IJMPR 2023, 7(5), 199-210

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

FORMULATION AND EVALUATION OF RAMIPRIL HYDROCHLORIDE FLOATING BEADS BY FOAM TECHNIQUE

***[1]Priya Singh, [2]Dr. Dilip Agrawal and [3]Mohit Khandelwal**

[1]Research Scholar, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.
[2]Principal, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.
[3]Asso. Prof., Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.

Received on: 21/04/2023
Revised on: 11/05/2023
Accepted on: 01/05/2023

***Corresponding Author**
Priya Singh
Research Scholar, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.

ABSTRACT

The objective of this research was to develop an intra gastric floating drug delivery system of Ramipril hydrochloride and also effort were made to sustain its release. Multiple-unit floating beads of Ramipril hydrochloride were prepared from sodium alginate solution containing polaxamer 188 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 Four Second and shows total floating duration more than 15 hours. It was observed that entrapment efficiency, drug loading and buoyancy was greater with formulation containing sodium alginate 375 mg and 1% calcium chloride solution along with 100 and 150 mg polaxamer. Result of in-vitro dissolution studies reveals that the formulation B1 give sustained release pattern of Ramipril hydrochloride upto 15 hrs.

KEYWORDS: Ramipril hydrochloride, Sodium alginate, Polaxamer 188, Floating Beads.

INTRODUCTION

Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them.[5,6]

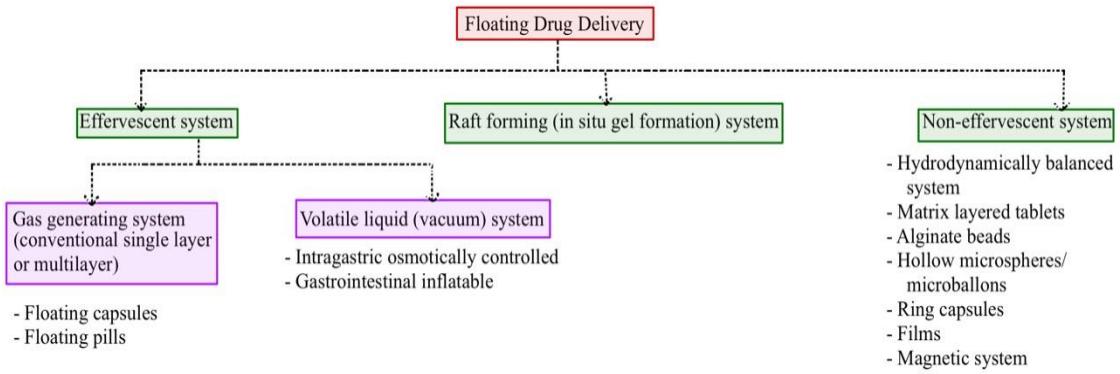

Fig. 1: Classification of FDDS.

Marketed Formulations Of Floating Drug Delivery System[14]
Table 1: List of marketed formulations of floating DDS.

S.N.O	BrandName	Drug	Dosage Form
1.	Topalkan	Aluminium Magnesium Antacid	Floating liquid Alginate Preparation
2.	Liquid Gavison	AluminiumHydroxide, Magnesium Carbonate	Effervescent Floating liquid Alginate Preparation
3.	Valrelease	Diazepam	Floating Capsule
4.	Madopar	Levodopa,Benserazide	Floating Controlled Release Capsule
5.	Cifran OD	Ciprofloxacin	Gas-generating Floating Tablet
6.	Conviron	Ferrous Sulphate	Colloidal Gel Forming FDDS
7.	Cytotec	Misoprostal	Bilayer Floating Capsule
8.	Amalgate Float Coat	Antacid	Floating Dosage Form

Applications of floating drug delivery system

1. FDDS are claimed for the increased efficacy of drugs as recent studies show that the administration of Diltiazem floating tablets twice a day would be more effective compared to normal tablets in hypertensive patients.
2. In case of Parkinson patient, FDDS is effective in absorption of the drug over a period of 6-8 h and maintained substantial plasma concentration.[25]
3. FDDS is site-specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine, e. g., Riboflavin and Furosemide.
4. FDDS served as an excellent drug delivery system in the eradication of *Helicobacter pylori*, blamed for chronic gastritis and peptic ulcers.

MATERIALS AND METHOD

Materials

Ramipril was procured as a gift sample from Solus Pharmaceutical Ltd. India. Sodium alginate, Poloxamar 188 and Calcium chloride were purchased from Central Drug House, Delhi, Merck Life Science Private Limited, Mumbai. All reagents used were of analytical reagent grade.

Method

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

RESULT AND DISCUSSION

Preformulation Studies

1. Melting Point Determination: Melting point of Ramipril Hydrochloride was found to be 108-110 °C which is almost under the reported value indicating that no impurity is present in the sample.

2. Partition Coefficient: It was reported as lop P = 3.93 with the below formulae

$$K_{o/w} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

3. Solubility Studies: Solubility data of Ramipril Hydrochloride at 25 ^oC

Table 2: Solubility of Ramipril in different solvent.

