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R E S E A R C H A R T I C L E

Design and *In-Vitro* Characterization of Cyclobenzaprine Floating Microspheres

D. Keerthi Raj*, B. Ramya Sree, S. Anusha, T. Anil Goud

Assistant Professor, Department of Pharmaceutics, Vijay College of Pharmacy, Nizamabad, Telangana, India

A B S T R A C T

In the present work, floating microspheres of Cyclobenzaprine using sodium bicarbonate, HPMCK100M, HPMCK15M, HPMC K4M as copolymers were formulated to deliver Cyclobenzaprine via oral route. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Cyclobenzaprine microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The *In-vitro* mucoadhesive study demonstrated that microspheres of Cyclobenzaprine using sodium alginate along with HPMCK100M as copolymer adhered to the mucus to a greater extent than the microspheres of Cyclobenzaprine using sodium alginate along with HPMCK15M and HPMC K4M as copolymers.

Keywords: Cyclobenzaprine, HPMC, Micrspheres

A R T I C L E I N F O

Corresponding Author
D. Keerthi Raj
Assistant Professor,
Department of Pharmaceutics,
Vijay College of Pharmacy, Nizamabad

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C O N T E N T S

1. Introduction

To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odour masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against environment (moisture, heat, light and oxidation), separation of

incompatible materials, to improve flow of powders, production of sustained release, controlled release and targeted medications. Cyclobenzaprine HCl, chemically it is 3-(5H-dibenzo [a,d] cyclohepten-5-ylidene)-N, N dimethyl-1-propanamine hydrochloride. Cyclobenzaprine HCL is a skeletal muscle relaxant and a central nervous system (CNS) depressant. Cyclobenzaprine HCL has a long half life up to 18 hrs and the absorption slowly but well absorbed after oral administration in the upper part of GIT hence it is suitable for gastro-retentive system. The present work consists of design and development of floating microspheres of Cyclobenzaprine HCl using ethyl cellulose in different proportions.

2. Materials and Methods

Drug, HPMC K4M, HPMC K15M, HPMC K100M, Calcium chloride, Sodium bicarbonate, Methanol, Water chemicals were Laboratory grade made of SD Fine chemicals Pvt Ltd

Method of Preparation Ionotropic Gelation Method

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Cyclobenzaprine (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

3. Results and Discussion

Determination of λmax

Calibration curve of Cyclobenzaprine in simulated gastric fluid pH 1.2 Table 6.1 shows the calibration curve data of Cyclobenzaprine in simulated gastric fluid pH 1.2 at 252nm. Fig. 6.1 shows the standard calibration curve with a regression value of 0.998 slope of 0.028 and intercept of 0.004 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

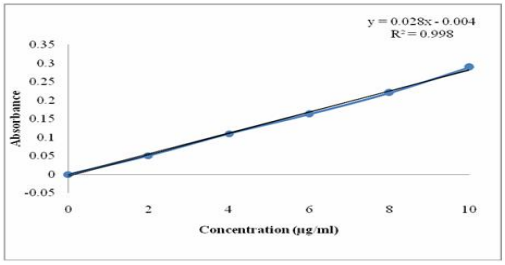

Figure 1: Standard graph of Cyclobenzaprine in simulated gastric fluid pH 1.2

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in. Table 6.14 that with an increase in polymer concentration, the percentage of swelling also increase. Thus we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with HPMC K100M as copolymer, 24 to 64% for microspheres containing sodium alginate along with HPMC K15M as copolymer and 31 to 85 for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage of swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in Figure.

In-Vitro Mucoadhesion Test

As the polymer to drug ratio increased, microspheres containing sodium alginate along with HPMC K100M as copolymer exhibited % mucoadhesion ranging from 65 to 85%, microspheres containing sodium alginate along with HPMC K15M as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with HPMC K 4 M as copolymer exhibited % mucoadhesion ranging from 60 to 80%. The rank of order of mucoadhesion is HPMC K100M > HPMC K4 M>HPMC K15M. The results of in-vitro mucoadhesion test are compiled in Table 6.15.

