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Oral sustained delivery of Ranitidine from *in-situ* gelling sodium-alginate formulation

Remya P. N.*, Damodharan N. and Venkata Anjaneyulu M.

Department of Pharmaceutics, SRM College of Pharmacy, SRM Nagar, Kattankulathur, Kanchipuram District, Tamil Nadu, India

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ABSTRACT

The experiment was conducted to make the formulation to release drug (Ranitidine) for an extended period of time and buoyant, thus prolong the residence time. Sodium alginate used as a polymer. Sols of Sodium Bicarbonate and Calcium carbonate was prepared. In the present study the Calcium ions released from Calcium carbonate are complexed by Citrate. The conversion of complexed Calcium into free Calcium cause gelation of Alginate. The gelled material floats upwards in the stomach, with a potential to release the drug from the formulation. It is established that the formulation containing Calcium carbonate produce a significant stronger gel than those containing Sodium bicarbonate due to internal gelation effect of calcium on gellan. Ranitidine from floating in-situ gels with D-sorbitol is the best suitable form for paediatrics and geriatrics and also for patients with difficult in swallowing.

Keywords: Ranitidine, Calcium carbonate, Sodium-alginate, Gelation, Sustained release.

INTRODUCTION

The oral route of drug delivery is typically considered the preferred and most patient convenient means of drug administration. The reality is that many compounds are either incompletely or ineffectively absorbed after oral administration or that the required dosing frequency is too short to enable once or twice-daily administration (i.e., pharmacokinetic half-life is an issue). Modified-release formulations technologies offer an effective means to optimize the bio-availability and resulting blood concentration-time profiles of drugs that otherwise suffer from such limitations [1]. With most orally administered drugs, targeting is not a primary concern, and it is usually intended for drugs to permeate to the general circulation and perfuse to other body tissues (the obvious exception being medication intended for local gastro intestinal tissue treatment). For is reason, most systems employed art of the sustained-release variety. It is

assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels which, in turn, promotes greater concentrations of drug at site of action [2].

Sustained release forms: The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. That Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An approximately designed sustained release drug delivery system can be a major advance toward sowing these two problems. Most sustained-release forms are designed so that the administration of a single dosage unit provides the immediate release of an amount of drug that promptly produces the desired therapeutic effect and gradual and continual release of additional amounts of drug to maintain this level of effect over an extended period, usually 8 to 12hrs. In general, the drugs best suited for incorporation into a sustained release product have following characteristics.

1. They exhibit neither every slow nor very fast rates of absorption and excretion.
2. They are uniformly absorbed from the gastro intestinal tract.
3. They possess a good margin of safety. They are used in the treatment of chronic rather than acute conditions.

The basic strategy adopted in this study involved incorporation of calcium carbonate and sodium citrate in sodium alginate dispersion. Initially, the calcium carbonate becomes soluble in the acidic environment of the stomach, and the released calcium ions then are complexed by the citrate. However, a slow conversion of the complexed calcium into free calcium causes gelation of alginate. The gelled material floats upwards in the stomach, with a potential to release its drug over a period of time. The calcium carbonate present in the formulation, releases carbon dioxide in the gastric environment, thereby making the formulation buoyant, thus prolonging the residence time. Hydrogels are hyrophilic polymeric networks, with chemical or physical crosslinks, that are capable of swell and can retain a large amount of water. , Polysaccharides suitable for different applications in the wide field of pharmaceutics [5]. There are several stimuli sensitive Swelling-controlled released systems[6,7].

1.Temperature sensitive hydrogels
2.Electrical signal sensitive hydrogels
3. Light sensitive hydrogels
4. Ion and pH sensitive hydrogels.

There are various applications of environment sensitive hydrogels in drug delivery system[8,9].

