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Optimisation of floating matrix tablets and evaluation of their gastric residence time

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Abstract

The present investigation concerns the development of the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of irritating drugs. The importance of the composition optimisation, the technological process development for the preparation of the floating tablets with a high dose of freely soluble drug and characterisation of those tablets (crushing force, floating properties in vitro and in vivo, drug release) was examined. Tablets containing hydroxypropyl methylcellulose (HPMC), drug and different additives were compressed. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release. With the incorporation of a gas-generating agent together with microcrystalline cellulose, besides optimum floating (floating lag time, 30 s; duration of floating, >8 h), the drug content was also increased. The drug release from those tablets was sufficiently sustained (more than 8 h) and non-Fickian transport of the drug from tablets was confirmed. Radiological evidence suggests that, that the formulated tablets did not adhere to the stomach mucus and that the mean gastric residence time was prolonged (>4 h).

Keywords: Tablet; Floating; Matrix; Non-Fickian diffusion; Gastric residence time

1. Introduction

Using current release technology, oral delivery for 24 h is possible for many drugs; however, the substance must be absorbed well throughout the whole gastrointestinal tract. A significant obstacle may arise if there is a narrow window for drug absorption in the gastrointestinal tract, if a stability problem exists in gastrointestinal fluids, or the drug is poorly soluble in the intestine or acts locally in the stomach. Thus, the real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the

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presence of the dosage forms in the stomach or somewhere in the upper small intestine until all the drug is released for the desired period of time (Deshpande et al., 1996; Hwang et al., 1998).

Controlling the residence of a drug delivery system in a particular region of the gastrointestinal tract can utilise several approaches: intragastric floating systems, high density systems, mucoadhesive systems, magnetic systems, unfoldable, extendable or expandable systems and superporous, biodegradable hydrogel systems. Some of these devices are of practical use; whereas others are more or less in the development and theoretical stages. Whenever extending the gastric residence time is considered, the physiology of the gastrointestinal tract must be well understood and all limitations should be taken into account. Factors such as pH, the nature and volume of gastric secretions, food, gastric mucosa and motility play an important role in drug release and absorption and also in dosage form placement (Deshpande et al., 1996). To validate in vitro simulations, in vivo studies must be conducted (Desai and Bolton, 1993; Jiménez-Castellanos et al., 1994; Hwang et al., 1998).

A previously described formulation, the hydrodynamically balanced systems, were designed to prolong the gastric residence time utilising floating behaviour (Gerogiannis et al., 1993; Rouge et al., 1997). Various attempts have been made to develop a floating system. Researchers used empty globular shells with a lower density than that of gastric fluid (Watanabe et al., 1976). The other group of researchers developed a system comprising a drug and hydrocolloid mixture, which swells and forms a soft mass floating on the top of gastric fluid (Sheth and Tossounian, 1978). Another possibility is to make gel-type matrix in which light oil and drug are incorporated (Desai and Bolton, 1993), or to produce a bilayer capsule (one layer is a release layer and the other one is a floating layer) (Oth et al., 1992).

The present study focused on development of a matrix floating tablet with an incorporated high dose of a freely soluble active substance with a high density, achieving the sustained drug release and determining the drug release mechanism, optimising the dosage form in the physical and technological sense, and proving the prolongation of the gastric residence time on beagle dogs.

2. Materials and methods

2.1. Materials

Pentoxyfilline was used as a model drug (Fermion, Finland); hydoxypropylmethyl cellulose: HPMC K4M (Premium Methocel K4M, Colorcon, England); $BaSO_4$ (Merck); cross-linked carboxymethylcellulose sodium: Ac-Di-Sol® (FMC, USA); microcrystalline cellulose: Avicel® PH 101 (FMC, USA); cetostearol (Lanette 0, Lek, Slovenia); sodium carboxymethyl starch: Primojel® (Avebe, The Netherlands); sodium bicarbonate, citric acid, hydrochloric acid 36.2% and sodium chloride were all of a pharmaceutical grade.

