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FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF CEFIXIME TRIHYDRATE

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ABSTRACT

The objective of the present investigation was to formulate and evaluate gastro retentive floating tablets of cefixime trihydrate. A novel gastro retentive drug delivery system of cefixime trihydrate was formulated in an effort to increase gastric residence time and thereby increase drug bioavailability. Rapid gastro intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Nine formulations of floating tablets were prepared using direct compression method containing 200 mg of cefixime trihydrate and various polymers like hydroxypropyl methylcellulose (HPMC K 100M), xanthan gum and fenugreek mucilage in varying proportions. Micro crystalline cellulose was used as swelling agent and buoyancy was achieved by adding fixed amount of an effervescent agent sodium bicarbonate. All the formulations were evaluated for physicochemical properties, *in vitro* buoyancy and *in vitro* drug release. Floating lag time observed for all the tablets was less than 1 minute and the duration of floating was greater than 12 hrs. Formulation F5 containing equal ratio of xanthan gum and fenugreek mucilage (25mg) showed optimum *in vitro* drug release of 83.53% at the end of 12 hrs.

KEYWORDS: Gastro retentive floating tablets, Cefixime trihydrate, Fenugreek mucilage, Xanthan gum, Buoyancy, *In vitro* release.

INTRODUCTION

Oral drug administration is still the most common and most popular pathway of drug administration due to several advantages such as ease of administration, less invasive

treatment and greater patient's compliance. Drugs for chronic condition are often administered orally for ease of long term use (Arora *et al*., 2005). Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastro intestinal transit time, drug release from the dosage form and site of absorption. Variable and too rapid gastro intestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose (Streubel *et al*., 2006).

To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. (Hirtz *et al*., 1985).The controlled gastric retention of solid dosage forms may be achieved by the mechanism of floating system, high density system, bio/mucoadhesive system, swelling system that delays gastric emptying. Based on these approaches, floating drug delivery systems seems to be one of the promising delivery systems for control release of drugs (Narang *et al*., 2011).

Floating drug delivery system was first described by Davis in 1968. Floating system or Hydro dynamically controlled system are low density system that have sufficient buoyancy to float over the gastric content and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This resultant increased GRT and a better control of the fluctuations in plasma drug concentration (Mushiroda *et al*., 2000).

Cefixime trihydrate is an orally active third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated gonorrhea, uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis. The biological half life of cefixime trihydrate is 3 to 4 hrs. Cefixime trihydrate having pKa value of 2.5 is a weak acid which will remain unionized at acidic pH thus increases absorption in the stomach region. It is primarily absorbed from the stomach and upper part of intestine (Rao *et al*., 2010). In view of this absorption characteristic, the hypothesis of current investigation is that if the gastric residence time of cefixime trihydrate containing formulation

is prolonged and allowed to float in the stomach for a long period, the oral bioavailability might be increased.

MATERIALS AND METHODS

Cefixime trihydrate and Xanthan gum were obtained as gift sample from Franklin Laboratories Pvt. Ltd. Ludhiana. HPMC K100 M was obtained as gift sample from Magbro Healthcare Pvt. Ltd. Solan. Fenugreek mucilage was isolated in the lab. Sodium bicarbonate was obtained from S D Fine Chemicals Pvt. Ltd. Mumbai. Cellulose microcrystalline, Lactose monohydrate and Magnesium stearate were obtained from Loba Chemicals Pvt. Ltd. Mumbai.

METHODS

Method for extraction of fenugreek mucilage

The seeds were powdered using pestle and mortar and 100 g of the powder was extracted with hexane to remove lipophilic compounds using a soxhelet apparatus. To remove pigments and to deactivate enzyme, the defatted powder was boiled in ethanol for 20 min. This treated powder was then soaked in 10 liters water and the pH was adjusted to 3.5 using 0.5 M Hydrochloric acid. The mixture was stirred by a mechanical stirrer for 12 hrs and then filtered through filtration paper. The filtrate was centrifuged (5000 g) and the supernatant was concentrated in vacuum to 50% of its initial volume. The resulting solution was mixed with the same volume of 96% ethanol and stored in a refrigerator for 4 hrs. The precipitated mucilage was separated by centrifugation (5000 g). The collected mucilage was re-suspended in distilled water, agitated for 20 min and re-precipitated one more time to eliminate chloride ions and other impurities. Finally the residue was washed with diethyl ether and acetone and dried overnight at 45°C, resulting in an off-white powder (Kumar *et al*., 2009).

