Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 336 (2007) 159–165
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form

Yong-Dan Tang [a], Subbu S. Venkatraman [a,*], Freddy Y.C. Boey [a], Li-Wei Wang [b]

[a] School of Materials Science & Engineering, Nanyang Technological University, Blk N4.1-02-06, 50, Nanyang Avenue, Singapore 639798, Singapore
[b] Amaranth Medical, Bioinnovation Centre, 180 Ang Mo Kio Avenue 8, Singapore 569830, Singapore

Received 1 June 2006; received in revised form 19 November 2006; accepted 23 November 2006
Available online 3 December 2006

Abstract

Floating dosage forms enable the sustained delivery of drugs in the gastro-intestinal tract. In this study, a type of multi-unit floating gel bead was synthesized with calcium alginate, sunflower oil, and a drug of interest through an emulsification/gelation process. The alginate beads with oil addition were able to continuously float over the medium for 24 h under constant agitation while the non-oily beads could not. Three kinds of drugs with different hydrophilicities, ibuprofen, niacinamide and metoclopramide HCl, were tested in the study. The hydrophobic drug ibuprofen was released in a sustained manner for 24 h, due to the oil partitioning. With suitable modification, the beads were able to also release the hydrophilic drugs, niacinamide and metoclopramide HCl, for a similar duration. Therefore a floating dosage form that is able to sustain release both hydrophobic and hydrophilic drugs within its extended gastric retention time has been developed.

Keywords: Gastric retentive dosage form (GRDF); Floating system; Alginate; Sustained release

1. Introduction

Limited gastrointestinal (GI) transit time often restricts the complete absorption of oral drugs, or limits the duration of absorption. Thus dosage of a few times a day is generally needed (Khosla and Davis, 1989). Prolonged gastric residence time (GRT) and controlled release of drugs within the GI tract helps to reduce dosing frequency and total dose, improve patient compliance and convenience, maintain a less fluctuating plasma level, as well as reduce GI side effects (Gupta and Robinson, 1992). Prolonging the GRT of therapeutic agents is thought to be beneficial especially under several circumstances such as for drugs acting topically on the gastric region, for drugs with a narrow therapeutic window or for drugs with the major absorption site in the upper GI tract (Klausner et al., 2003).

Methods or forms for prolonging the gastric retention of drug doses have been attempted based on different mechanisms such as buoyancy (Hilton and Deasy, 1992), expansion/plug type (Chen et al., 2000), high density (Singh and Kim, 2000), or adhesion to mucosa (Peppas et al., 2000). The floating system in particular has been extensively researched, mainly because the floating system does not adversely affect the motility of the GI tract. Calcium alginate (Ca-Alg) is the result of the complexation of the polyguluronic sequences by calcium ion, known to be insoluble and resistant to acidic media (Grant et al., 1973). An alginate floating dosage form was introduced as early as in the 1980s (Stochwell and Davis, 1986). Its benefits are obvious: cheap and abundant sources, excellent biocompatibility, and total degradation without hazardous by-products. Recent development of alginate floating dosage forms by three different groups (Whitehead et al., 1998; Iannuccelli et al., 1998; Murata et al., 2000) is schematically illustrated in Fig. 1.

Whitehead et al. (1998) developed the calcium alginate (Ca-Alg) gel beads by freeze-drying. The beads were approximately 2.5 mm in diameter and floated on agitated acidic media (0.1N HCl + 0.05% Tween 80) for over 12 h. The floating beads were radiolabelled with pertechnetate ($^{99m}TcO_4^-$) and in vivo test revealed gastric retention of these beads ranged from 5.5 to 9 h. Amoxycillin release from these alginate beads was conducted spectrophotometrically in 0.1N HCl, pH 1.2 at $37 \pm 1\,^{\circ}C$. In most samples, however, there was little sustained release of the drug: the majority of drug was released in a burst during the first

* Corresponding author. Tel.: +65 67904259; fax: +65 67909081.
E-mail address: assubbu@ntu.edu.sg (S.S. Venkatraman).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.11.060