2.2. Tablet preparation for in vitro testing

The hydoxypropylmethyl cellulose polymer and the active ingredient were mixed homogeneously and granulated in a laboratory mixer (Multipraktik, Iskra-Braun, Slovenia) for 2 min at the highest speed. One percent (w/w) HPMC K4M colloid dispersion was used as the granulating agent. The granules were dried in dry hot air for 5 h at a temperature of 45°C (Instrumentaria, Sterimatic ST-11, Croatia). Dry granules were sieved at a matching interval of 0.2 mm $< d <$ 1 mm using a vibrating sieve (MLV, Germany) for 10 min at the highest value of vibration without intervals and sieving aids. The sieves of 100, 200, 500 and 1000 μm were used. A total of 0.6% (w/w) of magnesium stearate was added as a lubricant to each granulate before compressing it into tablets (Erweka-Apparatebau, EKO, Korsch, Berlin, Germany). The tablets weighed 0.50 g $\pm$ 0.03 were circular, flat-faced, 12 mm in diameter and 0.47–0.49 mm thick. The tablets of each series were tested for resistance to crushing expressed as crushing force (VanKel VK 200, USA)

and average values and standard deviations (S.D.) were calculated ($n = 6$).

When the tablets with cetostearol were prepared, the cetostearol melt was added as a granulating agent to the homogeneously mixed powders of HPMC K4M and the drug. Granules were dried at the room temperature on the air. Then the procedure of preparing was the same as described before.

When the tablets with superdisintegrants (Ac-Di-Sol® or Primojel®) were formulated, these substances were added into the dry granulate together with lubricant before compression.

The nonaqueous conditions for granulation were required when tablets contained a gas-generating agent. Therefore 99% (vol./vol.) ethanol was used as a granulating agent. Granules of matching size were dried and stored in a dessicator until the lubricant was added and the tablets were compressed.

2.3. Floating properties

The time the tablets took to emerge on the water surface (floating lag time) and the time the tablets constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel (dissolution tester; Erweka, Type DT6, Germany) filled with 500 ml of artificial gastric fluid without pepsin (USP XXIII), pH 1.2; $T = 37°C \pm 0.5$, paddle rotation = 100 rpm. The measurements were carried out for each series of tablets ($n = 6$).

2.4. Drug release testing

The drug release studies were carried out using the dissolution tester (Erweka, Type DT6, Germany). The dissolution vessels were filled with 500 ml of the artificial gastric fluid (USP XXIII); pH 1.2; $T = 37°C \pm 0.5$, paddle rotation = 100 rpm. The samples were taken at preselected time intervals. The collected samples were diluted and the absorbance was measured spectrophotometrically (UV-VIS, Perkin-Elmer 554), $\lambda = 274$ nm. The released drug concentration was calculated using a calibration curve.

2.5. Tablet preparation for in vivo studies

The tablets with diameter ($d = 12$ mm) and 350 mg in weight were prepared. To make the tablets X-ray opaque the incorporation of $BaSO_4$ was necessary. Barium sulphate has a high relative density (4.4777 g/cm^3) and poor floating properties. For in vivo tests tablets with the following composition were prepared: 22.9% drug, 15.4% $BaSO_4$, 53.5% HPMC K4M, 3.9% citric acid, 3.9% $NaHCO_3$ and Mg-stearate (crushing forces 45 N; the floating lag time was 12 min $\pm$ 2 and the duration of floating was more than 8 h). The amount of the X-ray opaque material in these tablets was sufficient to ensure visibility by X-ray, but at the same time this amount of $BaSO_4$ was low enough to enable tablets to float. The analyses confirmed that these tablets were similar to the tablets for in vitro testing, i.e. the mechanical strength, floating properties, controlled drug release.