Solvents	Solubility (mg/ml)
Distilled Water	0.004
0.1N HCL	0.197
DMSO	1.76
Methanol	0.61

UV Scan of Ramipril

7.1.4.1. Determination of absorption maxima (λ_{max})

Table 3: List of marketed formulations of floating DDS.

Solvent	Absorption maxima
In 0.1 N HCl	210 nm
In Methanol	209 nm
6.8 Phosphate buffer	210 nm

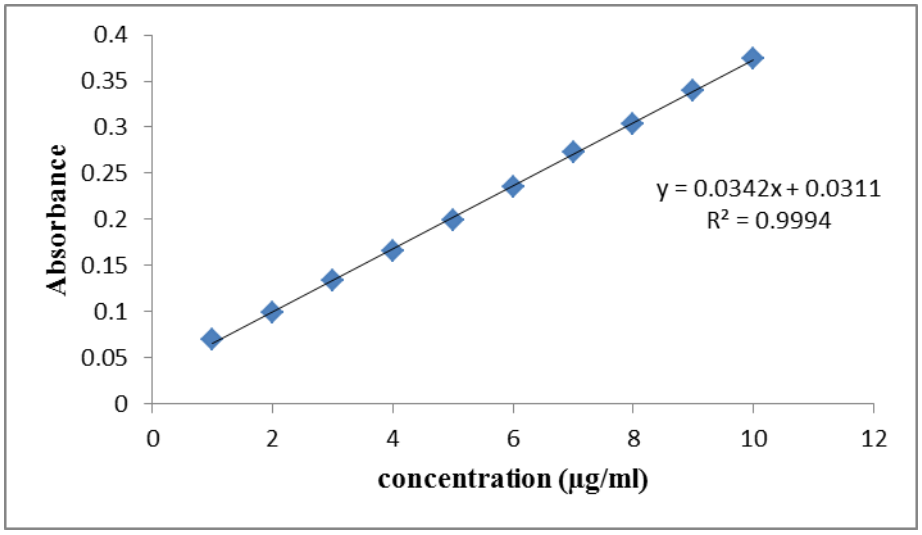

Fig. 2: Standard curve of Ramipril in 0.1N HCl.

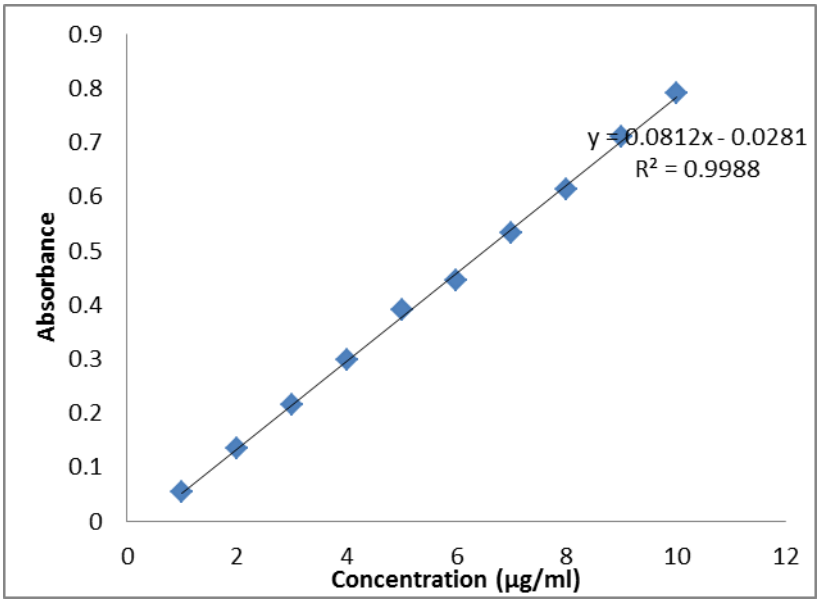

Fig. 3: Standard curve of Ramipril in Methanol.

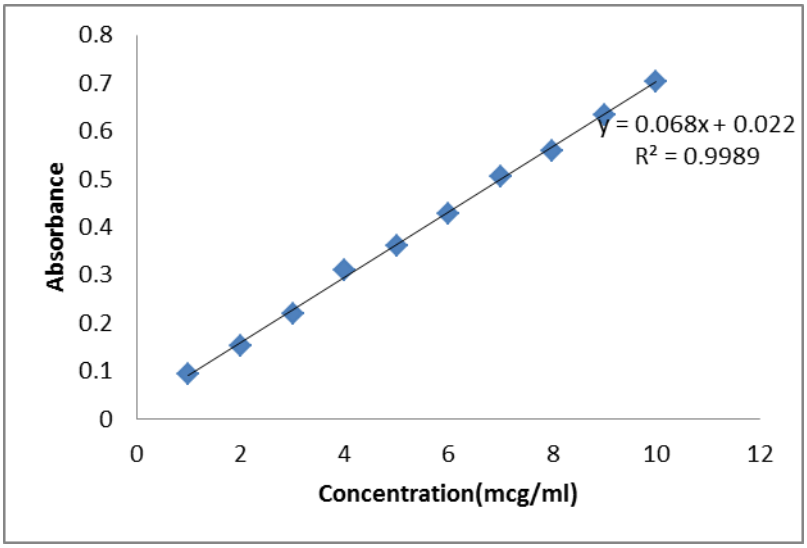

Fig. 4: Standard curve of Ramipril in 6.8 Phosphate buffer.

