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Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas-forming agents

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Abstract

Floating beads were prepared from a sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas-forming agents. The solution was dropped to 1% $CaCl_2$ solution containing 10% acetic acid for CO_2 gas and gel formation. The effects of gas-forming agents on bead size and floating properties were investigated. As gas-forming agents increased, the size and floating properties increased. Bead porosity and volume average pore size, as well as the surface and cross-sectional morphology of the beads were examined with Mercury porosimetry and Scanning Electron Microscopy. $NaHCO_3$ significantly increased porosity and pore diameter than $CaCO_3$. Incorporation of $CaCO_3$ into alginate solution resulted in smoother beads than those produced with $NaHCO_3$. Gel strength analysis indicated that bead strength decreased with increasing gas-forming agent from 9 to 4 N. Beads incorporating $CaCO_3$ exhibited significantly increased gel strength over control and $NaHCO_3$-containing samples. Release characteristics of riboflavin as a model drug were studied in vitro. Release rate of riboflavin increased proportionally with addition of $NaHCO_3$. However, increasing weight ratios of $CaCO_3$ did not appreciably accelerate drug release. The results of these studies indicate that $CaCO_3$ is superior to $NaHCO_3$ as a gas forming agent in alginate bead preparations. The enhanced buoyancy and sustained release properties of $CaCO_3$-containing beads make them an excellent candidate for floating drug dosage systems (FDDS). © 2002 Published by Elsevier Science B.V.

Keywords: Alginate bead; Floating bead; Floating drug dosage system (FDDS); Gas-forming agent; $NaHCO_3$; $CaCO_3$

1. Introduction

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine (Rouge et al., 1996).

To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as: floating drug dosage systems (FDDS) (Baumgarter et al., 2000; Bulgarelli et al.,

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2000; Deshpande et al., 1997; Singh and Kim, 2000; Timmermans and Moes, 1994), swelling or expanding systems (Chen and Park, 2000), mucoadhesive systems (Akiyama et al., 1998; Chickering et al., 1997), modified-shape systems (Kedzierewicz et al., 1999), high-density systems (Rouge et al., 1998), and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.

FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating in the gastric content, the drug is released slowly from the system at a desired rate.

Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds) (Baumgarter et al., 2000; Chen and Park, 2000, Johnson et al., 1997), highly swellable hydrocolloids and light mineral oils (Desai and Bolton, 1993; Murata et al., 2000). Multiple unit systems (Iannuccelli et al., 1998; Ichikawa et al., 1991; Rouge et al., 1998) and hollow systems prepared by solvent evaporation methods (El-Kamel et al., 2001; Kawashima et al., 1992; Thanoo et al., 1993) have also been developed.

In this paper the floating drug delivery system employs calcium carbonate ($CaCO_3$) or sodium bicarbonate ($NaHCO_3$) as a gas-forming agent dispersed in an alginate matrix. Alginate is a polysaccharide which contains varying amounts of 1,4′-linked β-D-mannuronic acid, α-L-guluronic acid residues. As biocompatible and biodegradable biopolymer, it forms a bio-adhesive and stable gel with divalent cations such as Ca^{2+}, Sr^{2+}, and Ba^{2+} (Grant et al., 1973; Smidsrod and Haug, 1965). These properties have enabled widespread use for sustained release of drugs (Badwan et al., 1985; Gray and Dowsett, 1988). They can also function as carriers of *Bifidobacteria* (Sultana et al., 2000) since alginate beads are stable in acidic media and easily depredated in alkaline media. Floating alginate beads are particularly effective for site-specific controlled release of antibacterial agents effective against harmful stomach bacteria such as *H. pylori* (Katayama et al., 1999; Whitehead et al., 2000).

During formation of the floating drug beads, carbonate salts are reacted with acetic acid to produce carbon dioxide. The evolving gas permeates through the alginate leaving gas bubbles or pores. $NaHCO_3$ has frequently been employed as a gas-forming agent for FDDS (Baumgarter et al., 2000; Chen and Park, 2000; Mandel et al., 2000; Park et al., 2001; Zaniboni et al., 1995). However, its effect on physical properties such as size, mechanical strength and dissolution rate of FDDS has not been reported. There are few records of research on $CaCO_3$ or other gas-forming agents. Until now, $CaCO_3$ has only been used as a gelling agent to make alginate gel (Catherine and Peter, 2001; Poncelet et al., 1999).

