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Formulation and Evaluation of Cinnarizine Floating Tablet Dosage form for Improved Absorption of Cinnarizine

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Abstract:

The purpose of this research was to prepare a floating drug delivery system of cinnarizine in order to increase the gastric residence time for enhance solubility in gastric HCL because of cinnarizine have lower solubility in intestine. Cinnarizine floating tablet prepared by direct compression method using HPMC K4M as matrix formers, sodium bicarbonate as gas generating agent. The formulated tablets were evaluated for physical characteristics such as weight variation, hardness, friability, floating lag time and total floating time. The *in-vitro* release of the tablets was evaluated in 0.1N HCl for 10hrs. The drug release kinetic was fitted in three different mathematical models like- zero order, first order, Higuchi model. Amongst all the formulations, F2 and F3 were found to be better formulations and both contain same concentration of HPMC K4M (100 mg) with different concentrations of sodium bicarbonate (30 mg and 45 mg respectively). Formulation F2 and F3 showed 93.85% and 96.32% drug release at 10 hrs. Thus, it may be concluded that the cinnarizine floating tablet can be successfully formulated for improve absorption of cinnarizine with increase in the gastric residence time.

Keywords: Floating Tablet, Cinnarizine

INTRODUCTION

Out of all route of drug administration, oral route is the most convenient and commonly used route. [1] But this route has many problems such as an unpredictable gastric emptying rate, gastrointestinal transit time, and the existence of an absorption window in the upper small intestine for several drugs that way very difficult to prepare such a doses form which stay in the stomach for long period of time. For the solution of such problem, many approaches have been developed such as swelling system, bioadhesive system, floating system, high density approach. [2] Among from all approaches, name of floating system itself suggest its work like it will remain float or buoyant on stomach fluid providing desire retention and drug release.

Cinnarizine is the most widely used drug for management of motion sickness. [3] Chemically, cinnarizine is piperazine derivative which has short half-life (4 to 6 hrs) as well as small dose. [4] Related to pharmacokinetics of cinnarizine which provide anti-histaminic activity and calcium channel blocking activity by higher affinity towards H1 and calcium channel receptor. But it suffers from incomplete and variable oral absorption which occurs mainly in the proximal small intestine thus it is

a good candidate to be formulated as a floating dosage form. [5] Cinnarizine is weakly basic in nature and has a lower pka value that's why it remains in ionized form at stomach pH and thereby it provides higher solubility in stomach and it remains in un-ionized form at intestinal pH so it has lower solubility in intestine. [6]

The main objective of this research work is to formulate cinnarizine floating tablet as floating tablet remains for longer period of time in stomach which provides larger acidic environment and thereby it increases the solubility of cinnarizine and hence absorption of cinnarizine in small intestine increases.

MATERIALS AND METHODS

Materials

Cinnarizine, HPMC K4M, $NAHCO_3$, Magnesium stearate, Talc were gifted from Balaji Drugs, Surat.

Methods

1. Preparation of Cinnarizine Floating Tablets

The cinnarizne floating tablets were prepared by direct compression method using HPMC as matrix former and sodium bicarbonate as gas generating agent. The compositions of different formulations are given in Table 1. Cinnarizine, HPMC K4M and PVPK 30 were mixed homogeneously using a pestle and mortar then mixed talc and magnesium stearate added as lubricant and glidant respectively. The granules were compressed to form a tablet using tablets compression machine.

