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Formulation and i*n Vitro* evaluation of Gastroretentive drug delivery system of Cefixime Trihydrate

Yash Paul[1], Manoj Kumar[1] and Bhupinder Singh[2]
[1]Lord Shiva College of Pharmacy, Sirsa (Haryana)
[2]University Institute of Pharmaceutical sciences, Panjab University, Chandigarh

Abstract

A gastroretentive, controlled release drug delivery system of Cefixime trihydrate was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Various grades of HPMC *viz.,* HPMCK100M, HPMCK15M, HPMCK4M were incorporated for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. *In vitro* drug release studies were performed, and drug release kinetics was evaluated using the zero order, first order, Higuchi's model and Korsmeyer-peppas kinetic models. The kinetic study results suggested that the drug was released by fickian diffusion in case of all the developed floating matrix tablet formulations of Cefixime trihydrate. The optimized intragastric floating tablet composed of 15% w/w of HPMC K4M exhibited 94.71±0.20% drug release in 12 h, while the buoyancy lag time was < 1 min, and the tablets remained buoyant for >12 h. All the formulations showed hardness, friability, weight variation and drug content values well within the prescribed limits, indicating that the prepared tablets were of standard quality. FTIR studies of the pure drug, its physical mixture with polymer blend showed that no polymorphic changes occurred during manufacturing of tablets. Optimized tablet formulation exhibited no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

*Corresponding author, Mailing address:
Dr. Yash Paul Singla
Professor & Principal
Lord Shiva College of Pharmacy, Sirsa-125055 (Haryana), INDIA
E-mail: ypsingla@yahoo.co.in
Phone: +91-1666-329204(O); 232684(R);
Fax 242695 (O)

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INTRODUCTION

It has been suggested that compounding the drugs with narrow absorption window in a unique pharmaceutical dosage form with gastroretentive properties, would enable an extended absorption phase of these drugs.

After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in the upper GIT. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs.[1] Gastroretentive dosage form 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 of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients.[2] Thus one of most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.[3] Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of GI tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, swelling systems, bioadhesive systems and high density systems.[4,5] The floating drug delivery system (FDDS) have a bulk density less than gastric fluid and hence, remain buoyant in the stomach without effecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at desired rate from the system.[3] After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentration.[6]

Potential drug candidates for Gastroretentive drug delivery systems

- Drugs those are locally active in the stomach e.g. misoprostol, antacids, etc.
- Drugs that have narrow absorption window in GIT e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin, etc.
- Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole
- Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori
- Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl[7]

Cefixime, the first oral third-generation cephalosporin available, is commonly used for the treatment of upper and lower respiratory tract infections, otitis media, sinusitis, urinary tract infections, gonorrhea, etc. The drug has a number of characteristics that make it effective when administered once or twice daily: a half-life of 3 to 4 h, activity against most common pathogens involved in the infections for which it is indicated, and serum and interstitial concentrations greater than the minimum inhibitory concentration of most of the common pathogens of these infections for up to 24 h after a 400 mg dose.[8] Therefore, in the light of above background it was decided to develop gastroretentive floating matrix tablets of Cefixime trihyrate.

MATERIALS AND METHODS

Materials used in the development of Cefixime trihydrate tablets.

Material	Manufacturer/ Supplier
Cefixime trihydrate	M/S Macleods Lab. Ltd, Baddi, H.P
HPMC K4M, HPMC K15M, HPMC K100M	M/S Leo chem, Bangalore, Karnataka
Sodium bicarbonate	M/S Nice Chemicals Pvt. Ltd, Cochin, Kerala
Microcrystalline cellulose	M/S Leo chem, Bangalore, Karnataka
Magnesium Stearate	M/S Titan Biotech Ltd, Bhiwadi, Rajasthan
Hydrochloric acid	M/S Nice Chemicals Pvt. Ltd, Cochin, Kerala
Sodium CMC	M/S Otto chemicals , Mumbai, Maharashtra
Sodium Alginate	M/S Otto chemicals , Mumbai, Maharashtra
Citric acid	M/S Nice Chemicals Pvt. Ltd, Cochin, Kerala

FORMULATION OF CONTROLLED RELEASE MATRIX TABLETS OF CEFIXIME TRIHYDRATE

Matrix tablets of Cefixime trihydrate with other excipients were prepared by direct compression. The weight of Cefixime trihydrate was kept constant in all the prepared tablets at 40% w/w/tablet. Different viscosity grades of HPMC namely HPMC K4M, HPMC K15M or HPMC K100M 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 500 mg. 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. Microcrystalline cellulose (5% w/w) was used as a filler. Sodium alginate (3% w/w) was used as gel forming agent. Citric acid (4% w/w) was used as acid source. Magnesium stearate (2% w/w) was employed as a lubricant and sodium CMC (4%) was incorporated as swelling agent. To make powder mixtures, the drug, polymer, MCC, sodium carboxymethylcellulose, sodium bicarbonate, sodium alginate, citric acid and lactose were thoroughly mixed for 10 min. This powder mixture was then lubricated with magnesium stearate then compressed into tablets in 12 mm flat face round tooling. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 6-7.5 kg/cm^2. The detailed compositions of the prepared matrix tablets formulations are given in table 1.

