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Formulation design, Development and Evaluation of Gastro Retentive Floating Matrix Tablets of Cefpodoxime Proxetil using Different Polymers

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ABSTRACT

In this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailability. A simple visible Spectrophotometric method has been employed for the estimation of Cefpodoxime Proxetil at 263nm and Beer's law is obeyed in the concentration range of 5- 40 µg/ml. Preformulation studies were carried out to optimize the required quantity for HPMC K4M,K15M, K100M.In these Cefpodoxime Proxetil GRDDS we are prepared Total 12 formulations. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as Hydroxy Propyl Methyl Cellulose (HPMC K4M, K15M, K100M) with other standard excipients like Sodium bicarbonate, MCC and Magnesium Stearate used as gas generating agent, as filler and as lubricant respectively. Tablets were evaluated for physical characterization viz. hardness, friability, swelling index, floating capacity, thickness and weight variation. Further tablets were evaluated in-vitro drug release for 12 hr. The effect of polymer concentrations on buoyancy and drug release pattern was also studied. All the matrix tablets showed significantly greater swelling index and exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than12 hr. The paddle speed affected the floating lag time and floating duration it had a negative effect on the floating properties. The optimized formulation followed the higuchi release model and showed non-fickian diffusion mechanism. It also showed no significant change in physical appearance, drug content, floatability or in-vitro dissolution pattern after storage at 45 °C at 75 % RH for three months.

Keywords: *Cefpodoxime Proxetil, Swelling index, Floating Capacity, HPMC.*

INTRODUCTION

Oral route is the most convenient and extensively used route for drug administration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS).This route has high patient acceptability, due to ease of administration. Controlled release drug delivery system release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This helps in achieving predictable drug plasma concentration required for therapeutic effect. A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation Cefpodoxime proxetil is a third generation cephalosporin prodrug, having a white to light brownish white powder, odourless, slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in acetonitrile & in methyl alcohol which is administered orally. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%.Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve. Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime Proxetil [3]. The half life of cefpodoxime proxetil is 2.2 hours. Cefpodoxime Proxetil is a lactum antibiotic. Its action is by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes [1-3].

The gastro-retentive floating matrix tablet of Cefpodoxime proxetil was design by using Cefpodoxime proxetil, MCC, HPMC, Sodium bicarbonate and Magnesium stearate.

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MATERIALS AND METHODS

Materials:

Cefpodoxime proxetil was procured from Aurobindo Pharma Ltd,Hyderabad. HPMC obtained was purchased from S.D. fine chemicals Mumbai. All other solvents and reagents were used of analytical grade.

Table No. 1: Standard graph of Cefpodoxime Proxetil in 0.1N HCl

Concentration	Absorbance
2	0.174
4	0.319
6	0.467
8	0.672
10	0.726
12	0.888

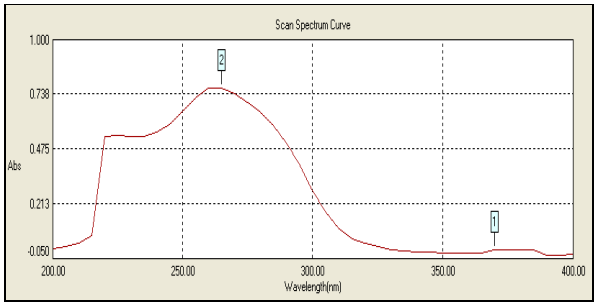

Fig. 1: Cefpodoxime Proxetil floating tablets standardization of by UV method

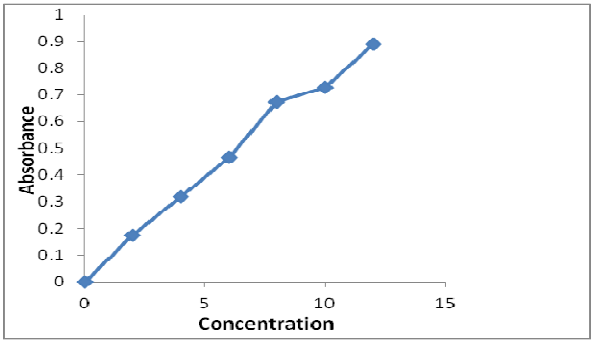

Fig. 2: Standard Graph of Cefpodoxime Proxetil in 0.1N HCl

Methods:

