Acta Pharm. **59** (2009) 345–354
10.2478/v10007-009-0021-z

Short communication

Floating drug delivery of a locally acting H_2-antagonist: An approach using an *in situ* gelling liquid formulation

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In the present work, a gastroretentive *in situ* gelling liquid formulation for controlled delivery of ranitidine was formulated using sodium alginate (low, medium and high viscosity grades), calcium carbonate (source of cations) and ranitidine. Prepared formulations were evaluated for viscosity, buoyancy lag time and buoyancy duration, drug content and *in vitro* drug release. Formulation variables such as concentration of sodium alginate, calcium carbonate and drug significantly affected the formulation viscosity, floating behavior and *in vitro* drug release. Analysis of the release pattern showed that the drug release from *in situ* gel followed a diffusion mechanism.

Keywords: gastroretention, *in situ* gelling, sodium alginate, ranitidine

Accepted June 24, 2009

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices (1). FDDS are widely explored for gastroretention purposes and have a bulk density lower 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 on gastric contents, the drug is released slowly at a desired rate from the system (1, 2).

Sodium alginate (SA) is a widely used natural polymer in various drug delivery systems. It exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and ulcer healing traits. Moreover, gelation of dilute solutions of SA occurs on addition of di- and trivalent metal ions by a co-operative process involving consecutive G-residues in the α-L-guluronic acid blocks of the alginate chain in a manner described by the 'egg-box' model (3). The procedure by which gelation is achieved is similar to the previously reported *in situ* gelling formulations of sodium alginate (4, 5).

H_2-antagonists or proton pump inhibitors are clinically used in treating chronic conditions like peptic ulcer and reflux oesophagitis. H_2-antagonists competitively inhibit his-

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tamine actions at all H_2-receptors, but are mainly used clinically as inhibitors of gastric acid secretion (6). Local availability of H_2-antagonists in stomach has a greater clinical significance in treatment of peptic ulcer. Ranitidine (RT), a H_2-antagonist, is widely prescribed in active duodenal ulcers, gastric ulcers and gastroesophageal reflux disease. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours and frequent administration leads to plasma fluctuations; hence, a sustained release dosage form of ranitidine is desirable. The short biological half-life of the drug (~2.5–3 hours) also favors development of a sustained release, gastroretentive formulation (7, 8).

In the present study, an attempt was made to develop a gastroretentive *in situ* gelling liquid formulation using ranitidine for local release in the stomach. Gastroretentive *in situ* gelling liquid formulations were formulated using different grades and concentrations of sodium alginate.

EXPERIMENTAL

Materials

Ranitidine (RT) was received as a gift sample from Torrent Pharmaceuticals Ltd (India). Low viscosity (0.25 Pa s), medium viscosity (6.5 Pa s) and high viscosity (14.0 Pa s) grades of sodium alginate (SA) were purchased from Sigma-Aldrich (USA). Calcium carbonate, sodium citrate and calcium chloride were purchased from S.D. Fine Chem. Ltd (India). All other chemicals used in the study were of analytical grade.

Methods

Preparation of in situ *gelling solution.* – SA solutions (0.5–1.0 %, *m/V*) were prepared in deionized water by heating to 60 °C under continuous stirring (3). After cooling below 40 °C, various concentrations of $CaCO_3$ and the drug were dispersed/dissolved under continuous stirring. A few formulations were prepared in deionized water previously containing 0.45 % (*m/V*) sodium citrate and 0.15 % (*m/V*) calcium chloride (Table I). The resulting formulations were finally stored in amber coloured bottles until further use.

Viscosity of in situ *gelling solutions.* – The viscosity of formulations was determined by a Brookfield viscometer DV-III (Brookfield, USA) using spindle number 21 with cup and bob setting at 50 rpm (Table II).

Floating behavior. – The buoyancy lag time and buoyancy duration of the formulations were determined in simulated gastric fluid (0.1 mol L^{-1} HCl, pH 1.2). The time in minutes taken by the formulation to emerge on the dissolution medium surface (buoyancy lag time) and buoyancy duration was noted.