7.1.5. Characterization of Ramipril hydrochloride by FT-IR spectroscopy: The spectra obtained from FT-IR spectroscopy studied at wavelength from 4000 cm-1- 400 cm^{-1}

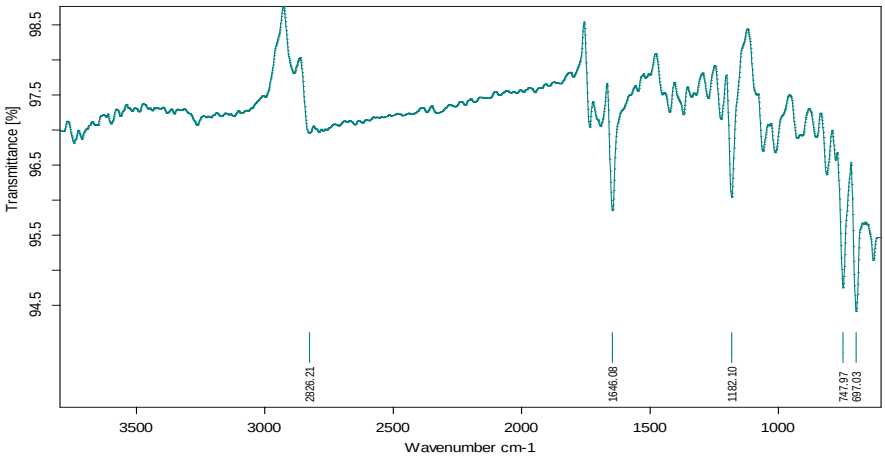

Fig. 5: FT-IR spectrum of Ramipril hydrochloride.

7.1.6 Drug-Excipient Compatibility Study

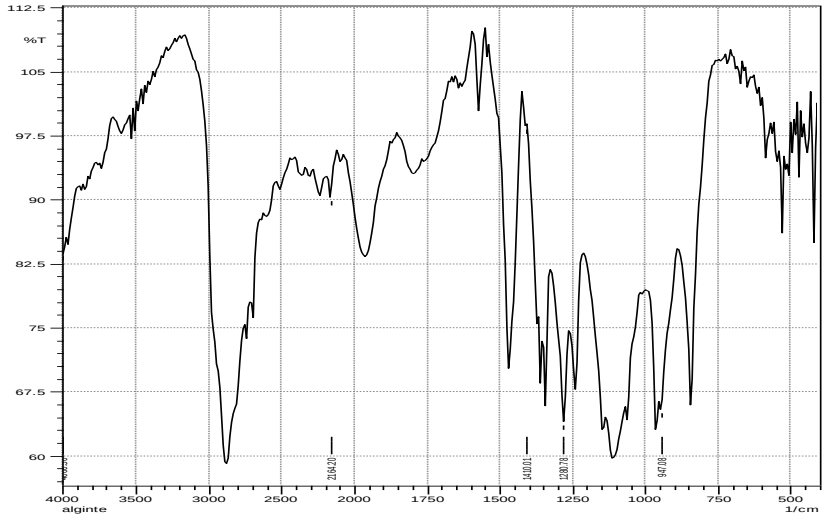

Fig. 6: FT-IR Spectrum of Sodium Alginate.

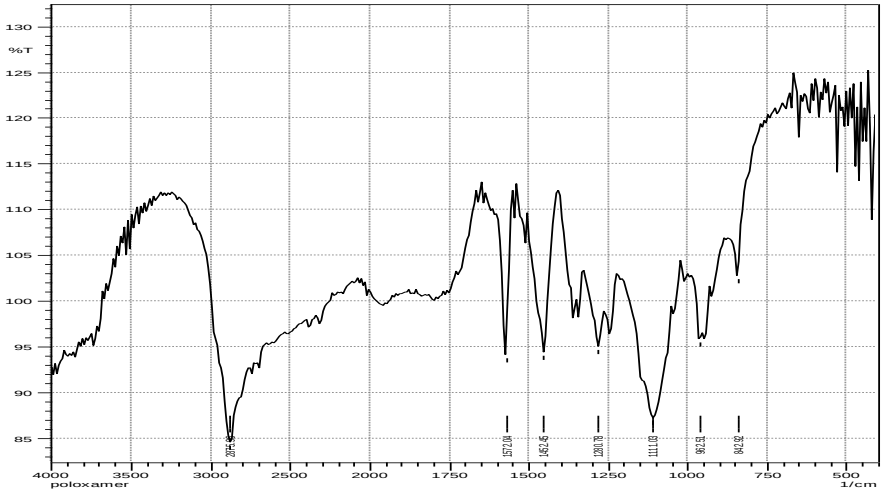

Fig. 7: FT-IR Spectrum of Poloxamer 188.

