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Floating microparticles based on low density foam powder

A. Streubel, J. Siepmann, R. Bodmeier *

College of Pharmacy, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany

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Abstract

The aim of this study was to develop a novel multiparticulate gastroretentive drug delivery system and to demonstrate its performance in vitro. Floating microparticles consisting of (i) polypropylene foam powder; (ii) verapamil HCl as model drug; and (iii) Eudragit RS, ethylcellulose (EC) or polymethyl methacrylate (PMMA) as polymers were prepared with an O/W solvent evaporation method. The effect of various formulation and processing parameters on the internal and external particle morphology, drug loading, in vitro floating behavior, in vitro drug release kinetics, particle size distribution and physical state of the incorporated drug was studied. The microparticles were irregular in shape and highly porous. The drug encapsulation efficiency was high and almost independent of the theoretical loading. Encapsulation efficiencies close to 100% could be achieved by varying either the ratio 'amount of ingredients: volume of the organic phase' or the relative amount of polymer. In all cases, good in vitro floating behavior was observed. The release rate increased with increasing drug loading and with decreasing polymer amounts. The type of polymer significantly affected the drug release rate, which increased in the following rank order: PMMA < EC < Eudragit RS. A broad spectrum of release patterns could be obtained with the investigated formulations. In contrast, the effect of the volume of the aqueous phase on drug release was not very pronounced. The size of the microparticles was almost independent of the drug loading, but strongly depended on the amount of polymer. The drug was partly dissolved and partly in the amorphous form distributed throughout the system.

Keywords: Floating drug delivery system; Foam; Gastroretentive drug delivery system; Microparticle; Microencapsulation; Solvent evaporation method

1. Introduction

A modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs (i) which are locally active in the stomach; (ii) with an absorption window in the stomach or in the upper small intestine; (iii) which are unstable in the intestinal or colonic environment; and (iv) with low solubility at high pH values. Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time, these systems can also be used as sustained release

* Corresponding author. Tel.: +49-30-8385-0643; fax: +49-30-8385-0692

E-mail address: bodmeier@zedat.fu-berlin.de (R. Bodmeier).

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devices with a reduced frequency of administration and therefore, improved patient compliance.

Approaches to increase the gastric residence time include: (i) bioadhesive delivery systems, which adhere to mucosal surfaces (Chitnis et al., 1991; Akiyama and Nagahara, 1999); (ii) delivery systems, which increase in size to retard the passage through the pylorus (Urquhart and Theeuwes, 1984; Chen et al., 1999); and (iii) density-controlled delivery systems, which either float or sink in gastric fluids (Sheth and Tossounian, 1984; Krögel and Bodmeier, 1999). Most gastroretentive drug delivery systems are single-unit devices (Hwang et al., 1998) having in common the risk of loosing their effect too early due to their all-or-nothing emptying from the stomach. To overcome this problem, multiple-unit floating systems have been proposed (Singh and Kim, 2000). They distribute uniformly within the gastric content and gradually empty from the stomach, possibly resulting in longer lasting effects and reduced intersubject variabilities.

A multiple-unit, oral, floating system, which generates carbon dioxide was developed by Atyabi et al. (1996a,b). Ion-exchange resin particles were loaded with bicarbonate and coated with a semipermeable membrane. Upon exposure to gastric media, exchange of bicarbonate and chloride ions took place and led to the formation of carbon dioxide. The gas was trapped within the membrane causing the particles to float. However, effervescent systems generally suffer from the disadvantage not to float immediately, because, the gas generation takes some time.

An interesting approach was developed by Kawashima et al. (1991, 1992). They prepared hollow microspheres (microballoons) consisting of Eudragit S, an enteric polymer, loaded with drug in the outer polymer shells. A solution of polymer and drug in ethanol/methylene chloride was poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitioned into the external aqueous phase and the polymer precipitated around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride led to the formation of internal cavities within the microparticles. However, according to Lee et al. (1999) many drugs are not released in significant amounts from this type of microparticles at the pH of gastric fluids. A floating drug delivery system being less dense than gastric juice due to the incorporation of at least one porous structural element, such as foam or a hollow body has been patented by Müller and Anders (1989).

The major objectives of this study were: (i) to develop a multiparticulate, floating drug delivery system consisting of a highly porous carrier material (foam powder), drug and polymer; (ii) to characterize this system physicochemically; and (iii) to study the effect of various formulation and processing parameters on the system characteristics (internal and external morphology, drug loading, in vitro floating behavior, in vitro drug release kinetics, particle size distribution). A highly porous, hydrophobic polypropylene foam powder with open-cell structure and low inherent density was chosen as carrier material. Polypropylene is practically insoluble in cold organic solvents and resistant to alkalies (The Merck Index, 1996). For pharmaceutical purposes it is used as packaging material, approved for parenteral dosage forms (European Pharmacopoeia, 1997). Verapamil HCl, a papaverine derivative with a molecular weight of 491.08 Da, was used as model drug. Verapamil HCl has a distinct pH-dependent solubility in the pH-range of the gastrointestinal tract. The following values have been reported: >150, 2.71 and 0.75 mg/ml at pH 1.2, 6.8 and 7.4, respectively (Streubel et al., 2000). With conventional controlled release dosage forms, a possible decrease in the release rate when passing from the stomach into the intestine can result in in vivo variability and bioavailability problems. Building greater control into the dosage form by providing prolonged drug release at the low pH within the stomach, is thus highly desirable to assure a more reliable drug therapy. Eudragit RS, a relatively hydrophilic polymer with a modest permeability for water and the more hydrophobic ethylcellulose (EC)

and polymethyl methacrylate (PMMA) were chosen as polymers.

2. Materials and methods

2.1. Materials

Polypropylene foam powder (Accurel® MP 1002 and MP 1000, Membrana GmbH, Obernburg, Germany), verapamil HCl (Knoll AG, Ludwigshafen, Germany), Eudragit® RS PO (Röhm Pharma GmbH, Darmstadt, Germany), EC (Ethocel® 10 Standard FP premium, Dow Chemical Company, Midland, MI, USA), PMMA (Röhm Pharma GmbH, Darmstadt, Germany), polysorbate 20 (Tween 20; Serva Feinbiochemica GmbH & Co., Heidelberg, Germany), polyvinylalcohol (PVA; Mowiol® 40-88, Aventis S.A., Frankfurt/Main, Germany), ethanol, ethyl acetate, methylene chloride, sodium hydroxide (all from Merck KGaA, Darmstadt, Germany). The polypropylene foam powder was sieved to obtain different size fractions prior to use, all other materials were used as received.