Drug content. – Ten mL of the solution was added to 900 mL of simulated gastric fluid (0.1 mol L^{-1} HCl, pH 1.2) and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined by using a UV-visible spectrophotometer a (UV-1601 Shimadzu, Japan) at 226 nm against a suitable blank solution.

Table I. Formulation composition

Formulation code	Sodium alginate		Ranitidine (%, *m/V*)	$CaCO_3$ (%, *m/V*)	$CaCl_2$ (%, *m/V*)	Sodium citrate (%, *m/V*)
	Grade	Concentration (%, *m/V*)				
F1	Low	0.50	1.00	1.00	–	–
F2	Low	0.75	1.00	1.00	–	–
F3	Low	1.00	1.00	1.00	–	–
F4	Medium	0.50	1.00	1.00	–	–
F5	Medium	0.75	1.00	1.00	–	–
F6	Medium	1.00	1.00	1.00	–	–
F7	High	0.50	1.00	1.00	–	–
F8	High	0.75	1.00	1.00	–	–
F9	Low	0.75	1.00	0.50	–	–
F10	Low	0.75	1.00	1.50	–	–
F11	Low	0.75	2.00	1.00	–	–
F12	Low	0.75	3.00	1.00	–	–
F13	Low	0.75	1.00	1.00	0.15	0.45
F14	Medium	0.50	1.00	0.50	–	–
F15	Medium	0.50	1.00	1.50	–	–
F16	Medium	0.50	2.00	1.00	–	–
F17	Medium	0.50	3.00	1.00	–	–
F18	Medium	0.50	1.00	1.00	0.15	0.45

In vitro *release*. – The release of ranitidine from the formulations was determined using a USP/24 dissolution test apparatus (Tab Machines, India) with a paddle stirrer at 50 rpm. The dissolution medium used was 900 mL of simulated gastric fluid (0.1 mol L^{-1} HCl, pH 1.2) and temperature was maintained at 37 ± 0.2 °C. Ten mL of the formulation were placed into a Petri dish (4.5 cm i.d.) which was kept in the dissolution vessel and simulated gastric fluid was carefully added to the vessel avoiding any disturbance of the Petri dish. At each time interval, a precisely measured sample of the dissolution medium was pipetted out and replenished with fresh medium. Ranitidine concentration in the aliquot was determined spectrophotometrically. Each study was conducted in triplicate (9).

Mechanism of drug release. – To analyze the mechanism of drug release from the formulations, the *in vitro* dissolution data were fitted to zero-order ($F = kt$), first-order ($F = e^{-kt}$), Higuchi ($F = k\sqrt{t}$), and Korsmeyer and Peppas ($F = kt^n$) release models (10–12), where F is the fraction of drug released (≤ 60%), k is the release constant and t is time.

Table II. Properties of in situ *gelling formulations*

Formulation Code	Viscosity (Pa s) [a]	Buoyancy		Drug content (%)[b]
		Lag time (s)	Duration (h)	
F1	0.292	29	>24	101.9±1.1
F2	0.593	35	>24	99.4±0.6
F3	0.897	44	>24	97.6±0.3
F4	0.812	36	>24	97.6±0.9
F5	0.987	110	>24	99.5±1.3
F6	ND	226	>24	119.6±1.7
F7	0.995	175	>24	104.4±0.4
F8	0.812	226	>24	100.8±0.3
F9	0.245	316	>24	102.1±0.5
F10	0.985	17	>24	99.9±0.3
F11	0.503	205	>24	100.5±0.7
F12	0.413	317	>24	101.8±0.2
F13	0.696	22	>24	102.3±0.3
F14	0.326	265	>24	100.2±0.3
F15	ND	102	>24	102.1±0.3
F16	0.732	268	>24	101.8±0.3
F17	0.326	318	>24	112.7±0.2
F18	ND	240	>24	98.9±0.4

ND – not determined.
[a] 50 rpm.
[b] Mean of three trials ± SD.

RESULTS AND DISCUSSION

The viscosity of the formulations increased with an increase in sodium alginate concentration (Table II) from 0.5–1 % (*m/V)* within each grade (low, medium and high viscosity grades). This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium carbonate, which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to the proportional increase in the amount of dispersed calcium carbonate.