In-Vitro Drug Release Studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the in- vitro dissolution studies of formulations T1 to T4, T5 to T8 and T9 toT12 are shown in table. The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations T1 to T4, figure for formulations T5 to T8 and figure 6.26 for formulations T9 to T12. Korsmeyer-Peppas plots of Cyclobenzaprine microspheres formulations T1 to T12 are displayed in figures. The formulations T1, T2, T3 and T4 containing Sodium alginate along with HPMC K100M as copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 94.66% after 12 hours respectively. The formulations T5, T6, T7, T8 containing Sodium alginate along with HPMC K15M as copolymer showed a maximum release of 92.22% after 9 hours, 91.33% after 10 hours, 89.55% after 11 hours and 90.66% after 12 hours respectively. The formulations T9, T10, T11 and T12 containing Sodium alginate along with HPMC K4 M as copolymer showed a maximum release of 92.6% after 9 hours, 91.3% after 10 hours, 90% after 11 hours and 92.44% after 12 hours respectively. This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was

increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

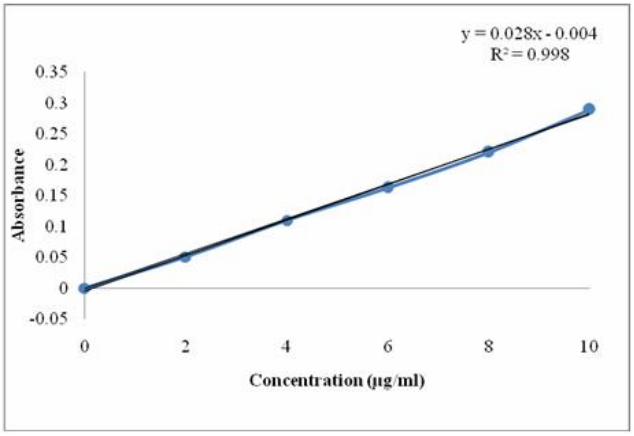

Figure 1: Standard graph of Cyclobenzaprine in simulated gastric fluid pH 1.2

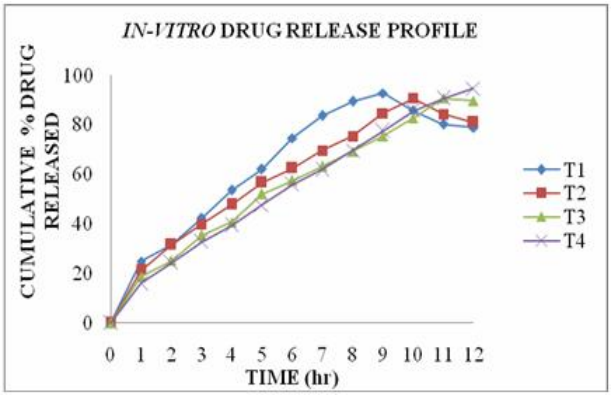

Figure 2: Comparison of In-Vitro drug release profile of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K100M as copolymer

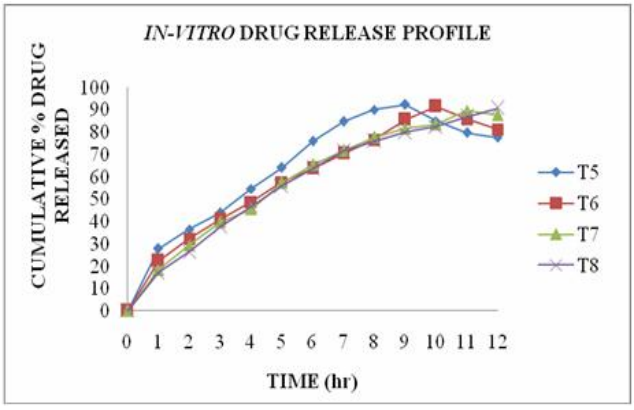

Figure 3 Comparison of In-Vitro drug release profile of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K15M as copolymer

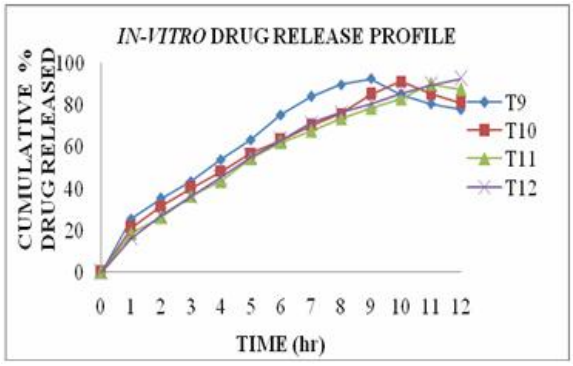

Figure 4: Comparison of *In-Vitro* drug release profile of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K 4 M as copolymer