Table 1: Composition of Floating Tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cinnarizine	50	50	50	50	50	50	50	50	50
HPMC K4M	100	100	100	125	125	125	150	150	150
NAHCO3	15	30	45	15	30	45	15	30	45
PVP K-30	12	12	12	12	12	12	12	12	12
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight (mg)	**181**	**196**	**211**	**206**	**221**	**236**	**231**	**246**	**261**

2. Evaluation Parameters

a. Hardness Test

The hardness of floating tablet was measured by Monsanto hardness tester. Hardness of tablet was measured in kg/cm^2 and it provides information about withstand ability during handling. [7]

b. Friability

The friability test was performed for all the formulated tablets using Roche Friabilator. Ten tablets were taken and their weight was determined (W_0) and then they were placed in a rotating drum. Then they were subjected to 100 revolutions. After completion of 100 revolutions or 4 min of time at 25 rpm, the tablets were again weighed (W). The percentage friability (f) was calculated by the formula:

$F = W_0 - W / W_0 \times 100$

Where, Wo = weight of the tablets before the test and W

= weight of the tablet after the test.

Acceptance criteria: the friability value should be less than 1.0 %. [8]

c. Buoyancy/Floating Studies

Buoyancy lag time means time interval between introduction of tablet into the dissolution medium and its floatation on top of the dissolution medium. Floating time means it is the duration of time up to which tablets floats on the dissolution medium. Both floating lag

time and floating time were carried out in 0.1N HCL in dissolution apparatus at 37°±1°C. [9]

d. Drug Content

Drug content of floating tablet was done by random selection of five tablets from each formulation and then fine powder of five tablets was made. From this powder equivalent to 50 mg of cinnarizine powder was weighed and makes desire concentration in 0.1N HCL then samples were analyzed in spectrophotometrically at 254 nm. [10

e. *In-vitro* Dissolution Studies

Release of cinnarizine was determined using USP (XXI) six stage dissolution rate test apparatus I (Electrolab, Mumbai) at 75 rpm. The dissolution rate was studied using 900 ml of 0.1N HCl. The temperature was maintained at 37±0.5°C. Samples of 5 ml each were withdrawn at different time intervals for 12 hrs and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and samples were suitably diluted and analyzed for cinnarizine content using double beam UV/Visible spectrophotometer (UV-1800 Shimadzu, Japan) at 254 nm. [11]

RESULT AND DISCUSSION

Compatibility Studies

The principal peaks for cinnarizine were observed at wave numbers 3180, 3017, 2960, 2880 cm^{-1}. Principal peaks of drug were also present in drug and HPMC K4M physical mixture, The study indicated that there was no interaction between drug and polymers or excipients, which were shown in Figure 1, 2 and 3.