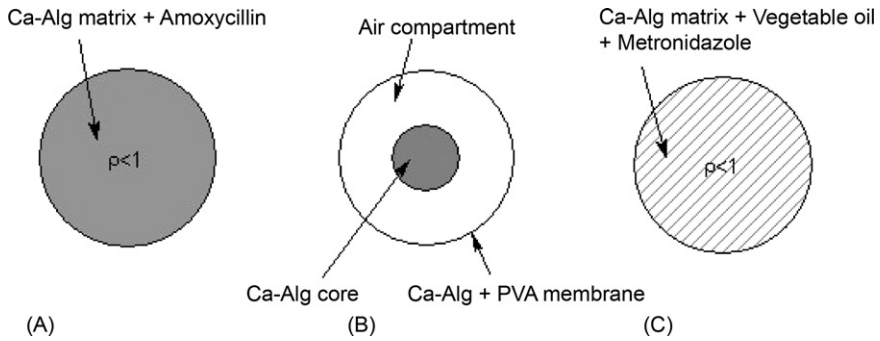

Fig. 1. Summary of design characteristics of three multi-unit floating systems based on calcium alginate. (A) Whitehead et al. (1998), (B) Iannuccelli et al. (1998), and (C) Murata et al. (2000).

60 min. Higher drug loadings could be achieved at the expense of faster release and lower buoyancy.

Iannuccelli et al. (1998) designed a different bubble type floating alginate dosage form with an alginate core. However, excellent buoyancy was only achieved in water. In acidic media, the units did not float. And even after modification of membrane permeability with PVA addition, buoyancy was still not as good as in water. No drug release characteristics were reported in this case.

Murata et al.'s (2000) design was in fact a modification to Whitehead et al.'s. Either vegetable oil for extra buoyancy or chitosan for extra bioadhesion (Gaserod et al., 1998) was added into the alginate gel beads. In contrast to the findings of Whitehead et al.'s, non-oily gel beads failed the buoyancy test. And they were found to have a lower loading of the drug metronidazole than the oily beads. The drug release profile was similar to the results Whitehead et al. had obtained, 80% of the drug was released during the first 60 min. Only chitosan-containing gel beads were administered orally to guinea pigs because oily gel beads were too big (diameter about 4 mm) for them to swallow. The floating gel beads were found to be able to maintain a stable serum concentration of metronidazole for 4 h rather than the 2 h of the conventional dosage. In a later study (Murata et al., 2003), the metronidazole release in vitro from alginate gel beads containing ethylcellulose lasted for less than 90 min.

Since buoyancy derived by trapping air bubbles in the alginate gel beads seems to be unreliable as indicated by Murata et al. (2000), this paper reports a preparation procedure for a multi-unit calcium alginate dosage form with enhanced buoyancy. Sunflower oil was utilized as a dispersed phase to generate a uniform emulsion to create multiple tiny chambers in the alginate matrix for better buoyancy.

The other issue addressed in this study is sustaining the release of both hydrophilic and hydrophobic drugs over a reasonable duration, since prolonged retention without sustained release is of little practical value. In this context, we also examined the relationship between the drug release profile and drug solubility since previous efforts (Whitehead et al., 1998; Iannuccelli et al., 1998; Murata et al., 2000) appeared not to produce sustained release of more than 2–3 h. Three drugs with different hydrophilicities, ibuprofen (less hydrophilic), niacinamide (hydrophilic) and metoclopramide HCl (highly hydrophilic) were studied as the model drugs. The intention was to achieve a controlled release profile that is consistent with prolonged retention time.

2. Materials and methods

Alginic acid sodium salt (Aldrich, Viscosity 200,000–400,000 cps), sunflower oil (Naturel®), polyvinyl alcohol (PVA, Aldrich, 87–89% hydrolysed, average Mw 13,000–23,000), ibuprofen (1 mg/ml in water, about 25 mg/ml in oil, Tokyo Kasei), niacinamide (50 mg/ml in water, Sigma), metoclopramide HCl (about 650 mg/ml in water, Sigma) and calcium chloride dihydrate (Fisher Scientific) were purchased and used as received. Eudragit® S100 (methacrylic acid–methyl methacrylate copolymer 1:2, Rohm Pharma, Germany) was a gift from Degussa Asia. The simulated gastric fluid (SGF) used for the experiment was made of 0.1 mol/l HCl solution (Merck) and 0.02% (w/v) Tween 20 (Tokyo Kasei).