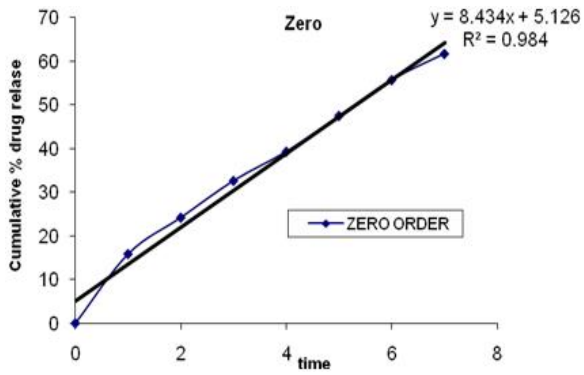

Figure 5: Zero order release kinetics

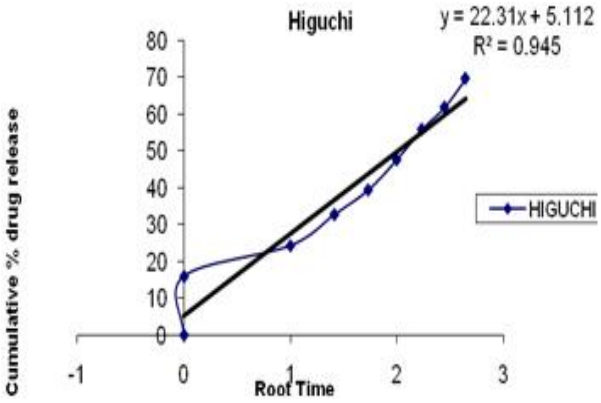

Figure 6: Higuchi release kinetics

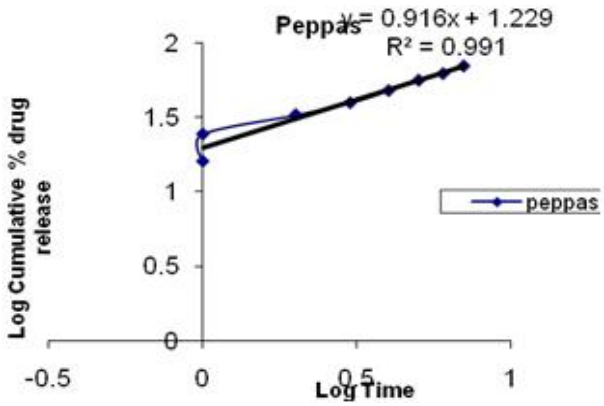

Figure 7: Kars mayer peppas

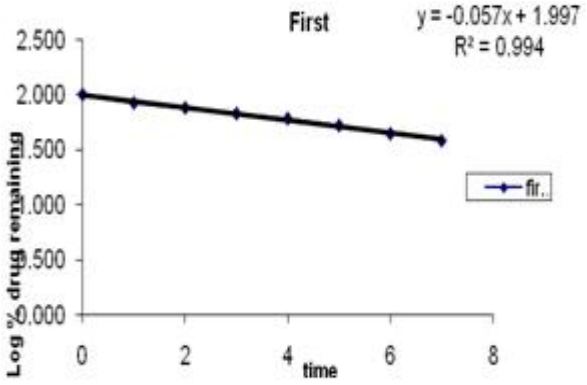

Figure 8: First order release kinetics

From the above graphs it was evident that the formulation T4 was followed first order release kinetics.

4. Conclusion

In the present work, floating microspheres of Cyclobenzaprine using sodium alginate along with HPMC K100M, HPMC K15M, and HPMC K4M as copolymers and sodium bicarbonate as floating polymer were formulated to deliver Cyclobenzaprine via oral route. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Cyclobenzaprine microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The in-vitro mucoadhesive study demonstrated that microspheres of Cyclobenzaprine using sodium alginate along with HPMC K100M as copolymer adhered to the mucus to a greater extent than the microspheres of Cyclobenzaprine using sodium alginate along with HPMC K15M and HPMC K4M as copolymers. The in-vitro drug release decreased with increase in the polymer and copolymer concentration. Based on the results of evaluation tests formulation coded T4 was concluded as best formulation.

Table 1: Prepared formulation of Floating Microspheres

S.NO	MATERIALS	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
1	Drug (mg)	100	100	100	100	100	100	100	100	100	100	100	100
2	HPMC K4M (mg)	250	300	350	400	-	-	-	-	-	-	-	-
3	HPMC K15M(mg)	-	-	-	-	250	300	350	400		-	-	-
4	HPMC K100M(mg)	-	-	-	-	-	-	-	-	250	300	350	400
5	5%Calcium chloride solution	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
6	Sodium bicarbonate(mg)	10	10	10	10	10	10	10	10	10	10	10	10
7	Methanol	10	10	10	10	10	10	10	10	10	10	10	10
8	Water	10	10	10	10	10	10	10	10	10	10	10	10

Table 2: Calibration curve data for Cyclobenzaprine in simulated gastric fluid pH 1.2