2.2. Microparticle preparation

The microparticles were prepared using a solvent evaporation method. The drug (verapamil HCl, 21–467 mg) and polymer (Eudragit RS, EC or PMMA, 50–500 mg) were dissolved in 3 ml methylene chloride. Then, polypropylene foam powder (different size fractions: 125–160, 250–315, 400–630 or 630–800 μm) was dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous PVA solution (200 ml, unless otherwise mentioned, adjusted to pH 12.5 with sodium hydroxide, 0.25% w/v PVA) and agitated for 1 h at room temperature (22 °C) under ambient pressure with a magnetic stirrer (Heidolph MR 2002, Heidolph Elektro, Kehlheim, Germany) to allow microparticle formation. The microparticles were separated by sieving (100 μm sieve), washed with water (adjusted to pH 12.5 with sodium hydroxide) and dried in a desiccator at room temperature for at least 48 h.

2.3. Film preparation

Thin, polymeric films were prepared by casting solutions of Eudragit RS (800 mg) and verapamil HCl (27% w/w, based on the mass of the film) in 6 ml methylene chloride into teflon dishes, and subsequent drying for 48 h at room temperature. The dried films were removed from the teflon dishes and stored for 24 h in a desiccator prior to DSC measurements. For the X-ray studies films were cast onto microscope slides.

2.4. Drug content of the microparticles

The drug content of Eudragit RS- and EC-microparticles was determined by dispersing 15–40 mg microparticles (accurately weighed) in 30 ml ethanol followed by agitation with a magnetic stirrer (Variomag Electronicrührer Multipoint HP 6, H + P Labortechnik GmbH, Oberschleißheim, Germany) for 12 h to dissolve the polymer and to extract the drug. After filtration through a 5 μm filter needle (Becton Dickinson & Co., Franklin Lakes, NJ, USA) the drug concentration in the ethanol phase was determined spectrophotometrically at 280 nm (UV-2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA) ($n = 3$). Eudragit RS, EC and the polypropylene powder did not interfere under these conditions. The drug content of PMMA-microparticles was determined by dispersing 15–40 mg microparticles (accurately weighed) in 3 ml ethyl acetate followed by agitation with a magnetic stirrer (Variomag Electronicrührer Multipoint HP 6, H + P Labortechnik GmbH, Oberschleißheim, Germany) for 12 h to dissolve the polymer and to extract the drug. Then, 57 ml 0.1 N HCl were added and stirring was continued for another 12 h. After filtration through a 0.22 μm filter (Sartorius AG, Göttingen, Germany) the drug concentration in the aqueous phase was determined spectrophotometrically at 278 nm (UV-2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA) ($n = 3$). PMMA, ethyl acetate and the polypropylene powder did not interfere under these conditions. The encapsulation efficiency was calculated as follows:

$$\text{encapsulation efficiency} = \frac{\text{actual drug content} \times 100\%}{\text{theoretical drug content}}$$

2.5. Microparticle morphology

The external and internal morphology of the microparticles was studied by scanning electron microscopy (SEM). The microparticles were coated for 120 s with gold–palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator (Sputter coater device 040, Balzers Union, Liechtenstein). The coated samples were then observed with a scanning electron microscope (Philips SEM 515, Type PW 6703, Philips Industrial Electronics, Kassel, Germany). Cross-sections were obtained by dispersing the microparticles within a solvent-free glue (UHU GmbH, Bühl, Germany), followed by cutting the dried matrix with a razor blade prior to coating.

2.6. Floating behavior of the microparticles

Floating behavior studies were performed by placing 60 particles into 30 ml glass flasks and subsequent addition of 30 ml preheated 0.1 N HCl pH 1.2, containing 0.02% w/v Tween 20 (37 °C) to exclude floating due to non-wetted surfaces, followed by horizontal shaking (37 °C, 75 rpm; GFL 3033, Gesellschaft für Labortechnik mbH, Burgwedel, Germany). At predetermined time intervals, the flasks were allowed to stand for 5 min without agitation and the number of settled particles was counted.

2.7. In vitro drug release studies

In vitro drug release studies were performed by placing 15–60 mg microparticles (accurately weighed) into 30 ml glass flasks and subsequent addition of 30 ml preheated release medium (0.1 N HCl pH 1.2 without additives, unless otherwise mentioned; 37 °C), followed by horizontal shaking (37 °C, 75 rpm; GFL 3033, Gesellschaft für Labortechnik mbH, Burgwedel, Germany). At predetermined time intervals, 2 ml samples were withdrawn and replaced with fresh medium (37 °C). Verapamil HCl was detected UV-spectrophotometrically at $\lambda = 278$ nm. All experiments were conducted in triplicate.

2.8. Particle size analysis

Particle size measurements were carried out on an image analysis system. An optical microscope (Axioskop, Carl Zeiss Jena GmbH, Jena, Germany) connected with a digital camera was used to produce pictures of the microparticles. The particle size distribution of each formulation was measured by determination of the Ferret diameter of 100 randomly selected particles using the EASY MEASURE software (1.0.15; INTEQ Informationstechnik GmbH, Berlin, Germany).

2.9. Differential scanning calorimetry (DSC)

Differential scanning calorimetric (DSC) measurements were carried out on a Mettler DSC 821^e scanning calorimeter equipped with a thermal analysis data system (Mettler Toledo, Giessen, Germany). The instrument was calibrated using indium as standard. Samples of 5–15 mg were placed in aluminum pans (Al-Crucibles, 40 μl) and sealed. The probes were heated from 25 to 200 °C at a rate of 10 K/min under nitrogen atmosphere.

2.10. X-ray diffraction

Wide-angle X-ray scattering measurements were carried out on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, $\lambda = 0.15418$ nm, 40 kV, 20 mA) fixed with a Philips PW 1710 diffractometer (Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The radiation scattered in the crystalline regions of the samples was measured with a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). A scanning rate of 0.02° 2θ per s over the range of 4–40° 2θ was used to determine each spectrum.