2.6. In vivo studies

Four healthy beagle dogs, weighing approximately 16 kg, were used throughout the study. In each experiment, an unanaesthetized animal was fasted for 24 h and the first radiograph was made to ensure the absence of radipaque material in the stomach. The dogs swallowed one of the tablets and immediately afterwards drank 100 ml of water. During the experiment the dogs were not allowed to eat, but water was available ad libitum. The in vivo tests were performed at the Veterinary Faculty, which has the authorisation to perform this kind of imaging, under the Law on animal health, Art. 78 and 79 (OJ SRS 37/85).

For radiographic imaging the animal was positioned in a right lateral or ventrodorsal recumbency. After the determined time intervals standard lateral and ventrodorsal radiographs of the abdomen were taken using an X-ray machine (General Electric Corporation, USA). The distance between the source of X-rays and the object was the same for all imaging. This allowed us to see the tablet in the body of stomach, antrum and/or pyloric part of the stomach so that observations of the tablet movements could be made.

The first picture was taken 30 min after the administration of the tablet and then every 30 min during the first 3 h, followed by 1 h intervals until the tablet disappeared from the stomach.

3. Results and discussion

3.1. The development of matrix floating tablet

On the basis of prior studies on the floating properties of matrix tablets, we concluded that the hydroxypropylmethyl cellulose K4M polymer is the best vehicle for the floating tablet design (Baumgartner et al., 1998). The floating properties of the tablet is, however, expected to be altered when a high dose of the active component is incorporated.

It is evident that the drug incorporation affects the tablet properties. The investigated model drug is highly water-soluble, true density is $\rho = 1.359$ g/cm^3 and the single dose is very high, so it was a real challenge to form a floating tablet which will ensure a constant drug release for more than 8 h.

Tablets with different ratios of the drug versus polymer were prepared to optimise the drug content and floating properties (Table 1). It was determined that besides the tablet composition, the tablet hardness has an essential role for floating properties. When just the drug and HPMC K4M are combined, it was impossible to incorporate more than 39.7 w/w% (S-4) of the drug into tablet, which would fulfil all the previously mentioned required properties (Table 1).

3.2. Drug release mechanism and drug release rate

Drug release studies of formulation S-4 were made to determine whether the release of the drug is slow enough, i.e. whether the polymer percentage is high enough to sustain the release of the drug for more than 8 h (Fig. 1). The drug compressed into the tablets was released in less than 1 h. From the comparison of drug release among tablets with and without added HPMC K4M, it is evident that the polymer prolonged the drug release for more than 8 h. In the time interval of 8 h the 75.55% $\pm$ 2.28 of the incorporated drug was released, and in 24 h the whole dose was released.

The tablet which is composed of a polymeric matrix on contact with water builds a gel layer

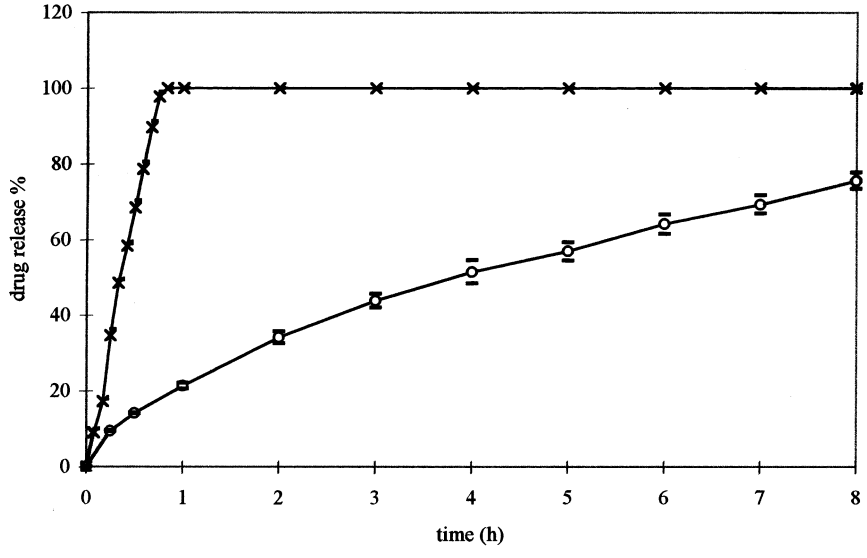

Fig. 1. In vitro drug release profiles of the pentoxyfilline in the absence (+ , —) or in the presence (S-4 = ○, —) of hydroxypropyl methylcellulose (HPMC) K4M.