Concentration (µg/ml)	Absorbance
2	0.051
4	0.110
6	0.163
8	0.221
10	0.290

Table 3: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	T_1	80	12.40	82.66
2	T_2	83.33	12.66	84.4
3	T_3	85	12.70	84.66

4	T_4	88	13.29	88.66
5	T_5	62.22	8.07	53.2
6	T_6	80	8.25	55
7	T_7	80	10.33	68.86
8	T_8	87	11.5	76.66
9	T_9	80	10.01	66.73
10	T_{10}	86	10.5	70
11	T_{11}	86.66	11.25	75
12	T_{12}	87.5	11.88	79.2

Table 4: Percentage swelling of the prepared microspheres

S.NO.	Formulation Code	Initial (Wt)	Final (Wt)	Percentage Swelling
1	T_1	10	12.8	28
2	T_2	10	14.2	42
3	T_3	10	16.2	62
4	T_4	10	18.5	85
5	T_5	10	12.4	24
6	T_6	10	13.9	39
7	T_7	10	15.5	55
8	T_8	10	16.4	64
9	T_9	10	13.1	31
10	T_{10}	10	15.3	53
11	T_{11}	10	16.7	67
12	T_{12}	10	18.5	85

Table 5: Percentage mucoadhesion of the prepared microspheres

S.NO.	Formulation Code	No. of Microspheres		Percentage Mucoadhesion
		INITIAL	FINAL	
1	T_1	20	13	65
2	T_2	20	14	70
3	T_3	20	15	75
4	T_4	20	17	85
5	T_5	20	12	60
6	T_6	20	13	65
7	T_7	20	14	70
8	T_8	20	15	75
9	T_9	20	12	60
10	T_{10}	20	14	70
11	T_{11}	20	15	75
12	T_{12}	20	16	80

Table 6: *In-Vitro* drug release data of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K100M as copolymer

TIME (h)	Cumulative Precent of Drug Released			
	T_1	T_2	T_3	T_4
0	0	0	0	0
1	24.88	21.11	18.66	15.88
2	31.55	31.55	25.11	24.22
3	42.44	39.77	35.44	32.66
4	53.55	47.77	40.66	39.33
5	62	56.66	52	47.55
6	74.66	62.44	57.33	55.77
7	83.55	69.55	63.11	61.77
8	89.33	75.33	69.11	69.55
9	92.66	84.66	75.33	77.55
10	85.55	90.66	82.66	85.55
11	80.22	84.22	90.66	90.66
12	78.88	80.88	89.55	94.66

Table 7: *In-Vitro* drug release data of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K15M as copolymer

TIME (h)	Cumulative Percent of Drug Released			
	T_5	T_6	T_7	T_8
0	0	0	0	0
1	27.77	22.44	18.44	17.11
2	36.44	32.22	29.33	26.44
3	43.77	40.88	39.55	37.55
4	54.66	48.66	45.55	46.88
5	64.01	57.55	57.33	55.77
6	75.77	63.55	65.33	63.55
7	84.65	70.44	71.55	71.33
8	90	76.55	77.56	75.77
9	92.22	85.55	81.55	79.77
10	84.88	91.33	83.33	82.44
11	79.55	85.77	89.55	86.88
12	77.55	81.11	87.55	90.66

Table 8: In-Vitro drug release data of Cyclobenzaprine microspheres containing sodium alginate along with HPMC K 4 M as copolymer

TIME (h)	Cumulative percent of drug released			
	T_9	T_{10}	T_{11}	T_{12}
0	0	0	0	0
1	25.77	21.55	18.66	16.44
2	35.33	31.77	26.55	27.11
3	43.55	40.44	36.55	36.44
4	54	48.44	43.66	45.55
5	63.55	57.11	54.55	55.33
6	75.33	63.11	62.33	63.11
7	84	70.22	67.68	71.55
8	89.77	76	73.55	76.44
9	92.66	85.11	78.55	80.66
10	85.11	91.33	83	85.55

11	80.66	85.33	90	89.55
12	78	81.11	87.55	92.44

Table 9: Application of Release Rate Kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
15.88	1	0.000	1.201	0.000	1.925
24.22	2	1.000	1.384	0.000	1.880
32.66	3	1.414	1.514	0.301	1.828
39.33	4	1.732	1.595	0.477	1.783
47.55	5	2.000	1.677	0.602	1.720
55.77	6	2.236	1.746	0.699	1.646
61.77	7	2.449	1.791	0.778	1.582
69.55	8	2.646	1.842	0.845	1.484
77.55	9	2.828	1.890	0.903	1.351
85.55	10	3.000	1.932	0.954	1.160
90.66	11	3.162	1.957	1.000	0.970
94.66	12	3.317	1.976	1.041	0.728

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