EXPERIMENTAL SECTION

Table No.1: The following materials used for the study

Materials	**Make**
Ranitidine	S.K.N. Organic Pvt. Ltd (Pondicherry)
Sodium alginate	Sigma-Aldrich (USA)
Calcium carbonate	Fine Chem. Ltd. (India)
Sodium bicarbonate	Fine Chem. Ltd. (India)
Sodium citrate	Fine Chem. Ltd. (India)

Table No.2: Formulation of in situ gelling sols of ranitidine

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Ranitidine(gm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium alginate(mg)	1	1	1	1.5	1.5	1.5	2	2	2	1	1	1	1.5	1.5	1.5	2	2	2
Sodium citrate(mg)	0.05	0.25	0.5	0..05	0.25	0.5	0.05	0.25	0.5	0.1	0.25	0.5	0.05	0.25	0.5	0.05	0.25	0.5
Sodium bicaronate(mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium cabonate(mg)	-	-	-	-	-	-	-	-	-	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium chloride(mg)	0.025	0.05	0.075	0.025	0.05	0.075	0.025	0.05	0.075	-	-	-	-	-	-	-	-	-

(a)Preparation of Sols Containing Sodium Bicarbonate($NaHCO_3$)

Sodium alginate of concentrations 1, 1.5 and 2% (w/v) were prepared by adding the sodium alginate to distilled water containing 0.5% (w/v) sodium bicarbonate, 0.05% (w/v) sodium citrate and heating to 40-60^{0}C while stirring. Appropriate amounts of Ranitidine (0.15% w/v) and flavouring agent (the optimized concentrations from 2, 4, 6, and 8% w/v of D-sorbitol) were then dissolved in the resulting solution.

(b)Preparation of Sols Containing Calcium Carbonate ($CaCO_3$)

Sodium alginate of concentrations 1, 1.5 and 2% (w/v) were prepared by adding the sodium alginate to distilled water containing 0.5% (w/v) calcium carbonate, 0.05% (w/v) sodium citrate and heating to 40-60^{0}C while stirring. Appropriate amounts of Ranitidine (0.15%` w/v) and flavouring agent (the optimized concentrations from 2, 4, 6, and 8% w/v of D-sorbitol) were then dissolved in the resulting solution.

PROCESS OPTIMIZATION:

Sodium alginate, Sodium citrate, $CaCO_3$ and $NaHCO_3$ were evaluated for their in-situ gelling ability and floating behaviour. Sodium alginate forms rigid gel structure and can be used as an in-situ gelling polymer.

Table-3: Optimization of concentrations of Sodium alginate and $NaHCO_3$

Formulations	Parameters
F_1	Maintains fluidity and gelation with less floating tendency at p^H 1.2 HCl buffer.
F_2	Poor gelation with low floating tendency.
F_3	Gelation occurred with a floating capacity of 3 min. when exposed to HCl buffer.
F_4	Shows less floating tendency and poor gelation.
F_5	Maintains fluidity with less gelation and less floating tendency
F_6	Less gelation with floating capacity of 8 min.
F_7	Gelation is poor.
F_8	Poor gelation occurred.
F_9	Gelation occurred with a floating tendency of 10 min.

Table-4: Optimization of concentrations of Sodium alginate and Calcium carbonate

F_{10}	Gelation occurred with less floating capacity at p^H 1.2 HCl buffer.
F_{11}	Gelation occurred with minimum floating capacity.
F_{12}	Forms thick gel with good floating tendency.
F_{13}	Maintains fluidity and results gelation with less floating tendency.
F_{14}	Gelation occurs with minimum floating tendency.
F_{15}	Shows good gelation with better floating tendency when exposed to pH 1.2 HCl buffer.
F_{16}	Maintains good gelation with a floating tendency of two hours.
F_{17}	Gelation occurs with good floating tendency.
F_{18}	Maintains gelation with more floating tendency.

Optimization of concentrations of polymer and excipients for the preparation of sols with $NaHCO_3$ and $CaCO_3$:

The various concentrations of sodium alginate (1%, 1.5%, 2% w/v) were added with the gas releasing agent $NaHCO_3$ to the various formulations(F_1, F_2, F_3, F_4, F_5,F_6, F_7, F_8,F_9) and gas releasing agent **$CaCO_3$** to various formulations (F_{10}, F_{11}, F_{12}, F_{13}, F_{14}, F_{15}, F_{16}, F_{17}, F_{18}) in both the cases the optimum concentration resulted in good gelation when the sol was added to pH 1.2 Hcl buffer. The optimum concentration also maintained good floating behaviour and fluidity. Among the above formulations F_9, F_{12}, F_{15}, F_{18} showed better gelation property, so this formulations has been studied for other evaluation parameters such as rheological studies, drug content, in-vitro studies, stability studies.