All gel beads described in this paper were prepared following the same gelation and freeze drying procedure. A pre-gelation liquid was prepared by mixing sodium alginate solution, the prescribed amount of sunflower oil, and the drug, either ibuprofen, niacinamide or metoclopramide HCl. Three millilitres of each of the pre-gelation liquid was then added, through a syringe, into 10 ml 0.3% (w/v) (unless otherwise stated) of $CaCl_2$ solution and kept for 30 min. The beads were then recovered from the $CaCl_2$ solution and washed with deionized (D.I.) water, freeze dried at −20 °C over night, then kept in desiccators. Selected niacinamide and metoclopramide HCl beads were dip coated in Eudragit ethanol solutions after freeze drying. Dipping was conducted thrice. Each time after the previous coating was air dried at room temperature.

The freeze dried beads were observed under a stereo zoom optical microscope (Leica MZ6 optical microscope) and under a scanning electron microscope (SEM, Joel JEM5410LV). Heywood diameters[1] (Wang and Liao, 2002) (Fig. 2) of the samples were obtained with the AIS4.0 Image Analysis software (Imaging Research Inc.). As most beads were not perfectly spherical (figure not shown), there was no uniform diameter. The Heywood diameter was employed as an approximation so that every

[1] Heywood diameter is defined as the diameter of a circle having the same area as the zone under consideration.

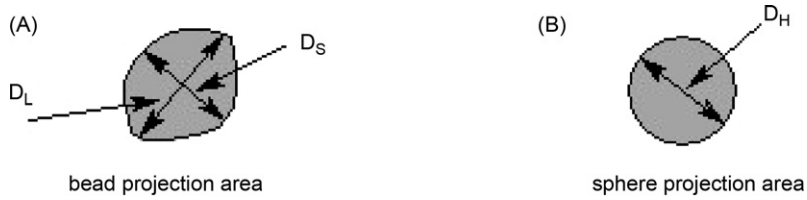

Fig. 2. Schematic illustration of Heywood diameter. Bead A has the same projection area as sphere B. Diameter of B is considered as the Heywood diameter of A.

bead could be evaluated with a single variable to quantify its size.

The buoyancy of the gel beads was tested by visual inspection. For each sample of gel beads, 20 individual beads were placed in the test bottles (10 ml volume capped bottle) filled with 10 ml SGF (about pH 1.0). The test bottles were kept in a water bath at $37 \pm 1\,^{\circ}C$ under constant agitation of 250 rpm with a magnetic stirrer for 24 h. The samples were considered buoyant only if 20 individual beads remained afloat after the prescribed test time.

The drug release test was carried out in the SGF. Each sample ($n = 20$) was put into 10 ml SGF, thermally controlled at $37 \pm 1\,^{\circ}C$. Experiments were done in duplicate to ensure the results were consistent, with the average values recorded. At prescribed times, all 10 ml SGF from the sample bottles containing the dissolved drug was taken out for analysis. And another 10 ml SGF was refilled. After completion of the release test, the residual amount of drug remaining in the samples was determined by solvent extraction. For ibuprofen, 20 individual beads were recovered and blended with 10 ml ethanol. The milky suspension was centrifuged and the clear solution was oven dried and the residue was dissolved with 50 ml SGF and the concentration was monitored. As for uncoated niacinamide beads, the extraction solvent was 10 ml SGF and measurement of drug concentration followed right after centrifugation. In this way, the actual drug loading (M_∞) was calculated. M_∞ of the Eudragit coated niacinamide and metoclopramide HCl beads were determined by depletion method. The drug concentration was assayed on a UV–vis spectrometer (UV-2501, Shimadzu) respectively at 261 nm for niacinamide, at 220 nm for ibuprofen and at 309 nm for metoclopramide HCl.

3. Results and discussion

3.1. Bead dimension and morphology

The Heywood diameter (D_H) was introduced as a single variable to evaluate the particle sizes of the beads as the beads were not perfect spheres (figure not shown).

There seems no obvious trend to the D_H dependence on oil concentration (figure not shown). The overall size differences between the samples with different alginate and oil concentrations were not significant. This is in agreement with Kikuchi et al. (1997).

Fig. 3 gives the details of the cross-sectioned beads without drugs. Non-oily beads in the upper two images of the figure were thin-shelled with large inner cavity. In comparison, oily beads had an "orange peel" appearance. Emulsification of sunflower oil in the alginate solution and fast gelation encapsulation of the oil with the alginate gel matrices resulted in a large number of tiny oil pockets either on the gel bead surface or deep within the bead matrices. The oil pockets spread evenly over the surface and in the kernel, giving the oily beads a fatter look in contrast to the non-oily beads. Leakage of a certain number of these tiny compartments would not necessarily result in a failure of the referred gel bead. This feature thus increases the margin of safety against premature sedimentation.

