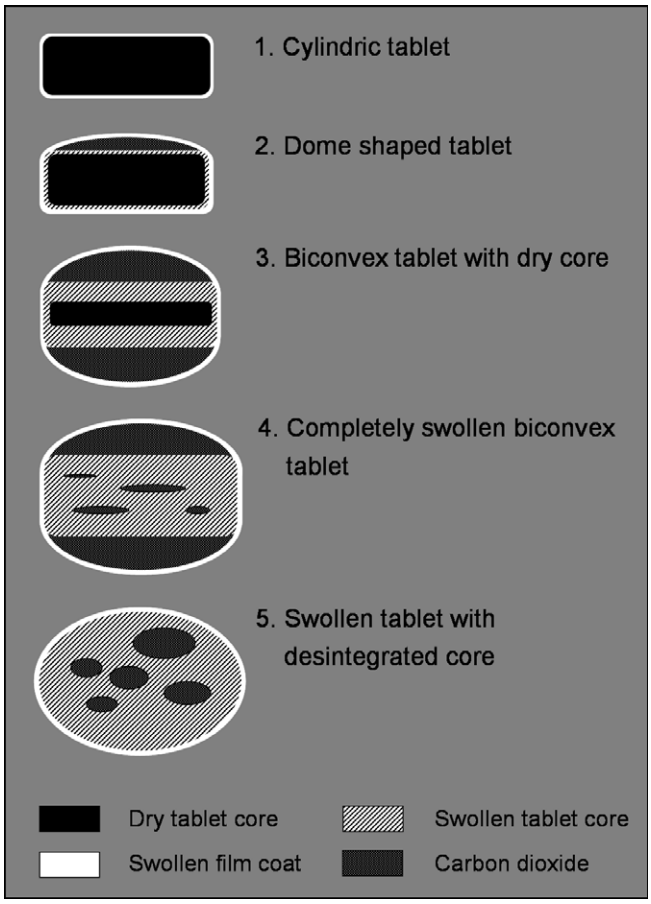

Fig. 10. Schematic process of tablet swelling and carbon dioxide development inside the floating devices.

with coating formulation SR/IR, 8.5:1.5, the required force exerted by the gas to expand the polymer network is lower than for tablet samples with 10% Kollicoat® IR. After 10–15 h the floating strength of the tablet samples with film coat SR/IR, 9:1 remains constant or decreases. Constant floating strength values over a certain time period indicate an equilibrium state between the carbon dioxide development and swelling of the device to keep the tablet afloat and the water penetration through the polymer film leading to a sinking of the tablet. The origin of reduced floating strength values lies in the removal of carbon dioxide from the inside of the polymer shell. Combining Fick's law of diffusion with Henry's law the volume of a gas diffusing through a membrane is given by the following equation:

$$\frac{dM}{dt} = \frac{D_G^* K_G^* A_F^* (p_1 - p_2)}{d} \quad (2)$$

where dM/dt is the diffusing gas amount per time unit, D_G the diffusion coefficient of the gas, K_G the solubility coefficient of the gas in the liquid, A_F the real flow-through area, p_1 the pressure of the gas above the liquid film, p_2 the pressure of the gas below the liquid film and d the thickness of the liquid layer. Thus, an increased porosity and a reduced thickness of the film coat will lead to higher permeating gas amounts. As the thinner polymer films on the tablets exhibit a higher porosity due to a more intensive expansion of the polymer network, the reduction in floating strength occurs earlier than for samples with a higher coating thickness. Another aspect lies in an increased tablet surface. As SR/IR, 8.5:1.5 tablet samples exhibit a stronger expansion of the polymer film, an increased tablet surface as well as a reduced diffusion path will increase the net mass transport through the membrane. Plateau phases regarding the floating strength of tablets with an SR/IR, 8.5:1.5 coat may be less pronounced due to a higher permeability of the film coat, reducing the ability to entrap the carbon dioxide within the polymer shell. In comparison to poly(vinyl acetate) based floating matrix tablets developed in previous studies, the floating strength for the coated tablets exhibits considerably higher values, reducing the risk of being accidentially emptied from the stomach [15]. Furthermore, the floating properties of the matrix devices are characterized by a proceeding decrease in floating strength. A disadvantage of the coated floating devices lies in a more or less pronounced lag time before floating onset, whereas Kollidon® SR based floating matrix tablets start to float immediately.

Drug release rates are a function of the coating thickness, the porosity and the surface area of the film coat. Thus, drug release as well as floating characteristics are affected by similar mechanisms. Therefore, samples with increased permeability for carbon dioxide will exhibit increased Propranolol HCl release rates as well.

Zero order drug release kinetics are related to a reservoir with undissolved drug amounts within a controlled drug release device. As all drug release curves showed linear characteristics, a certain Propranolol HCl amount will remain undissolved inside the tablet core. Lag times prior to drug release are shown in Table 3. Surprisingly, lag time values of tablet samples with the same coating thickness but different coating composition differ only marginally. The increased film coat permeability of the tablet samples coated with lower coating levels led to decreased drug release lag times.