RESULTS AND DISCUSSION

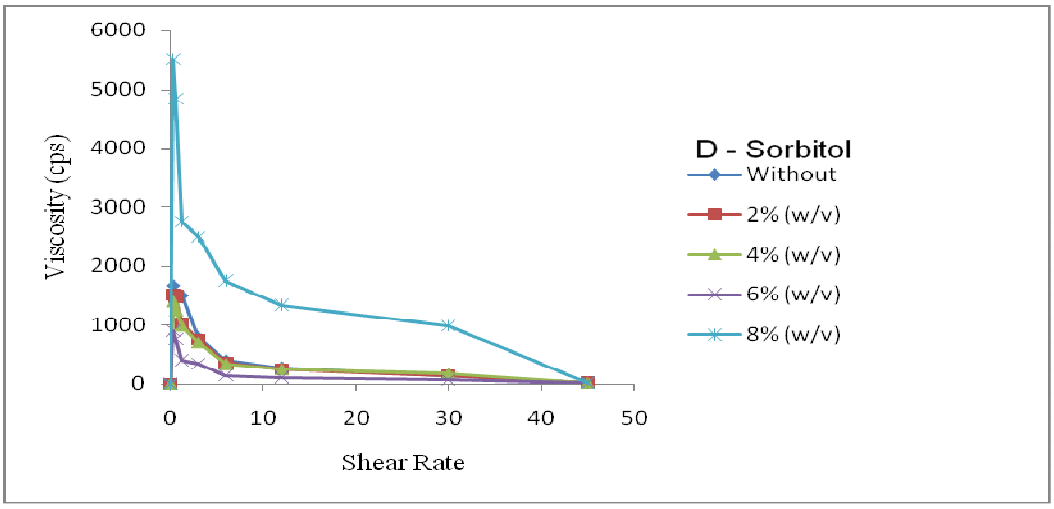
Table No.5: Pre formulation Studies for A.P.I

S. No.	Characteristics	Results
1.	Physical appearance	A light yellow colour powder, odourless, tasteless.
2.	Solubility	Freely soluble in water and iqaqnsoluble in other solvents

Compatibility studies

Samples and total mixtures were studied by using FT-IR and IR spectral studies. Samples retained their individual absorption characteristics, without undergoing any interaction with one another. From this study we can conclude that no untoward chemical reactions were observed.

Rheological behaviour of the sols:



The viscosities of the formulations at different rpm were determined by using Brookfield viscometer. The viscosity of 1%, 1.5% (w/v) sodium alginate containing various concentrations of D-sorbitol of $CaCO_3$ was found to decrease at increasing rpm exhibiting pseudoplastic behaviour. Increase in the concentration of the polymer has significant increase in viscosity of the sols.

The sols added with 2% (w/v) D-sorbitol shows no change in viscosity, which was found to have almost the same viscosity as resulted from the sols containing no D-sorbitol.

Table No.6: Rheological behaviour of 1% (w/v) Sodium alginate containing various concentrations of D-sorbitol of $CaCO_3$

Shear Rate	Viscosity (in cps)				
	Without D-sorbitol	With D-sorbitol			
		2% (w/v) D- sorbitol	4% (w/v) D-sorbitol	6% (w/v) D-sorbitol	8% (w/v) D-sorbitol
0.3	1667	1500	1400	900	5500
0.6	1500	1475	1250	750	4833
1.2	1500	1017	990	400	2750
3.0	791.7	750	700	333.3	2500
6.0	400	350	333.3	150	1750
12.0	275	250	250	110	1333.3
30.0	150	144.4	175	70	990
45.0	23.1	23.8	26.7	34.1	40.2

The results show there is a decrease in the viscosity but no significant reduction in viscosity of the sols due to addition of 4% (w/v) D-sorbitol.