Table 1: Detailed formula of various formulations of Cefixime trihydrate

Drug/ Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime (% w/w)	40	40	40	40	40	40	40	40	40
HPMC K100M (% w/w)	15	20	25	-	-	-	-	-	-
HPMC K15M (% w/w)	-	-	-	15	20	25	-	-	-
HPMC K4M (% w/w)	-	-	-	-	-	-	15	20	25
Sodium bicarbonate (% w/w)	15	15	15	15	15	15	15	15	15
Micro-crystalline cellulose (% w/w)	5	5	5	5	5	5	5	5	5
Sodium Carboxymethylcellulose (% w/w)	4	4	4	4	4	4	4	4	4
Citric acid (% w/w)	4	4	4	4	4	4	4	4	4
Sodium alginate (% w/w)	3	3	3	3	3	3	3	3	3
Magnesium stearate (% w/w)	2	2	2	2	2	2	2	2	2
Lactose q.s. (mg)	500	500	500	500	500	500	500	500	500

A. MICROMERITICS STUDIES

Various formulations before compression were evaluated for their flow properties in terms of following parameters.

(i) Angle of repose

Static angle of repose was measured according to the fixed funnel and free standing core method of Banker and Anderson. Blends were carefully poured through the Enar reposograph until the apex of the conical pile so formed just reached the tip of the funnel of reposograph. Height of instrument was fixed to 4 cm.[9] Thus, with r being the radius of the base of the granules conical pile and the angle of repose (θ) was calculated by using the eqn. 1

$\tan\theta = h/r$, therefore, $\theta = \tan^{-1} h/r$... (1)

(ii) Bulk density/Tapped density

Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of powder blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II (up to1250 taps). The tapping was continued until no further change in volume was noted. Volume of packing after tapping was noted. BD and TD were calculated using eqn. 2 and 3 respectively.

BD = weight of the powder / volume of the packing**... (2)**

TD = weight of the powder / tapped volume of the packing**... (3)**

(iii) Compressibility index

Compressibility index of the powder was determined by Carr's compressibility index[10] as given by equation 4

Carr's index (%) = [(TD – BD) x 100] / TD**... (4)**

It helps in measuring the force required to break the friction between the particles and the hopper.

(iv) Hausner's ratio

It is the ratio of tapped to bulk density[11] and was calculated by using the eqn. 5

Hausner's ratio = TD/BD **... (5)**

B. EVALUATION OF FLOATING MATRIX TABLETS OF CEFIXIME TRIHYDRATE

The prepared tablets of Cefixime trihydrate were evaluated for quality control tests like hardness, friability, weight variation, thickness, diameter, swelling index, floating or buoyancy test, drug content uniformity and *in vitro* dissolution studies.

(i) Tablet hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The crushing strength of prepared tablets was determined for ten tablets of each batch using Monsanto hardness tester.

(ii) Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined.

% loss = Initial wt. of tablets - Final wt. of tablets/ Initial wt. of tablets x 100**...(6)**

(iii) Weight variation

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to USP standards, not more than the percentage shown in the table 2 and none deviates by more than twice that percentage.[12]

Table 2: Weight variation table for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

(iv) Tablet Thickness/ Diameter

Thickness and diameter of tablets was important for uniformity of tablet size. Six tablets were examined for their thickness and diameter using vernier callipers and the mean thickness and diameter value was calculated.

(v) Swelling index

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation batch, one tablet was weighed and placed in a beaker containing 200 mL of 0.1 N HCl. After each interval the tablet was removed from beaker and weighed again up to 12 hours.[13] The swelling index was calculated using following equation 7.

Swelling Index % (S.I.) = (Wt-Wo)/Wo*100... (7)

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker.

(vi) Floating or buoyancy test

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT). The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37±0.5 ^{o}C in 900 mL of simulated gastric fluid at pH 1.2. The time of duration of floatation was observed visually.[6]

(vii) Drug content uniformity

For the drug content uniformity test ten tablets were weight and pulverised to a fine powder, a quantity of powder equivalent to 100 mg of Cefixime was dissolved in 100 mL methanol and liquid was filtered using whatman filter paper and diluted up to 50µg/mL. The cefixime content was determined by measuring the absorbance at 288 nm using UV spectrophotometer, after appropriate dilution with methanol.[14]

(viii) *In-vitro* dissolution studies

Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for Cefixime trihydrate was carried out as per USP method for dissolution test for tablets and capsules using apparatus II (paddle type). Dissolution medium used was 900 mL of 0.1 N HCl, rotating the paddle at 50 rpm at 37±0.5^{o}C. An aliquot of 5 mL of samples were withdrawn at different time periods. These samples were filtered and diluted. Absorbance of the resulting solution was measured at 288.0 nm. Contents of Cefixime trihydrate were calculated.[12] Percent drug release was calculated by using the eqn. 8 as follows

% Drug release = K × Absorbance **...(8)**

Where K can be calculated by using eqn. 9 as follows

K = Std. conc.×vol. of dissolution media×dilution factor×100/std. abs.×dose×1000 **...(9)**

Drug excepients compatibility studies

(i) Fourier transform infra-red (FT-IR) studies

The FTIR spectra of the drug and its physical mixtures with polymer blend of selected best formulation were recorded in KBR using an FTIR spectrophotometer.

Kinetic analysis of drug dissolution data

The dissolution profile of most satisfactory formulation was fitted to zero order, first order, Higuchi's model and Korsmeyer-peppas model to

ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model.

- Percent drug released versus time (zero-order kinetic model)[15]
- Log percent drug remaining versus time. (first-order kinetic model)[16]
- Percent drug released versus square root of time (Higuchi's model)
- Log percent drug released versus log time (Korsmeyer-Peppas model)[17]

Accelerated stability studies

It is imperative that the final product be sufficiently rugged for marketing worldwide under various climate conditions including tropical, subtropical temperature. Stability testing is done to check the physical, chemical and physiological properties of the product. Accelerated stability testing was carried out as per ICH guidelines (40°C/75% RH)[14] to ascertain the product stability for longer period in a shorter period of time. The most satisficatory formulation sealed in aluminum packing and kept in humidity chamber maintained at 40°C/75% RH for three months. At the end of studies, samples were analysed for colour, *in vitro* drug release, % friability, hardness and % drug content.