3.2. Buoyancy

Table 1 shows how the oil loadings affect the buoyancy of the alginate beads. All non-oily beads failed the buoyancy test as several specimens began sedimentation either upon contact with the SGF or soon after agitation started. In contrast, all oily samples stayed afloat for a 24 h test cycle. The results were similar to those obtained by Murata et al. (2000) so that it may be inferred that buoyancy attributed to air bubbles inside the alginate gel matrix were not reliable and persistent.

Table 1 also lists the buoyancy of the drug loaded beads. The results show that the buoyancy decreased for the beads with less oil inclusion or more drug incorporation. This was in agreement with what Whitehead et al. (1998) found: that drug loading impaired buoyancy to some extent. Similar outcomes were observed for Eudragit® coated beads too: thick coatings compromised the bead buoyancy (result not shown).

3.3. Bead water uptake

Bead water uptake in this case was presented as normalized weight gain ratio defined in Eq. (1).

$$Y = \frac{m_w}{m_d} \tag{1}$$

where Y is the normalized weight gain ratio, m_w the bead weight after swelling (including water uptake), and m_d is the initial dry bead weight.

In general, the beads achieved relatively low degrees of swelling as Fig. 4 shows, probably because the ionization of –COOH in alginate hydrogel was suppressed in acidic pH. And the maximum weight gain was achieved within 30 min.

The weight gains, Y values at equilibrium of beads of different compositions are also plotted in Fig. 4. In general the trend of water uptake of drug loaded and Eudragit coated beads remains similar to that of drug and coating-free alginate beads, as the weight gain decreases with the increase of oil concentra-

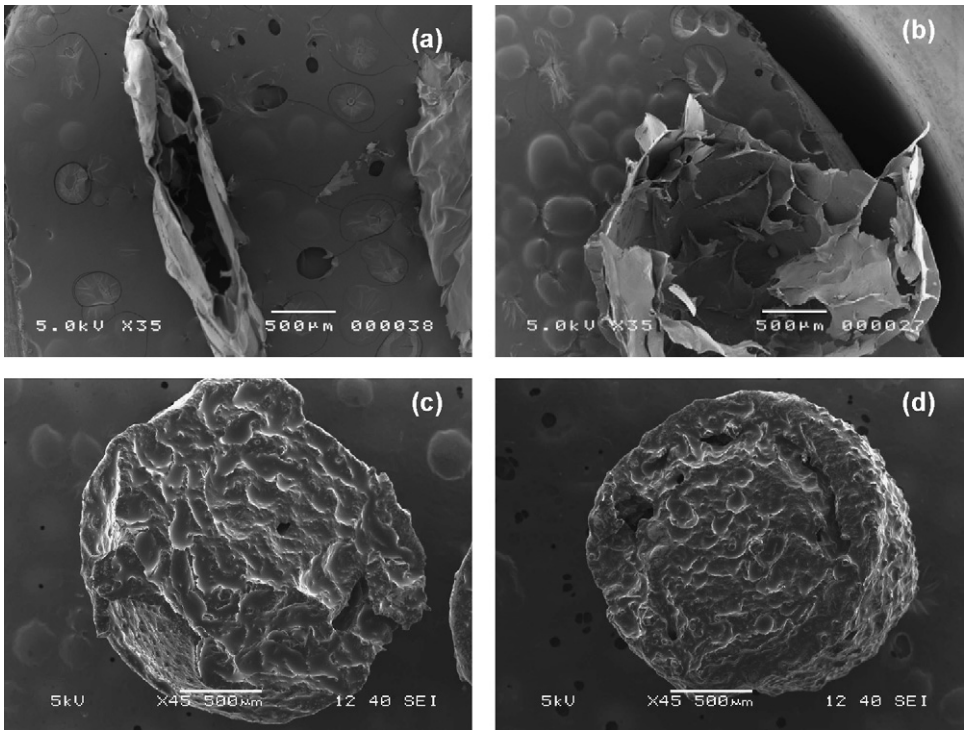

Fig. 3. Cross-sectional morphologies of oily and non-oily gel beads. (a) 2% (w/v) alginate, no oil, (b) 4% (w/v) alginate, no oil, (c) 2% (w/v) alginate, 20% (v/v) oil, and (d) 4% (w/v) alginate, 20% (v/v) oil.

