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FORMULATION AND IN-VITRO EVALUATION OF EFFERVESCENT FLOATING DRUG DELIVERY SYSTEM OF CIPROFLOXACIN TABLET.

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ABSTRACT

The effervescent floating drug delivery systems that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. Effervescent Floating tablets of Ciprofloxacin were prepared by using two different synthetic polymers such as HPMC K 100 M, and HPMC E15. Each polymer was used in combination with two different effervescent agents like $NaHCO_3$ and $CaCo_3$. The floating tablet is prepared by direct compression method. The mixture of Sodium bicarbonate with citric acid and calcium carbonate with citric acid was used as a gas generating agent. Floating properties and in-vitro drug release properties were optimized by changing the effervescent agent and total six formulations were developed. Pre formulation studies shows that all the formulation had poor flow property. In this study it was confirmed that the effervescent floating tablet of ciprofloxacin may be increase the retention time and absorption.

KEYWORDS: FDDS, effervescent agent, calcium carbonate, floating time.

INTRODUCTION

The oral route is most preferable route for administration of the drug but it may have some disadvantages like slow onset of action or slow absorption. This problem can be overcome by using alternative dosages form or administrating the drug via other routes. While we are selecting a dosage form or route for administration of drug there are some parameters should be consider like stability and bioavailability of the formulation as well as active

pharmaceutical ingredients. The Effervescent floating tablets can be used as alternative dosage form to minimize some problems associated with conventional dosage forms. The Effervescent floating tablets also reduce fluctuations of drug concentration and can be used to increase the bioavailability of drug.

Simply, Effervescence means release of carbon dioxide gas due to reaction of acids and bicarbonates in presence of water. Some common acids used in this reaction are citric, malic, tartaric, fumaric acid and bicarbonate used in the effervescent reaction is sodium bicarbonate, potassium bicarbonate, sodium carbonate and potassium carbonate. The most common reaction for pharmaceutical purpose is the acid base reaction between sodium bicarbonate and citric acid.

The present study outlines a systematic approach for design and development of effervescent floating drug delivery system of Ciprofloxacin using polymers such as HPMC K100M, HPMC E15, which increases the gastric residence time and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site to enhance the bioavailability and therapeutic efficacy of the drug. Formulations were evaluated in vitro for its buoyancy, dissolution, physical characteristic viz. Density, Hardness, Friability, Thickness and Weight variation.

EXPERIMENTAL

Ciprofloxacin is a gift sample of zip laboratory pvt Ltd., Nagpur. HPMC K100 M and HPMC E15 is gift sample of sanofi pharmaceuticals Ankleshwar, Gujarat. Sodium bicarbonates, calcium carbonate, Citric acid, and Talc were obtained from Loba chemicals, Mumbai, Maharashtra.

METHOD

Preparation of Ciprofloxacin effervescent Floating Tablets

Floating tablets of Ciprofloxacin were prepared by direct compression technique using polymers like HPMC K100M, HPMC E15, and different effervescent agent like sodium bicarbonate and calcium carbonate in combination with citric acid as gas generating agent. The different formulation F1 to F6 were prepared, the composition of each formulation is given in formulation Table No.1. Magnesium stearate used as a lubricant. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in mortar, After sufficient

mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Table no. 1 composition of all the formulation (F1 to F6).

Sr. no.	Excipient	F1	F2	F3	F4	F5	F6
1	Drug	250	250	250	250	250	250
2	HPMC K 100 M	130	-	65	130	-	65
3	HPMC E15	-	130	65	-	130	65
4	Sodium bicarbonate	30	30	30	-	-	-
5	Calcium carbonate	-	-	-	30	30	30
6	Citric acid	20	20	20	20	20	20
7	Magnesium stearate	1	1	1	1	1	1
8	Talc	4	4	4	4	4	4

*all the quantity of ingredient in mg.

I. PRE-COMPRSSION PARAMETER

1. Bulk Density

Bulk density of the powder was determined by pouring gently 2gm of sample through a glass funnel into a 10ml graduated cylinder. The volume is occupied by the sample was recorded. The bulk density was calculated by following formula:

Bulk density = weight of powder (gm)/ volume of powder in measuring cylinder.