The aim of this experiment is to prepare a floating controlled drug delivery system using gas-forming agents. The effects of CO_2 gas-formation on the physical properties, morphology, and release rate of alginate beads are examined. The comparative efficacy of $CaCO_3$ and $NaHCO_3$ as gas forming agents for FDDS is also evaluated. Riboflavin was chosen as a model drug for this study because its release must be specially targeted to the stomach and upper intestine (Akiyama et al., 1998; Deshpande et al., 1997; Zaniboni et al., 1995). The inefficiency of oral sustained-release riboflavin formulations has presented an ideal application for FDDS.

2. Materials and methods

2.1. Materials

Sodium alginate (low viscosity grade; 250 cp in 2% solution at 25 °C and hydroxypropylmethylcellulose (HPMC) were purchased from Sigma (St Louis, MO, USA). Riboflavin was obtained from Junsei Chemical (Tokyo, Japan). Calcium carbonate and sodium bicarbonate were purchased from Yakuri Pure Chemical (Osaka, Japan) and Duksan Pure Chemical (Kyungki,

Korea), respectively. All other chemicals were of analytical grade.

2.2. Preparation of floating alginate beads

A solution was prepared by dissolving 0.09 g riboflavin in 5 ml distilled water. The solution was dispersed in 30 ml alginate solution (3%, w/v) containing HPMC (alginate:HPMC = 9:1, w/w). Then, gas-forming agent such as $NaHCO_3$ or $CaCO_3$ was added to the solution with levels from 0:1 to 1:1 (gas-forming agent/alginate, w/w). The mixture was then degassed under vacuum. The resulting solution was dropped through a 26G syringe needle into 1% (w/v) $CaCl_2$ solution containing 10% (v/v) acetic acid. The solution containing suspend beads was stirred with a magnetic stir bar for 10 min to improve the mechanical strength of the beads and allowed to complete the reaction to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid (Scheme 1), thereby preventing premature gelation. The fully formed beads were collected, washed with ethanol and distilled water, and subsequently freeze-dried.

Mixture (alginate/HPMC, gas-forming agent, riboflavin)

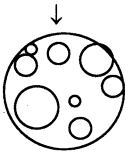
↓

Dropping into $CaCl_2$ /acetic acid solution

$NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2$

$CaCO_3 + 2CH_3COOH \rightarrow (CH_3COO)_2Ca + H_2O + CO_2$

↓



Separation

↓

Freeze dry

Scheme 1.

2.3. Bead characterization

2.3.1. 2.3.1. Size analysis

The average diameter of ten wet and dry beads was determined using a caliper (Mitutoyo, Japan) in triplicate.

2.3.2. Bead porosity and mean pore diameter

The bead porosity was assessed using mercury porosimetry (AutoPore IV 9500 V1.03, Micromeritics, GA, USA) ($n = 2$). The pressure was varied from 0 to 50 psi. A 10 s equilibration time was set for each intermediate data point. At each equilibrium point, mercury intrusion data were recorded and plotted against pressure. Standard values for the contact and surface tension of mercury were used.

2.3.3. Morphological analysis

Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope (SEM) (JSM-5310LV Scanning Microscope, Tokyo, Japan). Beads were mounted on metal grids using double-sided tape and gold coated under vacuum.

2.3.4. Mechanical strength study

To precisely measure mechanical strength of the alginate gel beads, large beads were prepared by replacing 26G syringe with 1 ml pipette aid (Gilson, Germany) as the method described above. However, the samples were not freeze-dried. Compression testing was performed with an Instron 4460 (Instron Corporation, Canton, MA). Ten beads of identical size were selected. Crosshead speed and probe diameter were set at 1 mm/min and 3.5 cm, respectively.

