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Floating Drug Delivery System of Ramipril Using Foam Technology

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Abstract

The objective of this research was to develop an intra gastric floating drug delivery system of ramipril and also effort were made to sustain the release of ramipril. Multiple-unit floating beads of ramipril were prepared from sodium alginate solution containing polaxamer by using foam technology method. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release. All formulations were the floating lag time below two minutes and shows total floating duration more than 18 hours. It was observed that entrapment efficiency, drug loading and buoyancy was greater with formulation containing sodium alginate 3% and 2% calcium chloride solution along with 100mg polaxamer F17 and also the result of in-vitro dissolution studies reveals that the formulation F17 give sustained release pattern of ramipril upto 18 hrs.

Keywords: Ramipril, Sodium alginate, polaxamer, formulations.

Contents

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1. Introduction

The drug bioavailability of pharmaceutical dosage forms is affected by various factors. One of which is gastric residence time (GRT) [1]. The gastric emptying process from the stomach to small intestine commonly ends from a few minutes to 12 h. This changeability leads to an unpredictable bioavailability of an orally administered dosage form[2] Furthermore, the comparatively short gastric emptying time can result in an incomplete release of drug from dosage form. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability [3].

FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach without influenced the gastric emptying rate for a prolonged period of time [4]. Over the years, various approaches have been pursued to increase the retention of an oral dosage form in the stomach. Gastro retentive systems remain in the gastric region for several hours and hence mainly prolong the gastric residence time of drugs [5,6]. These may be (i) Effervescent system and (ii)Non effervescent system.

Effervescent Floating Dosage Forms: [7,8]
These are matrix types of systems prepared with the help of swellable polymers (methylcellulose and chitosan) and various effervescent compounds (sodium bicarbonate, tartaric acid, and citric acid). They are formulated in such a way that when come in contact with acidic gastric contents, CO_2 liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

1. Gas-generatingSystems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

2. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

Non-effervescent Floating Dosage Forms: [9,10,11,12]

1. Colloidal gel barrier system:

A system that contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

2. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

3. Hollow microspheres / Microballons:

It is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug.

4. Intragastric / Microporous compartment system:

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach. Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

2. Materials and Method

2.1. Materials :

Ramipril was procured as a gift sample from Solus Pharmaceutical Ltd. India. Sodium alginate, Calcium chloride, Poloxamar 188 and Poloxamer 407 were purchased from Thomas baker pvt. Ltd., Thomas baker pvt. Ltd., Signet chemical corporation pvt. Ltd , Ludwigshfen/BASF Company. All reagents used were of analytical reagent grade.

2.2. Preparation of Floating Ramipril beads: [13]

Sodium alginate was dissolved in distilled water at then poloxamer was then added into the sodium alginate solution and agitated vigorously by using mechanical stirrer at 2600 rpm for 20 min. Then drug was added into the foam solution under vigorous stirring condition continuously. The foam solution was introduced using a 21 gauge syringe into the 1% $CaCl_2$ solution under gentle stirring condition. The distance between the edge of the needle and the surface of the $CaCl_2$ medium was about 10 cm. The beads formed were left in the solution with gentle stirring for 10

min at room temperature to be cured. The beads were collected, washed with distilled water twice and oven-dried subsequently (40 ^{o}C).

Table 1: Formulation

Formulation No.	Sodium alginate (mg)	Polaxamer 188 (mg)	Polaxamer 407 (mg)	Drug (mg)
F1	1%	100	-	50
F2	1%	-	100	50
F3	1.5%	100	-	50
F4	1.5%	-	100	50
F5	2.0%	100	-	50
F6	2.0%	-	100	50
F7	2.5%	100	-	50
F8	2.5%	-	100	50
F9	3.0%	100	-	50
F10	3.0%	-	100	50

Table 2: Optimization of formulation

Formulatio No.	Drug (mg)	Sodium alginate (mg)	Polaxamer 407 (mg)	Stirring speed	Stirring time (min)	$CaCl_2$
F11	50	3.0%	100	2000	10	1%
F12	50	3.0%	100	3000	20	1%
F13	50	3.0%	100	3000	30	1%
F14	50	3.0%	100	3000	20	1%
F15	50	3.0%	100	3000	20	1%
F16	50	3.0%	100	3000	20	2%
F17	50	3.0%	100	3000	20	3%

3. Evaluation parameters for floating beads:

1. Determination of drug entrappment efficiency: [14]

50 mg of beads from each formulation were weighed and crushed in a mortar and pastel and the crushed material was dissolved in 100 ml of hcl buffer at pH 1.2. This solution was mechanically agitated on shaker at 200 rpm for 2 hours. The resultant dispersions were filtered and analyzed at 210 nm using UV spectrophotometer (JASCO-V500, Kyoto, Japan). The encapsulationefficiency was determined by the following formula.[16]