Table 1
Influence of tablet composition on their crushing force and floating properties

Series no.	Drug (% w/w)	Hydroxypropyl-methyl cellulose K4M (% w/w)	Cetostearol (% w/w)	Microcrystalline cellulose (% w/w)	Gas-generating agent[a] (% w/w)	Crushing force (N)	Floating lag time (min)	Duration of floating (h)
S-1	29.7	69.7	0	0	0	80.0 ± 10.0	NO[b]	NO[b]
S-2	29.7	69.7	0	0	0	56.7 ± 1.2	6 ± 2	24
S-3	39.7	59.7	0	0	0	93.0 ± 10.0	NO[b]	NO[b]
S-4	39.7	59.7	0	0	0	54.1 ± 4.6	12 ± 3	24
S-5	44.7	54.7	0	0	0	63.5 ± 8.7	NO[b]	NO[b]
S-6	39.7	54.7	5	0	0	55.0 ± 5.0	6 ± 1	24
S-7	49.7	44.7	5	0	0	71.3 ± 3.24	NO[b]	NO[b]
S-8	49.7	44.7	5	0	0	53.5 ± 4.4	8 ± 3	24
S-9	54.7	39.7	5	0	0	65.0 ± 5.0	NO[b]	NO[b]
S-10	51.7	40.7	7	0	0	53.8 ± 2.3	NO[b]	NO[b]
S-11	49.7	29.7	0	15.0	5.0	42.7 ± 5.3	0.25 ± 0.2	24
S-12	54.7	30.0	0	9.7	5.0	45.5 ± 6.2	0.5 ± 0.2	24
S-13	59.7	23.0	0	10.0	7.0	42.2 ± 5.8	0.5 ± 0.2	24

[a] A mixture of citric acid and $NaHCO_3$.
[b] Tablets did not float.

Table 2
The results of the calculated number n (n is the release exponent indicative of the drug release mechanism) based on in vitro drug release experiments, and the results of the calculated kinetic constants k, which represent the drug release rate from the tablets, and Pearson coefficients

Series no.	n	r^2	k (%/$\sqrt{h}$)	r^2
S-4	0.60	0.9996	28.6	0.9995
S-6	0.63	0.9988	26.7	0.9996
S-8	0.62	0.9987	32.8	0.9987
S-12	0.59	0.9984	29.0	0.9992

around the tablet core, which governs the drug release. It is known that the drug release from HPMC matrices is controlled for water soluble drugs by diffusion through the gel layer or, for poorly soluble drugs, by erosion of the outer polymer chains (Mitchell et al., 1993). Therefore, the kinetics of swelling is important, because the gel barrier is formed with the water penetration.

Hydroxypropylmethylcellulose hydrogels have several important characteristics that play an essential role in drug diffusion including swelling ratio and specific mesh or pore size. Swelling ratio describes the amount of water that is contained within the hydrogel at an equilibrium and is a function of the network structure, hydrophilicity and ionisation of the functional groups. The pore size is the space available for drug transport. The drug characteristics are as important as those of the gel. The size, shape and ionisation of the drug affect its diffusion through the gel layer (Peppas and Wright, 1998).