2. Tap density

The 2gms of powder was introduce into a 10 ml of measuring cylinder. After firstly note down the initial volume, then tapping was continue until no further change in volume was noted.

Tap density = weight of powder (gm) / Tap volume of powder.

3. Angle of Repose

The angle of repose was determined by using fix funnel method. The accurately weighted powder were allowed to flow through the funnel. The funnel is adjusted to a stand at definite height. The diameter of powder cone was measured. The angle of repose was then calculated by following formula:

Tan θ = h /r

Where,

h = height of the heap

r = radius of the heap

4. Compressibility Index

The flow ability of powder can be determine by comparing the bulk density and tapped density of powder. Carr's index was calculated by =

Carr's index **=** (tap density – bulk density) ×100 / tap density.

5. Hausner ratio

Hausner ratio is related to inter particle friction and as such used to predict powder flow property. Hausner ratio calculated by using following formula:

Formula= tapped density / bulk density.

II. POST-COMPRESSION PARAMETER

6. Tablet thickness and diameter

Thickness and diameter were measured using a calibrated Vernier caliper. Twenty tablets of each formulation were picked and measure the thickness and diameter was individually.

7. Hardness

The hardness of the tablets was determined using Monsanto hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness was expressed in kg/cm2.

8. Friability test

The friability of tablets was determined by using Roche Friabilator. Twenty tablets were initially weighed and transferred into friabilator. Which was given 100 revolutions at 25rpm for 4 minutes. It was expressed in percentage (%). The tablets were reweighed. The % friability was then calculated by:

%Friability = (W_0 –W / W_0) 100.

Where,

W_0 = initial weight

W = final weight

% Friability of tablets less than 1% was considered acceptable.

9. Weight Variation Test

Twenty tablets were selected and weighted collectively and individually. From the collective weight, average weight was calculated. Each weight of tablet was compared with average weight to ascertain whether it was within permissible limit or not. The percentage deviation was calculated by following formula:

% deviation = individual weight – average weight / average weight × 100

10. Buoyancy / Floating Test

The tablet was introduce in to beaker containing 100ml of 0.1 N HCL. The time is taken by the tablet to come up to surface and floated was taken as the buoyancy time. The time taken for dosage form to emerge on surface of medium called Floating Lag Time and total duration of time by which dosage form remain buoyant is called Total Floating Time.

11. Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain as given by the equation.

$$WU = \frac{(W_1 - W_0) \times 100}{W_0}$$

Where

W_1= Weight of dosage form at time t.

W_0 = Initial weight of dosage form.

12. Buoyancy time

A tablet was introduce into a beaker containing 100ml of 0.1 N HCL. The time is required for tablet get floated was taken as the buoyancy time.

13. Determination of In – Vitro Dissolution Study

Dissolution study is carried out in USP dissolution testing apparatus II (basket type). Dissolution study was performed using 900ml 0.1(N) HCL, at 50 rpm. A 5ml of sample was withdrawn from the dissolution apparatus at a predetermined interval and the sink condition is maintain by adding same volume of dissolution medium. The sample diluted to a suitable

concentration with 0.1 N HCL. The absorption of withdrawn sample was measured spectrophotometrically, and the corresponding concentration was determined from the respective calibration curve.

RESULT AND DISCCUSION

Ciprofloxacin, a broad-spectrum fluroquinolones antibiotics used for gram- negative infection, diarrhea, mycobacterial infection, and urinary tract infection. Ciprofloxacin is absorb from stomach and the proximal part of small intestine. It has a short elimination half-life about 4 hrs. And the oral bioavailability is about 70%. The short biological half-life, low oral bioavailability and absorption site make ciprofloxacin an ideal candidate being designed in a sustained drug delivery system.

The effervescent floating tablets of ciprofloxacin were formulated in six different batches F1 to F6 by using hydrophilic polymers HPMC K100M, and HPMC E15 with effervescing agent sodium bicarbonate, calcium carbonate, and citric acid. All the formulations were prepared by direct compression technique.