tion. Oil encapsulation inhibits bead water uptake as equilibrium weight gains of beads of the same crosslink density decreases with increasing initial oil concentration. Ibuprofen incorporation seemed to have made the beads more hydrophobic compared with beads that are free of drugs and the equilibrium weight gain decreased with more ibuprofen. The effect was similar to more oil addition. Niacinamide incorporation has the opposite effect, and this is possibly due to the increased osmotic pressure caused by the hydrophilic niacinamide incorporation. The water uptake of the Eudragit coated beads is given in order to find out the possible influence on their drug release behaviour. The water uptake was largely inhibited by the coating compared with coating-free beads.

In conclusion, water uptake appeared to follow well-known patterns: decreases with crosslink density and hydrophobic additives.

3.4. Ibuprofen release profiles

The release profiles of ibuprofen beads are plotted in Fig. 5. All the samples released the ibuprofen in a controlled manner and no burst release was seen. The release profiles seemed dependent on the initial drug concentration C_0. Higher drug loadings achieved longer release. And it has been observed that ibuprofen release lasted for 24 h without much initial burst normally seen on spherical matrix drug carriers.

The initial ibuprofen loading has obviously exceeded its saturation in water. So if the excessive drug particles were exposed, there would have been a considerable burst effect, considering fast water infiltration into the porous alginate matrix. SEM observation did not detect drug crystals but only numerous oil pockets on the bead cross-section (picture not shown). Ibuprofen solubility in oil was determined experimentally by preparing a series of

Table 1
Buoyancy of beads with different alginate, oil and drug concentrations

Oil concentration (%)[a]	Alginate concentration (%)[b]			Niacinamide concentration (%)[c]				Metoclopramide concentration (%)[d]		
	2	3	4	2	8	100	200	2	100	200
0	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
10	F	F	F	NF	NF	NF	NF	F	NF	NF
20	F	F	F	F	F	NF	NF	F	F	NF
30	F	F	F	F	F	NF	NF	F	F	NF

NF: non-floating; F: floating.
[a] Oil concentration as in % (v/v) in alginate solution.
[b] Alginate concentration as in % (w/v) in D.I. water, drug free beads.
[c] Niacinamide concentration as in % (w/v) in alginate solution, beads of 3% (w/v) alginate.
[d] Metoclopramide concentration as in % (w/v) in alginate solution, beads of 3% (w/v) alginate

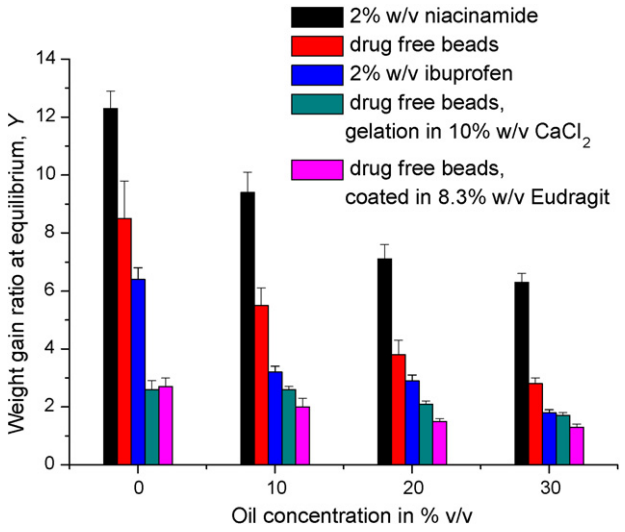

Fig. 4. Water uptake of beads of different compositions. Bead composition: 3% (w/v) alginate, gelation in 0.3% (w/v) $CaCl_2$ unless otherwise stated.

concentrations and the saturation concentration in oil was found to be about 25 mg/ml, well above the solubility in water 1 mg/ml. Hence the most reasonable explanation for the slow release is, most ibuprofen saturated and dispersed in oil domains that the bead could be considered as an ibuprofen-oil dispersed matrix. Thus the ibuprofen transportation from the carrier to the ambient medium underwent two steps. Firstly, it diffused out of the oil pockets into the swollen alginate. Secondly, it diffused out of the swollen alginate into the ambient. The second step is considered very fast compared with the first.