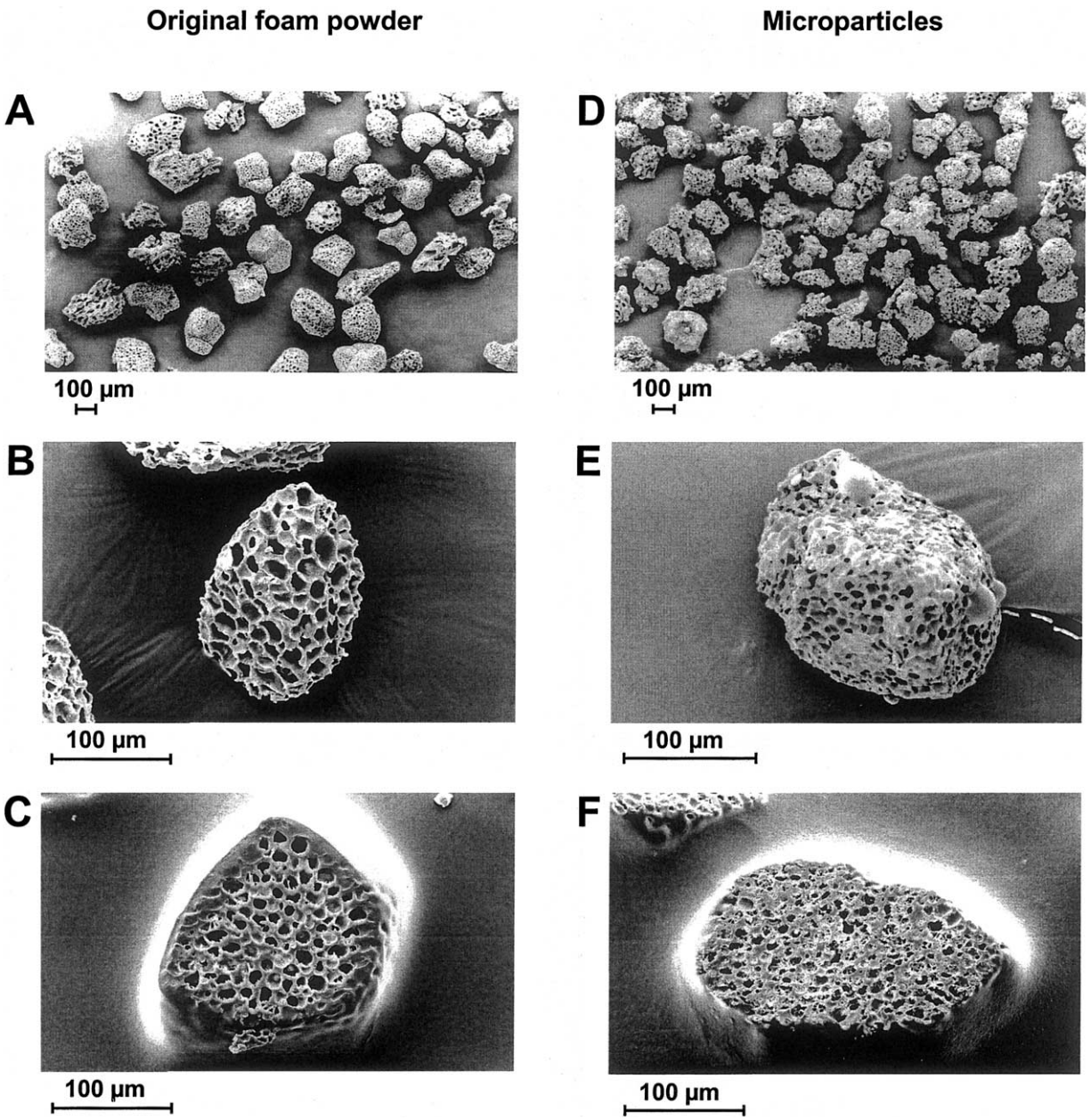

Fig. 1. SEM of the original polypropylene foam powder (A–C) and floating microparticles (D–F) (prepared with Eudragit RS, 10% theoretical drug loading): (A) and (D) particle populations; (B) and (E) surfaces of single particles; (C) and (F) cross-sections of single particles.

Table 1
Effect of the theoretical drug loading on the encapsulation efficiency of floating microparticles (200 mg polymer, 200 mg foam powder 125–160 μm, 3 ml organic phase)

Polymer	Aqueous phase (ml)	Theoretical loading (%)				
		5.0	7.5	10.0	15.0	20.0
		Encapsulation efficiency (%) (± S.D.)				
Eudragit RS	200	81.0 (± 1.4)	77.5 (± 0.1)	82.7 (± 1.9)	79.9 (± 0.0)	78.3 (± 0.2)
Eudragit RS	600	76.7 (± 2.2)	77.9 (± 0.4)	79.7 (± 0.9)	79.1 (± 1.8)	86.0 (± 0.2)
EC	200	95.7 (± 0.0)	94.2 (± 0.8)	93.0 (± 0.2)	95.6 (± 0.5)	94.7 (± 0.9)
PMMA	200	97.9 (± 0.9)	101.9 (± 6.8)	96.8 (± 0.6)	94.1 (± 1.0)	98.5 (± 3.3)

3. Results and discussion

3.1. Morphology studies

The polypropylene foam powder was irregular in shape and highly porous (Fig. 1A–B). Cross-sections revealed the characteristic open-cell structure of the particles (Fig. 1C). Also drug-loaded, polymer-containing microparticles were irregular in shape and highly porous (Fig. 1D–F). Eudragit RS-containing polypropylene foam particles (original size range: 125–160 μm) are shown. For these microparticles the theoretical drug loading was 10% (44 mg), and 200 mg foam powder and 200 mg polymer were used, representing a typical formulation. The open-cell structure is clearly visible with some of the pores being closed by the polymer. The latter only partially covers the porous foam particle surfaces at the investigated 'polymer: foam powder' ratio (1:1). This was the case independent of the original size of the foam powder (data not shown).

3.2. Encapsulation efficiency

As can be seen in Table 1, the encapsulation efficiencies were high in all cases (around 80% for Eudragit RS-containing systems) and independent of the theoretical drug loading in the investigated range (5–20%). In addition, no significant difference in the encapsulation efficiencies was observed when increasing the volume of the external aqueous phase from 200 to 600 ml (Table 1). The high encapsulation efficiencies probably result from the poor water solubility of the model drug in the alkaline external aqueous phase. Interestingly, EC and PMMA led to higher encapsulation efficiencies compared with Eudragit RS. This might be related to a faster precipitation of EC and PMMA, resulting in reduced drug diffusion into the aqueous phase.