Method for preparation of floating tablets

Matrix tablets of cefixime trihydrate were prepared by direct compression method. The weight of cefixime trihydrate was kept constant in all the prepared tablets at 40% w/w/tablet. Different concentrations of polymers viz. HPMC K100 M, Xanthan gum and Fenugreek mucilage were chosen as polymeric matrix materials. Lactose was selected as tablet diluent for increasing the compressibility and flowability of the ingredients as well as to maintain the tablets at constant weight of 500mg. Magnesium stearate was used as a lubricant at concentration of 1% by weight of tablet. Sodium bicarbonate was incorporated as an effervescent substance to aid buoyancy to the dosage form due to liberation of CO_2 when the

tablets come in contact with acidified dissolution medium which entrapped in the matrix. First the drug, polymer and other excipients selected were passed through 18 no. mesh sieve. Required quantity of drug, polymers and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The obtained blend was then lubricated by adding 1% magnesium stearate and again mixed for another 5 min. The tablets were compressed using 12 mm diameter punches by automatic punching machine. The detailed compositions of the prepared floating matrix tablets formulations are given in Table no. 1.

Table no. 1: Compositions for different batches of floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime trihydrate	200	200	200	200	200	200	200	200	200
HPMC K100M	50	50	50	50	50	50	50	50	50
Xanthan Gum	75	75	75	25	25	25	50	50	50
Fenugreek mucilage	50	75	25	75	25	50	75	50	25
Sodium bicarbonate	60	60	60	60	60	60	60	60	60
Cellulose microcrystalline	25	25	25	25	25	25	25	25	25
Lactose monohydrate	35	10	60	60	110	85	35	60	85
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total	500	500	500	500	500	500	500	500	500

Study of physical interaction between drug and polymer

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually as well as the combination of drug with individually all the polymers over a wave number range of 4000 to 400 cm–1using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated.

Evaluation of fenugreek mucilage

Fenugreek mucilage powder was evaluated in terms of Solubility, Loss on drying, Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio.

Evaluation of powder blend

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of

the powder cone was measured and angle of repose was calculated using the following equation (Paul *et al*., 2011).

$\tan\theta = h/r$

Where, h = height of the powder cone,

r = radius of the powder cone

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder blend were passed through a sieve no. 18 to break the clumps, if any. Accurately weighed 50 g of the powder blend was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14+2 mm. The tapped volume (Va) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tap volume was measured to the nearest graduated unit. The LBD and TBD were calculated in g per ml using following formulae (I.P, 1996).

LBD = weight of the powder/volume of the packing.

TBD = weight of the powder/tapped volume of the packing

Compressibility index (Carr's Index)

The compressibility of the powder was determined by the Carr's index. It is the simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down (Charyulu *et al*., 2011).The formula for Carr's index is as below

Carr's index (%) = [(TBD - LBD /TBD)] x 100

Hausner's ratio

It is the ratio of tapped to bulk density and was calculated by using the formulae (Kumari *et al*., 2012).

Hausner's ratio = TD/BD

Evaluation of floating tablets

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, drug content, swelling index, *in vitro* buoyancy and *in vitro* drug release study.

Dimensions

The dimensions of the tablets are thickness and diameter. The tablets should have uniform thickness and diameter. Thickness and diameter were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

Uniformity of weight test

Twenty tablets from each batch were randomly selected and weighed together. The tablets were then weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 5%). The percent deviation was calculated using the following formula (I.P, 1996).

% weight variation = [(Individual weight - Average weight /Average weight)] x 100

Table no. 2: Tablet weight variation test as per I.P.

S. No.	Average weight of tablet (mg)	Maximum % difference
1.	80 or less	±10
2.	80-250	±7.5
3.	Greater than 250	±5

Hardness test

Hardness of the tablets was determined at room temperature by diametric compression using a Monsanto tablet hardness tester. Ten tablets were selected randomly from the different batches of the tablets prepared and used for the experiment. A tablet was placed between the plate of the tester and the knob was screwed until contact was made after which there was enough pressure due to further screwing to cause breakage. The hardness was then read on the side scale of the tester. Results were taken only from tablets which split clearly into two halves without any sign of lamination. The hardness of the tablets should NLT 3.0 Kg/cm^2 as per I.P.

Friability test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. For tablets with a unit mass equal to or less than 650 mg a sample of whole tablets corresponding to 6.5 g, was taken. For tablets with a unit mass of more than 650 mg, a

sample of 10 whole tablets was taken. Tablets were weighed collectively and placed in the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using following formula (Lechman *et al*., 1987).

Friability = [(W1 – W2 /W1)] x 100

Where, W1 = weight of the tablet before test.

W2 = weight of the tablets after test.

Drug content

For the drug content uniformity test ten tablets were weighed randomly and powdered. The powder equivalent to average weight of cefixime trihydrate tablets was dissolved in 0.1N HCl buffer solution, pH 1.2 for 5 hrs with occasional shaking and diluted to 100 ml with buffer. The solution was filtered through whattman filter paper.1 ml of the filtrate solution was diluted to 100 ml with the 0.1N HCl buffer. The cefixime trihydrate content was determined by measuring the absorbance at 288 nm using UV spectrophotometer (Charyulu *et al*., 2011).