2.4. In vitro evaluation

2.4.1. Floating properties

Floating properties of wet and dry beads were evaluated in a dissolution vessel (USP dissolution tester) filled with 500 ml of simulated gastric fluid (pH 1.2) without pepsin and phosphate-buffered saline (PBS, pH 7.4). Paddle rotation speeds of 0 and 100 rpm were tested. Temperature was maintained at 37 °C. Fifty beads were placed in the

Table 1
The effect of gas-forming agents on bead size in wet and dry conditions

	Gas-forming agent/alginate (w/w)	Wet AVE (mm) ± S.D.	Dry AVE (mm) ± S.D.
Control	0	2.24 ± 0.01	1.10 ± 0.04
$CaCO_3$	0.25	2.23 ± 0.08	1.20 ± 0.02
	0.5	2.34 ± 0.03	1.58 ± 0.06
	0.75	2.42 ± 0.01	1.87 ± 0.05
	1	2.52 ± 0.07	1.88 ± 0.03
$NaHCO_3$	0.25	2.39 ± 0.05	1.29 ± 0.09
	0.5	2.49 ± 0.00	1.61 ± 0.05
	0.75	2.91 ± 0.02	2.45 ± 0.04

Table 2
Porosity and mean pore diameter of floating beads

	Gas-forming agent/alginate (w/w)	Porosity AVE (%) ± S.D.	Median pore diameter AVE (μm) ± S.D.
Control		80.08 ± 0.32	0.37 ± 0.03
$CaCO_3$	0.25	88.84 ± 3.21	0.50 ± 0.14
	0.5	89.10 ± 0.99	1.83 ± 0.38
	0.75	94.78 ± 4.70	6.14 ± 2.53
$NaHCO_3$	0.25	91.48 ± 3.09	1.28 ± 0.83
	0.5	91.85 ± 1.79	20.82 ± 0.33
	0.75	95.14 ± 0.89	39.72 ± 3.27

media and the percentage of floating samples was measured by visual observation ($n = 3$).

2.4.2. In vitro riboflavin release studies

Release studies were performed in triplicate using the USP paddle method at 100 rpm and 37 °C in 500 ml of PBS media. Approximately fifty beads were used for each experiment. Samples were taken at appropriate time intervals and assayed spectrophotometrically at 444 nm. Fresh media was added to replace the sample taken.

3. Results

3.1. The effects of CO_2 gas-forming agents on bead size

A range of weight ratios of $NaHCO_3$ and $CaCO_3$ was used to determine the effects of the gas-forming process on the size of beads formed (Table 1). Table 1 shows that both gas-forming agents significantly increased the size of the beads over the control (no gas-forming agent). This effect was especially remarkable in the case of $NaHCO_3$. Moreover, when $NaHCO_3$ was added to the alginate solution at a 1:1 ratio, spherical beads could not be formed because released CO_2 gas burst the bead before the wall was sufficiently hardened.

3.2. Porosity and pore size of floating beads

Porosity and volume average pore diameter was studied to determine the effects of gas-forming agents on pore structure of the floating beads. By increasing the ratio of incorporated gas forming agents from 0 to 0.75, the porosity and pore diameter of the beads were increased from 80.0% and 0.37 μm to 94.8% and 6.14 μm, respectively, with $CaCO_3$, and to 95.1% and 39.72 μm with $NaHCO_3$ (Table 2). Although the porosity of the beads was similar, it was clearly demonstrated that $NaHCO_3$ produced larger pores than $CaCO_3$.

3.3. The effects on floating ability of gas-forming agents

The floating ability of prepared beads was evaluated in simulated gastric fluid and PBS buffer (Table 3). While gas-forming agent free beads sink uniformly in both media, beads containing gas-forming agents in proportions ranging from 0.5:1 to 1:1 ratios demonstrated excellent floating ability (100% floating). The wet beads (0.25 gas-forming agent/alginate, w/w) had better floating ability than dry beads. Floating ability is directly related to the gas content of the polymer matrix. Wet beads can contain a greater proportion of CO_2 gas than dry ones and are thus more buoyant. These results were not affected by paddle speed (fixed at 0 and 100 rpm). The floating abilities persisted until disintegration of the beads began (over 30 min). In addition, differences between samples were not significant at any stage during the experiment.