The accumulative ibuprofen release M_t was applied to a simplified Higuchi expression (Koizumi and Panomsuk, 1995) which was derived specifically for non-degradable, spherical matrix (shown in Eq. (2). This equation can be rewritten into Eq. (3).

$$M_t = 4\pi r^2 \left[\sqrt{2(C_0 - C_S)C_S Dt} + \frac{4C_S Dt}{9r}\left(\frac{C_S}{2C_0 - C_S} - 3\right)\right] \quad (2)$$

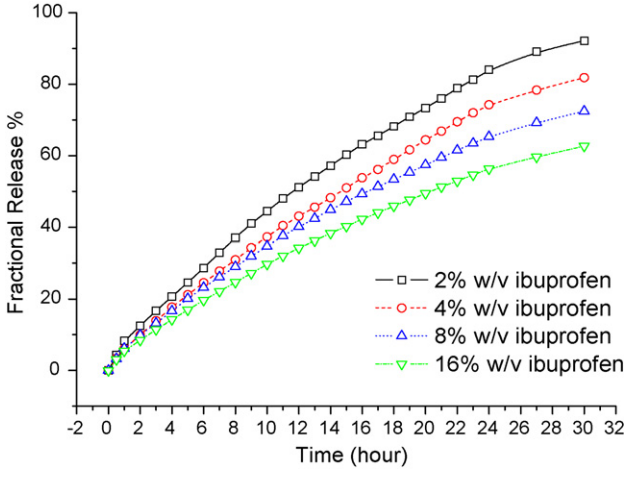

Fig. 5. Ibuprofen release from beads of different drug loadings. Bead composition: 3% (w/v) alginate, 20% (v/v) oil; gelation in 5% (w/v) $Cacl_2$.

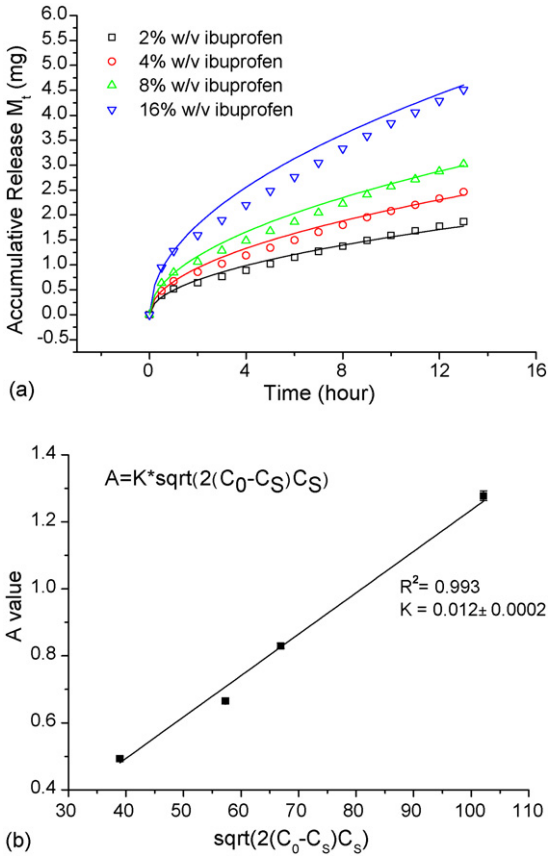

Fig. 6. First-order fitting of ibuprofen accumulative release. Bead composition: 3% (w/v) alginate, 20% (v/v) oil; gelation in 5% (w/v) $Cacl_2$.

$$M_t = At^{1/2} - Bt \quad (3)$$

where

$$A \sim \sqrt{(C_0 - C_S)C_S D} \quad \text{and} \quad B \sim \left|\frac{{C_S}^2}{2C_0 - C_S} - 3C_S.\right|$$

where C_0 is the initial ibuprofen concentration in oil, C_S the saturation concentration of ibuprofen in oil, and D is an overall average diffusion coefficient while r is the radius of the spherical matrix system, which can be approximated from the average Heywood diameter of the beads.

Fitting results (Fig. 6) denote that there is a strong dependence between the accumulative release amount M_t and the square-root-of-time when the zero-order part in Eq. (2) is equated to zero (shown in Table 2). Thus it is safe to claim that Fickian diffusion dominated the ibuprofen release from these oily beads. In short, a sustained release that is consistent with the increased retention/floatation time was achieved for the relatively hydrophobic ibuprofen. Assuming a pseudo-steady diffusion, the slope of Fig. 6(b) yields the diffusion coefficient, approximately 7.65×10^{-3} cm^2/h or 2.1×10^{-6} cm^2/s, which is indicative of diffusion of a drug of Mw about 200 through a non-viscous liquid.