The effect of the particle size of the original polypropylene foam powder on the encapsulation efficiency was studied by preparing different batches of microparticles with the same theoretical drug loading (10% w/w). Four fractions of foam powder were used with the following initial particle size ranges: 125–160, 250–315, 400–630 and 630–800 μm (200 mg Eudragit RS, 200 mg foam powder). The resulting actual loadings were 8.3 ± 0.2, 8.1 ± 0.2, 7.8 ± 0.2 and 7.3 ± 0.2%, thus, the encapsulation efficiencies were 82.7 ± 1.9, 80.7 ± 1.6, 77.6 ± 1.6 and 73.2 ± 1.6%, respectively. As can be seen the encapsulation efficiencies were similar in all cases. Only a slight decrease in the encapsulation efficiency with increasing particle size was observed. This might be attributed to the decreasing relative surface area with increasing particle size.

In contrast, the amount of ingredients (foam powder, drug and polymer) used at a constant volume of the organic phase significantly affected the encapsulation efficiency (Table 2). For the same theoretical drug loading of 10% and organic and external phase volumes (3 and 200 ml, respectively), the actual drug loading increased from 5.3 to 9.6% (corresponding to encapsulation efficiencies of 53.0 and 96.3%, respectively), when increasing the ratio 'amount of ingredients: volume of organic phase'

from 222:3 to 667:3. This phenomenon might be explained as follows. The solubility of verapamil HCl at pH 12.5 was determined to be 0.047 mg/ml (Streubel et al., 2000). Thus, 42, 21 and 14% of the total amount of drug can dissolve within the external aqueous phase when increasing the ratio 'amount of ingredients: volume of organic phase' from 222:3 to 444:3 to 667:3, respectively. Consequently, the relative amount of drug lost into the external water phase during microparticle preparation decreases with increasing 'amount of ingredients: volume of organic phase' ratio. Furthermore, with increasing amounts of foam powder at a constant organic phase volume the surface area available for polymer uptake increases. Thus, the fraction of the polymer which does not precipitate on the surfaces of foam particles, and which forms polypropylene foam powder-free, drug-containing microparticles (of smaller size, being separated from the floating microparticles during the sieving step) decreases. This hypothesis was confirmed by the experimentally determined yields (weight of obtained foam powder-containing microparticles/ weight of all ingredients used $\times$ 100%). When increasing the ratio 'amount of ingredients: volume of organic phase' from 222:3 to 444:3 and 667:3, the yield increased from 53.9 to 73.2 and 85.3%, respectively. Generally, with this floating drug delivery system, yields ranged from 54 to 95%.

The ratio 'polymer: drug' strongly affected the resulting encapsulation efficiency. Five microparticle batches with the same theoretical loading (10%), amount of polypropylene foam powder (200 mg), organic and external phase volumes (3 and 200 ml, respectively), but with different amounts of Eudragit RS (50–400 mg, corresponding to 18–60% polymer) and drug were prepared. With increasing amounts of polymer the actual drug loading and the encapsulation efficiency increased from 6.3 to 9.3%, and from 63.3 to 93.4%, respectively (Table 3). This can either be attributed to the increased probability for the drug to be entrapped within the microparticles with increasing relative amounts of polymer, and/or to the decreasing drug loss into the external water phase under these conditions. Based on the solubility of verapamil HCl and the volumes of the outer phases, 33, 28, 21, 17 and 14% of the drug can dissolve in the water phase when increasing the amount of Eudragit RS from 50 stepwise to 400 mg. However, as mentioned above the effect of the volume of the external aqueous phase on the encapsulation efficiency was not significant when increasing the volume from 200 to 600 ml (Table 1). Thus, the drug loss into the water phase might play a role, but is probably not dominating.

3.3. Floating behavior

Good in vitro floating behavior was observed in all cases. Fig. 2 shows the percentage of floating microparticles containing Eudragit RS versus time. More than 83% of the particles kept floating for at least 8 h. This is due to the low apparent density of the microparticles. The original foam powder as well as the polymer-containing particles have a highly porous internal and external structure (Fig. 1). The polymer partially covers the pores and entraps air within the system. Upon exposure to aqueous media the entrapped air is only slowly removed from the system leading to extended floating times (Fig. 2).

3.4. In vitro drug release

Various different drug release patterns were

Table 2
Effect of the ratio 'amount of ingredients: volume of organic phase' on the actual drug loading and encapsulation efficiency of floating microparticles (Eudragit RS: foam powder 125–160 μm = 100: 100, 200: 200, and 300: 300 mg, respectively, 3 ml organic phase, 200 ml aqueous phase)

Ratio (mg:ml)	Theoretical loading (%)	Actual loading (%) ($\pm$S.D.)	Encapsulation efficiency (%) ($\pm$S.D.)
222: 3	10.0	5.3 ($\pm$0.0)	53.0 ($\pm$0.4)
444: 3	10.0	8.3 ($\pm$0.2)	82.7 ($\pm$1.9)
667: 3	10.0	9.6 ($\pm$0.0)	96.3 ($\pm$0.3)

Table 3
Effect of the Eudragit RS amount on the actual drug loading and encapsulation efficiency of floating microparticles (200 mg foam powder 400–630 μm, 3 ml organic phase, 200 ml aqueous phase)

Eudragit RS (mg)	Theoretical loading (%)	Actual loading (%) (±S.D.)	Encapsulation efficiency (%) (±S.D.)
50	10.0	6.3 (±0.1)	63.3 (±0.5)
100	10.0	6.3 (±0.0)	62.8 (±0.3)
200	10.0	7.8 (±0.2)	77.6 (±1.6)
300	10.0	8.7 (±0.2)	86.7 (±1.8)
400	10.0	9.3 (±0.1)	93.4 (±0.6)

obtained (Figs. 3–5), most of them being biphasic: an initial rapid drug release phase ('burst effect') was followed by a second, slower drug release phase. Fig. 3 illustrates the drug release behavior from microparticles with different drug loadings (prepared in 200 ml aqueous phase). With increasing drug loading, the initial burst increased, whereas the second drug release phase was slowed down. Thus, at high loadings, major parts of the drug seem to be located close to the surface, easily accessible by the release medium. The subsequent decreasing relative drug release rates can be attributed to the resulting decreased drug concentration gradients, the driving forces for diffusion.