Characterization of drug ciprofloxacin

Determination of Melting point

The melting point of the drug was found to be 253-256^{0}C by using capillary method.

Spectrophotometric Determination

The wavelength of maximum absorbance (λ_{max}) for the solution of ciprofloxacin prepared in 0.1 N HCL was found to be 276 nm.

Preparation of calibration curve in 0.1 N HCL

The prepared calibration curve of ciprofloxacin in 0.1N HCL was prepare the concentration of 2, 4, 6, 8, and 10 µg/ml and is shown in following table and graph.

Table no. 2: concentration and absorbance of calibration curve of ciprofloxacin in 0.1 N HCl.

Sr. no.	Concentration(µg/ml)	Absorbance
0	0	0
1	2	0.114
2	4	0.228
3	6	0.321
4	8	0.41
5	10	0.506

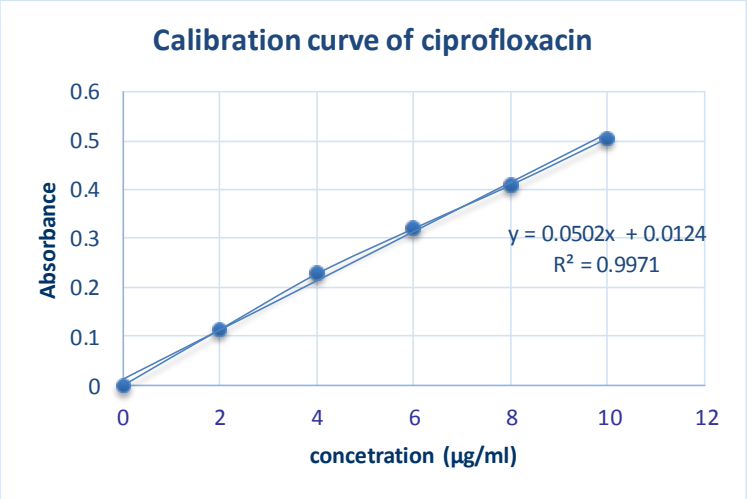

Figure no. 1: calibration curve of ciprofloxacin.

The prepared calibration curve obeyed beer's lambert law in the concentration range of 2, 4, 6, 8, and 10µg/ml. the value of regression coefficient (0.9971) shows the linearity of relationship between concentration and absorbance.

Evaluation of powder

The flow property and mechanical properties of all the formulation were evaluated like bulk density, tap density, angle of repose, hausner's ratio and Carr's index were shown in table no. 3.

Table no. 3 pre-formulation evaluation of ciprofloxacin.

Formulation batch	Angle of repose (Ø)	Bulk density (gm/cm3)	Tap density (gm/cm3)	Carr's index (%)	Hausner's ratio
f1	43.53	0.23	0.312	26.28	1.35
f2	38.65	0.24	0.322	25.46	1.34
f3	40.03	0.23	0.317	27.44	1.37
f4	43.83	0.24	0.33	27.27	1.37
f5	41.34	0.23	0.332	30.72	1.44
f6	42.61	0.23	0.322	28.57	1.4

The prepared floating tablet were evaluated. The pre compression parameter like the bulk density, tap density, angle of repose, hausner's ratio, and Carr's index. All the formulation shows the poor flow ability. Carr's index and hausner's ratio shows flowing ability was in acceptable range.

Evaluation of floating tablet (batches f1-f6)

Table no. 4 shows the results of hardness, diameter, thickness, friability, and weight variation. Tablet must have a certain amount of strength or hardness and resistance to friability to a tablet, so that it should not break during handling. The average hardness of tablet was found in between 2.5 to 2.8. The friability of the tablet was found to be less than 1% which was considered within the limit.

Table no. 4: evaluation of ciprofloxacin floating tablet.