RESULTS AND DISCUSSION

C. MICROMERITICS STUDIES

(i) Angle of repose

The angles of repose (θ) for the blend of various formulations F1 to F9 were calculated and the value of θ for each formulation is shown in Table 3. As vivid from Table 3, the angle of repose of precompressed blend of Cefixime trihydrate of formulations F1 to F9 was in the range 21.24±0.08° to 23.51±0.13°, indicating that the studied blends have excellent flow properties, because for a blend to have excellent flow properties, value of θ should be ≤ 25°.[9]

(ii) Bulk 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 3. As observed from the results, BD and TD for all the formulations were found in the range between 0.2824± 0.04 g/cm³ to 0.3499±0.03 g/cm³ and 0.3280±0.05 g/cm³ to 0.4091±0.04 g/cm³ respectively.

Table 3: Parameters evaluated for powder blend of Cefixime trihydrate

Formulation code	Angle of repose (θ) (n=3)	Bulk density (gm/cm³) (n=3)	Tapped density (gm/cm³) (n=3)	Carr's index (%) (n=3)	Hausner's ratio (H_R) (n=3)
F1	21.32 ± 0.12	0.3467±0.04	0.3994±0.04	13.29±1.14	1.1533±0.02
F2	23.51 ± 0.13	0.3389±0.03	0.4091±0.04	16.03±2.35	1.2065±0.03
F3	22.26 ± 0.02	0.3326±0.03	0.3798±0.03	12.38±1.56	1.1415±0.02
F4	21.24 ± 0.08	0.3499±0.03	0.4091±0.03	14.46±0.73	1.1691±0.01
F5	22.42 ± 0.06	0.3254±0.04	0.3740±0.05	12.96±0.77	1.1490±0.01
F6	22.12 ± 0.04	0.2938±0.07	0.3435±0.08	14.38±2.97	1.1689±0.04
F7	23.14 ± 0.02	0.3140±0.05	0.3659±0.04	14.35±3.81	1.1692±0.05
F8	21.65 ± 0.08	0.2883±0.05	0.3410±0.06	15.37±2.04	1.1820±0.03
F9	22.75 ± 0.05	0.2824±0.04	0.3280±0.05	13.95±0.85	1.1622±0.01

(iii) Compressibility index

The compressibility indexes for the blend of various formulations F1 to F12 were calculated and the value of compressibility index for each formulation is shown in Table 3. As vivid from Table 3, the compressibility index of precompressed blends of Cefixime trihydrate formulations F1 to F9 was in the range of 12.38±1.56% to 16.03±2.35%, indicating the good flow properties of powder blend. This is because for a blend to have good flow properties value of compressibility should be in the range of 11% to 15%.[18] Hence all the blends were found suitable for direct compression into matrix tablets.

(iv) Hausner's ratio

The Hausner's ratio 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 3. As vivid from Table 3, the Hausner's ratio of precompressed blends of Cefixime trihydrate formulations F1-F9 was in the range 1.1415±0.02 to 1.2065±0.03 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.[12]

EVALUATION OF PHYSICOCHEMICAL PARAMETERS

(i) Tablet Hardness:

Hardness of the developed formulations F1 to F9 varied from 6.2±0.08 to 7.3±0.05 kg/cm^2 (Table 4) in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling.

(ii) Friability:

The loss in total weight of the tablets due to friability was in the range of 0.62±0.08% to 0.87±0.07% (Table 4) in all the formulations F1-F9 and the friability value is less than 1% which ensures that formulated tablets were mechanically stable.[18]

(iii) Weight variation:

The maximum weight variation was found in the range of 497.67±3.79 to 503.00±1.00 (Table 4) from all the formulations. As none of the formulation showed a deviation of more than ±5% (I.P. limit) for any of the tablets tested, the prepared formulations comply with the weight variation test, thus it fulfills the USP requirements. [18]

(iv) Tablet Thickness/ Diameter:

Thickness and diameter of the developed formulations F1 to F9 varied from 4.12±0.03 mm to 4.20±0.04 mm and 12.10±0.06 mm to 12.16±0.04 mm respectively (Table 4) in all the formulation and the average thickness and diameter is within the range of ± 5%. Each sample was analyzed in triplicate.[18]

(v) Swelling index:

Swelling is also a vital factor to ensure buoyancy and drug dissolution of matrix tablets. The gastroretentive matrix tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. The gel layer governs the drug release from the matrix tablet. Table 4 showed the % swelling index values of all the nine formulations (F1-F9). It is evident that % swelling index values varies from 92.05±0.6% to 98.78±0.8% and also F7 has highest % swelling index value of 98.78±0.8%.

(vi) Floating or buoyancy test:

All formulations (F1- F9) shows the floating lag time less than one minute and good floating time of more than 10 h (Table 4).

(vii) Uniformity of drug content:

The drug content in different tablet formulations was highly uniform and in the range of 95.65 to 99.28 (Table 4) i.e within the permissible limits of IP.[19]