***In vitro* buoyancy study**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et a*l., (1994).The tablets were placed in 250 ml beaker containing 0.1N HCL. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1N HCL and the time during which the dosage form remain 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 time by which dosage form remain buoyant is called total floating time (TFT) (Mohapatra *et al*., 2013).

***In vitro* swelling study**

The swelling of polymers used were determined by water uptake. It was observed that the swelling increased with increases in polymer concentration. Usually swelling is essential to ensure floating. For floating of tablet, there should be appropriate balance between swelling and water uptake. Tablets were weighed individually and placed separately in glass beaker containing 250 ml of 0.1N HCl buffer pH 1.2 and incubated at 37±0.5°C. At regular intervals 1, 2, 3, 4, 5, 6, 7 and 8 and hours, the tablets were withdrawn from the basket and blotted with tissue paper to removed excess surface water and the swollen tablets were reweighed on analytical balance (Nanjwade *et al*., 2012).

Swelling index (SI) of tablets was calculated using the following formula.

% Swelling Index = [(Wet weight - Dry weight/ Dry weight)] ×100

In vitro drug release study

In vitro dissolution studies were carried out in USP type-II (Paddle) dissolution apparatus using 900ml 0.1N HCl buffer pH 1.2 as dissolution media. The paddle was rotated at 50 rpm and the temperature was maintained at 37±0.5°C throughout the study. 5 ml of the samples was withdrawn at every 1hr interval for 12 hrs and replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug releases by measuring the absorbance at 288 nm using UV-Visible spectrophotometer. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve (Mohapatra *et al*., 2013).

Drug release kinetics

The kinetic models used in the assessment of the dissolution data in this study were the Zero order, First order, Higuchi model, Hixson-Crowell models and Korsmeyer-Peppas model.

For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release (Martin, 2002).

RESULT AND DISCUSSION

Evaluation of fenugreek mucilage

Fenugreek mucilage powder was evaluated in terms of Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio. All the results are tabulated in Table no. 2. The angle of repose (25-30) indicates good flow properties and the value for prepared mucilage was 26.36. Hence it indicates good flow properties. For compressibility index the values up to 20% results good flow properties and values for prepared mucilage was 15.59 %. Hence it shows good flow properties.

Table no. 2: Physical Properties of fenugreek mucilage

Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose(°)
0.341	0.404	15.59	1.18	26.36

Evaluation of powder blend

Angle of repose

The angles of repose of various formulations F1 to F9 were calculated and the value of θ for each formulation is shown in Table no. 3. The results of angle of repose (25-30) indicate good flow properties and the values for prepared formulations ranges from 25 to 27. Hence it indicates good flow properties.

Bulk density and tapped density

The BD and TD for the powder blend of various formulations F1 to F9 were determined and their respective values are shown in Table no. 3. The results of bulk density and tapped bulk density were ranged from 0.348 to 0.405g/ml and 0.402 to 0.473g/ml.

Hausner's ratio

The Hausner's ratios for the blend of various formulations F1 to F9 were calculated and the value of Hausner's ratio for each formulation is shown in Table no. 3. The Hausner's ratio of precompressed blends of cefixime trihydrate formulations F1-F9 was in the range 1.15 to 1.19 indicating that the studied blends have fair to good flow rate. This is because for a blend to have good flow rate, values of Hausner's ratio should be 1.19 to 1.25 and for a blend to have fair flow rate, Hausner's ratio should be 1.12 to 1.18.

Compressibility index

The compressibility indexes for the blend of various formulations F1 to F9 were calculated and the value of compressibility index for each formulation is shown in Table no. 3. The compressibility index of pre compressed blends of cefixime trihydrate formulations F1 to F9 was in the range of 13.43% to 16.40%, indicating the good flow properties of powder blend. This is because, for a blend to have good flow properties value of compressibility should be up to 20%. Hence all the blends were found suitable for direct compression into matrix tablets.

Table no. 3: Physical properties of powder blend

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose(°)
F1	0.355	0.415	14.45	1.16	25.64 ± 0.11
F2	0.348	0.402	13.43	1.15	26.48 ± 0.10
F3	0.361	0.421	14.25	1.16	27.86 ± 0.15
F4	0.392	0.460	14.78	1.17	26.85± 0.05

F5	0.405	0.473	14.37	1.16	26.35± 0.03
F6	0.399	0.469	14.92	1.17	26.94±0.09
F7	0.368	0.437	15.78	1.18	25.12±0.12
F8	0.372	0.445	16.40	1.19	27.54±0.08
F9	0.381	0.453	15.89	1.18	25.41±0.11

Evaluation of the floating tablets

The tablet formulations were subject to various post-compressive evaluation tests, such as thickness, diameter, and uniformity of weight, drug content, and hardness, friability, *in vitro* buoyancy and *in vitro* dissolution studies. The results for all the formulations were shown in Table no. 4.