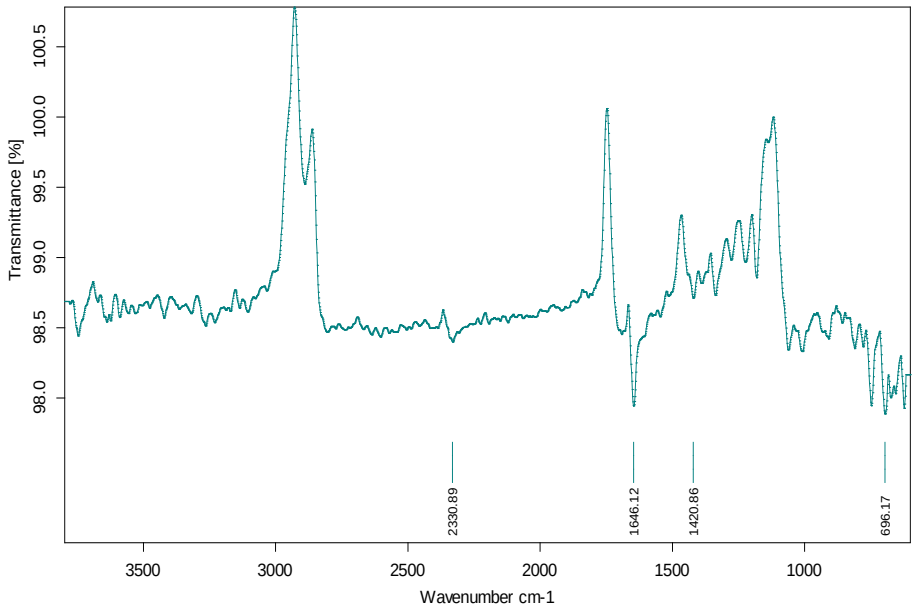

Fig. 8: FT-IR Spectrum of Physical mixture of Ramipril hydrochloride with sodium alginate and poloxamer 188.

Foambility And Foam Stability

Table 4: Data based on foambility and foam stability.

Poloxamer 188						
Amount (mg)	50	100	150	200	250	500
Foambility (%)	1.44	1.76	2.0	1.48	1.92	3.2
Foam Stability (min)	10	22	32	50	60	75

Optimization Of Floating Beads Of Ramipril Hydrochloride

Table 5: Batch specification of different batches of beads prepared using polymer at different ratios.

Batch No.	**Sodium Alginate (g)**	**Poloxamer 188 (g)**	**Drug (mg)**	**% $Cacl_2$ Solution**	**RPM**	**Appearance**
F 1	0.125	0.15	2.5	1	2600	Threads like bead formed
F 2	0.25	0.15	2.5	1	2600	Less spherical bead
F 3	0.375	0.15	2.5	1	2600	Spherical Bead formed
F 4	0.5	0.15	2.5	1	2600	Spherical Beads formed
F 5	0.625	0.15	2.5	1	2600	Less spherical Beads
F 6	0.375	0.15	2.5	0.5	2600	Spherical Bead formed
F 7	0.375	0.15	2.5	2	2600	Less Spherical Bead
F 8	0.375	0.15	2.5	2.5	2600	Spherical Bead formed
F 9	0.375	0.15	2.5	1	500	Spherical Bead formed
F 10	0.375	0.15	2.5	1	1500	Spherical Bead formed
F 11	0.375	0.15	2.5	1	2000	Spherical Bead formed
F 12	0.375	0.15	2.5	1	3000	Spherical Bead formed

Fig. 9: Image of Ramipril hydrochloride floating beads

From table 15 further batches namely B1, B2, B3, B4 were the best and selected to study various floating beads evaluation parameters.

Table 6: Composition of final formulations for optimization.

Formulation code	Drug (mg)	Sodium alginate (mg)	Poloxamer 188	Calcium chloride (1%)
B1	2.5	375	150	1
B2	2.5	375	100	1
B3	2.5	375	-	1
B4	2.5	375	-	1

7.2 Evaluation Parameters Of Ramipril Hydrochloride

7.2.1 % Entrapment efficiency and % Drug loading

The % entrapment efficiency for formulations B1- B4 was determined using 0.1 N HCl and the data is summarized below.

Table 7: % Entrapment efficiency and % Drug loading.

Formulation code	% Entrapment Efficiency	% Maximum drug loading
B1	73	3.95
B2	55	3.25
B3	35	1.92
B4	61	3.64

From the table, we can conclude that increase in poloxamer 188 ratio can improve the maximum loading capacity and its corresponding % EE.

7.2.2 % Yield: The prepared beads were collected, weighed and % yield was calculated.

Table 8: % Yield.

Formulation code	% Yield
B1	82.0
B2	79.52
B3	81.49
B4	80.91

7.2.3 Floating Lag time: Time required for the beads to rise to the surface and float was observed and summarized.

Table 9: Floating Lag time.