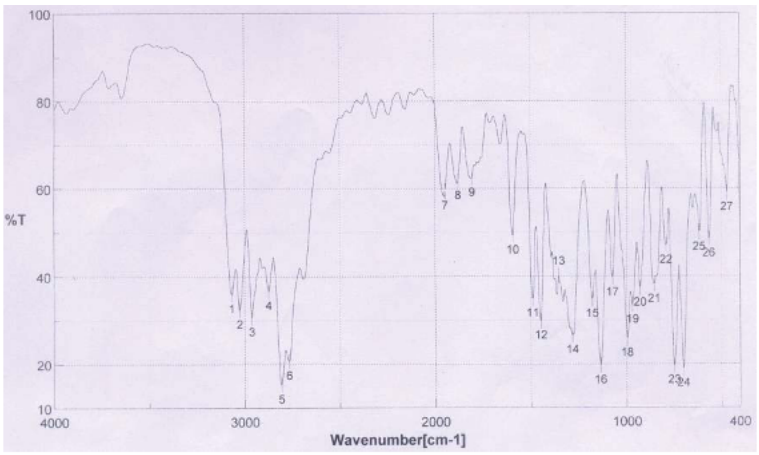

Figure 1: FTIR spectra of Cinnarizine

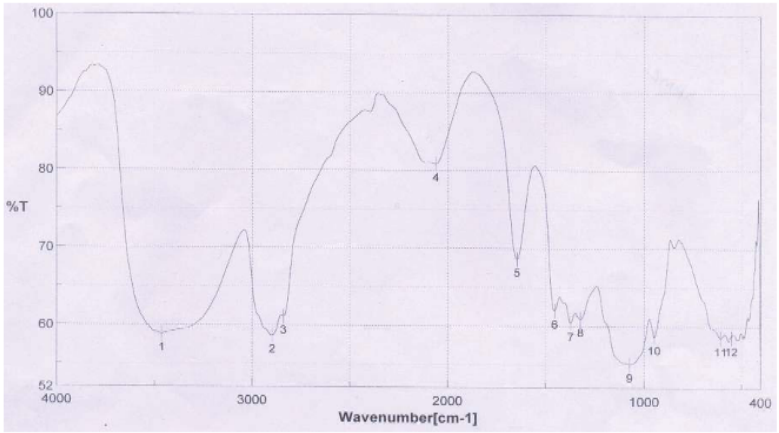

Figure 2: FTIR spectra of HPMC K4M

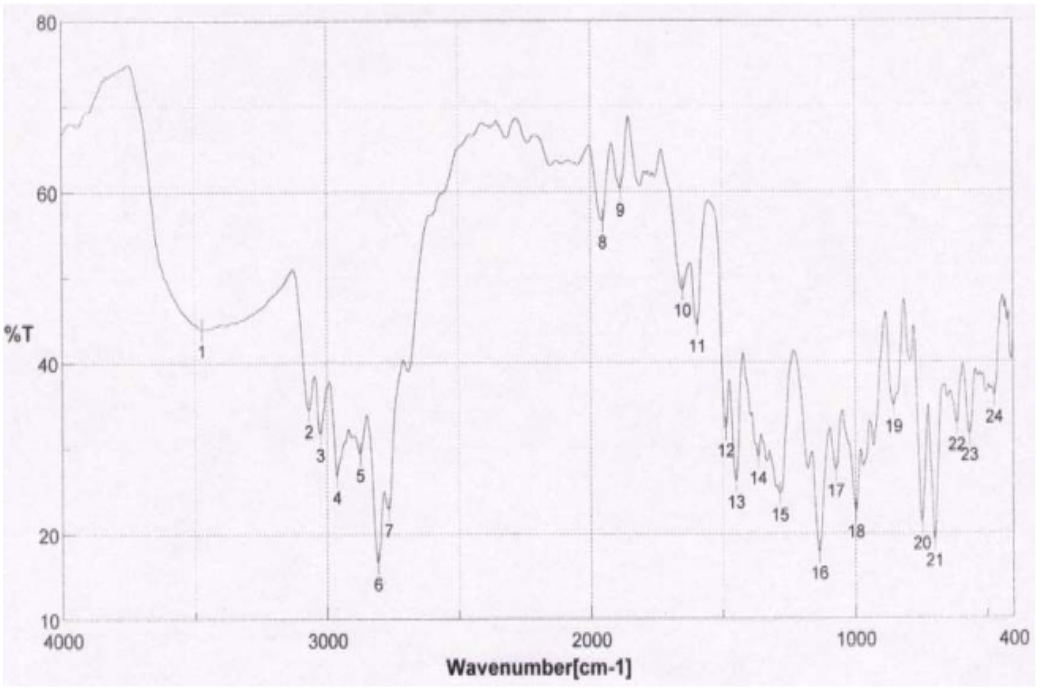

Figure 3: FTIR spectra of Cinnarizine and HPMC K4M

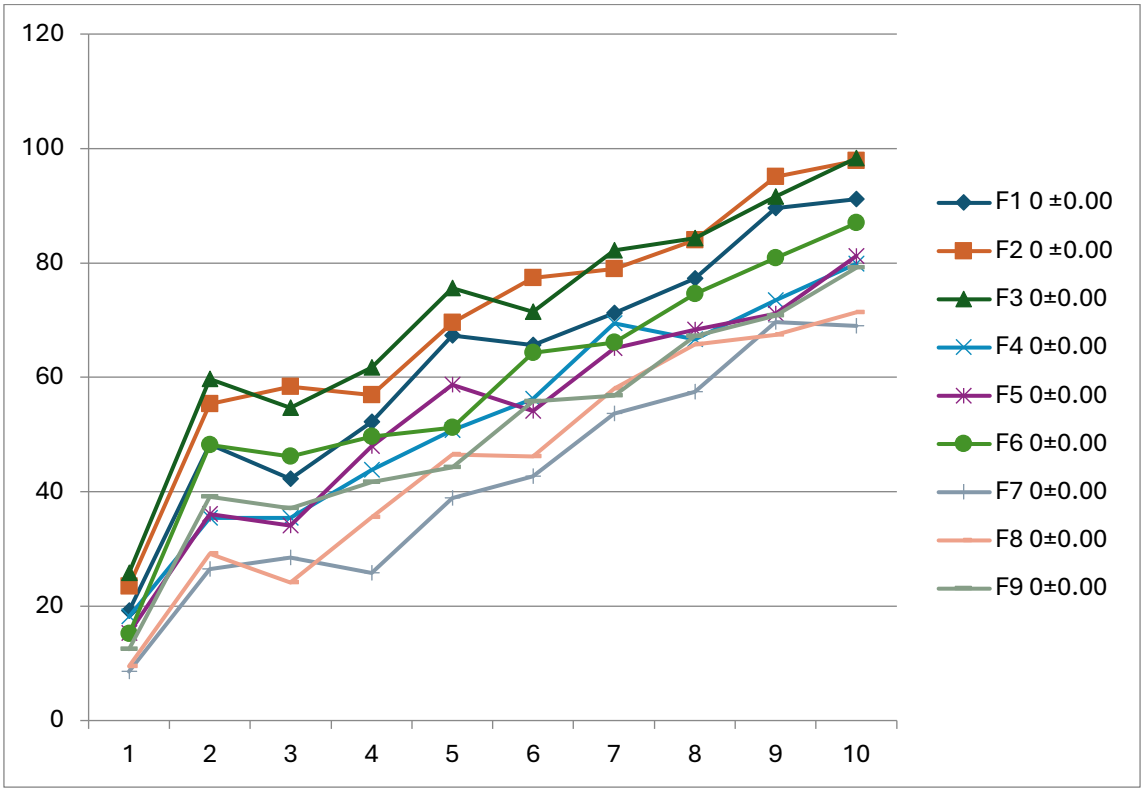

Figure 4: *In-vitro* drug release profile of Cinnarizine floating tablet

Table 4: Evaluation of Dissolution Data of Floating Tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0 ±0.00	0 ±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
1	19.17 ±0.73	23.5 ±0.37	25.8 ±0.48	18.15 ±0.18	15.28 ±0.86	15.12 ±0.47	8.57 ±0.49	9.48 ±0.58	12.47 ±0.41
2	48.24 ±0.47	55.3 ±0.27	59.67 ±0.82	35.37 ± 0.48	36.12 ±0.25	48.21 ±0.66	26.47 ±0.72	29.13 ±0.52	39.14 ±0.31
3	42.24 ±0.47	58.3 ±0.27	54.67 ±0.82	35.37 ± 0.48	34.12 ±0.25	46.21 ±0.66	28.47 ±0.72	24.13 ±0.52	37.14 ±0.31