The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but other processes in addition to diffusion are important. There is also a relaxation of the polymer chains, which influences the drug release mechanism. This process is described as non-Fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. A third class of the diffusion is Case II diffusion, which is a special case of non-Fickian diffusion (Peppas, 1985; Mitchell et al., 1993). A simple, semiempirical equation can be used to analyse data of controlled release of water-soluble drugs from polymer matrices (Eq. (1)). This equation predicts the mechanism of diffusional release (Peppas, 1985; Yang and Fassihi, 1997):

$$\frac{M_t}{M_\infty} = bt^n \tag{1}$$

where M_t is amount of the released drug at time t, M_∞ is the overall amount of the drug (whole dose), b is the constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent indicative of the drug release mechanism. For tablets of a known geometry (in this case a slab) $n = 0.5$ means Fickian diffusion, $0.5 < n < 1.0$ non-Fickian diffusion, and $n = 1.0$ Case II diffusion (Peppas, 1985). In this study the number n was calculated for the time interval from the first to the eight hour, because in the first hour the burst effect was recognised (the drug releases from the surface of the tablet, before gel layer formation). The result for S-4 has revealed that the calculated n is characteristic for the non-Fickian type of drug diffusion, which means that the processes of diffusion and relaxation run at comparable rates (Table 2).

The passage of a water-soluble drug through hydrated gel layer around the matrix tablet is approximately dependent on the square root of time and can be described in the following form (Shah et al., 1993):

$$Q_t = kt^{1/2} \tag{2}$$

where Q_t is the amount of the released drug in time t, k is the kinetic constant, and t is time. Many times this simple equation (Eq. (2)) is useful for the determination of the drug release rate. The release rate constants from Eq. (2) for the tested tablets ($t = 1$–8 h) are shown in Table 2.

3.3. The physical and technological optimisation of the floating matrix tablets

The results of floating properties and dissolution studies for tablets S-4 were encouraging, and

thus the next step was to improve the floating properties and to incorporate higher amounts of the drug into the tablets.

It is generally believed that incorporation of lipophilic substances, which have a relative density lower than 1, decrease the water intake and improve the floating properties (Moës, 1993; Hwang et al., 1998). The cetostearol melt was added as a granulating agent and the percentage of cetostearol ranged from 5 to 7% (w/w) of the total tablet mass (Table 1).

Tablets with cetostearol compared to tablets without cetostearol S-4 have better floating properties. Therefore, it was possible to increase the drug content from 39.6 to 49.7% and obtain floating tablets (S-8) at crushing forces from 50 to 60 N (Table 1). It has been stated that higher amounts of the drug could not be incorporated at a higher percentage of the cetostearol and a decreased tablet mechanical strength. The reason for this appeared to be the action of cetostearol which reduced ingress of water into the HPMC K4M reducing the polymer swelling.

The release studies were conducted to investigate if cetostearol influences the release mechanism or the release rate in comparison to tablets without cetostearol. From Fig. 2 it can be seen that cetostearol (S-6) slowed the release of the drug from the tablets in comparison to tablets without cetostearol (S-4). Even if there was less incorporated HPMC K4M, the release from tablets (S-8) was slow enough because of the added cetostearol. In 8 h 83.09% $\pm$ 2.73 of the drug was released. Cetostearol did not change the drug release mechanism and the kinetic constant was calculated from Eq. (2).

It is known that lipophilic substances may affect the gastric retention time-gastric emptying could become slower for all ingested food or drugs (Moës, 1993; Deshpande et al., 1996). This may be a side effect of the incorporation of the cetostearol into the floating tablets. Therefore one attempted to replace the cetostearol with the superdisintegrants cross-linked carboxymethycellulose Ac-Di-Sol® or sodium carboxymethyl starch Primojel® because those polymers swell fast. It was proved earlier that swelling is a vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored (Timmermans and Moës, 1990; Baumgartner et al., 1998). Superdisintegrants were incorporated into the dry granulate (in a