2. **Buoyancy test: [**15]

The obtained beads were studied for buoyancy and floating time using USP Apparatus II (paddle type). One hundred beads of each batch were placed in 900 ml of 0.1 N HCl (pH 1.2) containing and agitated at rpm, temperature was maintained at 37ºC**.**

3. FT-IR study:[16]

Drug polymer interactions were studied by FT-IR spectroscopy. The infrared spectra of sodium alginate,Ramipril and drug loaded beads were recorded on FT-IR (Shimadzu FTIR 8400S). The samples were prepared on KBr press and the spectra were recorded over the wave number range of 4,000 to 400 cm^{-1}.

4. Evaluation of swelling ratio: [17]

Swelling ratio was studied by measuring the percentage water uptake by the . About 50 mg of beads from prepared placebo beads were accurately weighed and placed in 100 ml of phosphate buffer (pH 6.8 and 0.1 N HCl(pH 1.2). Beads were removed from their respective swelling media after 8 h and weighed after drying the surface water using filter paper. The water uptake was calculated as the ratio of the increase in weight of beads after swelling to the dry weight.

$$Swelling\ ratio = \frac{Swollen\ w.t. - initial\ w.t.}{initial\ w.t.} * 100$$

5. Scanning electron microscopy analysis (SEM): [18]

The shape and surface characteristics were determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The particles were Vacuum dried, coated to 200 Ao thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

6. *In-vitro* release studies:[19]

In-vitro release studies of prepared micro beads were carried out using phosphate buffer (pH 6.8) using USP- basket type apparatus. Accurately weighed quantity of 250 mg of prepared micro beads put into the basket rotated at a constant speed at 100rpm and maintained temperaturem 37±5ºC in 900ml of the dissolution medium (phosphate buffer pH6.8).The sample was withdrawn at0.25hrs, 0.5hrs, 1hrs, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs, 7hrs,, 9hrs, 10hrs,.. Each time interval 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The withdrawn samples were suitably dilutedand measure the absorbance at 210 nm Spectrophotometrically. Then calculate the cumulative percentage drug release at regular time intervals.

7.Drug release kinetics: [20]

The release kinetic was studied by various kinetic models as zero order plot, first order plot, higuchi plot and korsmeyer-peppas. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release. To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi matrix, Korsemeyer-Peppas. By comparing the R2-values obtained from the above equations, the best-fit model was selected.

3. Results and Discussion

The aim of the study is to investigate possibility of using sodium alginate with Polaxamer 407, Polaxamer 188 as Foaming agent in sustained release system. We prepared Floating beads containing Ramipril by Foam technology and examined the effects of various factors (concentration of sodium alginate, concentration of Foaming agent like Polaxamer and concentration of drug Ramipril with effect of effect of stirring speed, stirring time and $CaCl_2$.)

Percentage Yield: The yield of all the formulations was within the range of 62.4 to 92.8.The values of production yield are depicted in Table- 3

Table 3: % yield of formulation

Formulation No.	% yield	Formulation No.	% yield
F1	62.4	F11	86
F2	60.3	F12	90
F3	67.2	F13	92
F4	68	F14	92.5
F5	72	F15	92.8
F6	76.4	F16	92.8
F7	74	F17	91.4
F8	78.2		
F9	82		
F10	88.5		

Entrapment efficiency:

The Entrapment efficiency of all the formulations was within the range of 4.5 to 89.4.The values of production yield are depicted in Table-4.

Table 4: Entrapment efficiency of formulation

Formulation No.	Entrapment efficiency	Formulation No.	Entrapment efficiency
F1	4.5	F11	72.5
F2	5.4	F12	76.5
F3	10.2	F13	78.2
F4	10.4	F14	82.5
F5	32	F15	88.2
F6	32.6	F16	89.4
F7	34.8	F17	87.3
F8	50.2		
F9	54.6		
F10	68		

Bead diameter:

The Bead diameter of all the formulations was within the range of 88..0±2.83 to91.0±0.87 .The values of production yield are depicted in Table-5

T**able 5:** Bead diameter of formulation

Formulation No.	Bead diameter ±SD	Formulation No.	Bead diameter ±SD
F1	90.0± 0.022	F11	90.0±0.378
F2	89.0±0.32	F12	89.0±0.574
F3	89.0±0.456	F13	88.0±0.732
F4	89.0±1.32	F14	90.0±1.43
F5	91.0±0.89	F15	90.0±1.76
F6	90.0±0.65	F16	90.0±0.675
F7	91.0±0.87	F17	90. ±0.834
F8	88.0±2.83		
F9	88.0±0.678		
F10	90.0±0.65		

Swelling index:

The Swelling index of all the formulations was within the range of 1.2to To3.5 .The values of production yield are depicted in Table-6.