Table 2
Correlation between ibuprofen M_t and $t^{1/2}$ in Eq. (3)

Ibuprofen concentration (%)[a]	C_0 (in oil) (mg/ml)	A value	B value	R^2
2	55.3	0.493 ± 0.006	0	0.989
4	90.6	0.665 ± 0.009	0	0.985
8	114.4	0.830 ± 0.008	0	0.988
16	233.6	1.278 ± 0.015	0	0.981

[a] Ibuprofen concentration as in % (w/v) in alginate solution, bead composition: 3% (w/v) alginate, 20% (v/v) oil, gelation in 5% (w/v) $CaCl_2$.

3.5. Niacinamide release profiles

Niacinamide releases from uncoated beads in a considerable "burst" during the first 30 min (figure not shown), due to rapid water ingress and creation of aqueous channels for the niacinamide to permeate out. Clearly, even if gastric retention time were prolonged for these formulations, sustained release is absent, hence the value of these formulations for release of hydrophilic drugs is limited; to overcome this, Eudragit® coating of the beads was studied.

It was found that the Eudragit coated beads were able to extend the release for a longer duration than uncoated niacinamide beads as Fig. 7 shows. Beads coated in 8.3% (w/v) Eudragit released niacinamide with a pronounced burst effect and after 6 h, all drug had been released. The release from beads coated in 16.7% (w/v) Eudragit differed as niacinamide was released (after a short initial burst) in a sustained manner for the first 5 h, followed by a slower release till drug was exhausted. The third sample, beads coated in 25% (w/v) Eudragit, showed virtually no burst and a seemingly zero-order profile for the entire duration of release. Interestingly, it seems that at about 6 h interval, there was a pulsatile minor burst for each formulation, whose cause is still unclear.

The rationale for the slow niacinamide release is as follows: the Eudragit coating makes the bead a reservoir/membrane system. When Eudragit concentration increased from 8.3% to 25% (w/v), the coating thickness increased accordingly from 21.1 ± 6.2 to 79.1 ± 21.9 μm. The thicker the Eudragit coating, the slower the permeation was through the membrane.

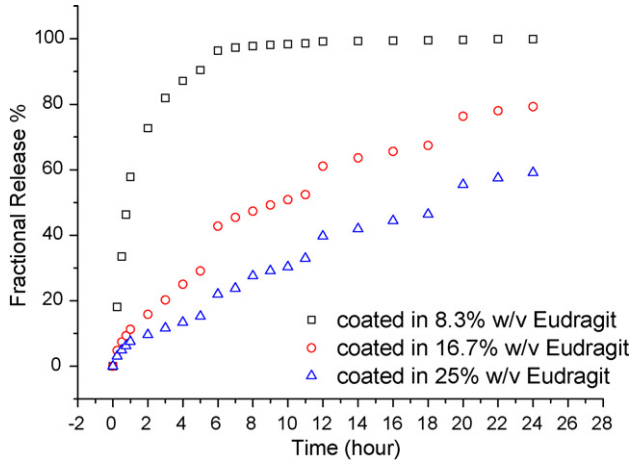

Fig. 7. Niacinamide release from beads with different Eudragit coating thicknesses. Bead composition: 3% (w/v) alginate, 20% (v/v) oil; 100% (w/v) niacinamide in alginate solution; gelation in 5% (w/v) $Cacl_2$.

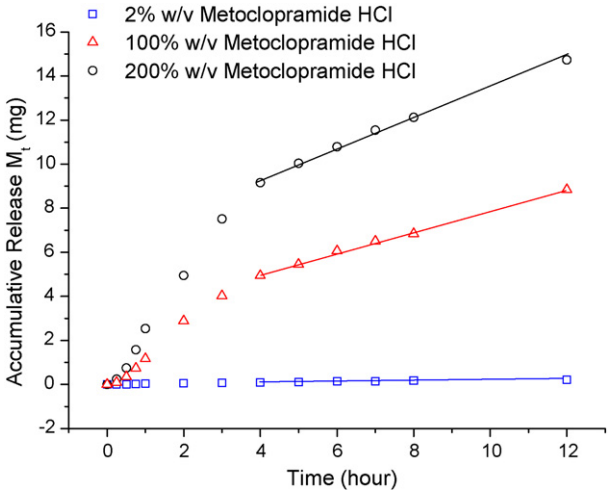

Fig. 8. Metroclopramide HCl release from Eudragit coated beads. Bead composition: 3% (w/v) alginate, 20% (v/v) oil; gelation in 5% (w/v) $Cacl_2$; coated in 16.7% (w/v) Eudragit.