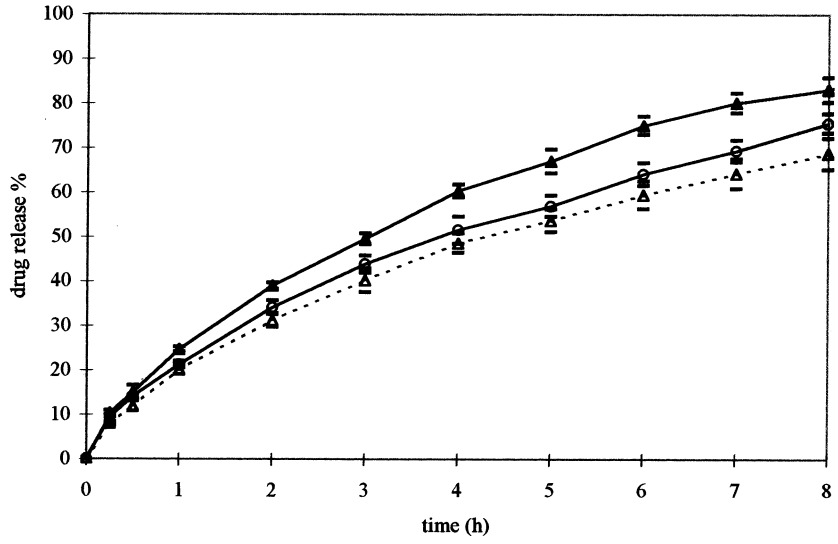

Fig. 2. Drug release profiles of the pentoxyfilline from the floating tablets without cetostearol (S-4 = ○, —) and with it (S-6 = △,-- -), and additionally with a different drug content (S-6 = △,-- -; S-8 = ▲, —).

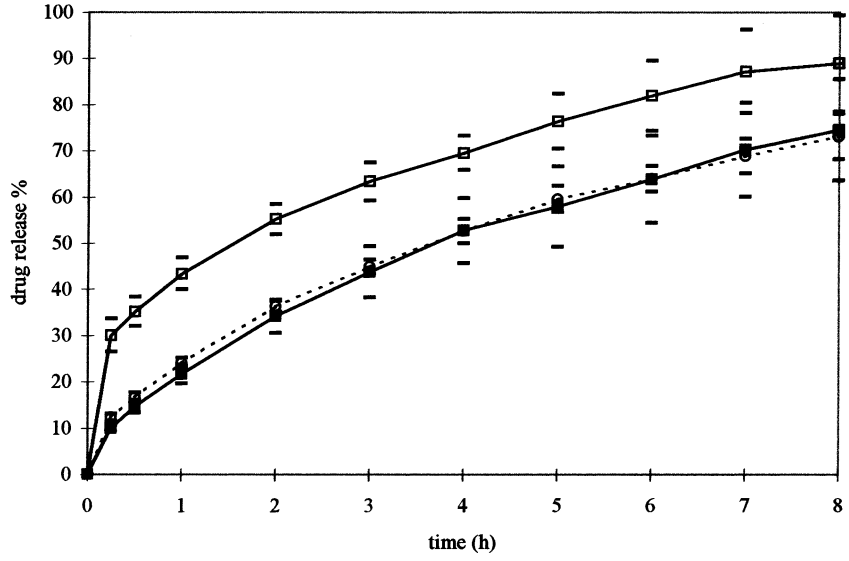

Fig. 3. Drug release profiles of the pentoxyfilline from floating tablets (S-11 = ○,-- -; S-12 = ■, —, and S-13 = □, —) with a different drug content.

concentration of up to 10%) before compression, but those tablets did not float. The possible reason was that Ac-Di-Sol® or Primojel®, even if they swell fast and accept a lot of water per 1 g of polymer, did not ensure that the density of the matrices was less than 1.

The floating properties of the tablets could be improved not just with fatty substance, but also with gas generating agent, which is a mixture of citric acid and $NaHCO_3$ (Moës, 1993; Deshpande et al., 1996; Hwang et al., 1998). These compounds generate CO_2 on reaction with water. The bubbles of gas first help the tablet to become buoyant and remain entrapped in the gel layer.