The buoyancy lag time varied with the formulation variables. Formulation F10 (SA 0.75 % *m/V*, $CaCO_3$ 1.5 % *m/V*) exhibited the least buoyancy lag time (17 s) while formulation F17 (SA 0.50 % *m/V*, $CaCO_3$ 1 % *m/V*) exhibited the highest lag time (318 s) (Table II). The decrease in the buoyancy lag time of an formulation F10 can be attributed to the availability of an increased amount of CO_2 as the concentration of calcium carbonate was increased, being entrapped in the formed gel to give rapid buoyancy. Irrespective of formulation variables, buoyancy duration was > 24 hours. The buoyancy lag time in-

creased with an increase in SA viscosity and concentration (1.0 > 0.75 > 0.5 % *m/V*). As the drug concentration was increased from 1–3 % *m/V*, the buoyancy lag time also increased from 35 to 318 seconds. It appears that with higher polymer content, excipients and drug, the bulk density of the gel increased, resulting in extension of the lag time from a few seconds to minutes.

In vitro drug release study was conducted on the formulations for a period of 8 hours during which the highest drug release of 96.5 ± 0.3 % (n = 3) was observed with formulation F1 (SA 0.5 % *m/V*, drug 1 % *m/V*) and the least drug release of 74.1 ± 0.1 % with F13 (SA 0.75 % *m/V*, drug 1 % *m/V*) during the 8 hour dissolution study. The influence of SA grades on *in vitro* drug release is shown in Figure 1. As the viscosity of the SA used in the formulation was increased from low to high, a decrease in the amount of drug release was observed. The drug release from the formulations with highly viscous SA was slower compared to formulations with medium and low viscous SA.

Figure 1 shows the cumulative percentage drug release from formulations containing different levels of sodium alginate. The drug release decreased with an increase in SA concentration in each grade. This can be explained by the fact that as the concentra-

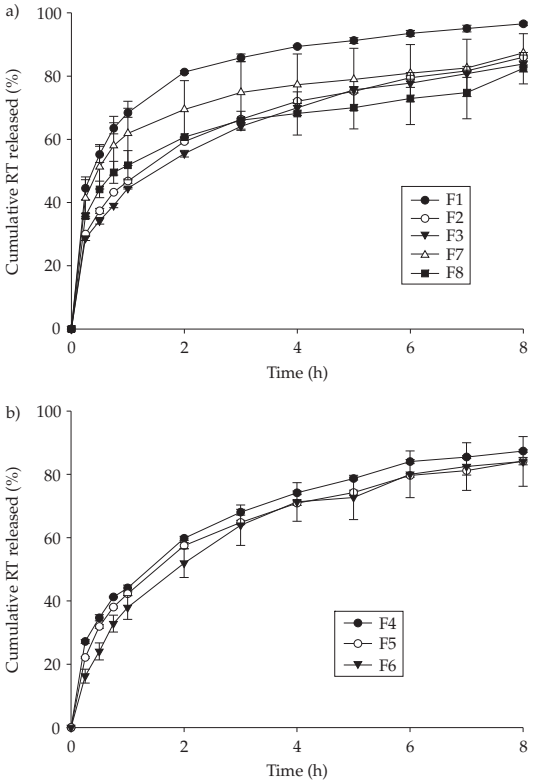

Fig. 1. Effect of SA grades and concentration on *in vitro* drug release from: a) F1–F3 and F7, F8, b) F4–F6 (mean ± SD, n = 3).

tion of polymer increases, more polymeric chains are available for crosslinking with the calcium ion. As the crosslinking increases, it forms a stronger gel, across which drug diffusion becomes difficult (13, 14). Among the eight formulations studied (F1 to F8) using different grades of sodium alginate, formulations F2 (SA low viscous, 0.75 % *m/V*) and F4 (SA medium viscous, 0.5 % *m/V*) were selected for further studies based on their viscosity, floating behaviour and *in vitro* drug release.