Table 4: Tablet formulations evaluated for different parameters

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tablet wt. (mg) , n=3	501.67±3.51	503.00 ±1.00	501.33±3.03	497.67±3.79	500.67±5.13	500.33±2.53	500.00± 4.36	501.33±3.51	500.33±4.51
Thickness (mm) , n=3	4.13 ±0.03	4.16 ±0.02	4.12 ±0.03	4.12 ±0.06	4.13 ±0.07	4.12 ±0.04	4.20 ±0.04	4.14 ±0.02	4.13 ±0.08
Diameter (mm) , n=3	12.16 ±0.04	12.14 ±0.02	12.10 ±0.06	12.14 ±0.02	12.14 ±0.02	12.14 ±0.04	12.12 ±0.08	12.12 ±0.06	12.12 ±0.04
Friability (%) , n=3	0.74 ±0.06	0.85 ±0.03	0.70 ±0.04	0.78 ±0.02	0.82 ±0.04	0.80 ±0.08	0.87 ±0.07	0.62 ±0.08	0.68 ±0.06
Hardness (Kg/cm²), n=3	6.4 ±0.04	6.9 ±0.03	7.3 ±0.05	7.2 ±0.06	7.1 ±0.03	6.6 ±0.02	6.2 ±0.08	6.9 ±0.04	6.9 ±0.04
Drug content (%)	96.80	97.43	98.17	97.25	98.59	96.09	99.28	98.87	95.65
Floating lag time (min)	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
Floating duration (min)	> 720	> 720	> 720	> 720	> 720	> 720	> 720	> 720	> 720
Tablet integrity	Intact	Intact	Intact	Intact	Intact	Intact	Intact	Intact	Intact
Swelling index (%) , n=3	92.05 ±0.6	94.06 ±0.2	98.02 ±0.6	94.22 ±0.4	98.12 ±0.6	95.04 ±0.3	98.78 ±0.8	98.32 ±0.2	97.06 ±0.5

(viii) *In vitro* dissolution studies

From *in vitro* drug dissolution profile of Cefixime trihydrate matrix tablet, it was found that more than 20% drug was released till 1 h from F1 to F9 formulations (Drug: various grades of HPMC in different ratios). After 8 h more than 60% of the drug was released from all the formulations. After 12 h the release rate decreased slightly and a sustained release pattern was observed for 12 h. The hydrophilic matrix of HPMC controlled the Cefixime trihydrate release effectively for 12 h. It was observed that formulation with the drug polymer ratio 40:15% w/w/tablet (F1, F4, F7) showed high drug release rates in the range of 94.71±0.20% to 88.13±0.18% when compared to 40:20% w/w/tablet (F2, F5, F8) which showed a drug release rates from 90.33±0.88% to 87.60±0.26% and those of 40:25% w/w/tablet (F3, F6, F9) which showed a drug release rates in the range of 88.30±1.32% to 83.93±0.15% over a period of 12 h. The order of drug release from the selected polymers were found to decrease in the following order HPMC K4M > HPMC K15M > HPMC K100M. Table 5 enlists the dissolution parameters of all the nine formulations developed using various polymers.

Table 5: *In vitro* drug release study: % drug released

Time (h)	F1 (%)± SD	F2 (%)± SD	F3 (%)± SD	F4 (%)± SD	F5 (%)± SD	F6 (%)± SD	F7 (%)± SD	F8 (%)± SD	F9 (%)± SD
1	20.36±0.09	25.64±0.13	20.31±0.09	25.87±0.13	22.33±0.15	28.65±0.09	31.33±0.09	25.74±0.54	23.36±0.13
2	29.45±0.14	30.86±0.09	26.53±0.14	32.20±0.96	27.52±0.18	34.46±0.08	38.80±0.04	31.91±0.54	30.85±0.13
3	34.51±0.18	35.36±0.13	33.97±0.80	41.64±0.11	34.59±0.23	40.10±0.09	45.39±0.09	40.05±1.07	38.78±0.12
4	39.90±0.18	42.71±0.43	41.44±0.12	49.36±0.13	42.50±0.22	48.56±0.08	52.99±0.02	47.60±0.09	45.39±0.13
5	44.42±0.15	48.60±0.18	48.51±0.12	56.50±0.11	50.29±0.15	54.69±0.10	58.60±0.04	54.66±0.10	52.90±0.11
6	51.33±0.20	54.86±0.18	53.79±0.15	62.80±0.95	57.46±0.13	60.90±0.03	64.32±0.05	58.35±0.36	57.29±0.05
7	58.54±0.13	58.65±0.13	57.33±0.14	70.63±0.11	62.96±0.10	65.26±0.08	71.10±0.54	63.01±0.10	63.46±0.14
8	65.43±0.10	65.50±0.18	64.45±0.12	76.22±0.13	69.76±0.22	70.52±0.10	77.56±0.04	70.51±0.09	70.52±0.11
9	74.66±0.13	71.67±0.11	70.63±0.13	82.95±0.18	74.41±0.14	74.97±0.08	82.88±0.04	76.23±0.10	75.79±0.12
10	80.75±0.12	78.14±0.52	77.69±0.13	88.13±0.18	80.23±0.15	80.23±0.04	87.98±0.42	82.85±0.09	81.10±0.12
12	88.13±0.18	87.60±0.26	83.93±0.15	92.53±1.76	89.04±0.54	86.48±0.63	94.71±0.20	90.33±0.88	88.30±1.32
16	86.03±1.00	85.57±1.36	81.36±0.15	90.01±0.85	87.30±0.28	84.00±0.34	92.30±0.44	88.93±0.18	86.70±0.78
20	84.14±0.69	83.77±2.64	79.16±0.92	88.30±0.79	85.07±1.44	82.57±0.64	90.77±0.64	86.09±0.42	84.94±1.28
24	82.82±0.38	81.01±1.22	77.73±1.69	86.27±2.16	83.38±0.62	80.64±0.63	88.71±0.20	84.44±0.62	82.66±4.30

Fig.1 shows *in vitro* drug release profile of various floating matrix tablet formulations (F1- F9) of Cefixime trihydrate.