Formulation of Floating Tablet:

Each floating tablets containing 200 mg Cefpodoxime Proxetil were prepared by direct compression method. Cefpodoxime pure drug was mixed with required quantity of HPMC K4M, K15M,K100M,Sodium bicarbonate and MCC by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2 min. The lubricated blend was compressed into tablets using 12 mm flat-face round tooling on Pilot Press rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 4 to 5 kg/cm^2 with 4.0 mm tablet thickness.

Pre-Compression Parameters:

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder, Vt is the tapped volume of the powder

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\text{Tan } (\theta) = h / r$$
$$\theta = \tan^{-1} (h / r)$$

Where; 'θ' is the angle of repose. 'h' is the height in cms,r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = Dt - Db / Dt \times 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = Dt / Db$$

Where, Dt is the tapped density, Db is the bulk density.
Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Evaluation of Tablets:

Physical properties like Weight variation, Hardness, Thickness, Friability and Drug content of tablet performed and results are evaluated.

Thickness:

Thickness of tablets was determined using Vernier caliper. Three tablets from each batch were used, and average values were calculated.

Average weight:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

Drug content:

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 263 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 263 nm.

Hardness:

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability:

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Determination of swelling index:

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37 .5 ^{0}C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation shows relationship between swelling index and time [4-7].

$$WU\ \% = \frac{\text{Wt of swollen tablet} - \text{Initial wt of the tablet}}{\text{Initial wt of the tablet}} \times 100$$

Buoyancy determination:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floatation i.e. as long the dosage form remains buoyant is called

Total Floating Time (TFT).The buoyancy test of tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at 37±0.5^{0}C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation [8, 9].

***In Vitro* Release Studies:**

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. *In* vitro dissolution studies of prepared drug were carried out in 900 ml of 0.1 N HCl as a medium using USP type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37.01°C was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5min interval, filtered using a 0.45-mm what man filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analyzed on UV/Visible spectrophotometer at 263nm [10-12].

Table No. 2: Formulation chart

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cefpodoxime proxetil	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4 M	12.5	25	-	-	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	12.5	25	50	75	100	-	-	-	-	-
HPMC K100 M	-	-	-	-	-	-	-	12.5	25	50	75	100
Sodium Bicarbonate	60	60	60	60	60	60	60	60	60	60	60	60
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
MCC	120.5	108	120.5	108	83	58	33	120.5	108	83	58	33
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

Table No. 3: Precompression parameters

Formulations	Bulk density	Tapped density	Hausner's ratio	Compressibility index%	Angle of repose
F1	0.434±0.002	0.633±0.04	1.39	32.7	32.2±0.01
F2	0.465±0.032	0.643±0.04	1.53	36.6	31.6±0.54
F3	0.422±0.006	0.656±0.03	1.49	29.5	35.8±0.95
F4	0.425±0.003	0.623±0.04	1.42	31.8	32.6±0.54
F5	0.435±0.002	0.634±0.06	1.46	34.4	36.4±0.49
F6	0.423±0.001	0.654±0.05	1.57	30.4	35.9±0.45
F7	0.433±0.003	0.632±0.08	1.53	33.9	32.3±0.38
F8	0.466±0.004	0.645±0.04	1.47	34.7	36.2±0.34
F9	0.455±0.005	0.655±0.06	1.56	22.4	36.5±0.56
F10	0.442±0.003	0.649±0.08	1.48	26.4	38.8±0.52
F11	0.431±0.004	0.637±0.03	1.51	32.1	33.7±0.59
F12	0.459±0.031	0.659±0.06	1.55	34.8	35.3±0.47