3.4. The effects on surface and cross-sectional morphology

Figs. 1 and 2 show the surface and cross-sectional SEM pictures of the beads prepared with $CaCO_3$ and $NaHCO_3$ components. The gas-forming agent free bead has a rough surface. While the $NaHCO_3$ treated bead did not show a significantly improved surface character, (Fig. 1f–h), increased ratios of incorporated $CaCO_3$ made the bead surface smoother (Fig. 1a–e). It is suggested that the presence of Ca^{2+} ions contributed to homogenous alginate bead formation. In some experiments $CaCO_3$ has been used as a gelling agent to aid the internal gelation of the alginate (Johnson et al., 1997; Poncelet et al., 1999). In acid conditions the salt dissociates to release divalent calcium cations that interact with the alginate. In spite of improved gellation, cracks were shown on surface of the 1:1 $CaCO_3$:alginate beads (Fig. 1e); and SEM photographs reveal the presence of riboflavin crystals on bead surface (Fig. 1a–h).

The cross-sectional morphologies of floating beads were also examined with SEM (Fig. 2).Many large closed pores are present in the alginate gel matrix. The number of observed pores appears to be directly related to the amount of incorporated gas-forming agent. Additionally, it

Table 3
Floating ability of beads in simulated gastric fluid (pH 1.2) and PBS buffer (pH 7.4): − − completely sink; − slightly float; +/− partially sink or float; ++ completely float; + slightly sink

Variables				Gas-forming agent/alginate (w/w)				
				0	0.25	0.5	0.75	1
Simulated gastric fluid (pH 1.2)	$CaCO_3$	Wet	Stand	− −	++	++	++	++
			100 rpm	−	+	++	++	++
		Dry	Stand	−	−	++	++	++
			100 rpm	−	+/−	++	++	++
	$NaHCO_3$	Wet	Stand	− −	++	++	++	
			100 rpm	−	+	++	++	
		Dry	Stand	−	+	++	++	
			100 rpm	−	+	++	++	
PBS buffer (pH 7.4)	$CaCO_3$	Wet	Stand	− −	++	++	++	++
			100 rpm	−	++	++	++	++
		Dry	Stand	− −	+/−	++	++	++
			100 rpm	− −	+/−	++	++	++
	$NaHCO_3$	Wet	Stand	− −	++	++	++	
			100 rpm	−	+	++	++	
		Dry	Stand	− −	+/−	++	++	
			100 rpm	− −	+/−	++	++	

