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Formulation and *in-vitro* evaluation of floating capsules of Loratadine

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Abstract

The present work focuses on the development of hydrodynamically balanced delivery system of loratadine as a single unit floating capsules. Sustained release floating capsules for loratadine were fabricated using drug:polymer ratio of 1:4. The hydrocolloids were used in different proportions using 3^2 full factorial design and formulations were prepared. These formulations were optimized on the basis of buoyancy, matrix integrity, duration of floating and *in vitro* drug release. All the nine formulations showed good buoyancy and matrix integrity. The duration of floating was more than 12 h for all formulations. *In vitro* drug release study of these formulations indicated controlled release of loratadine and about 90 percent drug was released at the end of 12 h.

Key-words: Loratadine, hydrodynamically balanced delivery system, single-unit floating capsules, 3^2 factorial design.

Introduction

Floating drug delivery system is oral dosage foam designed to prolong the residence time of dosage foam within the GI track. Such dosage form having density less than that of the gastric fluid floats on the gastric juice for an extended period of time while slowly releasing the drug. On contact with the gastric fluid, the intragastric floating capsule forms a water impermeable colloid gel barrier around its surface and maintains a bulk density of less than 1. So, it remains buoyant in the gastric fluid in stomach until the entire loading dose has been released. This drug delivery system not only prolongs GI residence time but does so in an area of the GI tract that could maximize drug reaching its absorption site in solution and hence ready for absorption [1].

The pH of the stomach in the fasting state is ~1.5 to 2 and in the fed state is 2 to 6. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6 to 9, and the stomach does not have time to produce sufficient acid to dissolve the drug before the liquid is emptied. In addition the meal also brings pH differences according to the type of meal consumed. Hence, in general, basic drugs have a better chance of dissolving in a fed state than in a fasting state [2].

In this present study, use of a hydrodynamically balanced system (HBS) is desirable where a prolonged GRT is required. The underlying principle of an HBS is that such a dosage form would swell to create a gel-like structure after administration and attain a density less than that of gastric fluids [3].

Loratadine, a H_1 receptor blocker, is absorbed in the proximal part of the gastrointestinal tract and has rapid first-pass hepatic metabolism; it is stable in acidic pH, has a narrow therapeutic absorption window in the GI tract and the presence of food enhances its bioavailability [4], meeting the primary criterion for selection of loratadine as the drug candidate to be formulated as a floating multiple unit dosage form. Loratadine peak effect occurs in 1–2 hours, and its biological half-life is on average 8 hours with its metabolite's half-life being 28 hours [5]. The objective of present study was to formulate floating capsules of Loratadine to deliver the drug continuously with set limits of dissolution profile and minimum floating time of 8 h.

Materials and methods

Materials

Loratadine was obtained as a gift sample from NIVIKA Chemo-Pharma Pvt Ltd, Ankleshwar, Gujarat, India. Other materials were used in study like HPMC K4M and Carbapol 934 polymers and all other chemicals used were of analytical grade.

Methods

Preparation of floating capsules

Floating capsules containing Loratadine were prepared by wet granulation technique using varying concentrations of different grades of polymers with Sodium bicarbonate. Before actual formulation, an initial study was carried out to find out the optimum combination of drug and polymers. For floating capsules, hydrocolloids of natural as well as semi synthetic origin were selected.

Table: 1 Drug: Polymer Combination

Formulation	Buoyancy	Matrix integrity	Duration of Floating (hr)
A(1:1)	-	-	3.5
B(1:2)	-	-	6.4
C(1:3)	+	-	8
D(1:4)	+	+	>12
E(1:5)	+	+	>12
F(1:6)	+	+	>12

- denotes non-buoyant/non-intact capsules and + denotes buoyant/intact

The hydrocolloids selected were Hydroxypropylmethylcellulose (HPMC K4M) and Carbopol 934. In addition to these hydrocolloids, Polyvinylpyrrolidone (PVP) was used as a binder. The drug and polymers were taken in a ratio ranging from 1:1 to 1:6. This was done to select the optimum combination of drug polymer ratio in the floating drug delivery device in such a way that it would pass the tests of buoyancy, matrix integrity and duration of floating in 0.1N HCl. The other excipients used were Sodium Bicarbonate, Lactose and Magnesium stearate. The hydrocolloids along with the excipients were blended homogenously with the drug. The blended mixture was used to prepared granules using wet granulation method and then filled in the white gelatin capsules.