Among the three grades of HPMC polymer used the tablets prepared with lower viscosity grade i.e. HPMC K4M, have shown drug release rate (94.71±0.20% to 88.30±1.32%) and the higher viscosity grade polymers i.e. HPMC K15M (92.53±1.76% to 86.48±0.63%) and HPMC K100M (88.13±0.18% to 83.93±0.15%). But the much difference was not found in the drug release profiles of tablets prepared with HPMC K4M and HPMCK15M. From the dissolution data of Cefixime trihydrate matrix tablet formulations F1- F9 it has been observed that when the viscosity and content of HPMC are increased, the release of drug tends to become slower. HPMC particles of increasing viscosity grades will swell more slowly and produce swollen particles of smaller volume; then matrices made of particles of HPMC with higher viscosity grade (HPMC K100M) will contain pores of smaller diameters and will show slower release rate then those made of HPMC particles with lower viscosity grades (HPMC K4M, HPMC K15M).

Increase in polymer level from 15% to 20% and to 25% further reduce the release of Cefixime trihydrate from matrix tablets. This finding might be due to increase in resistance of gel layer to drug dissolution and gel erosion. At a higher polymer level, formation of tightly swollen gel layer cause by more intimate contact between the particles of HPMC results in decreased mobility of insoluble drug particles in swollen matrices, which leads to decreased release rate.[20]

Formulation F7 containing 15% of HPMC K4M exhibited short buoyancy lag time, floated for more than 12 h, showed maximum swelling index (98.78± 0.8), and released its maximum drug content (94.71±0.02%) upto 12 h in a controlled manner without changing the physical integrity of tablets in the released medium. Hence formulation F7 was selected as the best formulation for development of controlled release matrix tablets of Cefixime trihydrate. Nevertheless, apart from floating properties of the tablet, the bioadhesion tendency of HPMC K4M could possibly, to some extent, assist the tablet to remain in upper part of GI tract and enhance the gastroretention.[21]

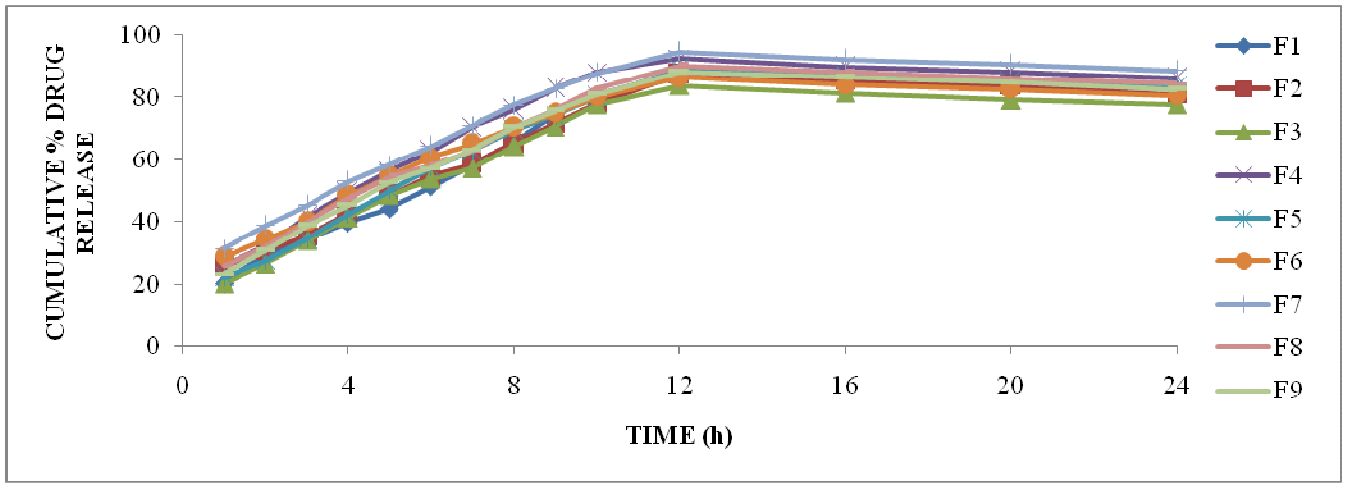

Fig. 1: *In vitro* drug release profiles of floating matrix tablet formulations (F1-F9) of Cefixime trihydrate

KINETIC ANALYSIS OF DISSOLUTION DATA

The *in vitro* drug release data of all the nine formulations (F1 to F9) were fitted in to zero order, first order, Higuchi's model and Korsemeyer-peppas model and the values of slope, intercept and r^2 were calculated in each case. These values are shown in

table 6 and the plots obtained for optimized formulation (F7) are given in Fig.2 to 5. On the basis of kinetic analysis it can be concluded that the drug release from the studied formulation followed Korsemeyer-Peppas 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 0.3870 to 0.5038, suggesting that the drug was released by Fickian diffusion in all the cases.

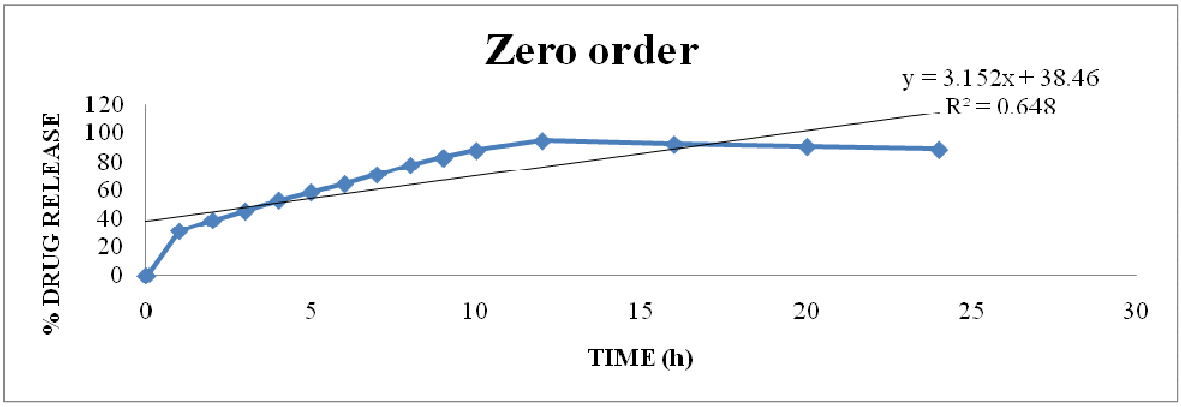

Fig. 2: % Drug release vs time plot of F7 showing zero order kinetics.