Formulation code	Floating lag time (seconds)
B1	2.0
B2	3.0
B3	4.0
B4	3.0

7.2.4 Swelling Study: The swelling behavior of floating beads was studied in 0.1 N HCl and swelling index was calculated.

Table 10: Swelling index.

Formulation code	Floating lag time (seconds)
B1	175
B2	133
B3	120
B4	141

7.2.5 Bead Size: The size of beads was determined using optical microscopy method. Approx 20 beads were counted for size determined.

Table 11: Bead size.

Formulation code	Bead size (mm)
B1	1.81
B2	1.09
B3	1.62
B4	0.52

7.2.6 Percent Floating: The number of sinking beads was observed visually. The % of floating beads was calculated.

Table 12: Percent Floating.

Formulation code	Time (Hrs)							
	0	**0.5**	**1**	**2**	**4**	**6**	**8**	**10**
B1	100	100	100	100	100	94	86	79
B2	100	100	100	100	100	95	89	75
B3	100	100	96	81	78	73	70	64
B4	100	100	98	95	93	91	88	85

B2 and B3 formulations show less % floating, B1 already showed good buoyancy; therefore high percent floating i.e. floating ability of beads is directly affected by foambility and foam stability of foam solution.

Selection of optimized formulation

The formulation B1 is optimized whose results are shown

Table 13: Evaluated parameters of optimized formulations.

Parameter	Optimized Value
% Entrapment efficiency	73
% yield	82
Floating lag time	2 sec
Percent floating	79%
Swelling index	175
Bead size	1.81

EVALUATION OF OPTIMIZED FORMULATION

7.3.1 Shape and Surface morphology

Particle size of formulations is given in a table 28.

Table 14: Particle size of different batches of Ramipril beads.

Formulation Code	Particle Size (mm)
B1	3.12
B2	4.49
B3	1.90
B4	3.20

The average particle diameter of beads was found to be in the size range of 1.90 to 4.46. The formed beads were sufficiently hard and spherical in shape.

The prepared beads of formulation B1 was subjected to scanning electron microscopy (SEM) and image is shown.

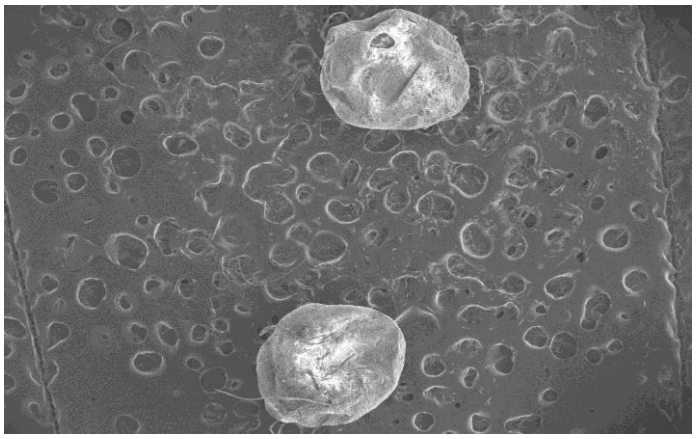

Fig.10: SEM image of floating beads.

7.3.2 In-vitro drug release: Beads equivalent to weight 100 mg were taken and in vitro dissolution study was carried out.

Table 15: Cumulative Percent Drug Release (CDR) for optimized formulation.

Time (Hrs)	Absorbance	% CDR
1	0.31	17.59
2	0.389	22.66
3	0.498	29.64
4	0.595	35.87
5	0.609	36.82
6	0.799	48.99
7	0.89	54.87
8	0.909	56.15

B1 formulation containing 2.5 mg Ramipril hydrochloride shows 60 % release in 9 hrs.

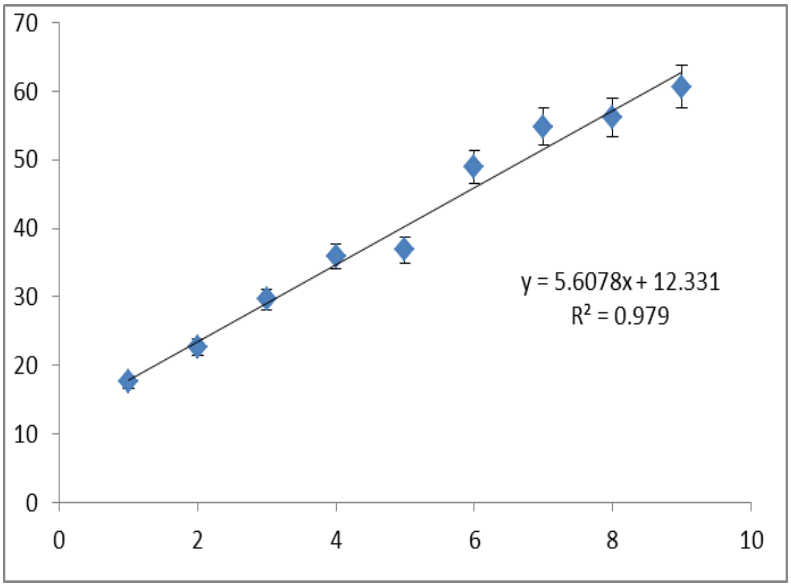

Fig. 11: Cumulative Percent Drug Release (CDR) for optimized formulation.