The filled capsules were then observed for buoyancy, matrix integrity and duration of floating [Table 1]. From the Table, it was clear that formulation D containing drug and polymers in the ratio of 1:4 remained buoyant in 0.1N HCl for more than 12 h and maintained the shape. So this combination was selected for further study to incorporate the dose of 10 mg of Loratadine. After selecting the ideal combination (1:4 drug: polymer), the actual formulations were prepared. The dose of Loratadine was taken to be 10 mg and the quantity of polymers was calculated which came out to be 40 mg. Based on such studies using above formulation D, take HPMC K4M:Carbopol 934 ratio were selected as release modifier polymeric fillers and sodium bicarbonate as the float accelerator and nine batches were formulated using 3^2 factorial design.

Factorial Design

In the present study, a 3^2 full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed at all 9 possible combinations. The formulation variables and their ranges were chosen from the knowledge acquired from the preliminary studies and from the experiments previously reported. The two independent variables selected were ratio of HPMC K4M: Carbopol 934 (X_1) and sodium bicarbonate (X_2) as per Table 2 and the nine formulations were formulated as per the experimental design (Table 3). All the nine formulations were prepared using factorial design and described in Table 4.

Table: 2 Variables in 3^2 Factorial Design Batches

Coded values	Actual Value	
	X_1 (HPMC K4M: Carbopol934)	**X_2** $NaHCO_3$ (%)
-1	7:1	5
0	3:1	7.5
+1	5:3	10

Evaluation of capsules

The capsules were evaluated for various parameters as follows and observations recorded in Table 5 and 6.

***In Vitro* Buoyancy Study**

All formulations were subjected to buoyancy test. Buoyancy test was done using USP type II apparatus at 50 rpm maintained at 37±0.5°C. Capsules were placed in 900 ml jar containing 0.1N HCl as dissolution medium. The amount of time during which the capsules remained buoyant was the floating time. The polymer that showed the best floating behavior was used for in vitro release studies.

Table: 3 Experimental Design by using 3^2 Full Factorial Design

Formulation Code	Coded values	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table: 4 Formulations of Factorial Design Batches

Ingredients	Formulation Code								
(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loratadine	10	10	10	10	10	10	10	10	10
HPMC K4M	35	35	35	30	30	30	25	25	25
Carbopol 934	5	5	5	10	10	10	15	15	15
Sodium bicarbonate	5	7.5	10	5	7.5	10	5	7.5	10
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Lactose	32	29.5	27	32	29.5	27	32	29.5	27
PVP	10	10	10	10	10	10	10	10	10
Total Weight	100	100	100	100	100	100	100	100	100

Weight Variation/uniformity of weight

To study weight variation, 20 capsules of each formulation were weighed using an electronic balance and the test was performed as per I.P. [6].

Uniformity of content

Five capsules were weighed and their contents were removed. An accurately weighed sample equivalent to 100 mg of Loratadine was taken in a volumetric flask (100ml). The content was dissolved in 0.1N HCl and the volume made upto 100 ml. This solution was filtered through Wattman filter paper No.41. The solution was diluted and the absorbance was measured at 274.0 nm. The drug content was calculated.

Dissolution Studies

The release rate of Loratadine from floating capsules was determined using USP dissolution test apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 50 rpm. The temperature of the medium was maintained at 37±0.5ºC and the study was carried out for 12 hrs. Aliquot of 5 ml were withdrawn at an interval of 1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr respectively. The withdrawn samples were replaced with previously warmed fresh dissolution medium. The samples were filtered through Wattman filter paper (No.41) and the

samples were analyzed at 274.0 nm [7]. The actual drug content in the formulations was then calculated from the standard curve prepared with Loratadine in 0.1 N HCl.

Similarity factor (f2) study

The similarity factor (f2) calculated as per the equation

$$f2 = 50 * \log \{[1+ (1/n) \sum (Rt-Tt)^2]^{-0.5} * 100\}$$

Table no.7 shows the results of similarity factor.

Table: 5 Evaluation of 3^2 Factorial Design Batches Formulation

Formulation	Buoyancy	Matrix Integrity	Floating Duration(h)	Drug Content uniformity	Average weight (mg) ± S.D.
F1	+	+	> 12	99.20	99.09 ± 0.56
F2	+	+	> 12	98.60	99.14 ± 0.58
F3	+	++	> 12	98.75	99.13 ± 0.59
F4	+	+	> 12	99.80	99.38 ± 0.51
F5	+	+	> 12	98.56	99.20 ± 0.48
F6	+	+	> 12	99.18	98.92 ± 0.55
F7	+	+	> 12	99.02	98.78 ± 0.55
F8	+	+	> 12	98.88	98.80 ± 0.52
F9	+	+	> 12	98.94	98.82 ± 0.55