Table 6: Swelling index of formulation

Formulation No.	Swelling index	Formulation No.	Swelling index
F1	1.2	**F11**	3.2
F2	1.5	**F12**	3.4
F3	1.3	**F13**	3.2
F4	2.4	**F14**	3.6
F5	2.2	**F15**	3.4
F6	2.6	**F16**	3.5
F7	2.6	**F17**	3.2
F8	2.1		
F9	2.7		
F10	2.8		

Buoyancy Studies:

The Buoyancy characteristics of all the formulations were within the range of this. The values of are Buoyancy Studies depicted in Table-7

Table 7: Buoyancy characteristics of formulation

Formulation No.	FLT(Min.)	Floating duration (h)
F1	0	>12
F2	0	>12
F3	0	>16
F4	0	>16
F5	0	>16
F6	0	>16
F7	0	>16
F8	0	>16
F9	0	>16
F10	0	>16
F11	0	>16
F12	0	>18
F13	0	>18
F14	0	>18
F15	0	>18
F16	0	>18
F17	0	>18

4 Drug Polymer Interaction (FTIR) Study:

4.1 FT-IR spectrum of Ramipril :

FT-IR spectrum of the pure drug sample was recorded with Shimadzu 8400S. Spectrum is displayed in figure 1.

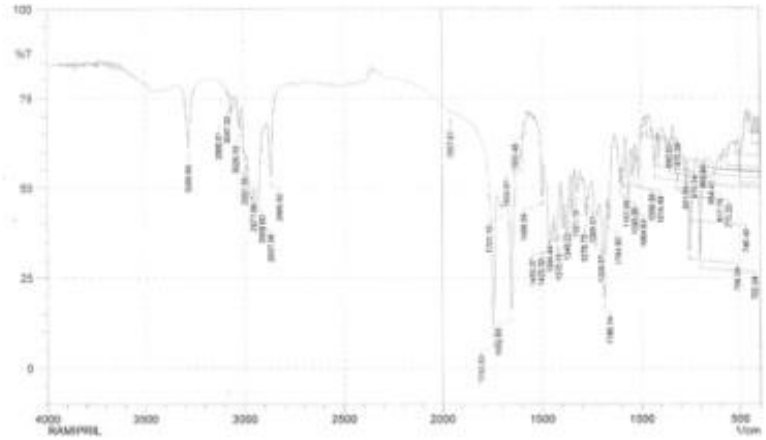

Figure 1: FT-IR Spectrum of Ramipril

4.2. FT-IR spectrum of pure sodium alginate FT-IR spectrum of the pure sodium alginate was recorded with Shimadzu 8400S. Spectrum is displayed in figure 2 .

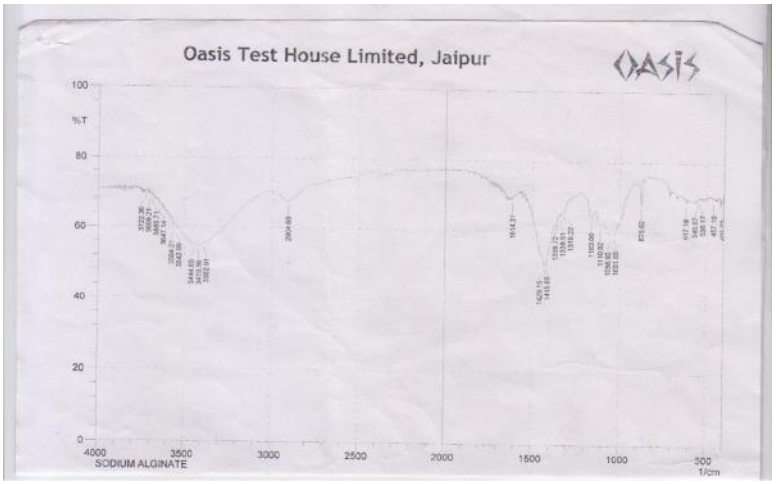

Figure 2: IR Spectrum of sodium alginate

4.3. FT-IR spectrum of pure polaxamer FT-IR spectrum of the pure polaxamer was recorded with Shimadzu 8400S. Spectrum is displayed in figure 3.