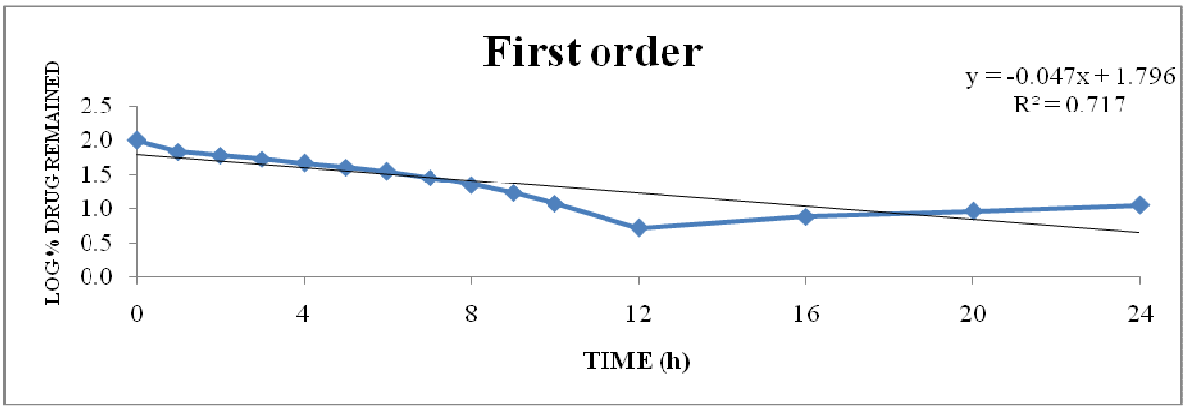

Fig. 3: Log % drug remained vs time plot of F7 showing first order kinetics.

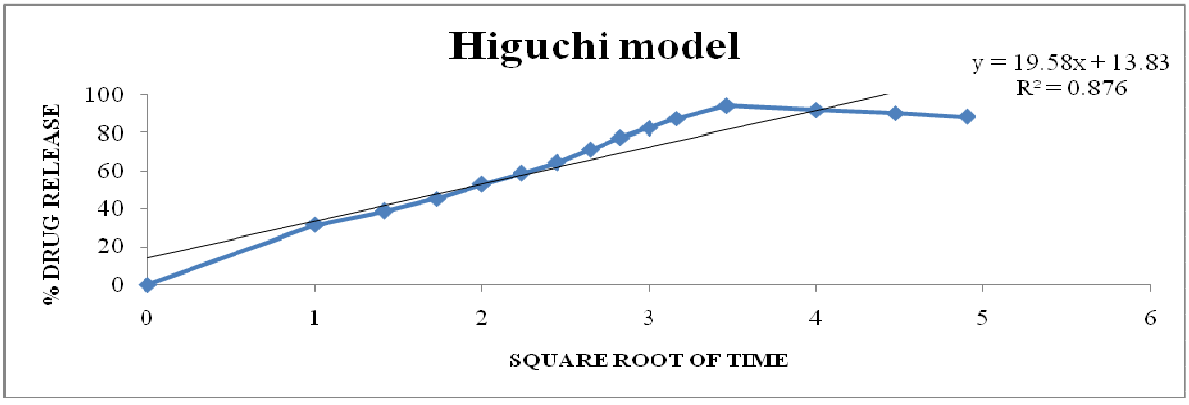

Fig. 4: % Drug release vs square root of time plot of F7 showing Higuchi's model

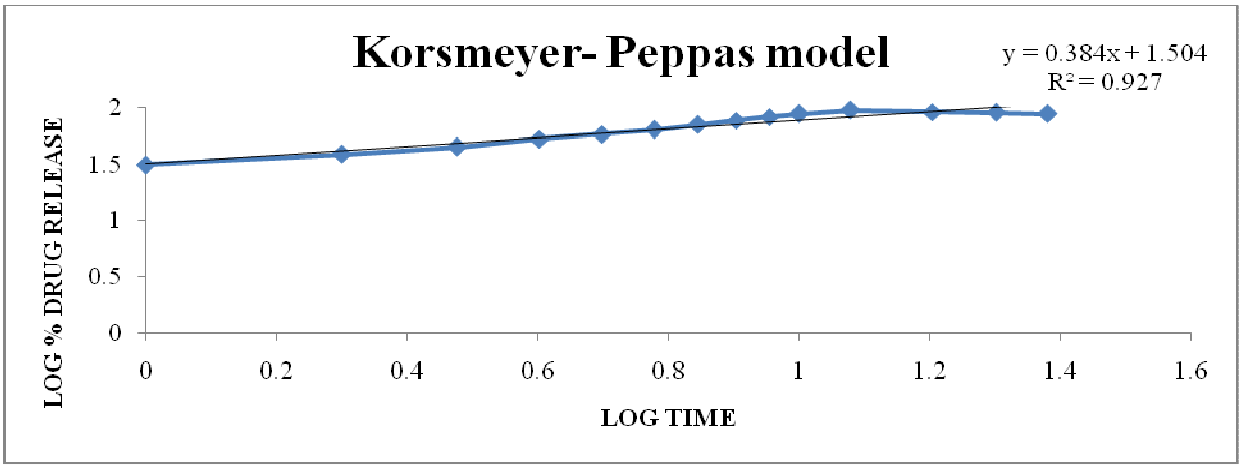

Fig. 5: Log % drug release vs time plot of F7 showing Korsemeyer-peppas model

Table 6: Modeling of dissolution data of all formulations (F1-F9)