- denotes non-buoyant/non-intact capsules and + denotes buoyant/intact

Table: 6 *In-Vitro* Drug Release Data of Loratadine Floating Capsules

Formula	% cumulative release			
	3 h	6 h	9 h	12 h
F1	43.36	61.18	76.99	90.08
F2	43.69	62.83	78.67	91.46
F3	44.68	62.86	80.34	93.5
F4	46.33	63.88	80.06	94.52
F5	47.32	64.56	82.4	95.92
F6	47.97	66.21	84.08	96.64
F7	50.29	66.25	82.48	98.62
F8	49.63	67.9	83.49	99
F9	49.97	67.9	84.48	99.68
Ref	40.2	60.1	80	99.9

Table: 7 Optimization of tablet formulation using F2 value

Batch no	F2
F1	67.13
F2	69.68
F3	**71.44**
F4	67.7
F5	65.26
F6	62.38
F7	59.94
F8	58.08
F9	57.44

Result and Discussion

Formulation of Floating Matrix Capsules

The primary objective of the study was to design a floating capsule of Loratadine with a release profile sufficient to maintain adequately high local concentration. Based on such studies, HPMC K4M and Carbopol 934 were selected as release modifier polymeric fillers and sodium bicarbonate as the float accelerator and nine batches were formulated using 3^2 factorial design. Sodium bicarbonate generates CO_2 gas in the presence of hydrochloric acid present in dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of HPMC K4 M), thus decreasing the density of the capsule. As the density of the capsule falls below 1 (density of water), the capsule becomes buoyant.

Weight variation and Drug content

The average weight of capsules within each formulation was found to be uniform. This indicates uniform filling of powder blend during capsule filling. Not more than two of the individual weights deviated from the average weight by more than 7.5% and none deviated by more than twice that percentage, which provided good weight uniformity [8-9].

In all the nine formulations, the values for drug content were found to be uniform among different batches of the floating drug delivery system (FDDS) and ranged between 98.5 and 101.0% of the theoretical value as per USP [10]. The value ensures good uniformity of the drug content in the capsules.

Dissolution studies

The in vitro release of all the factorial design batches was studied. (Table 6) Figures 1-3 clearly indicated that all the formulations follow a linear pattern of Loratadine release at least in their initial phase, which indicates the appropriate choice of the selected range of formulation variables.

Percentage drug release at 12 hr (Q_{12}) of the formulations F1, F4 and F7 containing ratio 7:1, 3:1 and 5:3 of the HPMC K4M: Carbopol 934 polymer showed significant difference indicating the rate retarding effect of polymer. The Q_{12} i.e. drug release after 12 hrs for formulations F1, F4 and F7 were 90.08, 94.52 and 98.62 %, respectively. So the concentration of HPMC K4M was higher in formulation, which was suitable for getting gel strength of the formulation of FDDS.

However, with constant polymer concentration F1-F3 (7:1) an increase in Sodium Bicarbonate concentration (5%, 7.5% and 10%, respectively) showed increase in Q12. Similar trend was observed for formulations bearing 3:1 polymer (F4-F6) and 5:3 polymer (F7-F9), (Figure 1-3). The release profile of the drug from the formulation was as follows, F3>F2>F1, F6>F5>F4 and F9>F8>F7 which depicts the significant effect of Sodium bicarbonate.

Initially no characteristic trend was observed. This may be due to the time taken by the polymer in the capsule to get hydrated before changing from glassy state to rubbery state. The sodium bicarbonate present in the capsule reacts with acidic medium leading to formation of channel with liberation of CO_2. This also explains the absence of lag phase in the release profile. Thus, by using rate retarding polymer HPMC K4M the drug release was controlled for 12 hrs and the desired release profile was achieved.