Table No. 4: Postcompression parameters

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	299.5 ± 1.28	4.25 ± 0.04	4.50± 0.07	0.70±0.065	102.48 ± 0.20
F2	298.7± 1.35	4.00 ± 0.05	4.62 ± 0.03	0.91±0.044	101.58 ± 0.20
F3	300.5± 1.23	3.90 ± 0.03	4.084 ± 0.06	0.71±0.080	99.38 ± 0.21
F4	300.2 ± 1.98	4.20 ± 0.06	4.11 ± 0.04	0.72±0.042	98.68 ± 0.20
F5	299.1± 1.57	4.10 ± 0.05	4.41 ± 0.07	0.80±0.066	102.28 ± 0.10
F6	300.6 ± 1.55	3.90 ± 0.04	4.27 ± 0.05	0.76±0.054	102.73 ± 0.13
F7	299.7± 1.16	3.85 ± 0.07	4.10 ± 0.03	0.75±0.045	103.36 ± 0.14
F8	300.1± 1.97	3.90 ± 0.03	4.04 ± 0.06	0.71±0.080	99.38 ± 0.21
F9	299.7± 1.24	4.20 ± 0.06	4.21 ± 0.04	0.72±0.042	98.68 ± 0.20
F10	298 ± 1.79	4.10 ± 0.05	4.69 ± 0.07	0.80±0.066	102.28 ± 0.10
F11	299.4± 1.11	3.90 ± 0.04	4.44 ± 0.05	0.76±0.054	103.73 ± 0.13
F12	299.9± 1.47	3.85 ± 0.07	4.15 ± 0.03	0.75±0.045	103.36 ± 0.14

RESULT AND DISCUSSION

All formulation from F1 to F12 was evaluated with thickness and diameter of tablets measured by vernier calipers. Thickness and diameter was in range of 3.90 ±0.04 to 4.20±0.04.The hardness was in range of 7.0±0.23 to 9.2±0.40kg/cm^2,which was measured on Monsanto hardness tester. Drug content release was in the range of 96.38±0.12 to 104.73±0. The percentage drug release was found 50% after 7 hrs. In view of this absorption characteristics, the hypothesis of current investigation is that if the gastric residence time of cepfodoxime proxetil containing formulation is prolonged and allow to float in the stomach for a long period, the oral bioavailability might be increased hence the present research work was to study systematically the effect of formulation variable on the release and floating properties of cepfodoxime proxetil drug delivery system.

In vitro dissolution studies of all floated formulations of Cefpodoxime Proxetil were carried out in 0.1 N HCl, by using USP dissolution apparatus Type-II.at 50 rpm. Percentage drug release was calculated at two hour time intervals for 12 hours.

Formulation F1, F2 contains Drug: Polymer ratio of 1: 2.2, 1: 1.1 prepared with HPMC K4M. Formulation F1, F2 exhibited 93.5%, 88.2% of drug release in 12 hours respectively. Formulations F3, F4, F5, F6 and F7 were prepared with HPMC K15M are in the ratio of 8:1, 4:1, 2:1, 1:1.3, 1:1. But these formulations exhibit only 78.2%, 87.3%, 85.5%, 89.8%, 87% of drug release at the end of 12th hr when they are placed in 0.1N HCL.

Formulation F8, F9, F10, F11, F12 is prepared with HPMC K15M in Drug: Polymer ratio of 8:1, 4:1, 2:1, 1:1.3, 1:1. These formulations exhibit 98%, 89.7%, 85.4%, 75.7%, 85.8% of drug release at the end of 12th hr when they are placed in 0.1N HCL.

Total floating time depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to $NaHCO_3$ firmly. Due to high viscosity and content of the polymer

bursting effect of the tablet was decreased and float for longer duration of time. From the result of floating lag time it was concluded that, as the concentration of gas generating agent increase the floating lag time get shortens this finding were supported by the study that reported that as the concentration of gas generating agent ($NaHCO_3$) was increased the floating lag time get shortened and at the same time floating ability get increased

From the overall dissolution profiles it was observed that as the concentration and of the polymers increased, there is decrease in the drug release rate, where use of less concentration could cause rapid release. From the above results formulations F8 is found to be satisfactory with dissolution profile results. Hence these formulations was said to be optimized formulations.