Nevertheless, even with improved floating properties, we were unable to increase the drug content. Tablets with higher amounts of the drug rapidly emerged to the water surface, but sank after 2 or 3 h because the gas-forming substances were depleted.

Microcrystalline cellulose (Avicel®PH 101) has a very porous structure. With this substance more air would be present in the tablets S-11, S-12, and S-13 and this could help the tablets to float (Table 1). The results in Table 1 have proved the expectations. The tablets had very good floating properties and contained higher amounts of the drug. Therefore the dissolution tests were performed (Fig. 3). The release kinetic was suitable for tablets S-11 and S-12 and was not significantly different as proved by the statistical calculations. For S-13 tablets the burst effect in the first hour was too big and the standard deviation was too high, and this formulation was discarded.

The release rate constant for tablets S-12 was the lowest among all those calculated (Table 2). This result was a bit surprising. A faster release was expected for two reasons. First, with the evolution of gas the matrix would become more relaxed allowing water penetration and the drug diffusion might be easier; and second, the drug content was higher in comparison to the previous one (Table 1). However, the improved floating properties of tablets S-12 were associated with an even slower drug release.

3.4. Intragastric behaviour of the floating tablet

The behaviour of the tablet in the dog stomach was observed in real time using a radiographic imaging technique. On radiographic images made 0.5 h after the administration, the tablets were

observed in the animal's stomach (Fig. 4A). In the next picture taken at 1 h significant changes were detected: the tablet had altered its position and turned round (Fig. 4B). This provided evidence that the tablets did not adhere to the gastric mucous, but, on the contrary, floated on the gastric fluid. Additionally the swelling of the tablet is visualised very well together with the white dry core and translucent swelling layer around it (Fig. 4C). As the swelling continued, the glassy core diminished, the swelling layer eroded from the outer surface and a size reduction was seen. The investigations showed that during the tablet observation only animal 4 responded differently to the others. For this animal no prolongation of the gastric residence time was obtained.

The major limitation to the upper gastrointestinal residence time of solid single unit dosage forms administered in the fasted state or with non-caloric fluids constitutes the third phase of