Addition of 6% (w/v) concentration of D-sorbitol to the sols caused significant decrease of viscosity and the sols gelled at room temperature after storage for a week.

There is a marked increase in viscosity after addition of 8% (w/v) D-sorbitol which is nearly 2 fold increase from that of the sols containing no D-sorbitol. . It was also observed that 1% (w/v) sodium alginate showed less viscous comparatively the sols containing 1.5% (w/v) sodium alginate.

Drug content

Table No.7: Determination of drug content of Formulation F12

S.No.	Batch	Drug content (mg)
1.	Without D-sorbitol	149.98
With D-sorbitol		
2.	2% (w/v)	149.98
3.	4%(w/v)	149.96
4.	6%(w/v)	149.97
5.	8%(w/v)	149.92

Table No.8: *In vitro* dissolution profile of Formulation F12

Time (hr)	Cumulative Drug Release (%)				
	Without D-sorbitol	With D-sorbitol			
		2% (w/v)	4% (w/v)	6%(w/v)	8%(w/v)
0.25	7.23	12.32	14.51	19.98	20.30
0.5	14.53	18.42	26.64	27.07	27.20
1.0	20.32	24.53	34.08	44.59	46.18
2.0	34.93	38.20	44.26	65.60	68.80
3.0	47.81	51.23	65.45	79.62	82.18
4.0	57.82	59.59	78.89	82.40	93.97
5.0	65.68	72.34	93.52	94.07	100.02
6.0	80.23	83.56	99.59	100.53	-
7.0	91.57	94.59	-	-	-
8.0	95.26	98.42	-	-	-

Significant decrease in the rate and extent of drug release was observed with the increase in polymer concentration in in-situ gels and is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse. The release of drug from these gels was characterized by an initial phase of high release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of moderate release. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics.

Effect of drug release without addition of taste masking agent

The amount of drug release from 1%, 1.5% and 2% (w/v) of sodium alginate at the end of 8 hrs was found to be 96.5%, 68.19% and 63.81% respectively at pH 1.2. The results were shows that an increase in alginate concentration causes decrease in release rate of drug.

Effect of drug release with addition of taste masking agent:

The *in vitro* drug release from 1%, 1.5% and 2% (w/v) sodium alginate containing 2% D-sorbitol was found to be 98.42%, 70.06% and 65.32% respectively at the end of 8 hrs. By the addition of D-sorbitol the formulations does not show any change in the release rate of drug.