Table 5: Dissolution Profiles of different formulations

%Drug Release Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	**0**	0	0	0	0
30	24.8	25.5	21.4	17.7	18.9	24.03	17.7	**25.4**	21.5	19	19.5	20.2
60	33.3	34.9	29.2	25.8	25.5	32.2	25.8	**38.4**	29.6	29.2	30.3	28.9
120	44.8	48.6	36.1	41.8	34.6	42.8	41.8	**45.7**	38.4	40.7	40.3	36.7
240	50	65.7	44.8	50.5	42.3	54.9	50.4	**54.8**	44.3	46.7	50.7	43.8
360	59.9	72.7	50.7	56	48.2	60.8	59.9	**61.8**	54.6	55.4	55.7	49.1
480	68.4	78.8	56.9	62.1	56.7	71.9	70	**72.7**	62.6	67.04	63.3	59.3
600	77.3	84.5	68.3	73.2	69.3	84.8	76.2	**91.1**	80.9	75.9	70.5	73
720	93.5	88.2	78.2	87.3	85.5	89.8	87	**98.1**	89.7	85.4	75.7	85.8

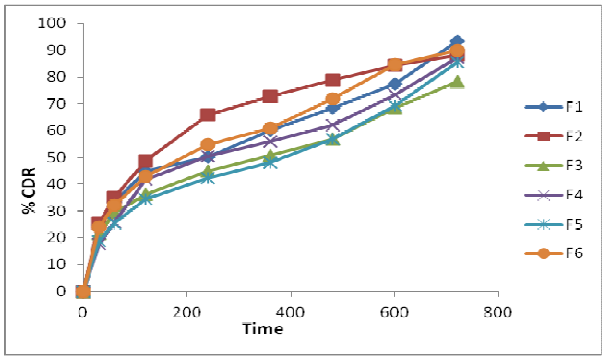

Fig. 3: Dissolution graphs of F1, F2, F3, F4, F5 & F6 Formulations

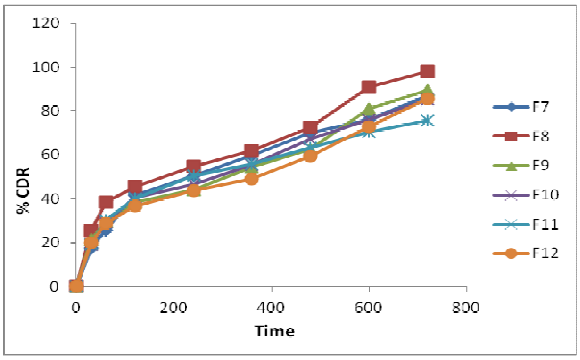

Fig. 4: Dissolution graphs of F7, F8, F9, F10, F11 & F12 formulations

Table No. 6: Swelling index of different formulations

Time (Min)	% SWELLING INDEX											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
15	38	38	39.6	32.14	40.38	37	31.5	44.4	49.01	42.3	47.16	50.98
30	53.38	51.9	49	35.71	51.92	40	53.7	51.85	54.9	53.84	56.6	58.82
60	67.73	71.15	64.15	55.35	69.23	68.5	72.2	66.66	72.54	76.92	73.58	82.35
120	84.61	84.6	84.9	76.8	88.46	85.18	101.9	85.16	94.11	92.3	100	103.9
180	103	101.9	105.7	91.07	119.2	107.4	122.2	109.3	113.7	111.5	107.5	127.5
240	115.4	119.2	128.3	101.8	123.1	125.9	142.6	116.7	127.5	126.9	128.3	147.1
300	121.2	126.9	132	108.9	134.6	133.3	157.4	118	139.2	140.4	141.5	152.9
360	134.6	136.5	137.7	116	150	140.7	161.1	127.8	141.2	146.2	145.3	160.8
420	138.5	142.3	143.4	123.2	153.8	142.6	175.9	138.9	152.9	151.9	152.8	164.7
480	145.8	146.8	150.1	121.7	160.4	148	178.8	141	159.3	160	158	172
540	153.8	153.8	157.7	115.8	171.2	153.7	181.5	144.4	168.6	171.2	167.9	180.4
600	151.2	150	150.9	105.7	170	151.9	182.4	151.9	166.7	167.3	150.9	182.2
660	148	148	150.9	104.8	166	150	185.9	150.6	165	167	147.2	182
720	136	138	140	102.6	160	140	194.9	140	155	150	137	170