Regarding the benchtop MRI experiments it was observed, that positioning tablets into 0.1 N HCl led in all cases to an initial sinking of the tablets. Only magnetic resonance images for samples with 10 mg polymer/cm^2 SR/IR, 8.5:1.5 coat were floating after 12 min. The swollen polymer film was visible as a bright edge surrounding the core due to the immediate water diffusion into the tablet. For the tablet core a signal with a short T_1 relaxation time was detected, which leads to the conclusion that the hydration of the inner part of the tablet had not yet begun. It was possible to monitor the continuing water diffusion into the tablet over time as can be seen in an increasing water diffusion layer. CO_2 development due to the neutralization reaction between hydrochloric acid diffusing from the dissolution medium and sodium bicarbonate in the tablet core led to a strong increase in tablet size, forming a kind of balloon. Tablet size increased primarily in axial direction and only slightly in tangential direction. The increasing sig-

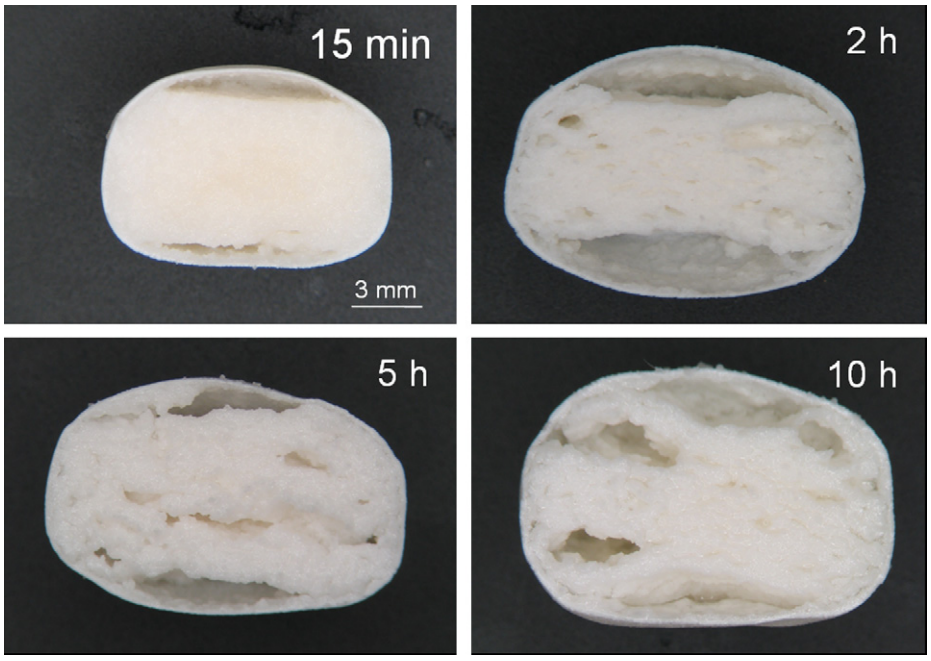

Fig. 11. Impinging light micrographs of axial cut tablet samples with coat SR/IR, 8.5:1.5 of 10 mg polymer/cm^2 after different time intervals of contact with 0.1 N HCl.

nal intensity inside the tablet core in the last images of each MRI series may be caused by a high amount of aqueous dissolution medium bound by the polymer network. Even if the shape of the tablet core is no longer visible, the polyvinyl acetate structure of the disintegrated tablet core is still strong enough to entrap gas bubbles inside the polymeric shell. The reduced volume of the floating device, which was observed for some formulations, is caused by the diffusion of carbon dioxide from the core.

Impinging light micrographs underlined the findings of the benchtop MRI study (Fig. 11). A cylindrical shaped tablet with undisintegrated core and only slight CO_2 formation was observed after 15 min of contact with dissolution medium. After 2 h the floating device forms a biconvex tablet, of which the tablet core is disintegrating slightly after 5 h and nearly completely after 10 h. The 10-h micrograph shows clearly the cavities, where the carbon dioxide is entrapped. Additionally, an all in all increase in tablet size can be observed as well.

5. Conclusions

The present study demonstrates the exceptional attributes of poly(vinyl acetate) as an excipient for floating devices showing controlled drug delivery. Kollidon® SR is able to ensure a low initial density of the floating system and to overcompensate the sinking characteristics of the model drug Propranolol HCl. The high elasticity of Kollicoat® SR films reduces the risk of dose dumping even for expanding, carbon dioxide developing systems. The Kollicoat® SR film simultaneously provides a controlled release of the drug and ensures an effective capture of the CO_2 within the tablet. Although a variety of gastroretentive systems have been developed until now, most of the published studies neglect floating strength studies and focus only on the monitoring of floating lag time and floating duration. Applying floating strength measurements to the developed floating tablets it was possible to quantify and to compare floating characteristics of different systems. Though the application of MRI is widely accepted to study drug release mechanisms, until now no studies regarding the monitoring of floating drug delivery systems are available. Therefore, the performance of MRI experiments led to a more profound understanding not only of swelling poly(vinyl acetate) based drug delivery systems but of carbon dioxide developing floating devices in a noninvasive and continuous manner. The study is also one of the first experimental proofs, that the newly developed low cost benchtop MRI machines can provide information on drug delivery systems, which is comparable to results of superconducting MRI machines. It can be anticipated that MRI will be used more frequently in formulation research due to the low installation and running costs of the new benchtop systems.