Formulation batch	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^3)	weight variation (%deviation)	Friability (%)
f1	12.04 ± 0.161	3.21±0.09	2.83± 0.35	441.05±7.74	0.3
f2	11.94 ±0.234	3.14±0.10	2.6±0.48	439.7±6.95	0.28
f3	12.13 ± 0.214	3.07±0.07	2.5± 0.38	441.15±7.49	0.31
f4	12.01 ±0.082	3.23±0.08	2.78± 0.62	440.5±7.57	0.25
f5	12.05± 0.079	3.17±0.08	2.73±0.62	442.05±11.22	0.3
f6	12.09± 0.091	3.15±0.08	2.73±0.39	443.15±7.41	0.16

Tablet diameter and thickness varying from 12.01 to 12.13 mm and 3.07 to 3.23 mm respectively. The hardness of tablet varying from 2.5 to 2.83 kg/cm^3. The weight variation of tablets within the limit of uniformity.

Floating lag time and floating time

The floating lag time is determined by the prepared tablet was kept in 100ml of 0.1 N HCL and time taken to reach the surface of solution was recorded. The result of all formulations showed in table no. 5.

Table no. 5 the floating lag time and floating time formulation.

Formulation	Floating lag time(min)	Floating time(Hrs.) Up to
F1	18.30	12
F2	13.26	11
F3	35.47	13
F4	24.17	12
F5	21.38	12
F6	41.25	13

Formulation f1 to f6 shows the floating lag time ranges from 13 to 42 min. the floating time of formulation f3 and f6 shows up to 13 hrs.

In vitro dissolution studies

In order to investigate the effect of effervescent agents such as sodium bicarbonate and calcium carbonate on effervescent floating tablet of ciprofloxacin, there are six formulation were prepared F1-F6 as generated from experimental design. Formulation F1-F6 was subjected to dissolution studies as shown in table no. 6, and figure no. 2 & 3.

Table no.6: dissolution profile of ciprofloxacin floating tablet.

Hrs.	f1	f2	f3	f4	f5	f6
0	0	0	0	0	0	0
1	9.55	12.56	12.92	14.08	14.80	8.32
2	14.49	24.32	17.26	22.59	23.82	12.82
3	27.13	31.15	23.18	28.94	28.66	22.56
4	30.43	38.45	33.62	35.29	39.68	32.56
5	42.15	45.90	42.37	45.94	51.88	37.81
6	50.88	59.76	47.53	50.50	60.38	48.95
7	63.29	71.56	58.72	57.00	66.35	53.63
8	71.85	80.53	64.25	62.71	80.29	62.28
9	79.88	88.32	71.44	71.84	86.73	70.55
10	87.51	94.08	80.26	85.37	91.91	82.37
11	92.04	98.46	91.30	91.30	96.57	91.94
12	96.77	-	97.26	99.93	99.33	96.96
13	-	-	100.17	-	-	104.90