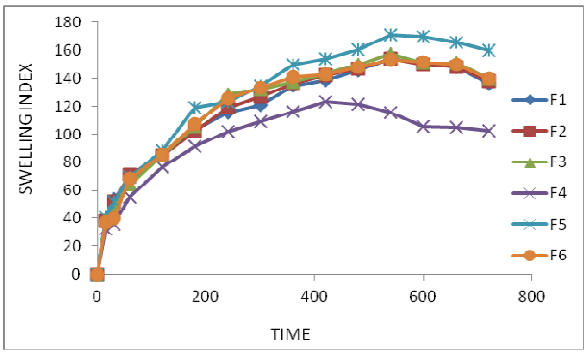

Fig. 5: Relationship between swelling index and time of F1-F6

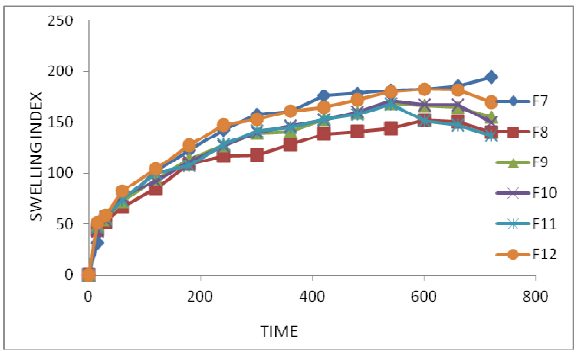

Fig. 6: Relationship between swelling index and time of F7-F12

Drug Excipient Interaction studies:

Fourier Transform Infrared spectroscopic studies (FTIR):

The FTIR spectra of drug, excipients, and drug loaded formulation were recorded. The characteristic peaks of the optimized formulation followed the same trajectory as that of the drug alone with minor differences. Thus there may be no drug-excipient interactions.

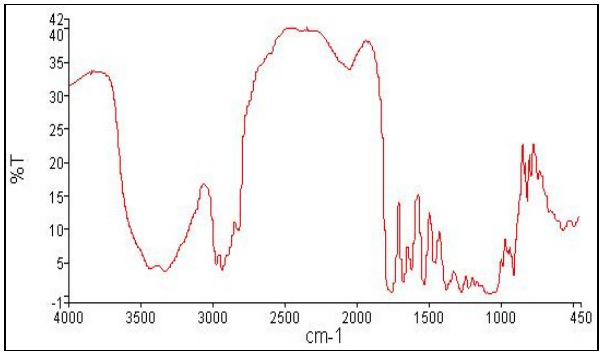

Fig. 7: FTIR of Cifodoxime proxetil

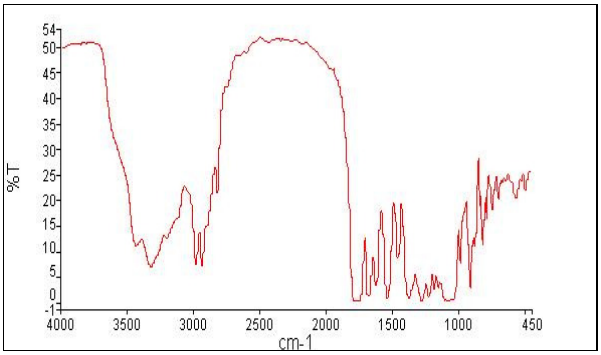

Fig. 8: FTIR of Cifodoxime proxetil with HPMC

CONCLUSION

From the drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F8 i.e. the formulation containing HPMC K100M, $NaHCO_3$, Magnesium stearate, MCC, Aerosil is the best formulation. F8 possessed quick buoyancy lag time of 45 sec and good total floating time of 12 hrs. The results showed that the drug release rate was decreased by increasing viscosity of the polymer combination.

As a result of this study it may be concluded that the floating tablets using HPMC K100M is a hydrophilic polymer increase the GRT of the dissolution fluid in the stomach to deliver the drug in a sustained manner. The concept of formulating floating tablets of Model drug offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

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