Acknowledgement

The authors thank BASF Ludwigshafen, Germany, for the kind polymer supply.

References

[1] N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136 (1996) 116–122.
[2] J. Drewe, C. Beglinger, T. Kissel, The absorption site of cyclosporin in the human GIT, Br. J. Clin. Pharmacol. 33 (1992) 39–43.

[3] S. Harder, U. Fuhr, D. Bergmann, Ciprofloxacin absorption in different regions of the human GIT. Investigations with hf capsule, Br. J. Clin. Pharmacol. 30 (1990) 35–39.
[4] E.A. Klausner, E. Lavy, D. Stepensky, E. Cserepes, M. Barta, M. Friedman, A. Hoffman, Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration in healthy volunteers, J. Clin. Pharmacol. 43 (2003) 711–720.
[5] G.L. Chen, W.H. Hao, In vitro performance of floating sustained-release capsule of verapamil, Drug Dev. Ind. Pharm. 24 (1998) 1067–1072.
[6] S.A. Elkheshen, A.E. Yassin, S. Alsuwayeh, F.A. Alkhaled, In vitro and in vivo evaluation of floatin controlled release dosage forms of verapamil hydrochloride, Pharm. Ind. 66 (2004) 1364–1372.
[7] R. Singh Matharu, N.M. Sanghavi, Novel drug delivery systems for captopril, Drug Dev. Ind. Pharm. 18 (1992) 1567–1574.
[8] L. Whitehead, J.H. Collett, J.T. Fell, Amoxycillin release from a floating dosage form based on alginates, Int. J. Pharm. 210 (2000) 45–49.
[9] M. Oth, M. Franz, J. Timmermans, A. Moës, The bilayer floating capsule: a stomach-directed drug delivery system for misoprostol, Pharm. Res. 9 (1992) 298–302.
[10] A. Streubel, J. Siepmann, R. Bodmeier, Gastroretentive drug delivery systems, Expert Opin. Drug Deliv. 3 (2) (2006) 217–233.
[11] J.W. Lee, J.H. Park, J.R. Robinson, Bioadhesive-based dosage forms: the next generation, J. Pharm. Sci. 89 (2000) 850–866.
[12] A.A. Deshpande, N.H. Shah, C.T. Rhodes, W. Malick, Development of a novel controlled-release system for gastric retention, Pharm. Res. 14 (1997) 815–819.
[13] E.A. Klausner, E. Lavy, M. Friedman, A. Hoffman, Expandable gastroretentive dosage forms, J. Control. Release 90 (2003) 143–162.
[14] S. Desai, S. Bolton, A floating controlled-release drug delivery system: in vitro-in vivo evaluation, Pharm. Res. 10 (1993) 1321–1325.
[15] S. Strübing, H. Metz, K. Mäder, Characterization of polyvinyl acetate based floating matrix tablets, J. Control. Release. (2007), doi:10.1016/j.jconrel.2007.11.013.
[16] E. Draganoiu, M. Andheria, A. Sakr, Evaluation of new polyvinylacetate/povidone excipient for matrix sustained release dosage forms, Pharm. Ind. 63 (2002) 624–629.
[17] W. Sawicki, R. Lunio, Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D, Eur. J. Pharm. Biopharm. 60 (2005) 153–158.
[18] W.E. Baille, C. Malveau, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 1. Swelling and water uptake, Biomacromolecules 3 (2002) 214–218.
[19] C. Malveau, W.E. Baille, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 2. Effect of tablet size, Biomacromolecules 3 (2002) 1249–1254.
[20] H. Thérien-Aubin, W.E. Baille, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 3. Initial diffusion and temperature effects, Biomacromolecules 6 (2005) 3367–3372.
[21] M. Fukuda, N.A. Peppas, J.W. McGinity, Floating hot-melt extruded tablets for gastroretentive controlled drug release system, Pharm. Res. 115 (2006) 121–129.
[22] J. Timmermans, A.J. Moës, How well do floating dosage forms float? Int. J. Pharm. 62 (1990) 207–216.
[23] J. Timmermans, A.J Moës, Apparatus and method for resultant-weight measuring system. US Patent 5,076,107, 1991.
[24] S. Strübing, H. Metz, K. Mäder, Mechanistic analysis of drug release from tablets with membrane controlled drug delivery, Eur. J. Pharm. Biopharm. 66 (1) (2007) 113–119.
[25] S. Strübing, H. Metz, K. Mäder, Monitoring of dissolution induced changes in film coat composition by ^{1}H NMR spectroscopy and SEM, J. Control. Release 119 (2) (2007) 190–196.