Calcium carbonate (0.5–1.0 % *m/V*) was used as a gas generating agent and a source of cations for gelation in the formulation. Calcium ions cause *in situ* gelation by interacting with sodium alginate during which carbon dioxide is entrapped within this gel matrix attributing to the gel buoyancy. The desired buoyancy (> 24 h) was achieved with calcium carbonate concentration of 0.5 % (*m/V)* while a concentration up to 1.5 % (*m/V)* provided sustained release of ranitidine (Fig. 2). The drug release decreased as the concentration of calcium carbonate in the formulation was increased. This may be attributed to the fact that as the concentration of calcium ions increases, cross-linking also increases. Although formulations F2 and F10 contain the same proportion of low viscous sodium alginate (0.75 % *m/V*), they differed in the calcium carbonate concentration. It is likely that the entire carboxylic acid group is cross-linked by free Ca^{2+} ions when added in a concentration of 1 % *m/V* (formulation F2). Therefore, addition of a higher proportion of Ca^{2+} source in formulation F10 (1.5 % *m/V*) might not have altered the cross-linking density, which could be the reason for the observed not significant change in drug release from formulations F2 and F10.

Ranitidine was incorporated in three different concentrations (1, 2 and 3 % *m/V*) to evaluate the effect of drug loading on the release profile (Fig. 3). An initial burst release of ~60 % was observed from the studied formulations F2 (drug 1 % *m/V*), F11 (drug 2 % *m/V*) and F12 (drug 3 % *m/V*) representing low viscous SA and F4 (drug 1 % *m/V*), F16 (drug 2 % *m/V*) and F17 (drug 3 % *m/V*) representing medium viscous SA. However, at the end of 8 hours, the drug release from the formulations with low viscous SA was in the range of 77–86 % and formulations with medium viscous SA ranged between 87–93 %.

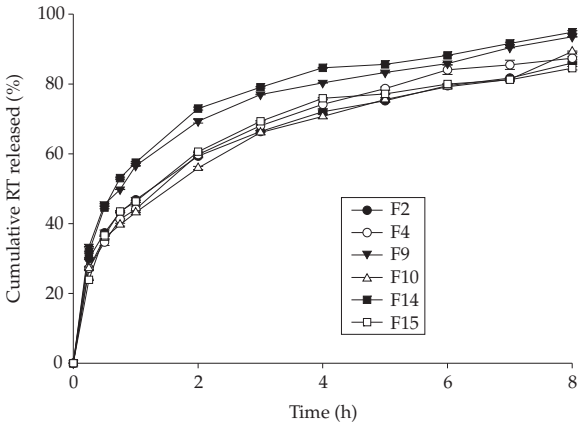

Fig. 2. Effect of calcium carbonate concentration on drug release from the formulations (mean ± SD, n = 3).

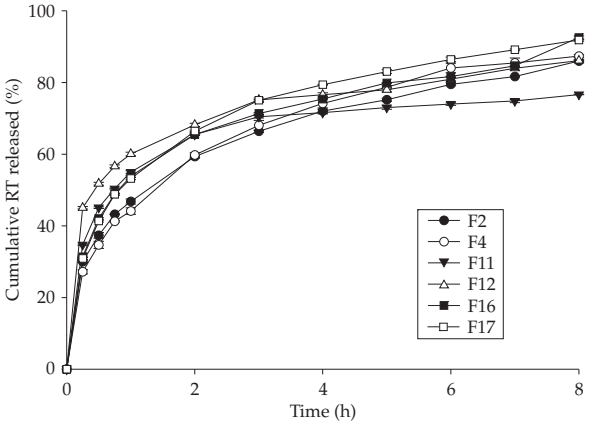

Fig. 3. Effect of drug loading on drug release from the prepared formulations (mean ± SD, n = 3).

This indicates that, except for the initial burst release which was due to the channeling effect of ranitidine, the drug release in the next 5 hours was significantly sustained ($p < 0.05$).

Fig. 4 shows the comparative drug release profiles of formulations with (F13 and F18) and without (F2 and F4) sodium citrate (0.45 %, *m/V*) and calcium chloride (0.15 %, *m/V*). Incorporation of sodium citrate and calcium chloride in the formulations, further sustained the drug release irrespective of the sodium alginate viscosity. This decrease in drug release was due to the availability of additional calcium ions supplied by the incorporation of $CaCl_2$ in the formulation, which further increased the extent of gelation.