4	52.23 ±0.83	56.94 ±0.32	61.73 ±0.86	43.8 ±0.93	47.92 ±0.52	49.63 ±0.58	25.78 ±0.48	35.56 ±0.97	41.73 ±0.19
5	67.32 ±0.21	69.5 ±0.58	75.53 ±0.39	50.79 ±0.28	58.73 ±0.74	51.19 ±0.53	38.93 ±0.21	46.52 ±0.84	44.28 ±0.42
6	65.59 ±0.47	77.35 ±0.52	71.43 ±0.27	56.23 ±0.29	54.13 ±0.79	64.23 ±0.29	42.64 ±0.22	46.12 ±0.63	55.73 ±0.89
7	71.23 ±0.69	78.98 ±0.83	82.23 ±0.18	69.45 ±0.17	65.1 4±0.83	66.12 ±0.18	53.71 ±0.15	57.98 ±0.72	56.84 ±0.72
8	77.22 ±0.85	83.98 ±0.91	84.27 ±0.29	66.64 ±0.53	68.27 ±0.94	74.62 ±0.12	57.44 ±0.28	65.72 ±0.34	67.19 ±0.63
9	89.59 ±0.27	95.05 ±0.33	91.59 ±0.38	73.49 ±0.51	71.15 ±0.13	80.83 ±0.54	69.65 ±0.63	67.47 ±0.58	70.76 ±0.59
10	91.14 ±0.18	97.85 ±0.64	98.32 ±0.30	79.86 ±0.47	81.22 ±0.12	86.94 ±0.33	68.99 ±0.52	71.37 ±0.51	79.16 ±0.28