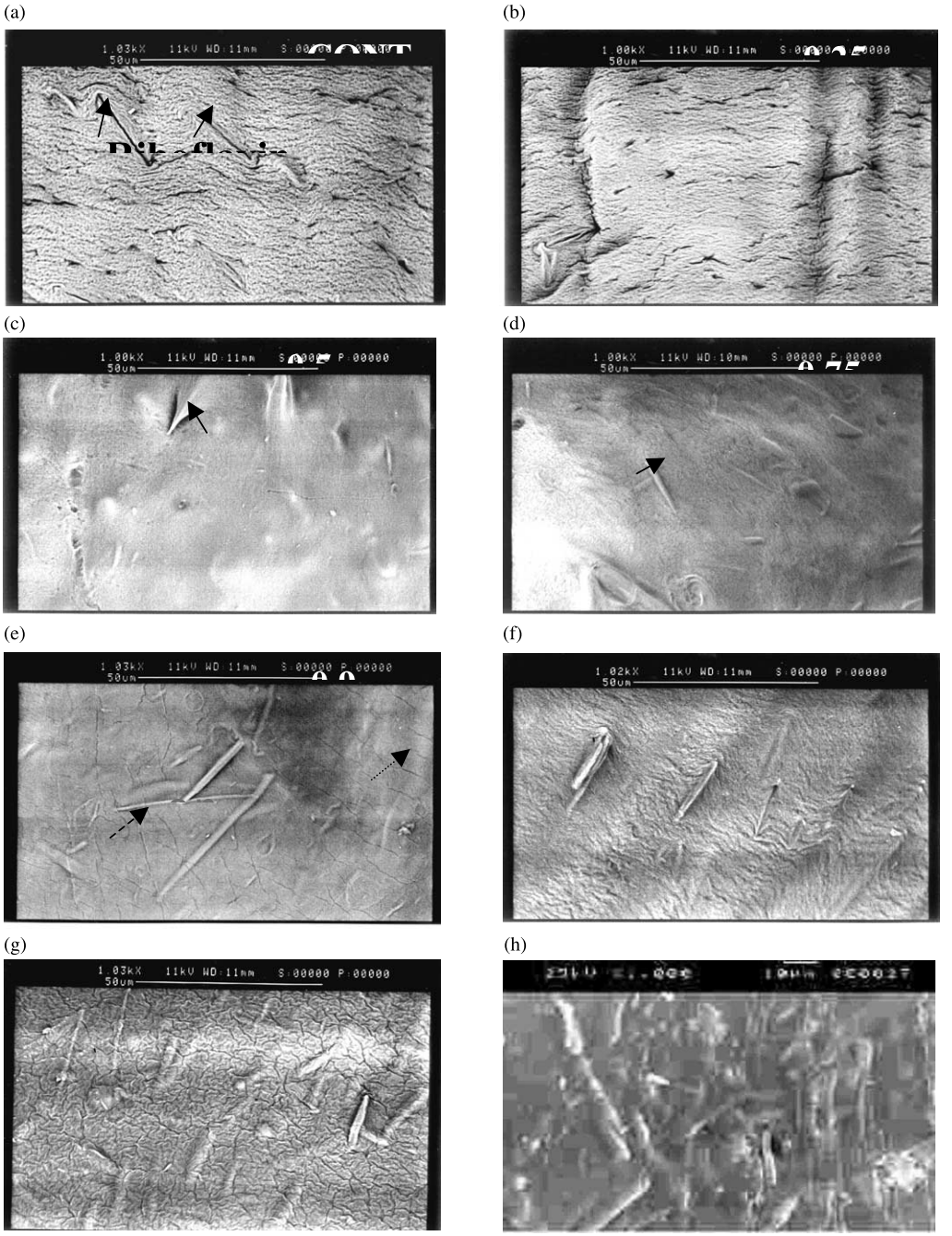


Fig. 1. SEM photographs, surface morphologies. Bar, 50 μm: (a) Control; (b) 0.25 $CaCO_3$/alginate (w/w); (c) 0.5 $CaCO_3$/alginate; (d) 0.75 $CaCO_3$/alginate; (e) 1 $CaCO_3$/alginate; (f) 0.25 $NaHCO_3$/alginate; (g) 0.5 $NaHCO_3$/alginate; (h) 0.75 $NaHCO_3$/alginate (⟶: Riboflavin crystal, - - ▶: Crack).