Similar tendencies were observed for foam powder-free microparticles (Fig. 4). These are a by-product of the manufacturing process. As can be concluded from the experimentally determined yields (see above), generally maximally 46% m/m of the prepared microparticles do not contain any foam powder. As foam powder-free microparticles are much smaller in size than foam powder-containing microparticles, they are separated during the sieving step. Interestingly, both types of microparticles (foam powder-containing ones and foam-powder-free ones) show similar drug release profiles (Figs. 3 and 4) indicating similar drug release mechanisms. Fig. 4 shows the dependence of drug release from foam powder-free microparticles on the initial drug loading.

Increasing the volume of the external water phase from 200 to 600 ml did not significantly affect the resulting drug release kinetics from the investigated microparticle formulations (data not shown). A potential advantage of using large volumes of the external aqueous phase is the reduction of the required stirring times. The solubility of methylene chloride in water is 1% w/v. Thus, the 3 ml (= 3.99 g) organic solvent used can completely be taken up within 600 ml, but not within 200 ml external aqueous phase. Using 600 ml, the diffusion of methylene chloride into the aqueous phase and hence solidification of the particles occurs faster compared with 200 ml. Thus, the particles can be separated after shorter stirring times. As can be seen in Table 1, the encapsulation efficiency is not significantly affected by the increase of the volume of the external phase.

Interestingly, the addition of a wetting agent (0.02% Tween 20) to the release medium did not significantly affect the resulting drug release patterns from the investigated microparticle formulations (data not shown).

Also the effect of the particle size of the original

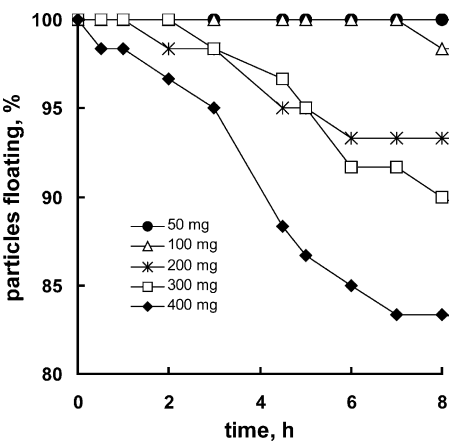

Fig. 2. Floating behavior of the microparticles depending on the amount of Eudragit RS (10% theoretical drug loading, 200 mg foam powder 400–630 μm).

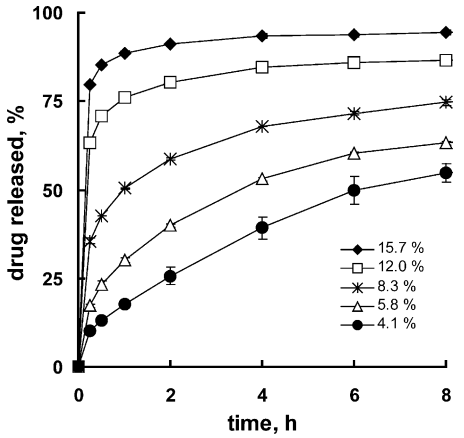

Fig. 3. Effect of the actual loading on drug release in 0.1 N HCl from floating microparticles (200 mg Eudragit RS, 200 mg foam powder 125–160 μm).

polypropylene foam powder on the drug release kinetics was studied (using Eudragit RS as polymer, data not shown). Four foam powder fractions were investigated with the following initial particle size ranges: 125–160, 250–315, 400–630 and 630–800 μm (200 mg Eudragit RS, 200 mg foam powder, 10% theoretical drug loading). The release behavior was very similar in all cases.

The effect of the amount of polymer relative to the amount of drug on the drug release profiles is shown in Fig. 5 for the case of Eudragit RS. Five microparticle batches were investigated. The

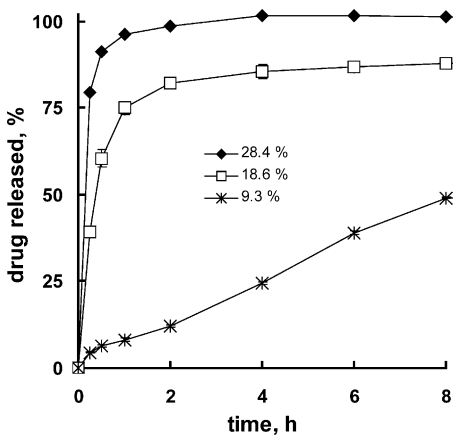

Fig. 4. Effect of the actual loading on drug release in 0.1 N HCl from foam powder-free microparticles (prepared with Eudragit RS).

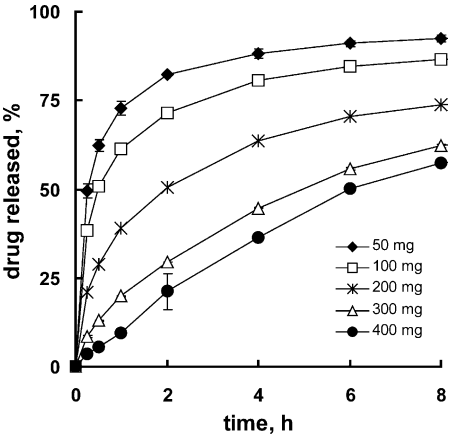

Fig. 5. Effect of the amount of Eudragit RS on drug release in 0.1 N HCl from floating microparticles (200 mg foam powder 400–630 μm, 10% theoretical drug loading).

amount of polymer was varied between 50 and 400 mg (corresponding to 18–60% related to the total weight, and 180–600% related to the drug), the theoretical drug loading and the amount of foam powder were kept constant at 10% and 200 mg, respectively. With increasing absolute amounts of polymer, the initial rapid drug release ('burst') significantly decreased. With 400 mg polymer, no burst effect was visible. This might be attributed to the fact that at this polymer level no direct access of the release medium to the drug within the microparticles is given, the polymer completely covers the drug.

In conclusion, different formulation parameters such as the initial drug loading and the amount of polymer can be used to effectively adjust the resulting drug release profiles to achieve optimal therapeutic effects.