***In vitro* release kinetics**

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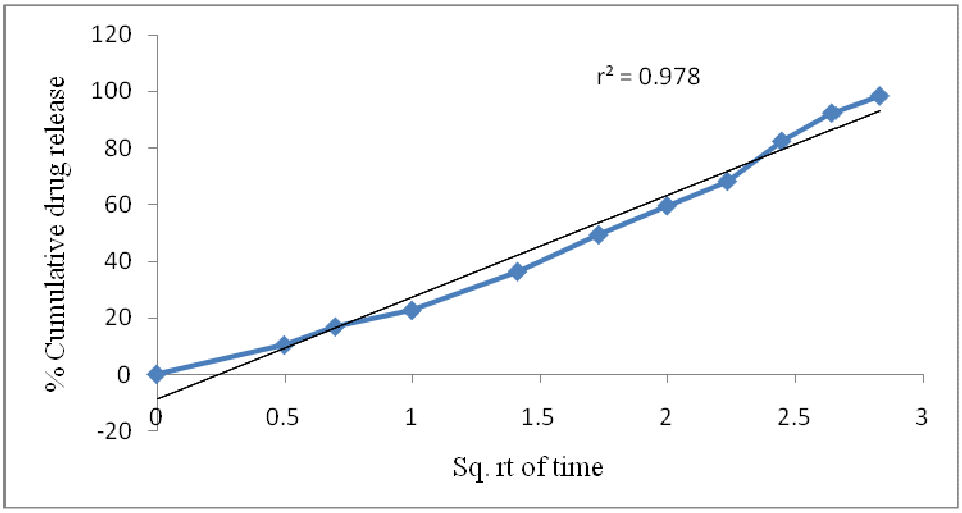
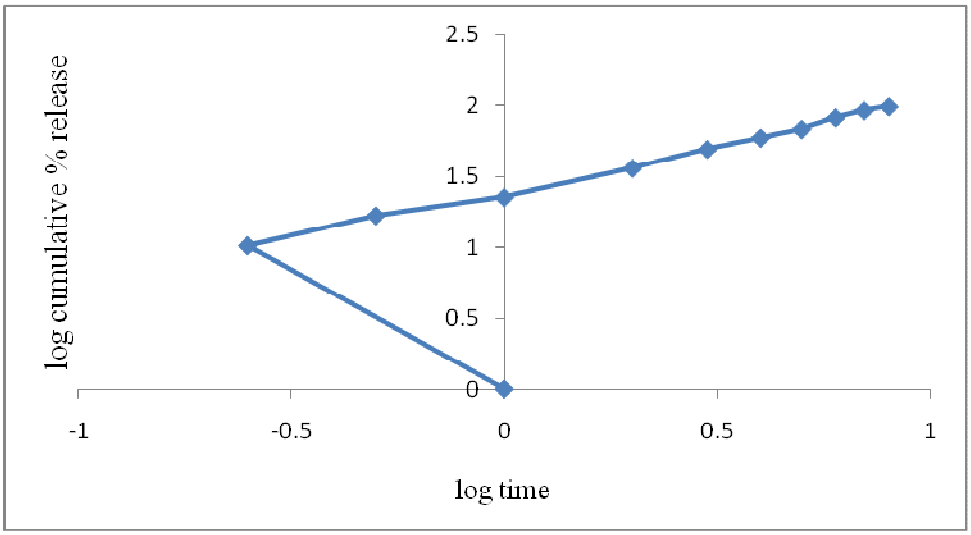
Determination of release kinetics for 1% (w/v) Sodium alginate (Higuchi model)



Determination of release kinetics for 1% (w/v) Sodium alginate (Peppas model)



The correlation values obtained from Higuchi's model for formulation F12 was found to be 0.978. This value shows that mechanism of release from the gels formed in-situ after addition into acidic medium follows Higuchi's diffusion controlled release. The slopes for F12 formulation obtained from the linear plot of Peppas model was found to be 0.780 thus, the value follows diffusion controlled mechanism confirming Fickian's law. Thus, when we consider the *in vitro* dissolution kinetic data, it is seen that, the release followed diffusion controlled release mechanism.

Floating behaviour

The floating ability of the prepared formulations was evaluated in stimulated gastric fluid. Formulations containing calcium carbonate demonstrated excellent floating ability, while formulations not containing this agent settled at the bottom of the medium.

The floating time of the prepared formulation took to emerge on the medium surface (floating lag time) was found to be 60sec.The time the formulation constantly floated on the dissolution medium surface (duration of floating) was evaluated to be 12hrs resulting the formation of thick gel with good floating tendency .

STABILITY STUDIES

Stability studies at 40^0C ± 75% RH for 1month indicated that there is no significant change in physical appearance, viscosity, drug content, *in vitro* drug release and Floating behaviour in the optimized formula F12 (1% (w/v) sodium alginate with 2% (w/v) D-sorbitol).

CONCLUSION

The developed formulations met all the pre-requisites to become an insitu gelling floating system, gelled and floated instantaneously at the pH conditions of the stomach.

The formulation containing Calcium carbonate produce a significant strong gel then those containing Sodium bicarbonate due to internal gelatine effect of Calcium on gellan.

The present study has demonstrated that 1% (w/v) alginate gels sustained the release of Ranitidine with a drug release of 98.4%. Sustained release of ranitidine from insitu gelling formulations was obtained with alginate concentrations of 1% (w/v) and a Sorbitol concentration of 2% (w/v). The formulation F12 follows the Higuchi diffusion controlled release and Diffusion controlled mechanism confirming Fickians law.

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