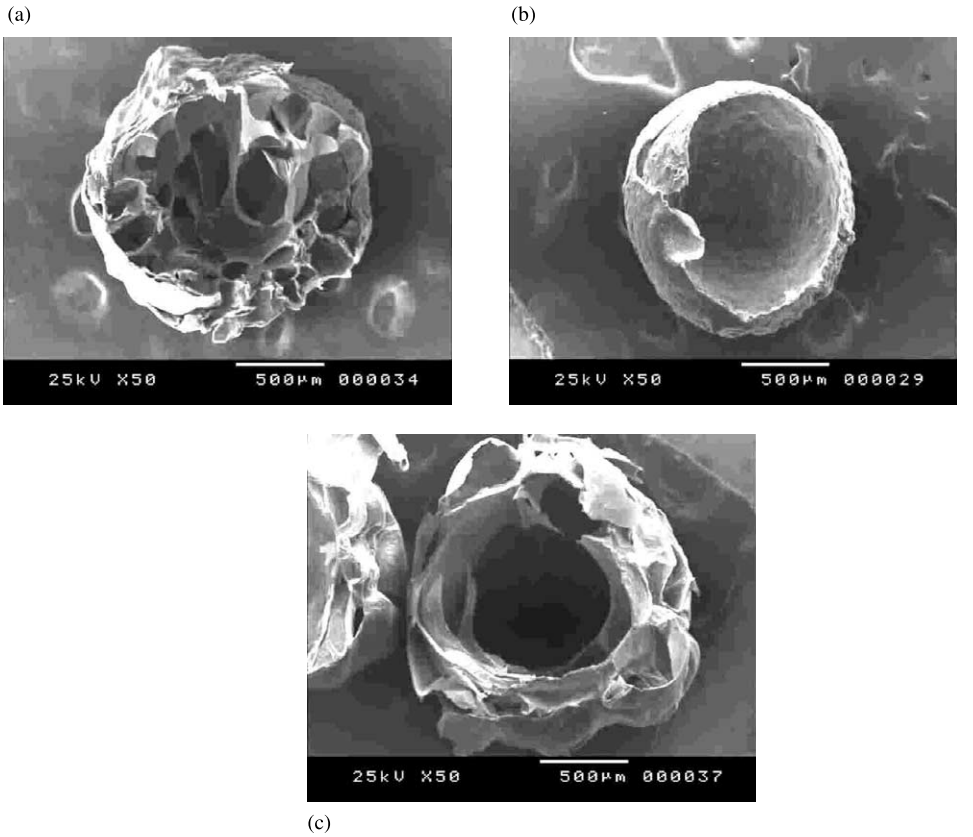


Fig. 2. SEM photographs (cross-sectional morphologies): (a) 0.5 $CaCO_3$/alginate (w/w); (b) 0.5 $NaHCO_3$/alginate; (c) 1 $CaCO_3$/alginate.

was established that $NaHCO_3$ produced much larger pores than $CaCO_3$. This result is in accordance with the porosity and pore size data of Table 2.

3.5. Mechanical strength of gas-forming agent treated beads

Mechanical testing was performed in order to study the effect of gas forming agents on the gel strength of floating beads. Fig. 3 shows the tendency for gel strength to decrease with increasing gas forming agent content. A high proportion of gas-forming agent made the beads highly porous and fragile. As also shown in Fig. 3, it was established that $CaCO_3$ containing beads possessed a significantly stronger gel than those containing $NaHCO_3$. This is due to the internal ionotropic gelation effect of $CaCO_3$ on alginate. It has been shown that Ca divalent ions make stronger alginate gels than Na ions. Johnson et al. (1997) investigated the mean maximum breaking strengths of rafts formed using a range of alginates, carbonates and bicarbonates. In the case of a LFR5/60 alginate sample, the gel strength of $NaHCO_3$-treated rafts was 44.6 mN, but the gel strength of $CaCO_3$-treated rafts was 58.9 mN.

3.6. Release profiles of floating beads

The release rates of riboflavin from wet and dried alginate beads with different amounts of $NaHCO_3$ and $CaCO_3$ are shown in Fig. 4. Riboflavin was exhausted from dried beads more quickly than from wet beads. The freeze drying process tends to make samples more porous.

Freeze dried beads disintegrate more readily in the dissolution tester due to increased water uptake. In addition, dry beads are more fragile and susceptible to shear stress from rotating paddles. In the absence of gas-forming agent the release rate was very slow. The rate of drug release was found to increase with increasing weight ratios of $NaHCO_3$. This is a direct result of the porous nature of the $NaHCO_3$ containing beads. The highly dense internal structure of the alginate beads prepared without gas forming agents was expected to retain the drug more effectively. Conversely, increasing the $CaCO_3$ weight ratio prolongs the release rate of riboflavin from the alginate matrix. The effect is observed in spite of increased bead porosity and pore size and may be due to the internal ionotropic gelation effect of $CaCO_3$ (Poncelet et al., 1999). $CaCO_3$ is present as an insoluble dispersion in neutral pH aqueous alginate solution; however, in acidic media, the $CaCO_3$ becomes water-soluble. The ionized Ca^{2+} ions then promote internal gelation by cross-linking with the alginate carboxyl group. More significant differences in release profile would be expected from in vivo experiments or more suitable in vitro tests. Standard dissolution methods based on USP or British Pharmacopoeia (BP) have been shown to be poor predicators of in vitro release for floating dosage forms due to reduced shear stress on the floating beads (Pillay and Fassihi, 1998).