3.5. Particle size

The mean particle sizes were 156.2 ± 23.2 μm for the original foam powder (sieve fraction 125–160 μm), and 204.5 ± 53.0, 205.2 ± 49.3 and 196.0 ± 50.8 μm for Eudragit RS-containing microparticles with 4.1, 8.3 and 15.7% drug loading. As can be seen, the addition of Eudragit RS (at a 'polymer: foam powder' ratio = 1:1 = 200:200 mg) led to slightly increased particle sizes compared with the original foam powder. Increasing the initial drug loading had no significant effect.

The influence of the amount of polymer on the particle size was also studied. Here, a larger foam powder fraction (400–630 μm) was used, and the amount of Eudragit RS stepwise varied from 200 to 400 mg. The theoretical drug loading (10%) and the amount of foam powder (200 mg) were kept constant. The mean particle sizes were 620.0 ± 105.4 μm for the original foam powder, and 606.1 ± 122.2, 689.1 ± 153.3 and 816.3 ± 169.1 μm for microparticles containing 200, 300 and 400 mg Eudragit RS, respectively. The size of the microparticles significantly increased. The extent of the increase in particle size indicates that besides the increasing polymer deposition on the surfaces also microparticle agglomeration occurs at higher polymer amounts. This phenomenon could be confirmed by SEM pictures (data not shown).

3.6. Physical state of the drug within the system

Differential scanning calorimetry was used to elucidate the physical state of the drug within the system. Thermograms of the single components, a physical mixture and microparticles are shown in Fig. 6. A sharp melting transition of verapamil HCl was observed at 145 °C (curve A). Polypropylene foam powder showed a broad melting transition with a peak maximum at 165 °C (curve B). Eudragit RS also showed a broad transition with a peak maximum at 59 °C, corresponding to the glass transition temperature overlapped by relaxational processes in the polymer (curve C). A physical mixture of the three components (containing 27% drug) showed the Eudragit RS, verapamil HCl and polypropylene peaks (curve D). From these observations it can be concluded that (i) verapamil HCl did not completely dissolve in the molten Eudragit RS during the DSC measurements, otherwise the drug peak would have disappeared in the physical mixture (Bodmeier and Chen, 1989); and that (ii) there was no major interaction between the components during heating. A DSC thermogram of the microparticles showed only the polypropylene peak, but no drug peak (curve E). As a complete dissolution of the incorporated verapamil HCl in the polymer melt can be excluded from the above mentioned, the drug is partly dissolved in the polymer and partly in the amorphous form. To strengthen this hypothesis a polypropylene foam powder-free film, consisting of polymer and drug only was prepared from organic solution. No transition peaks at all were visible in its DSC thermogram (curve F).

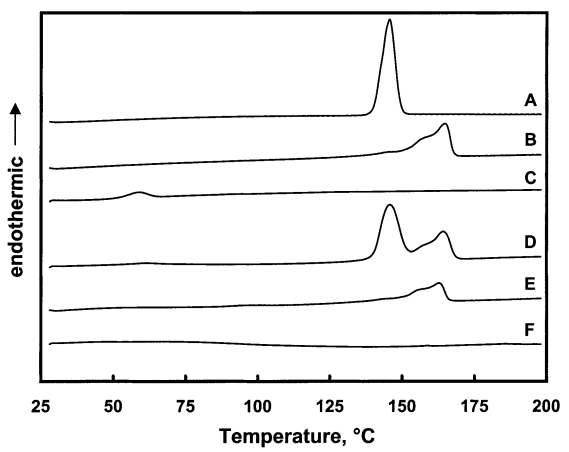

Fig. 6. DSC thermograms of: (A) verapamil HCl; (B) polypropylene foam powder; (C) Eudragit RS; (D) a physical mixture of A–C (27% drug); (E) microparticles with 27% drug; (F) Eudragit RS film containing 27% drug.

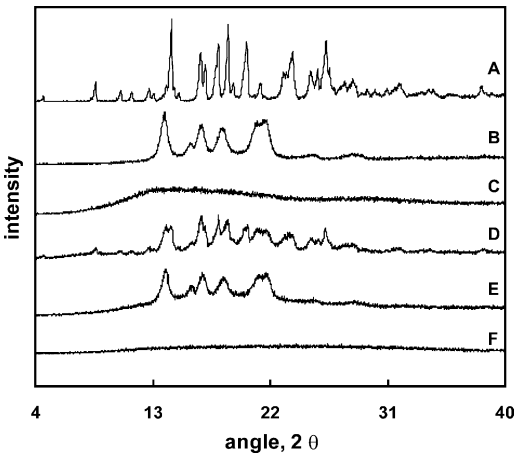

Fig. 7. X-ray diffraction patterns of: (A) verapamil HCl; (B) polypropylene foam powder; (C) Eudragit RS; (D) a physical mixture of A–C (27% drug); (E) microparticles with 27% drug; (F) Eudragit RS film containing 27% drug.

Also, X-ray diffraction was used to study the physical state of the drug within the microparticles. Diffraction patterns of the single compo-

nents, a physical mixture and drug-loaded microparticles are shown in Fig. 7. Verapamil HCl showed various characteristic peaks (curve A), polypropylene foam powder was partly crystalline, indicated by broader peaks (curve B), whereas Eudragit RS showed the patterns of an amorphous substance (curve C). In the diffraction patterns of a physical mixture of the three components (containing 27% verapamil HCl), the drug peaks and the polypropylene foam powder peaks were still visible (curve D). In contrast, the X-ray patterns of microparticles showed only the characteristic peaks of polypropylene foam powder, but no drug peaks (curve E). Thus, the drug is not in a crystalline form (at least not at a higher percentage). Also, a foam powder-free Eudragit RS film prepared from organic solution containing 27% verapamil HCl did not show any crystallinity peaks (curve F). These observations are in good agreement with the SEM pictures (Fig. 1, no drug crystals visible).

Thus, it can be concluded that the drug is not present in a crystalline form in the microparticles. It is partly dissolved within the polymer and partly in the amorphous form distributed throughout the system.

3.7. Effect of the type of polymer

In addition to Eudragit RS, the suitability of EC and PMMA to serve as polymers for the formation of floating microparticles was studied. As mentioned above, the obtained encapsulation efficiencies were close to 100% with both polymers, independent of the theoretical drug loading in the investigated range (5–20%). Excellent in vitro floating behavior was observed in all cases: 96–100% PMMA-containing, and 98–100% EC-containing microparticles kept floating for at least 8 h.