Evaluation of Floating Tablet

1. Hardness Test

The measured hardness of tablets of each batch ranged between 4.44 to 4.56 kg/cm^2 as reported in Table 2. This ensures good handling characteristics of all batches.

2. Friability Test

The % friability was found to be in the range of 0.54% to 0.49% ensuring that the tablets are mechanically stable. The values of friability test are tabulated in Table 2.

3. Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation. The values of weight variation are shown in Table 2.

4. *In-vitro* Buoyancy Studies

The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid pH 1.2. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The overall floating time was calculated during the dissolution studies which were given in Table 2.

5. *In-vitro* Drug Release Study

The values of dissolution profile were shown in Table 3. The *In-vitro* drug release profile of

cinnarizine floating tablet is shown in Figure 4. Amongst all the formulations, formulation F2 and F3 showed 93.85% and 96.32% drug release at 10 hours.

6. Drug Release Kinetic Studies

The drug release data of cinnarizine were fitted to Zero order, First order, and Higuchi model kinetics. The results were given in Table 4.

Sr. no.	Formulation	Average Weight (mg)	Mean Hardness of Tablets	Friability %w/w	Mean Drug Content (%)	Floating Tag Time (Sec)	Floating Time (Hrs)
1	F1	180	4.45	0.54	97	52	12
2	F2	191	4.46	0.62	98	48	12
3	F3	250	4.52	0.68	99	35	12
4	F4	265	4.75	0.48	98	39	12
5	F5	254	4.85	0.45	97	45	12
6	F6	261	4.95	0.57	98	40	12
7	F7	245	4.25	0.58	99	45	12
8	F8	257	4.56	0.56	98	12	12
9	F9	259	4.86	0.49	97	15	12

Conclusion

In the present study, an attempt has been made by formulating floating tablet of cinnarizine by addition of various combinations of HPMC K4M and $NAHCO_3$ and their effectiveness on floating tablets were studied. Total 9 formulations of floating tablets of cinnarizine were prepared by direct compression method and using conventional equipments and were subjected to various evaluation tests.

Thus, the following conclusions have been drawn from "Results and Discussion".

1. The FTIR spectra of the physical mixture of Cinnarizine and excipients confirmed the absence of the interaction between the drug and the excipients.
2. All 9 formulations of floating tablet prepared by direct compression method. Among all formulations F2 and F3 were found to be good with dissolution profile.
3. Concentration of HPMC K4M directly affects on hardness, floating lag time and dissolution.
4. As the concentration of HPMC K4M is increased there is an increase in hardness with decrease in floating lag time and drug release.
5. Sodium bicarbonate directly affects on floating lag time. Floating lag time is decreased with decrease in the amount of sodium bicarbonate.

Thus, it may be concluded that the floating tablets of cinnarizine can be successfully formulated using conventional methods and evaluated to prove that it will surely enhance gastric residence time.

In future need, In-vivo studies will clearly provide the justification for the formulation of floating tablets of cinnarizine and it also increases its industrial applicability and productivity.

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