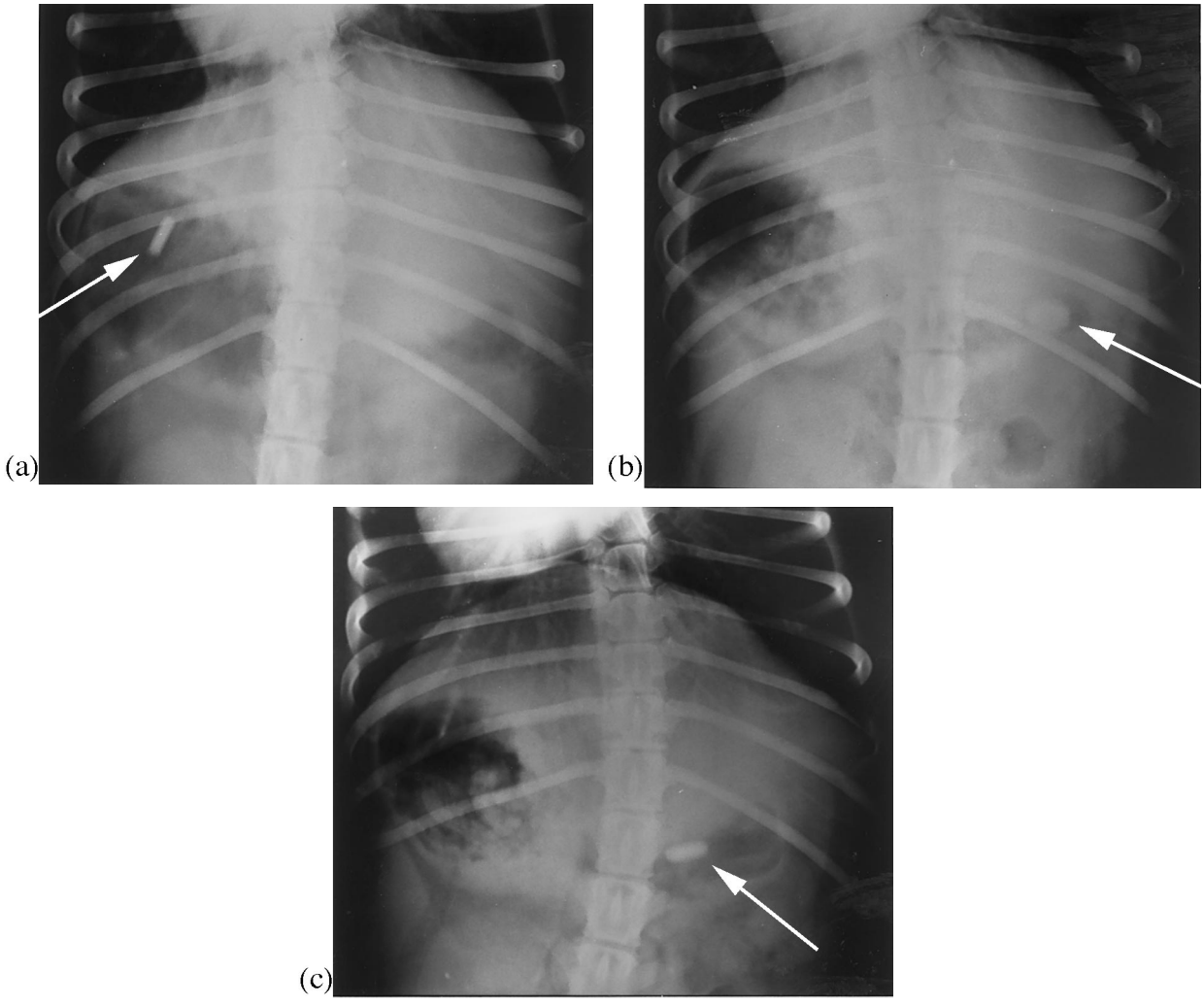

Fig. 4. Intragastric behaviour of the $BaSO_4$-loaded floating tablets represented by typical radiographic images after definite time intervals (the tablet is pointed by an arrow). (A) The tablet edges are sharp, no gel layer is seen after 0.5 h of the tablet administration. (B) After 1 h of the tablet administration the tablet altered its position and turned round. (C) After 4 h of the tablet administration the tablet edges are not sharp any more, the translucent swelling layer is clearly seen, the tablet did not adhere to the gastric mucous.

the migrating myoelectric complex, since it occurs approximately every 2 h in humans (Hwang et al., 1998) and approximately every 1 h in dogs (Cunningham, 1997). For this phase the intense activity that empties large, non-disintegrating particles including dosage forms from the stomach to the small intestine is characteristic. But the results have shown that the mean gastric residence time for the developed floating tablets was 240 min $\pm$ 60 ($n = 4$). The comparison of gastric motility and stomach emptying between humans and dogs shows no big differences (Cunningham, 1997; Hwang et al., 1998). Therefore, it might be speculated that experimentally proven increased GRT in beagle dogs can be compared to known literature data for humans, where this time is less than 2 h (Davis, 1985).

4. Conclusion

In the current work a matrix floating tablet incorporating a high dose of freely soluble active substance is described. The most successful mixture (S-12) contained 54.7% of drug, HPMC K4M, Avicel®PH 101 and a gas-generating agent. This formulation took 30 s to become buoyant and have an appropriate resistance to crushing. The non-Fickian diffusion was confirmed as the drug release mechanism from these tablets. This means that water diffusion and also the polymer rearrangement have an essential role in the drug release. The release rate constant of this formulation (S-12) was low enough prolonging drug delivery. In vivo experiments supported the expectations in prolonging the gastric residence time in the fasted state in beagle dogs. The mean gastric residence time for the tested tablets was 240 min $\pm$ 60 ($n = 4$). This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the prolonged or controlled release dosage forms.

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