Shape of the tablet

Microscopic examination of tablet from each formulation showed circular shape with no cracks.

Weight uniformity test

The maximum weight variation was found in the range of 498±3.74 to 502±3.03 from all the formulations. It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per Pharmacopoeia standard the deviation should not be more than 5% for tablet having weight 500 mg). All formulations showed values within ranges.

Thickness and diameter test

Thickness and diameter of the developed formulations F1 to F9 varied from 4.10±0.04 mm to 4.19±0.02 mm and 12.08±0.02 mm to 12.15±0.05 mm respectively. Thickness and diameter test reveals that all the formulations showed uniform thickness and diameter.

Hardness test

Hardness of the developed formulations F1 to F9 varied from 6 to 8 kg/cm2 in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling. The hardness of the tablets should NLT 3.0 Kg/cm2 as per I.P.

Friability test

Another measure of tablet hardness was the friability. The loss in total weight of the tablets due to friability was in the range of 0.129 to 0.511%. Compressed tablets that lose less than 1

% of their weight are generally considered acceptable. All the formulations showed weight loss less than 1%.

Table no. 4: Physical properties of tablets

Batch No.	Weight variation (mg) ± SD (n=20)	Diameter (mm) ± SD (n=10)	Thickness (mm) ± SD (n=10)	Hardness (kg/cm²) ±SD (n=10)	Friability (%) ± SD (n=10)	Drug content (%) ± SD (n=10)
F1	498±3.74	12.08±0.02	4.19±0.02	6.38±0.29	0.421	95.83
F2	500±2.46	12.10±0.03	4.14±0.02	7.05±0.27	0.342	96.56
F3	502±3.03	12.14±0.04	4.13±0.04	7.07±0.18	0.356	97.53
F4	501±3.12	12.12±0.03	4.15±0.03	6.98±0.16	0.436	102.13
F5	501±3.60	12.14±0.05	4.16±0.04	6.67±0.16	0.511	98.73
F6	499±3.81	12.12±0.03	4.17±0.04	6.71±0.17	0.181	99.88
F7	500±2.22	12.14±0.05	4.10±0.04	8.17±0.19	0.304	98.26
F8	502±2.90	12.15±0.05	4.13±0.03	7.12±0.26	0.281	98.69
F9	498±3.30	12.14±0.04	4.12±0.05	7.55±0.12	0.129	99.42

***In vitro* buoyancy study**

The *in vitro* buoyancy was determined by floating lag time and total floating time. Floating lag time and duration of floating of various formulations were tabulated in Table no. 5. All formulations F1- F9 shows the floating lag time less than one minute and the duration of floating was greater than 12 hrs. Sodium bicarbonate was used as an effervescent agent that maintains the buoyancy of the tablets. It was observed that floating lag time increases with the increase in the concentration of polymers. Xanthan gum showed good buoyancy as compared to fenugreek mucilage. Formulation F2 showed only 05 second to float over the medium because the concentration of both the polymers increased. Prepared floating tablets of cefixime trihydrate were floated over the medium were showed in Figure no. 2.

Table no. 5: Floating lag time and duration of floating of various formulations

Formulation Code	Floating lag time (sec)	Duration of floating (hrs)
F1	10	>12
F2	05	>12
F3	10	>12
F4	20	>12
F5	30	>12
F6	30	>12
F7	20	>12
F8	20	>12
F9	25	>12

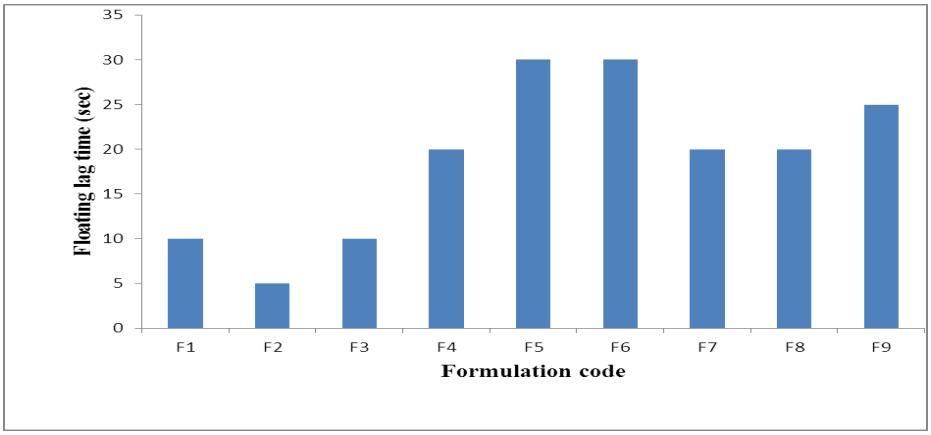

Figure no. 1: Floating lag time of various formulations

At initial time **After 10 sec** **After 8 hrs**

Figure no. 2: Tablets float in 0.1N HCl at initial time, after 10 sec and after 8 hrs