The resulting in vitro drug release strongly depended on the type of polymer (Fig. 3 vs. Fig. 8A and B). At similar actual drug loadings the release rate increased in the following rank order: PMMA < EC < Eudragit RS, which can be attributed to the different permeabilities of the drug within these polymers and/or drug distribution within the systems. In all cases the release rate increased with increasing drug loading (Figs. 3 and 8). Similar to Eudragit RS-containing systems, EC-containing microparticles showed biphasic drug release patterns in all cases: an initial rapid drug release phase ('burst effect') was followed by a second, slower drug release phase. With increasing initial drug loading the burst increased. In contrast, PMMA-containing microparticles showed more sustained drug release patterns which were not biphasic (no initial burst) which might again be attributed to different drug permeabilities and structures of the microparticles (Figs. 3 and 8A and B). Analogous to Eudragit RS-containing systems, the initial particle size of

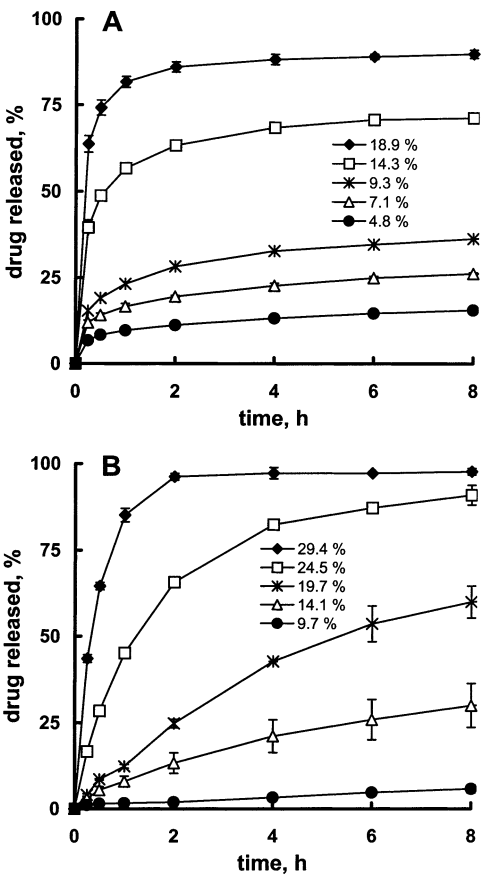

Fig. 8. Effect of the type of polymer and actual loading on drug release in 0.1 N HCl from floating microparticles: (A) EC-containing; and (B) PMMA-containing systems (200 mg polymer, 200 mg foam powder 125–160 μm, actual drug loadings are given in the figure legends).

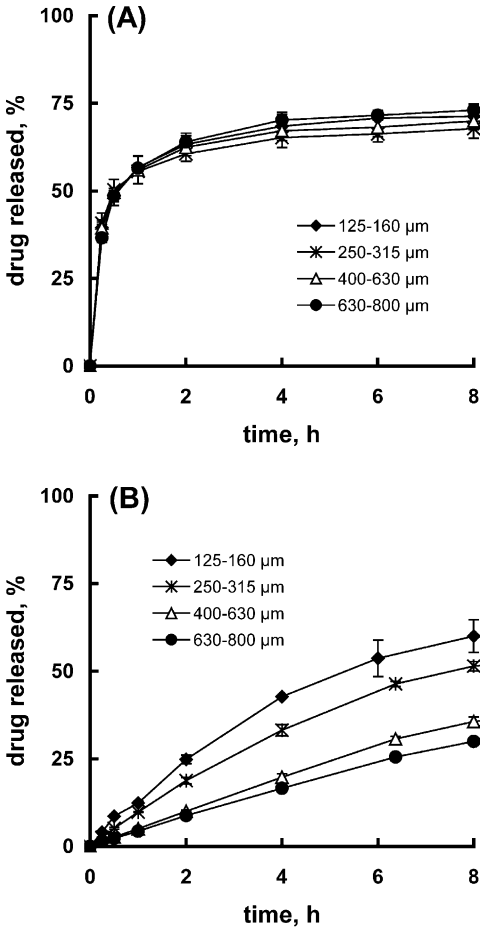

Fig. 9. Effect of the type of polymer and initial particle size of the foam powder (given in the figure legends) on drug release in 0.1 N HCl from (A) EC-, and (B) PMMA-containing floating microparticles (200 mg polymer, 200 mg foam powder).

the original polypropylene foam powder had no significant effect on drug release from EC-containing microparticles (Fig. 9A). In contrast, in the case of PMMA-containing microparticles drug release decreased with increasing particle size of the original foam powder (Fig. 9B). This might be explained as follows. PMMA-containing microparticles do not show any burst effect. Thus, drug release is purely diffusion-controlled. According to Fick's law of diffusion increasing diffusion pathways led to decreased diffusion rates. In contrast, the Eudragit RS- and EC-containing microparticles showed a significant 'burst' release: approximately 40–50% of the drug were released within the first hour. This 'burst' release cannot solely be attributed to drug diffusion through the polymer, but is probably related to the dissolution of drug aggregates located close to the particle surfaces. Thus, an increase in particle size does not significantly affect the initial burst, and only marginally influences the subsequent slower drug release phase.

Analogous to Eudragit RS-containing microparticles, drug release from PMMA-containing systems significantly depended on the amount of polymer (Fig. 10). The drug release kinetics from microparticles with 25, 30, 35, and 40% (Fig. 10A–D) theoretical drug loading (encapsulation efficiencies were close to 100% in all cases) are shown for different amounts of the polymer. Importantly, varying the initial drug loading and the amount of polymer, a large range of different drug release patterns can be achieved.

The effect of the type of polymer on the microparticle size is illustrated in Fig. 11. PMMA-containing systems (mean particle size 214.1 ± 60.0 µm) showed a rather narrow particle size distribution and only a small increase in size compared with the original foam powder, similar to Eudragit RS-containing devices. In contrast, a significant increase in particle size and a much broader size distribution was observed with EC-microparticles (mean particle size 564.7 ± 216.8 µm). This might be explained by the higher viscosity of the organic phase in the case of EC compared with Eudragit RS and PMMA, resulting in the formation of agglomerates during preparation. The higher viscosity hinders the entrance of the organic phase into the inner pores of the system. Thus, more polymer solution is present at the surface of the particles, increasing the probability to form agglomerates. This could be confirmed by SEM pictures: Fig. 12 shows an agglomerate of EC-containing microparticles.