4. Discussion

There were two principle objectives to this study. Firstly, the use of $CaCO_3$ and $NaHCO_3$ for the production of floating alginate beads was investigated using a simple dripping method. The data presented here has established that these gas-forming agents are highly effective for floating bead formation. The second objective was to assess the effects of formulation variables on bead characteristics and to compare $CaCO_3$ and $NaHCO_3$ as gas-forming agents. The study has clearly shown that the kind and amount of gas-forming agent has a profound effect on size, floating ability, pore structure, morphology, release rate and mechanical strength of floating beads. In general, $CaCO_3$-formed smaller and

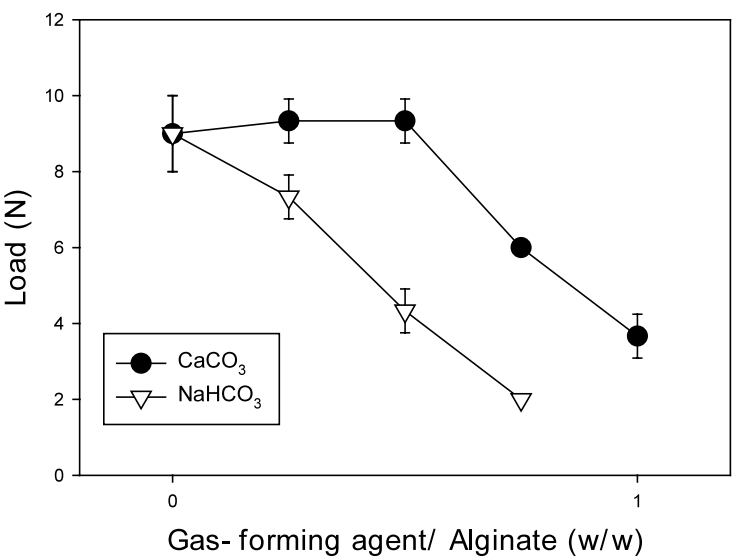


Fig. 3. The effect of gas-forming agents on mechanical strength of beads.

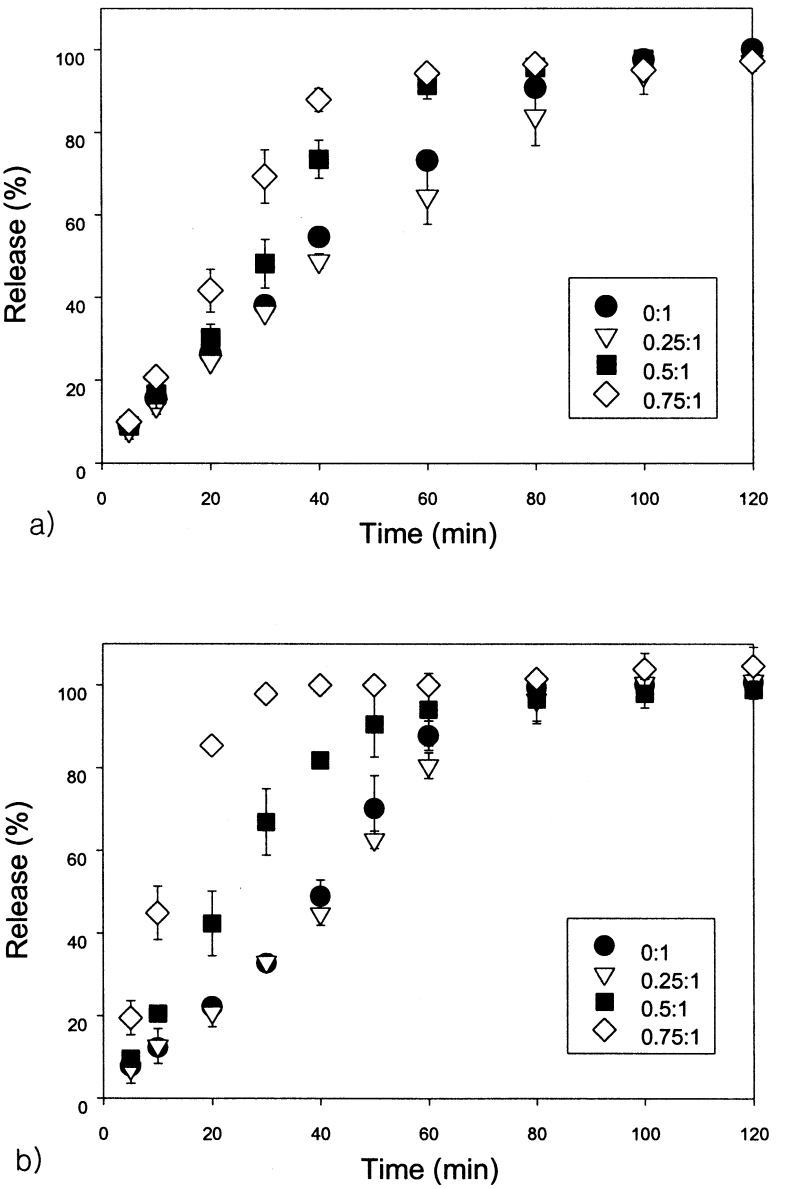
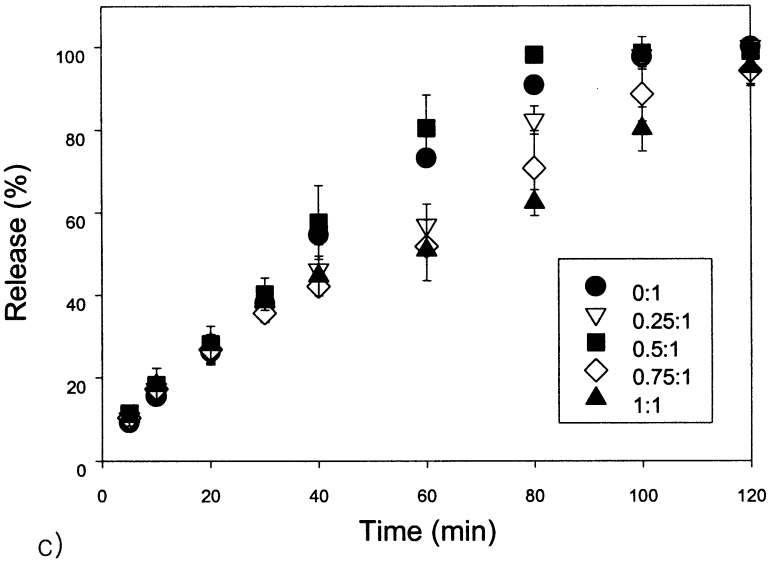