Figure No.: 1. Comparative Dissolution Profiles of F1, F2, F3 and Reference

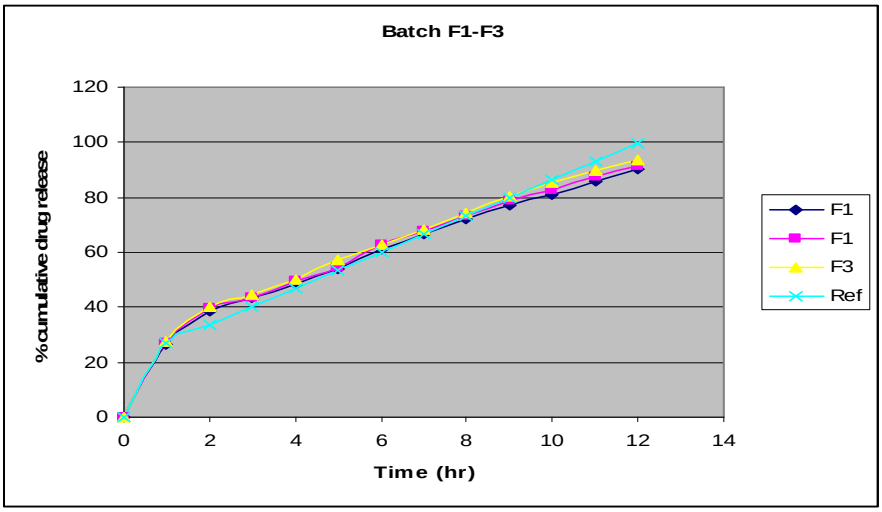


Figure No.: 2. Comparative Dissolution Profiles of F4, F5, F6 and Reference

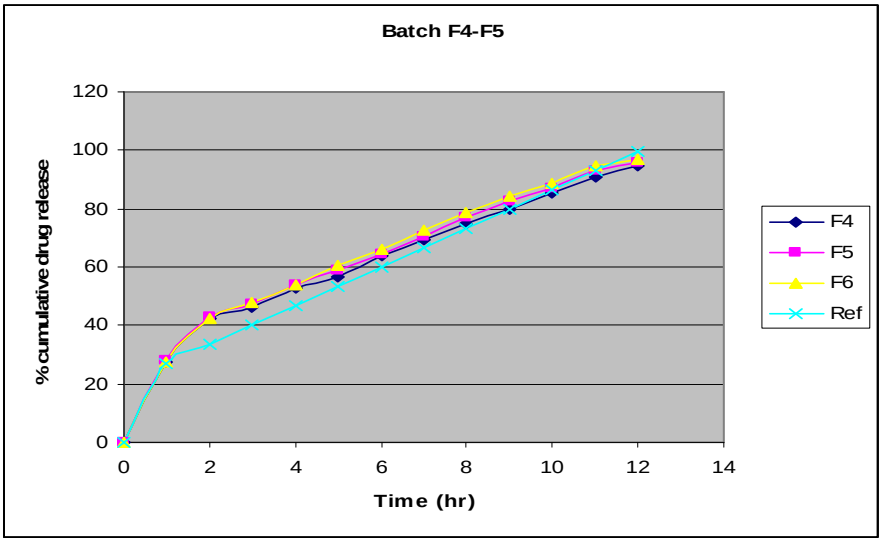
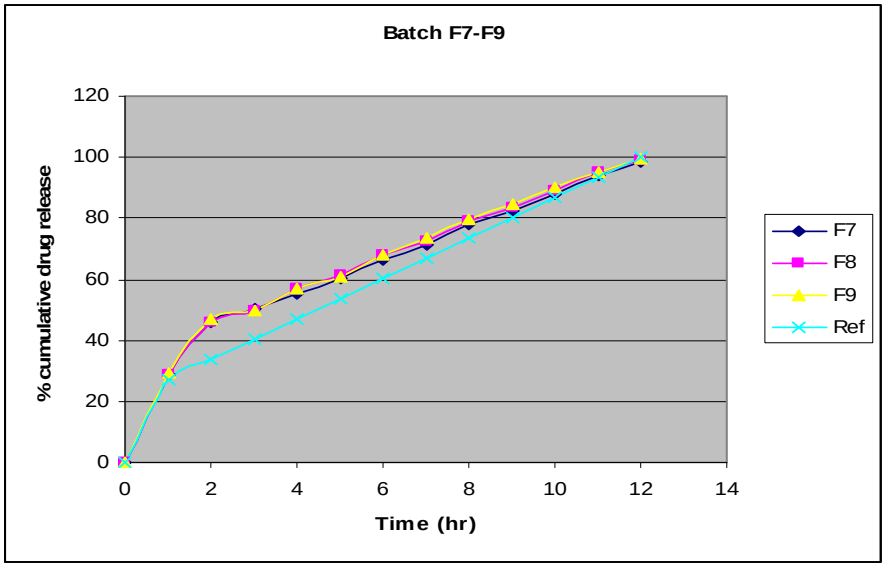


Figure No.: 3. Comparative Dissolution Profiles of F7, F8, F9 and Reference



Similarity factor (f_2)

We calculated the similarity value (f_2 value) of all the formulation, the table no.7 shows the results, according to that results the F3 formulation give the 71.44 % similarity value.

So finally, from all above evaluation parameters, Batch F3 was optimized as best sustained release single unit floating capsule for floating drug delivery system of loratadine.

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