***In vitro* swelling study**

Swelling study was performed on all the batches (F1 to F9) for 8 hrs. Cefixime trihydrate floating tablets showed higher swelling index in the first 5 hrs but could not maintain up to 8 hrs due to continuous erosion of the polymer. All the formulations showed constant increase in swelling index up to 5 hrs. Formulations F1, F2 and F3 which were prepared with increase in the concentration of xanthan gum showed higher swelling as compared to other batches. Formulations F4 and F7 which were prepared with increase in the concentration of fenugreek mucilage and decrease in the concentration of xanthan gum showed less swelling index. It was observed that xanthan gum show high swelling as compared to fenugreek mucilage. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. The results of swelling index are given in Table no. 6.

Table no. 6: *In vitro* swelling study of various formulations

Time (hour)	Swelling index (% weight gain)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	32	35	31	29	25	26	30	29	28
2	41	44	39	37	33	34	39	37	37
3	52	53	49	45	41	44	47	45	45
4	60	61	57	54	47	52	54	54	53
5	67	69	64	60	54	58	60	61	59
6	72	75	70	67	60	63	67	67	65
7	78	81	75	73	65	67	74	73	72
8	83	86	81	79	69	72	80	79	77

***In vitro* drug release study**

All the formulations of prepared floating tablets of cefixime trihydrate were subjected to *in vitro* release studies and results are tabulated in Table no. 7. These studies were carried out using dissolution apparatus paddle method containing 0.1N HCl buffer pH 1.2. Optimized formulation F5 prepared with equal amount of xanthan gum (25mg) and fenugreek mucilage (25mg) showed maximum drug release of 84.53% after 12 hrs. While the formulation F2 prepared with increase the concentration of both the polymers (75mg) showed minimum drug release of 67.72% after 12 hrs. The results indicate that an increase in drug release with decrease in the polymer concentration. It could be due to increase in polymer concentration leads to the formation of thick gel barrier, causing the difficult drug diffusion through the matrix and thus decreasing the overall drug release from the matrix. Formulation F3 prepared with increase the concentration of xanthan gum (75mg) and decreases the concentration of fenugreek mucilage (25mg) showed drug release of 73.52 after 12 hrs. Formulation F4 prepared with increase the concentration of fenugreek mucilage (75mg) and decreases the concentration of xanthan gum (25mg) showed drug release of 80.55 after 12 hrs. The results indicated an increase the drug release with decrease the concentration of xanthan gum and increase the concentration of fenugreek mucilage. Formulation F6 prepared with decrease the concentration of xanthan gum (25mg) and increases the concentration of fenugreek gum (50mg) showed drug release of 82.32% after 12 hrs. While the formulation F9 prepared with decrease the concentration of fenugreek gum (25mg) and increases the concentration of xanthan gum (50mg) showed minimum drug release of 79.84% after 12 hrs. From the results, it is evident that double the concentration of fenugreek mucilage (50mg) showed nearly same result as that of (25mg) of xanthan gum.