3.6. Metoclopramide HCl release profiles

In order to confirm the efficacy of Eudragit coating for sustained release, metoclorpramide HCl release from Eudragit coated beads was studied and the results are shown in Fig. 8. The release patterns appear to be typical of a reservoir/membrane system, with the Eudragit coating acting as the membrane in this case. Compared with niacinamide, the overall release is faster for metoclorpromide HCl; this may be attributed to a higher partitioning coefficient (into Eudragit).

4. Conclusions

A completely erodible multi-unit floating GRDF has been developed. Gel beads made solely of calcium alginate was found to lack sufficient and consistent buoyancy over long hours of administration. In contrast, oil incorporated alginate gel beads floated constantly under the condition of body temperature and continuous agitation for more than 24 h. Drug release profiles were influenced by the relative hydrophilicities of drugs. A slow first order ibuprofen release was achieved with drug encapsulation in oil. Sustained release for more than 12 h was also achieved for hydrophilic drugs such as niacinamide and metoclopramide HCl, with the rate-control being achieved by means of an acid-resistant Eudragit® coating. Such an alginate based GRDF is hence thought to be able to sustain the release of both hydrophobic and hydrophilic drugs over 12 h, while remaining afloat in the gastric fluid.

References

Chen, J., Blevins, W.E., Park, H., Park, K., 2000. Gastric retention properties of superporous hydrogel composites. J. Control. Release 64, 39–51.

Gaserod, O., Jolliffe, I.G., Hampson, F.C., Dettmar, P.W., Skjak-Brak, G., 1998. The enhancement of the bioadhesive properties of calcium alginate gel beads by coating with chitosan. Int. J. Pharm. 175, 237–246.

Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J.C., Thom, D., 1973. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Lett. 32, 195–198.

Gupta, P.K., Robinson, J.R., 1992. Oral controlled-release delivery. In: Kydonieus, A. (Ed.), Treatise on Controlled Drug Delivery. Marcel Dekker, New York.

Hilton, A.K., Deasy, P.B., 1992. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxicillin trihydrate. Int. J. Pharm. 86, 79–88.

Iannuccelli, V., Coppi, G., Bernabei, M.T., Cameroni, R., 1998. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. Int. J. Pharm. 174, 47–54.

Khosla, R., Davis, S.S., 1989. Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects. Int. J. Pharm. 52, 1–10.

Kikuchi, A., Kawabuchi, M., Sugihara, M., Sakurai, Y., Okano, T., 1997. Pulsed dextran release from calcium-alginate gel beads. J. Control. Release 47, 21–29.

Klausner, E.A., Lavy, E., Friedman, M., Hoffman, A., 2003. Expandable gastroretentive dosage forms. J. Control. Release 90, 143–162.

Koizumi, T., Panomsuk, S.P., 1995. Release of medicaments from spherical matrices containing drug in suspension: theoretical aspects. Int. J. Pharm. 116, 45–49.

Murata, Y., Sasaki, N., Miyamoto, E., Kawashima, S., 2000. Use of floating alginate gel beads for stomach-specific drug delivery. Eur. J. Pharm. Sci. 50, 221–226.

Murata, Y., Kofuji, K., Kawashima, S., 2003. Preparation of floating alginate gel beads for drug delivery to the gastric mucosa. J. Biomater. Sci. Polym. Edn. 14 (6), 581–588.

Peppas, N.A., Little, M.D., Huang, Y., 2000. Bioadhesive controlled release systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker, New York, pp. 255–269.

Singh, B.N., Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release 63, 235–259.

Stochwell, A.F., Davis, S.S., 1986. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. J. Control. Release 3, 167–175.

Wang, G., Liao, W., 2002. Automatic identification of different types of defects in radiographic images. NDT&E Int. 35, 519–528.

Whitehead, L., Fell, J.T., Collett, J.H., Sharma, H.L., Smith, A.-M., 1998. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J. Control. Release 55, 3–12.