DSC- and X-ray measurements of drug-loaded, EC- and PMMA-containing microparticles (data not shown) gave similar results as Eudragit RS (Figs. 6 and 7). Thus, the drug is not present in a crystalline form.

In conclusion, a new type of multiparticulate gastroretentive drug delivery system (floating mi-

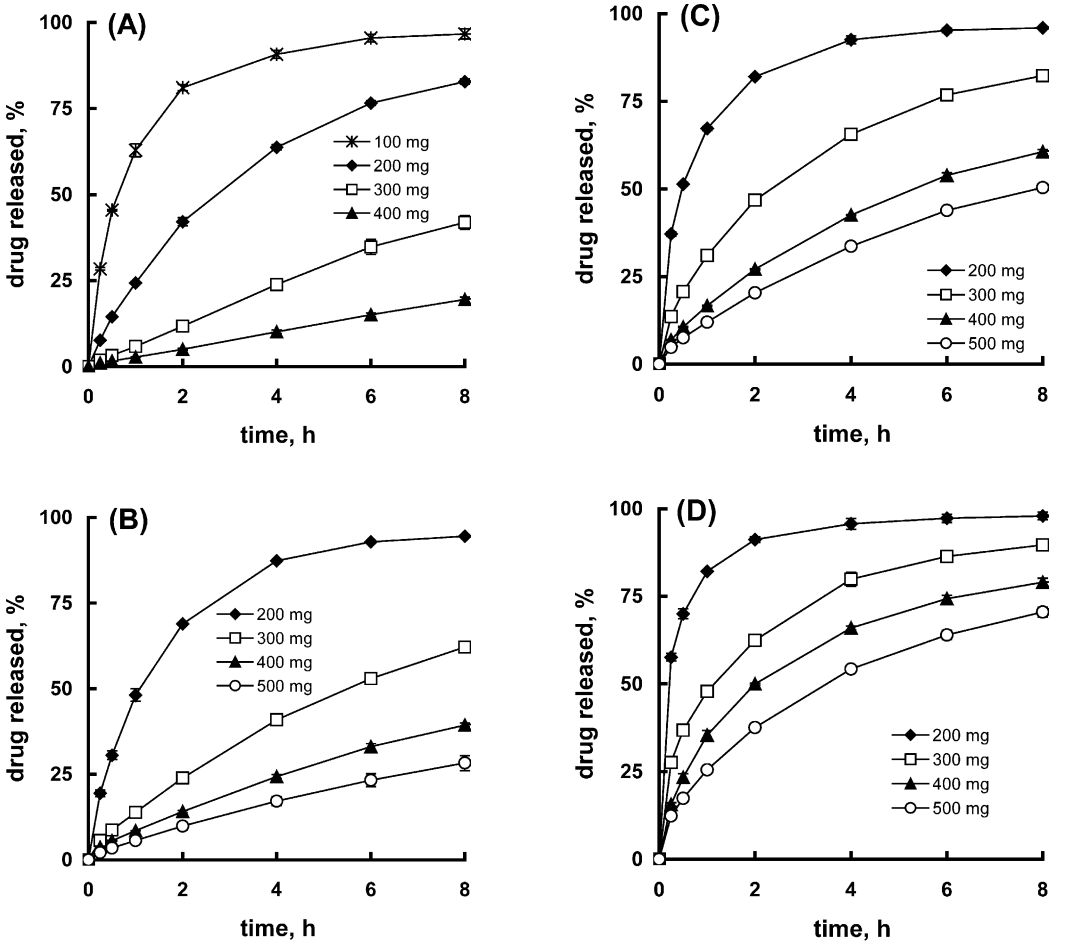

Fig. 10. Effect of the amount of PMMA (given in the figure legends) on drug release in 0.1 N HCl from floating microparticles. (A) 25%, (B) 30%, (C) 35%, and (D) 40% theoretical drug loading (200 mg foam powder 400–630 μm).

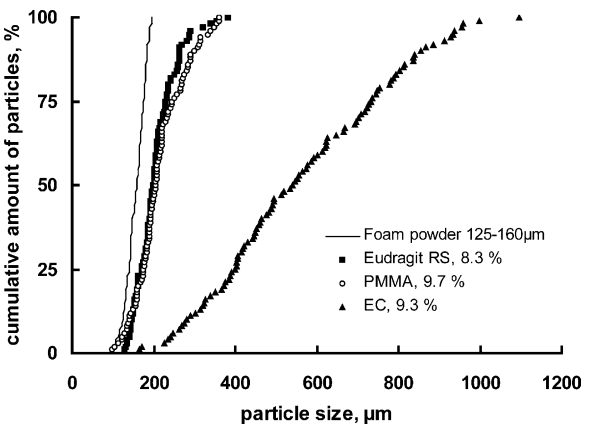

Fig. 11. Cumulative particle size distributions of original foam powder and floating microparticles: effect of the type of polymer (200 mg polymer, 200 mg foam powder 125–160 μm, actual drug loadings given in the figure legend).

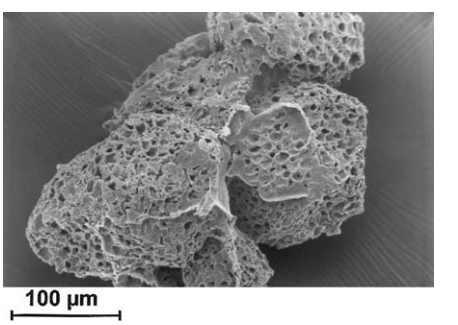

Fig. 12. SEM of an agglomerate of EC-containing microparticles (200 mg EC, 200 mg foam powder 125–160 μm).

croparticles) has been developed. The performance of these devices was demonstrated and the effect of various formulation parameters was studied. Major advantages of the system include: (i) easiness of preparation; (ii) good floating properties; (iii) high encapsulation efficiencies; (iv) high payloads of the drug; and (v) sustained drug release over several hours. The microparticles (which showed release rates suitable for oral use) could be compressed into tablets, filled into capsules, or formulated into oral suspensions.

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