Drug release kinetic study: Raw data obtained from in-vitro release studies were analyze, wherein data were fitted to different equations and kinetics model to calculate the percent drug release and release kinetics of Ramipril hydrochloride from floating beads.

Table 16: Drug release kinetic data of formulation B1.

Time (Hrs)	Square root of time	Log time	Cumulative Percent Drug Release	Log Cumulative Percent Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent Drug Remaining
0	0	-	0	-	100	2
1	1	0	17	1.2	82.41	1.915
2	1.414	0.301	22.66	1.35	77.34	1.888
3	1.732	0.477	29.64	1.471	70.36	1.847
4	2	0.602	35.87	1.554	64.13	1.807
5	2.236	0.698	36.82	1.566	63.18	1.8
6	2.449	0.778	48.99	1.69	51.01	1.707
7	2.645	0.845	54.87	1.739	45.13	1.654
8	2.828	0.903	56.15	1.749	43.85	1.641
9	3	0.954	60.7	1.783	39.3	1.594

Zero order

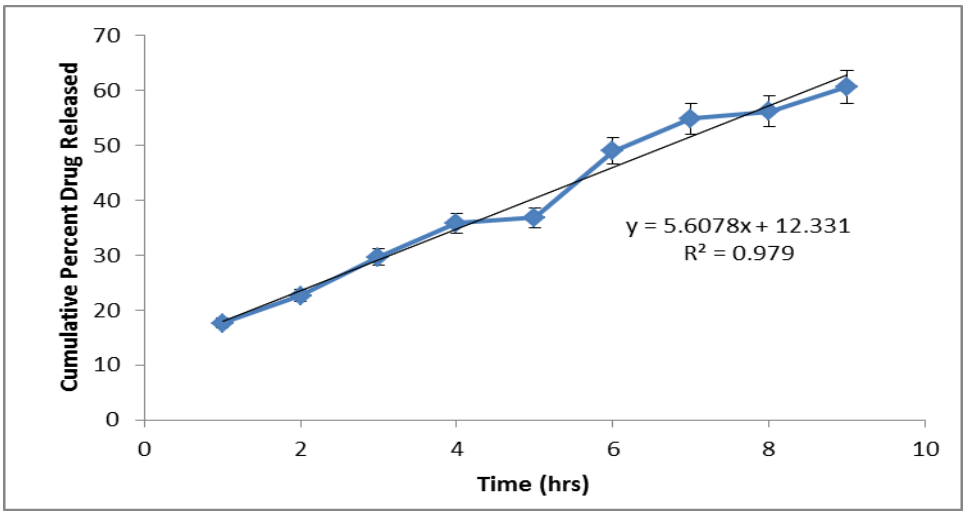

Fig. 12: Cumulative Percent Drug Release Vs Time Plot (Zero order).

First order

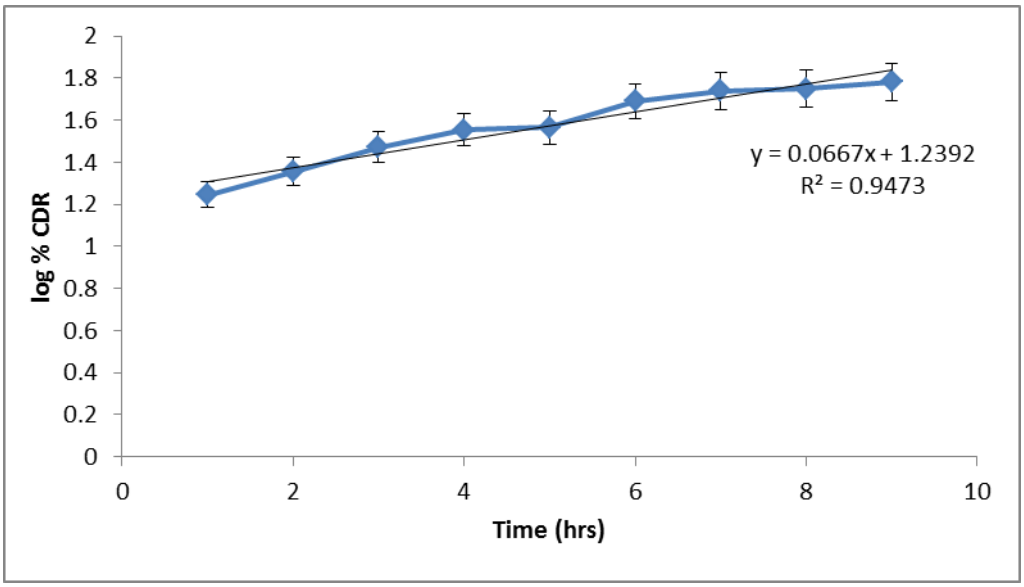

Fig. 13: Log Cumulative Percent Drug Remaining Vs Time Plot (1st order).