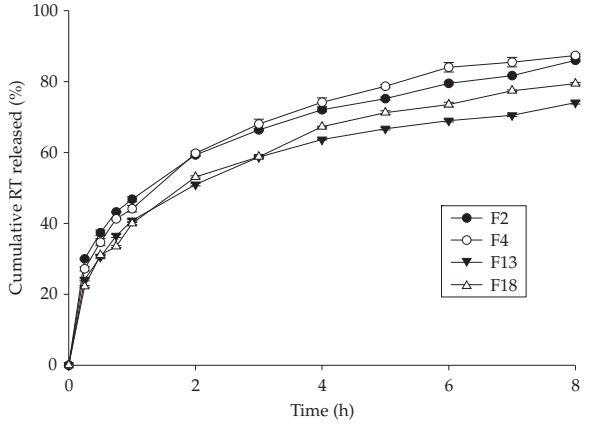

Fig. 4. Effect of incorporation of sodium citrate and calcium chloride on drug release from the formulations (mean ± SD, n = 3).

Table III. Release analysis

Formulation Code	R^2			n
	Zero-order	First-order	Higuchi	
F1	0.8395	0.8010	0.9225	0.1579
F2	0.9315	0.8799	0.9821	0.2840
F3	0.9290	0.8801	0.9816	0.3073
F4	0.8975	0.8342	0.9640	0.3267
F5	0.9054	0.8402	0.9646	0.3233
F6	0.8986	0.8303	0.9628	0.3852
7F	0.9164	0.8930	0.9607	0.1560
F8	0.9351	0.9110	0.9579	0.2082
F9	0.9155	0.8689	0.9697	0.2301
F10	0.9315	0.8811	0.9807	0.3325
F11	0.7733	0.7360	0.8701	0.1473
F12	0.9145	0.8839	0.9659	0.1663
F13	0.9051	0.8539	0.9680	0.2820
F14	0.8678	0.8145	0.9398	0.2250
F15	0.9315	0.7901	0.9303	0.2800
F16	0.9459	0.9098	0.9772	0.2390
F17	0.9038	0.8526	0.9677	0.2570
F18	0.9201	0.8629	0.9761	0.3294

[a] Mean of three trials ± SD. After 8 hours.

As shown in Table III, the coefficient of determinations (R^2) for the zero-order model ranges from 0.7733 to 0.9497 and that for the Higuchi model ranges from 0.8701 to 0.9911, suggesting the square root of the Higuchi time model for drug release from dosage forms. The drug release was further analyzed by the Korsmeyer-Peppas model to define the mechanism of drug release; n values obtained were in the range of 0.15–0.42, which further confirms the drug release by the diffusion mechanism.

CONCLUSIONS

In the present study, various *in situ* liquid oral formulations of ranitidine were prepared. The study has shown that by modifying parameters like the initial drug loading, concentration of gas generating agent and polymer content, the release can be modulated to the desired rate. By observing various evaluation parameters for the studied formulations, it can be stated that incorporation of sodium citrate and calcium chloride in the formulations is required to control and sustain the drug release from *in situ* gel.

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SAŽETAK

Isporuka tekućeg pripravka H_2-antagonista s lokalnim djelovanjem: Primjena tekućeg ljekovitog oblika koji gelira *in situ*

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U radu je opisana priprava tekućeg pripravka za kontroliranu isporuku ranitidina s produljenim zadržavanjem u želucu. Pripravak gelira *in situ*, a načinjen je iz natrijeva alginata niske, srednje i visoke viskoznosti, kalcijeva karbonata (izvor kationa) i ranitidina. Pripravcima je ispitana viskoznost, vrijeme plutanja, sadržaj ranitidina i oslobađanje

ljekovite tvari *in vitro*. Koncentracije natrijeva alginata, kalcijeva karbonata i ljekovite tvari značajno utječu na viskoznost, vrijeme plutanja i oslobađanje ranitidina. Utvrđeno je da se ljekovita tvar iz gela oslobađa difuzijom.

Ključne riječi: gastroretencija, *in situ* geliranje, natrijev alginat, ranitidin

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