Table no. 7: Percent cumulative drug release of various batches

S. No.	Time (hrs)	% DRUG RELEASE								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2.	1	10.23±0.08	8.89±0.07	12.05±0.06	14.01±0.04	16.11±0.04	14.15±0.05	12.14±0.05	13.15±0.04	14.92±0.05
3.	2	18.76±0.14	16.35±0.10	21.36±0.04	24.66±0.10	27.15±0.05	25.04±0.09	21.79±0.06	22.27±0.03	24.47±0.05
4.	3	26.77±0.09	23.71±0.13	28.10±0.07	33.55±0.11	36.52±0.04	34.08±0.03	29.15±0.04	31.59±0.07	32.24±0.09
5.	4	33.13±0.15	30.22±0.12	35.47±0.10	41.05±0.04	45.84±0.10	42.72±0.04	36.85±0.11	38.29±0.07	40.53±0.14
6.	5	40.06±0.16	36.96±0.11	42.69±0.09	48.22±0.05	52.49±0.12	49.71±0.12	43.50±0.09	44.07±0.05	45.03±0.08
7.	6	46.61±0.17	42.75±0.10	48.04±0.10	54.27±0.08	58.57±0.12	56.90±0.13	49.14±0.10	50.82±0.11	51.21±0.06
8.	7	52.45±0.09	47.11±0.15	54.60±0.06	59.22±0.14	63.37±0.09	61.79±0.15	54.03±0.10	55.09±0.17	57.44±0.08
9.	8	57.81±0.14	52.65±0.16	59.29±0.09	64.86±0.11	68.59±0.05	66.06±0.06	60.82±0.08	61.79±0.16	62.99±0.08
10	9	61.12±0.13	57.68±0.09	63.04±0.11	69.55±0.08	73.38±0.06	71.28±0.04	64.23±0.08	65.63±0.11	67.26±0.11
11.	10	65.15±0.19	61.33±0.13	67.36±0.11	73.15±0.09	77.18±0.13	75.89±0.08	68.94±0.09	69.76±0.13	73.29±0.11
12.	11	68.04±0.23	65.46±0.22	70.57±0.10	77.52±0.09	81.12±0.07	79.92±0.06	72.49±0.07	73.26±0.08	77.76±0.08
13.	12	71.70±0.17	67.72±0.27	73.52±0.13	80.55±0.07	84.53±0.10	82.32±0.07	74.90±0.10	77.97±0.09	79.84±0.10

*Mean ± SD, n=3

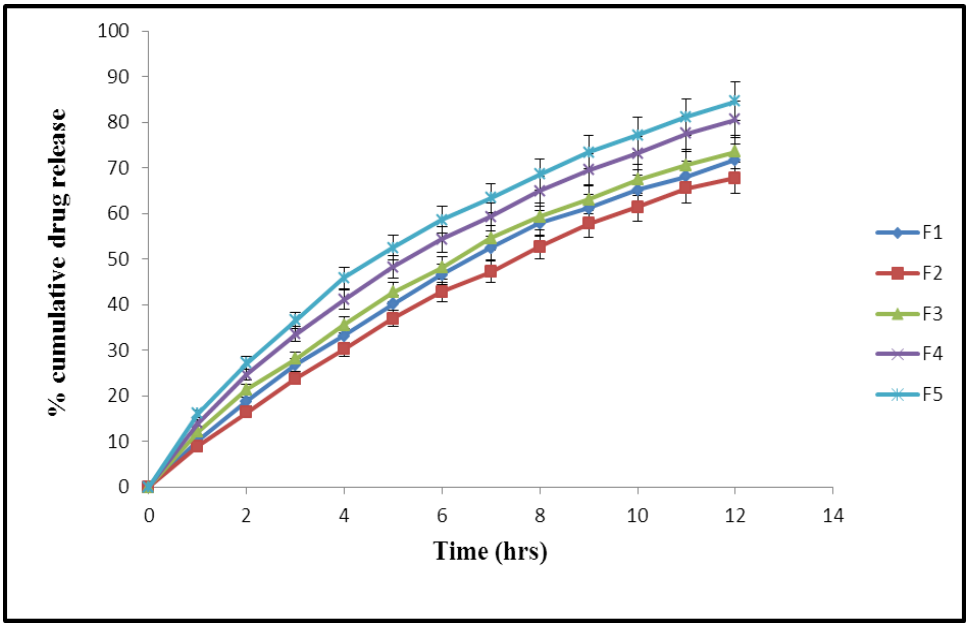

Figure no. 3: Drug release profile of batches (F1-F5)