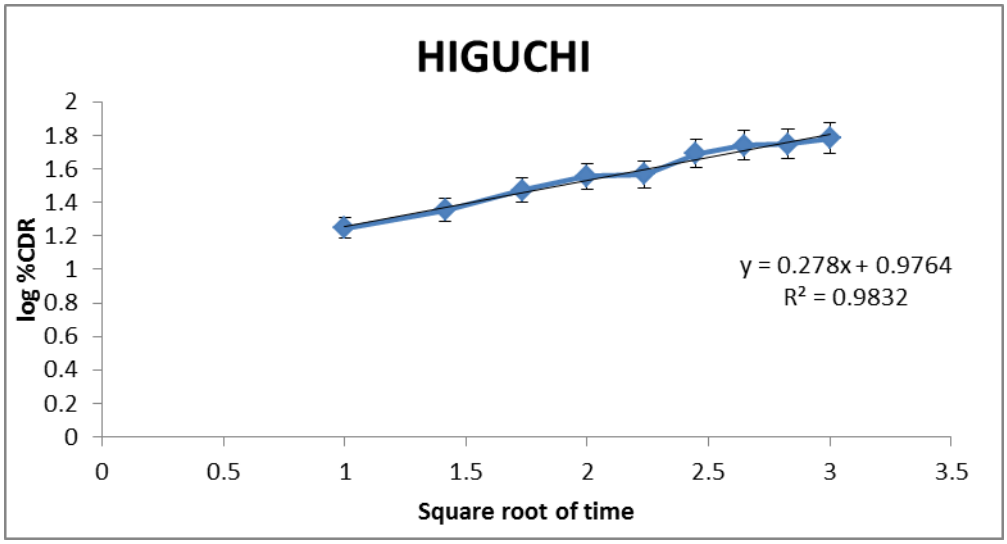

Fig. 14: Log Cumulative Percent Drug Remaining Vs Square Root of Time (Higuchi's).

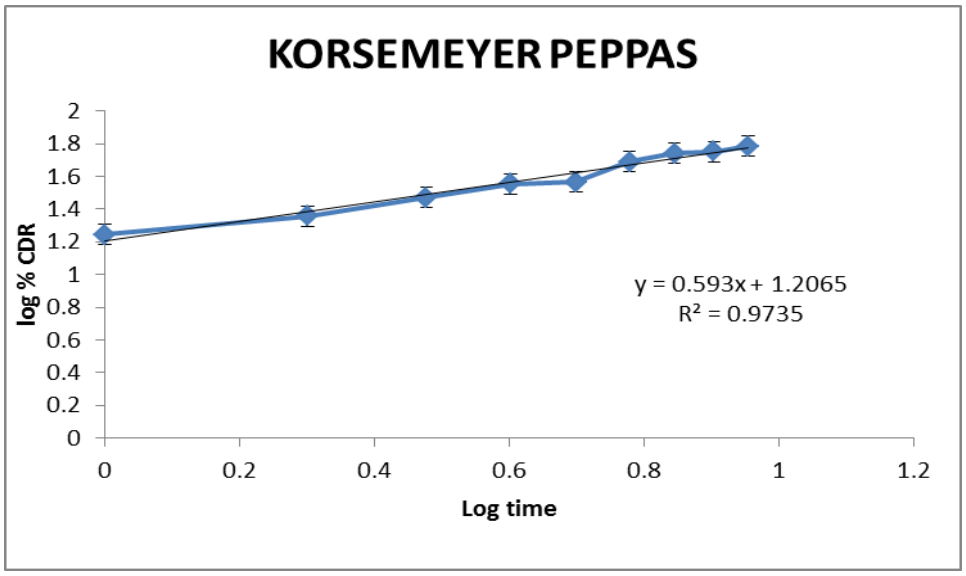

Fig. 15: Log Cumulative Percent Drug Remaining Vs Log Time (Peppas Plot).

Linear regression analysis and model fitting shows that formulation B1 follows Higuchi kinetics, which has higher value of correlation coefficient (R^2). The final results are reproduced in Table.

Table 17: Regression Coefficient (R^2) values of drug release data obtained from various kinetics models.

Formulation Code	Zero Order (R^2)	Higuchi Model (R^2)	First Order (R^2)	Peppas Mode (R^2)
B1	0979	0.983	0.947	0.9735

7.3.3 Accelerated Stability Studies

The optimized formulation was stored at 40/75 RH in HDPE bottles for 6 weeks. Beads were analyzed at specified time intervals (0, 1,2,4,6 weeks) for entrapment efficiency, % yield, floating lag time, percent floating and in-vitro dissolution study.

Table 18: Effect on various parameters during accelerated stability studies.

Time intervals (Weeks)	Entrapment efficiency (%)	% Yield	Floating lag time (Sec)	Percent floating	% CDR
0	73	82	2	79	60.7
1	72.95	81.9	2	79.14	60.45
2	72.4	81.79	2	78.3	60.23
4	71.65	81.54	1	77.79	60
6	70.23	78	1	75.43	58.63

Comparison of floating beads of Ramipril with pure drug and marketed drug

Table 19: Comparison of floating beads of Ramipril with pure drug and marketed drug.