Model	Paramete-rs	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	Slope (K)	3.3157	3.1225	3.0298	3.2132	3.2767	2.8655	3.1528	3.1684	3.1414
	Intercept	27.959	30.225	28.803	35.689	30.045	35.207	38.469	33.221	32.205
	r²	0.7187	0.7079	0.6849	0.6421	0.6985	0.642	0.6484	0.6825	0.6795
First order	Slope (K/2.303)	-0.038	-0.0356	-0.0312	-0.0429	-0.0387	-0.0326	-0.0472	-0.0397	-0.0371
	K	-0.087514	-0.080605	-0.071393	-0.096726	-0.087514	-0.073696	-0.108241	-0.089817	-0.085211
	Intercept	1.8739	1.8569	1.8553	1.8042	1.857	1.8081	1.7964	1.8352	1.838
	r²	0.7617	0.7583	0.7364	0.6981	0.7603	0.7272	0.7177	0.7449	0.7512
Higuchi model	Slope (K)	19.784	18.81	18.406	19.927	19.799	17.852	19.588	19.35	19.2
	Intercept	4.193	7.3759	6.228	10.681	5.9102	12.692	13.838	9.3445	8.4954
	r²	0.8961	0.8997	0.8853	0.8648	0.8931	0.8726	0.8766	0.8915	0.8889
Korsemeyer-Peppas model	Slope (n)	0.5038	0.4409	0.4874	0.4426	0.4921	0.3870	0.3842	0.4364	0.4556
	Intercept (log K)	1.3254	1.3901	1.3293	1.4343	1.3504	1.4624	1.5047	1.4202	1.3932
	K	20.36	25.60	20.31	25.81	22.30	28.65	31.37	62.38	23.66
	r²	0.9348	0.9324	0.9265	0.9116	0.9275	0.9213	0.9273	0.9328	0.931

DRUG EXCIPIENTS COMPATIBILITY STUDIES

Fourier transform infra-red (FTIR) studies

FT-IR spectrum (Fig.6) of Cefixime (in KBr) displays a characteristic $-NH_2$ absorption peak at 3284 cm^{-1}, which is a normal range of absorption of primary amines. It exhibits a strong band for C=O stretching of the non- conjugated carboxylic acid at 1769 cm^{-1} whereas the second band which is expected to shift to lower frequency (owing to conjugation) appears as a overlapping band. The carbonyl of cyclic as well as acyclic amide appears at 1666 cm^{-1}. The corresponding to C-H stretching appears in the region 1540-1600 cm^{-1}. FT-IR spectrum of formulation F7 (Fig.7) do not show any appreciable change in the position of assigned bands. It can be inferred that drug and the polymer do not exhibit significant chemical interaction and therefore, are compatible with each other.