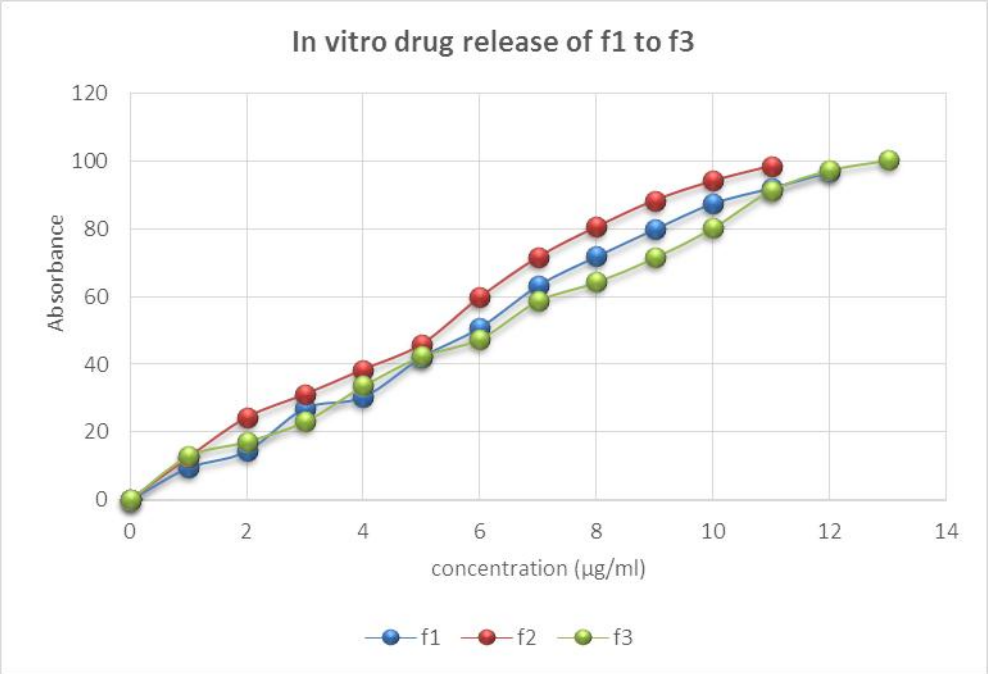

Figure no 2: dissolution profile of formulation f1 to f3.

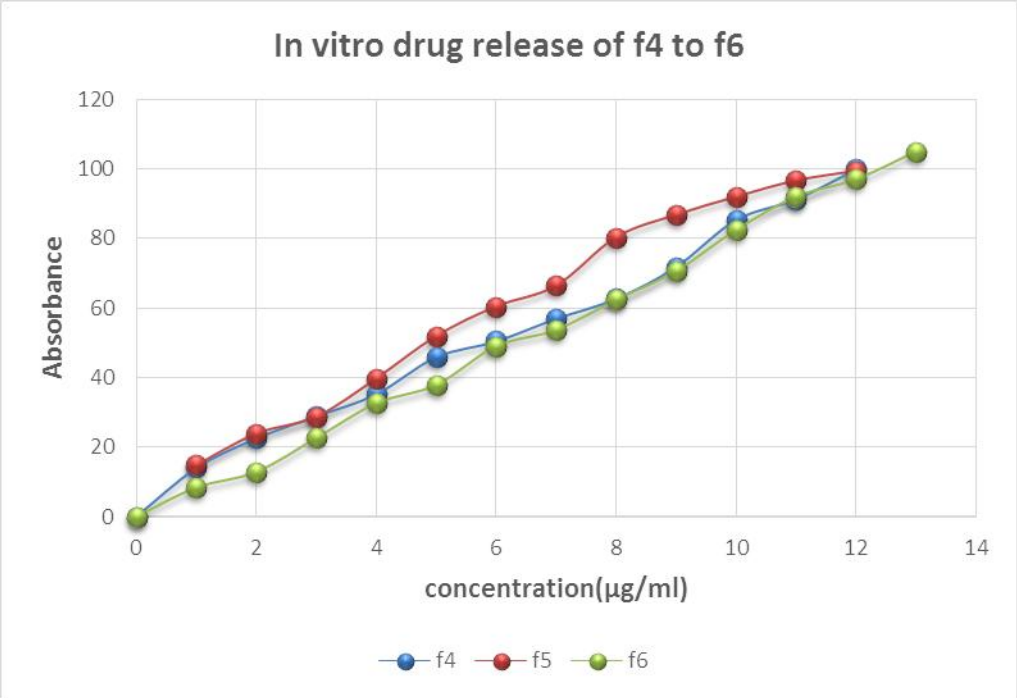

Figure no. 3: dissolution profile of formulation f4 to f6.

CONCLUSION

In present study, the new effervescent floating system of ciprofloxacin was formulated and evaluated, by using synthetic polymer like HPMC K 100M, and HPMC E 15 with combination of sodium bicarbonate and calcium carbonates with citric acid as an effervescent agent. The formulations f6 containing HPMC K100M, HPMC E15 with combination of $CaCO_3$ have shown better floating properties, in-vitro release properties and the buoyancy studied showed that tablet remain float for more than 12 hrs. It can be conclude that effervescent floating tablet of ciprofloxacin may be increase the retention time and absorption by using the formula f3 and f6.

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