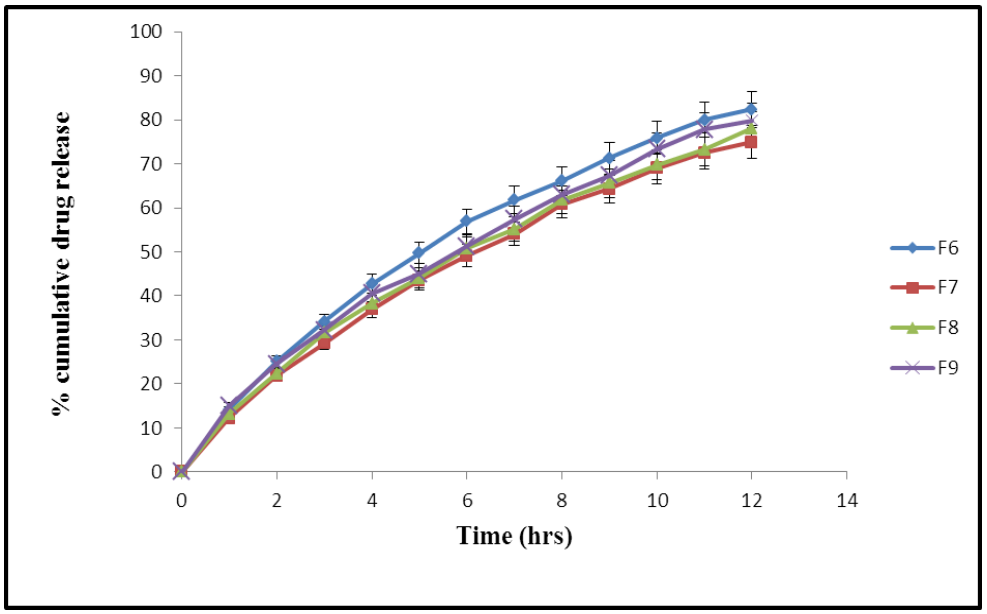

Figure no. 4: Drug release profile of batches (F6-F9)

Drug release kinetics

The kinetic models used in the assessment of the dissolution data in this study were the Zero order, First order, Higuchi and Hixson-Crowell models while Korsmeyer-Peppas model was used to determine the mechanism of drug release. The results of determinations are summarized in Table no. 8.

On the basis of kinetic analysis it can be concluded that the drug release from the studied formulations followed Higuchi model as it has highest value of R^2. Hence, we can say that diffusion is the predominant mechanism of drug release from cefixime trihydrate formulations. From the Korsmeyer-peppas plots it has been observed that regression value (n-value) of all the formulations (F1 to F9) ranges from 0.6573 to 0.8194, suggesting that the drug was released by non-fickian diffusion in all the cases. An increased the *n* value that is indicative of the release mechanism from diffusion toward a relaxation and erosion controlled process.

Table no. 8: Kinetic data of cefixime trihydrate floating tablets

B. No.	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Hixon-crowell (R^2)	Peppas plot	
					(R^2)	n-value
F1	0.9684	0.9693	0.9761	0.9695	0.9972	0.7808
F2	0.9789	0.9800	0.9698	0.9802	0.9981	0.8194
F3	0.9612	0.9609	0.9820	0.9615	0.9981	0.7270
F4	0.9484	0.9478	0.9879	0.9485	0.9972	0.6927
F5	0.9314	0.9311	0.9918	0.9316	0.9965	0.6573
F6	0.9468	0.9465	0.9873	0.9470	0.9964	0.7005
F7	0.9610	0.9613	0.9824	0.9616	0.9979	0.7279
F8	0.9578	0.9576	0.9849	0.9581	0.9982	0.7063
F9	0.9564	0.9561	0.9863	0.9568	0.9994	0.6741

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated floating tablets of cefixime trihydrate were wrapped in aluminum foil and stored at temperature 40^0 C ± 5^0 C / 75 % RH for a period of one month. After the period of one month floating tablets were evaluated for physical appearance, drug content, *in vitro* buoyancy study and *in vitro* drug release.

The physical stability was assessed by the appearance and there was no change in color or shape of the tablets. The chemical stability was assessed by change in drug content and drug release and there was no much change in chemical properties. *In vitro* buoyancy study showed the tablet was float over the medium less than 1 minute. So the formulation F5 and F6 was stable at end of one month.

FTIR study

IR spectra of pure drug and physical mixture of drug and excipients are given in Fig. 8. The characteristic peaks of cefixime trihydrate at: 3294 cm-1 for N-H stretching, 1771 cm-1 for C=O stretching, 1669 cm-1 for C=C alkenes, 1458 cm-1 for C-C stretching, etc. The results of the FTIR spectra analysis showed that the peaks and the pattern of the spectra were similar in pure drug and mixture of drug and excipients, which indicated that there was no chemical interaction or decomposition of cefixime trihydrate during the preparation of the tablets.