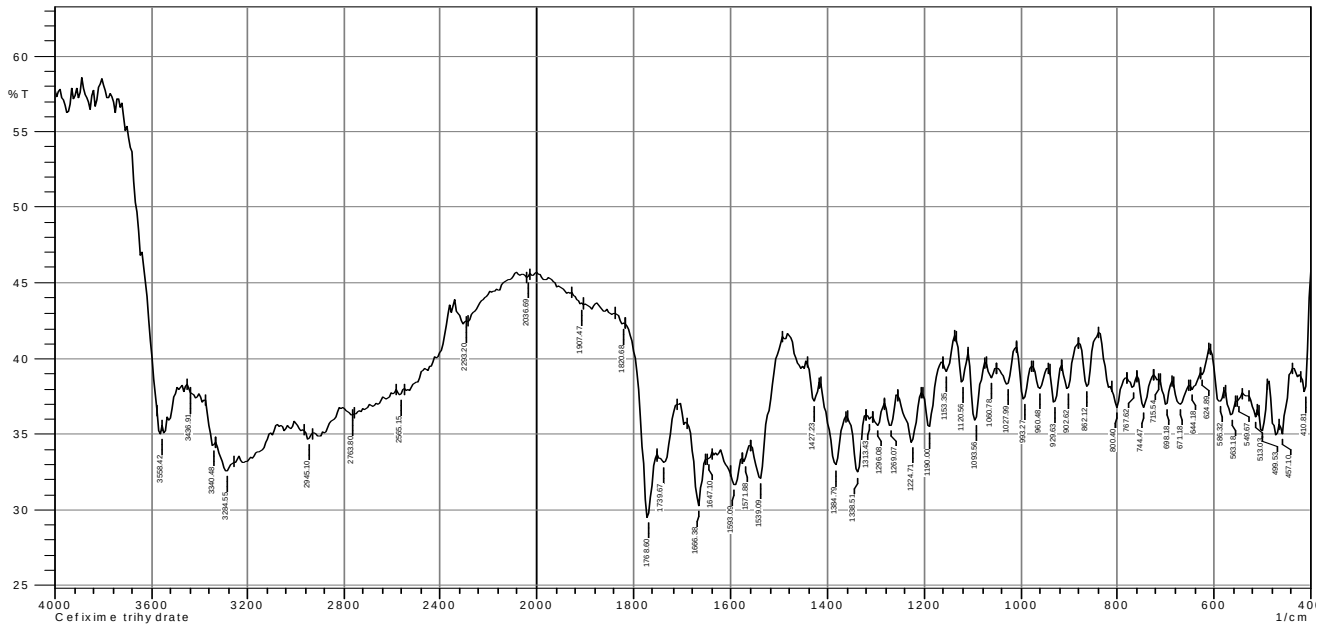

Fig. 6: FTIR Spectra of pure drug Cefixime trihydrate

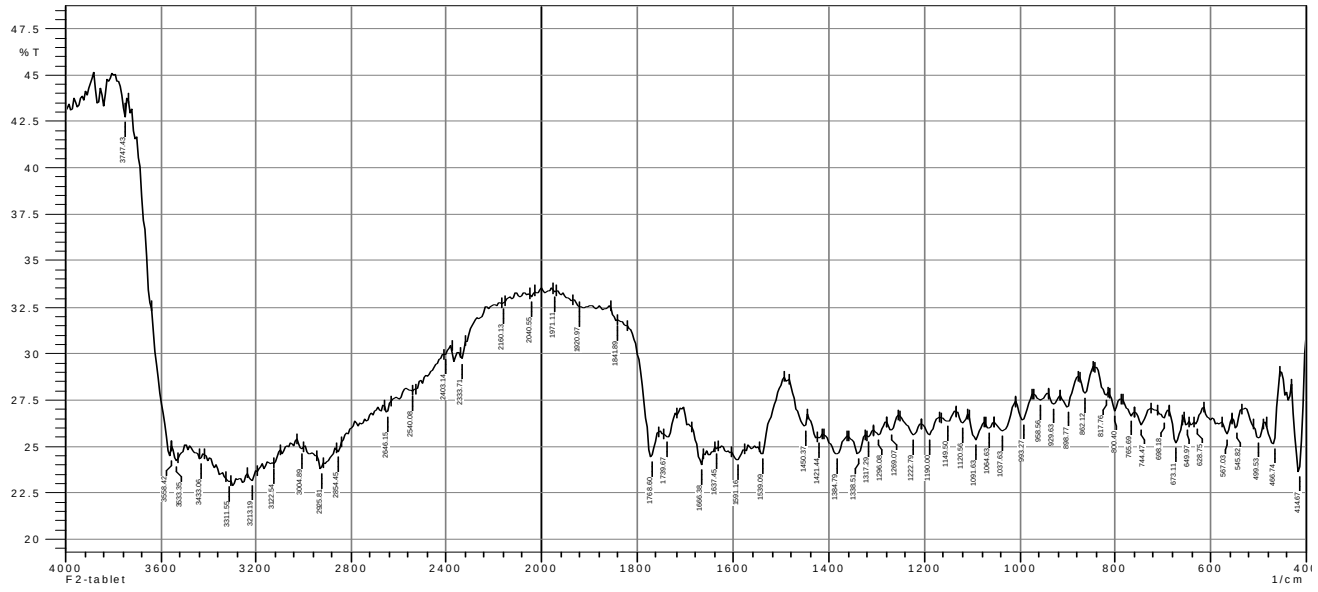

Fig. 7: FTIR Spectra of formulation 7

Accelerated stability study of floating matrix tablets of Cefixime trihydrate

Formulation F7 was selected for stability studies till 3 months. Various physical parameters are evaluated as shown in table 7. As evident from table 7, tablets did not show any change in colour, remain intact throughout the study period. Also, the friability, hardness and *in vitro* % drug release of tablets were well within the range and were almost similar to initial time point sample throughout the study period. No significant variation in drug content has been observed with respect to time the studied formulation. So, it can be concluded that floating matrix tablet formulation of Cefixime trihydrate (F7) developed during current investigation is stable enough.

Table 7: Parameters of the selected formulation (F7) analyzed at different time points during accelerated stability studies

Time point (month)	Conditions	Colour	Drug release (%) n=3	Friability (%) n=3	Hardness (Kg/cm^3) n=3	Drug content (%)n=3
Initial	40°C/75%RH	Light Yellow	94.71±0.20	0.87±0.07	6.2±0.08	98.28
1	40°C/75%RH	Light Yellow	94.08±0.04	0.85±0.03	6.1±0.02	97.85
2	40°C/75%RH	Light Yellow	93.05±0.03	0.86±0.02	6.4±0.04	97.25
3	40°C/75%RH	Light Yellow	93.72±0.06	0.82±0.08	6.3±0.06	97.26

CONCLUSION

Controlled release gastroretentive floating matrix tablets of Cefixime trihydrate can be successfully prepared using various viscosity grades of HPMC *viz.* HPMC K4M, HPMC K15M or HPMC K100M. The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel forming polymer (methocel) and gas generating agent sodium bicarbonate along using citric acid was essential to achieve *in vitro* buoyancy. All the nine formulations had desired floating lag time (<1 minute) regardless of viscosity and content of polymeric matrices. All the tablet formulations get swelled while come in contact with aqueous medium. All the formulations showed values within the prescribed limits for tests like hardness, friability, weight variation and drug content indicating that the prepared tablets were of standard quality. FTIR studies of the pure drug, its physical mixture with polymer blend showed that no polymorphic changes occurred during manufacturing of tablets. It was concluded that the rate of drug release from all formulations were depend on viscosity and concentrations of polymers used. It was found that as the viscosity and concentration of polymer increased, the drug release rate decreased. Formulations developed using various grades of HPMC (HPMCK4M, HPMCK15M, HPMCK100M) exhibited extended drug release till 12 h. The kinetic study results suggest that the drug was released by fickian diffusion in case of all the developed floating matrix tablet formulations of Cefixime trihydrate. Formulation F7 was found to be optimum because it had shown most consistant drug release (94.71±0.20%) upto 12 h with floating lag time of <1 min. and good swelling index (98.78±0.8%). The selected formulation F7 was found to be stable during the short term stability testing. On the basis of this investigation finally, it can be concluded that controlled release floating matrix tablets of Cefixime trihydrate may be used in clinical practice for various infectious diseases, thereby improving the bioavailability and more patient compliance. However, long term stability studies and *in vitro* studies in human subjects need to be carried out on floating matrix tablets of Cefixime trihydrate.

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