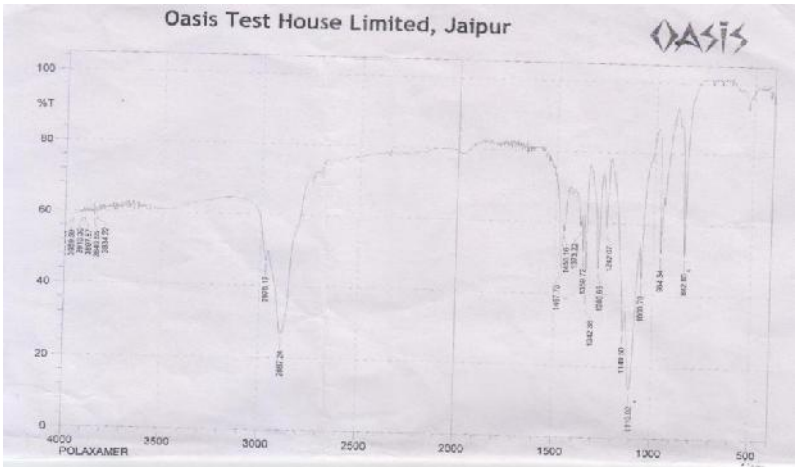

Figure 3: IR Spectrum of pure polaxame

4.1.3.4. FT-IR spectrum of Physical mixture FT-IR spectrum of the Physical mixture was recorded with Shimadzu 8400S. Spectrum is displayed in figure 4. and spectral interpretation is indicated in table 8.

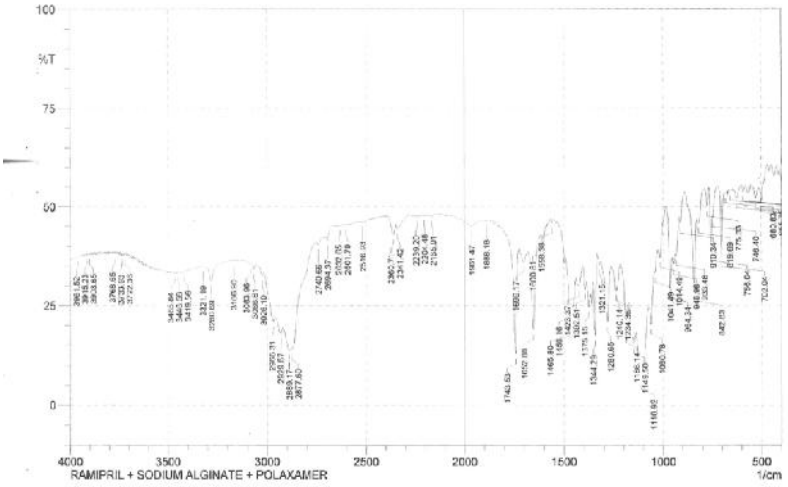

Figure 4: IR Spectra of Ramipril+sodium alginate+polaxamer

Table 8: FT-IR interpretation of Physical mixture

Functional group	Reference peak range	Observed peak	
		Pure drug	Physical mixture
-COOH	3300-2800	3280.69	3280.69
-C-C-(alkane)	1300-800	1107.06	1110.92
-C-H	2960-2850	2866.02	2877.60
C=C	1600	1600.81	1600.81
-COOR	1750-1735	1743.53	1743.53

***In vitro* drug release study**

The *In-Vitro* drug release studies of the different formulations cumulative percentage drug release was observed in the range of 75.26- 87.20.

Table 9: In vitro drug release

Time	% Cumulative drug release				
	F10	F12	F13	F15	F17
1	17.15	13.5	14.6	15.6	12.89
2	26.5	19.4	36.4	36.8	32.67
3	32.14	32.8	47.7	46.67	48.10
4	48.70	40.67	56.8	56.89	58.40
5	54.67	44.76	59.6	60.78	64.10
6	59.78	48.56	64.7	65.65	67.45
7	64.67	56.76	68.5	67.78	76.78
8	69.12	60.76	73.78	73.67	82.89
9	75.40	65.78	79.67	76.40	85.76
10	78.25	75.56	85.34	79.67	87.20

4. Conclusion

The foam technology was successfully utilized for formulation of floating alginate beads of ramipril. The adopted method for estimation of ramipril showed good linearity. The formulated floating alginate beads have shown higher percentage of drug loading, encapsulation efficiency, particle size.. The beads formed have a spherical shape with rough surface as evidenced by SEM. FT IR did not reveal any significant drug interaction it was observed that floating beads formulation (F17) exhibits greater in vitro drug release than other formulation .The result of *in-vitro* release and release kinetic indicated sustained release and exhibited zero kinetic followed by super case II transport reveal any significant drug interaction. F17 released ramipril for prolonged duration (18 h). Formulated floating beads of ramipril showed good swelling behavior. The optimized formulation F17 showed best fit in zero order model.

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