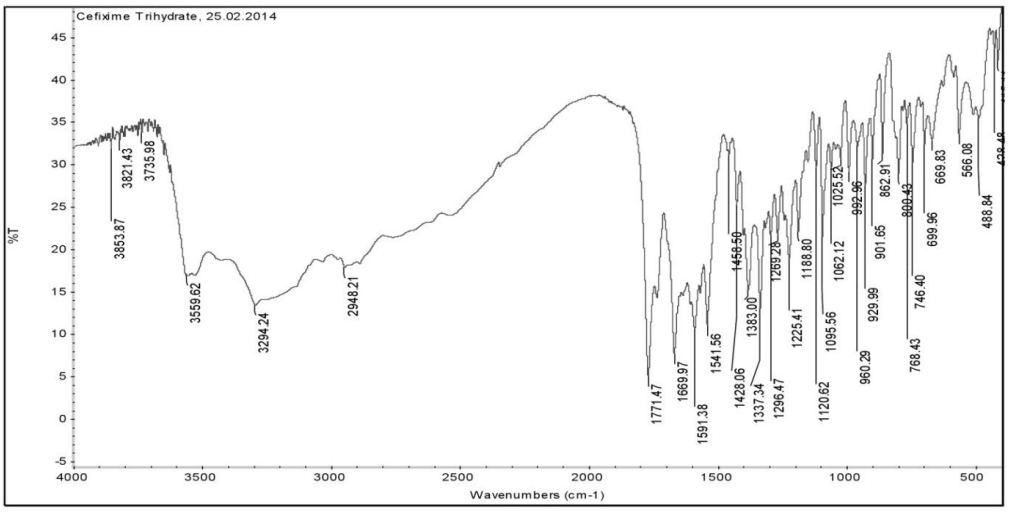

Figure no. 5: FTIR spectra of cefixime trihydrate

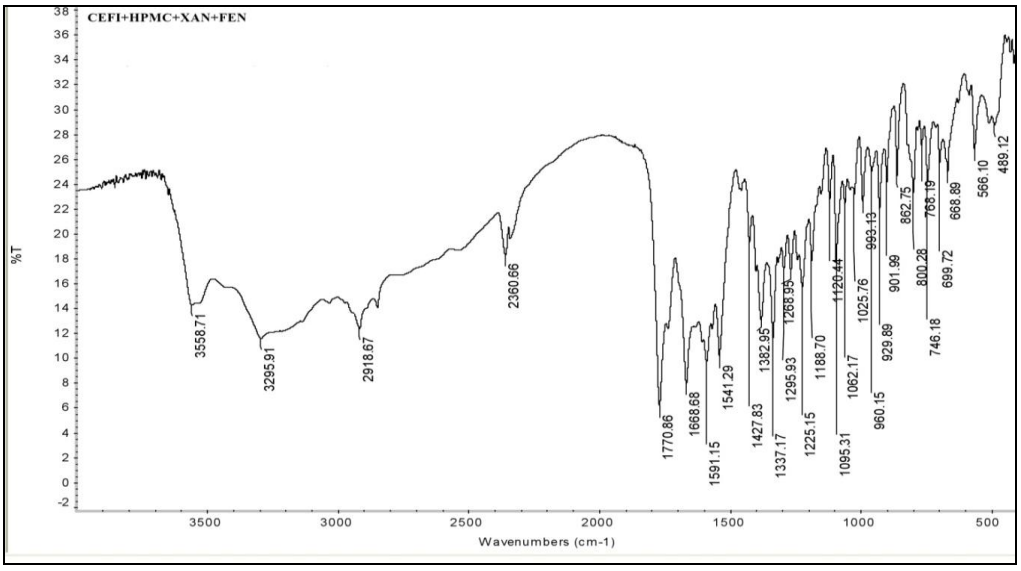

Figure no. 6: FTIR spectra of physical mixture of drug and polymers

CONCLUSIONS

Controlled release gastro retentive floating matrix tablets of cefixime trihydrate can be successfully prepared using HPMC K100 M, xanthan gum and fenugreek mucilage.

Prepared floating tablets of cefixime trihydrate were evaluated for weight uniformity test, thickness, hardness, friability, drug content, swelling index, *in vitro* buoyancy and *in vitro* drug release. All the results showed within ranges. FTIR spectra of pure cefixime trihydrate and the polymers individually as well as the combination of drug with all the other polymers are shown. No significant changes in intensity of the FTIR bands of cefixime trihydrate were observed with polymers indicating the absence of interaction. *In vitro* buoyancy results indicated that floating lag time observed for all the tablets was within 0-1 minute after immersion into gastric media and the duration of floating was greater than 12 hrs for all the batches. Sodium bicarbonate was used as an effervescent agent that maintains the buoyancy of the tablets.

In vitro drug release studies showed optimized formulation F5 prepared with equal amount of xanthan gum and fenugreek gum (25mg) showed maximum drug release of 83.53% after 12 hrs. While the formulation F2 prepared with increase the concentration of both the polymers (75mg) showed minimum drug release of 66.72% after 12 hrs. The results indicated an increase in drug release with decrease in the polymer concentrations. On the basis of kinetic analysis it can be concluded that the drug release from the studied formulations followed Higuchi model as it has highest value of r^2. Hence, we can say that diffusion is the predominant mechanism of drug release from cefixime trihydrate formulations. From the Korsmeyer-peppas plots it has been observed that regression value (n-value) of all the formulations (F1 to F9) ranges from 0.6573 to 0.8194, suggesting that the drug was released by non-fickian diffusion in all the cases. Short term stability studies of formulation F5 and F6 indicated that there were no significant changes in physical appearance, drug content, *in vitro* buoyancy and *in vitro* drug release values after 30 days storage at 40^0 C ± 5^0 C /75 % RH.

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