Time	% CDR (Beads)	% CDR (Pure Drug)	% CDR (Marketed)
0	0	0	0
1	17.59	46.66	9.6
2	22.66	53.59	10.15
3	29.64	80.29	14.05
4	35.87	97.12	22.81
5	36.82	97.12	23.95
6	48.99	97.2	27.73
7	54.87	97.2	30.05
8	56.15	97.2	35.16
9	60.7	97.2	43.52

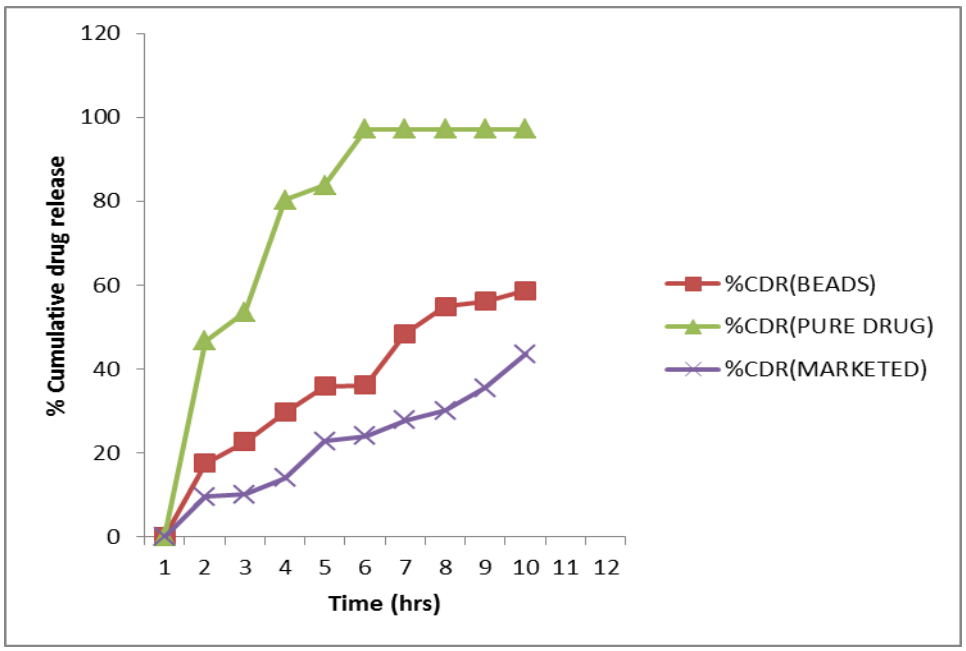

Fig. 16: Comparison of floating beads of Ramipril with pure drug and marketed drug.

CONCLUSION

The foam technology was successfully utilized for formulation of floating alginate beads of ramipril hydrochloride. The adopted method showed good linearity. B1 formulation SEM cross-section pictures of the beads showed that the beads were inner-porous and composed of bubble with a very thin wall bubbles stacked together have a spherical shape with rough surface. The formulated floating alginate beads have shown higher percentage of drug loading, encapsulation efficiency, particle size and good swelling behavior. The floating beads release behavior in vitro showed that drug release from the beads in a sustained-release fashion for 9 hours. Application of kinetic modeling revealed that formulation follows Higuchi Model for drug release. Stability studies showed that the formulation was competent enough to withstand the accelerated conditions and gave comparable results in terms of drug release. The result of in-vitro release and release kinetic indicated sustained release and exhibited zero kinetic.

REFERENCES

1. Dixit N. Floating Drug Delivery System. Journal of current pharmaceutical research, 2011; 7(1): 6-20.
2. Suryawanshi. A. Floating Drug Delivery System-a review. American journal of pharmaceutical research, 2012; (1): 138-152.
3. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system I: Preparation and in vitro evaluation of floating and sustained-release kinetics. J Pharm Sci., 1991; 80: 1062-1066.
4. Kuccherkar B.et al. Mouth dissolving tablets: A novel drug delivery system. Pharma times, 2003; 35: 3-10.
5. Brahmankar DM and Jaiswal SB: Biopharmaceutics and Pharmacokinetics a Treatise. Vallabh Prakashan, First Edition, 1995; 336-337.
6. Jeyabalan G, Gastro retentive beads of Indomethacin a Non-steroidal anti- inflammatory agent for increased bioavailability, 2018; (6): 31.
7. Jain NK: Controlled and Novel Drug Delivery. CBS Publishers and Distributors, First Edition, 1997.

8. Martin A. Physical pharmacy. 4th ed. New Delhi: B.I. Waverly Pvt. Ltd, 1994.
9. Indian Pharmacopoeia, volume II. Government of India, ministry of health and family welfare, Delhi: The controller of publications, 1996.
10. Roughe N, Buoyancy and drug release patterns of floating mini tablets containing piretanide and atenolol as model drugs, 2008; 74-84.
11. Park HJ, Choi BY, Hwang SJ, Park JB, Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas forming agents, Int J Pharm, 2002; 2(4): 332-336.