Fig. 4. The effect of gas forming agents on releasing rate: (a) wet, $NaHCO_3$; (b) dry, $NaHCO_3$; (c) wet, $CaCO_3$; (d) dry $CaCO_3$.

stronger floating beads than $NaHCO_3$. Consequently, beads formed with $CaCO_3$ significantly extended drug release. Overall, it was demonstrated that although $CaCO_3$ is a less effective gas-forming agent than $NaHCO_3$, it produced superior floating beads with enhanced control of drug release rates. By delineation of the formulation variables, it is hoped that further research with a variety of gas-forming agents and new preparation methods for floating microspheres will lead to the development of more effective FDD Systems.



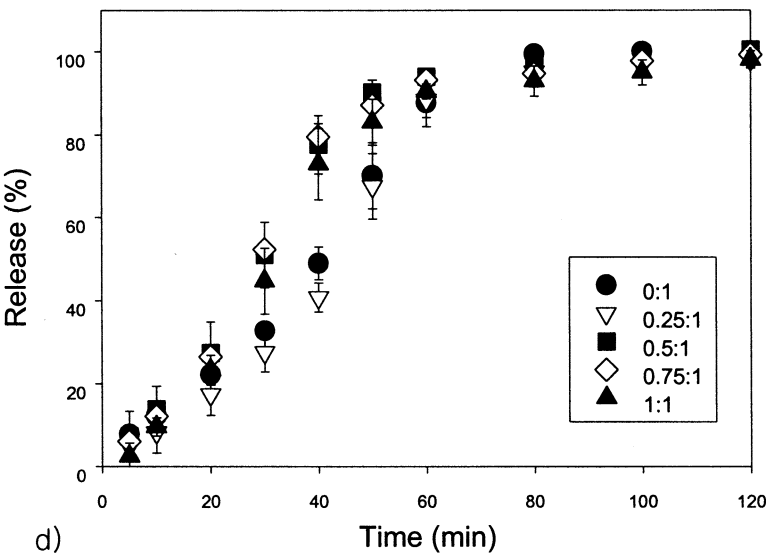


Fig. 4. (*Continued*)

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