ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

PHARMACEUTICS

FORMULATION, EVALUATION AND STUDY OF EFFECT OF HYDROPHILIC POLYMERS ON RELEASE RATE OF CEFIXIME FLOATING TABLETS

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

YASH PAUL
Lord Shiva College of Pharmacy, Sirsa (Haryana)

*Corresponding author

ABSTRACT

Floating matrix tablets of cefixime trihydrate were developed to prolong gastric residence time and to increase drug absorption and hence bioavailability. Hydrophilic polymers viz. HPMC K4M and Xanthan gum were incorporated in varied proportions to develop floating matrix tablets of cefixime by direct compression method. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. *In vitro* drug release studies were performed, and the drug release data were fitted into zero order, first order, Higuchi,s model and Korsmeyer-peppas kinetic models. The optimized formulation composed of 15% w/w of HPMC K4M exhibited maximum drug release (94.71±0.20%) in 12 h, buoyancy lag time was < 1 min, and the tablets remained buoyant for >12 h. All the formulations exhibited 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.

KEYWORDS

Cefixime, gastroretention, floating matrices, xanthan gum, HPMC

INTRODUCTION

Oral ingestion is the predominant and most preferable route for drug delivery. Importantly, it allows unassisted administration by the patient without the need for trained personnel. Time-controlled oral drug delivery systems offer several advantages over immediate release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency, leading to improved patient compliance.[1] Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this problem, the development of oral controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT.[2]

Gastroretentive systems can remain in the gastric region for several hours and hence can 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 of small intestine.[3] It has applications also for local drug delivery to the stomach and proximal small intestine.[4] 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.[5] After the release of drug, the residual system is emptied from the stomach. This results in an increase in the Gastric residence time (GRT) and a better control of fluctuations in plasma drug concentration.[6]

Cefixime trihydrate is a third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. 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. 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. Cefixime trihydrate is not soluble in water after its oral administration, it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability around 40-50 %. So, in order to improve the therapeutic effect of the drug by increasing its bioavailability, safe and effective levels are to be maintained for a long period time. It gives constant blood levels of active ingredient as compared to uncontrolled fluctuations observed when multiple dosage of quick releasing conventional dosage forms are administered to a patient. It not only reduces the frequency of dosing but may reduce the severity and

frequency of side effects.[7] Hence it was planned to develop floating matrix tablets of Cefixime trihydrate using HPMC K4M and Xanthan gum.

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	M/S Leo chem, Bangalore, Karnataka
Xantan Gum	M/S Titan Biotech Ltd, Bhiwadi, Rajasthan
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

1. ***Preparation of Cefixime trihydrate 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 K4M and Xanthan gum 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. Magnesium stearate was used as a lubricant at concentration of 2% 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. Microcrystalline cellulose (5% w/w) was used as a tablet disintegrant. 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 by means of pestle mortar. 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 6-7.2 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
Cefixime (% w/w)	40	40	40	40	40	40
HPMC K4M (% w/w)	15	20	25	-	-	-
Xanthan gum (% w/w)	-	-	-	15	20	25
Sodium bicarbonate (% w/w)	15	15	15	15	15	15
Microcrystalline cellulose (% w/w)	5	5	5	5	5	5
Sodium Carboxymethylcellulose (% w/w)	4	4	4	4	4	4
Citric acid (% w/w)	4	4	4	4	4	4
Sodium alginate (% w/w)	3	3	3	3	3	3
Magnesium stearate (% w/w)	2	2	2	2	2	2
Lactose q.s. (mg)	500	500	500	500	500	500

2. *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.[8] 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[9] as given by eqn. 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[10] 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.[11]

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 wascalculated.

(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.[12] The swelling index was calculated using following eqn 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 weighed and pulverised to a fine powder, and a quantity of powder equivalent to 100 mg of Cefixime was dissolved in 100 mL methanol and the 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.[7]

(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^{0}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.[11] 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 excipients 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

.

(ii) ***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 adopted for deciding the most appropriate model were:

- Percent drug released versus time (zero-order kinetic model)[13]
- Log percent drug remaining versus time. (first-order kinetic model)[14]
- Percent drug released versus square root of time (Higuchi's model)
- Log percent drug released versus log time (Korsmeyer-Peppas model)[15]

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 (40^0C/75% RH)[7] 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 40^0C/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

A. Micromeritics studies

(i) Angle of repose

The angles of repose (θ) for the blend of various formulations F1 to F6 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 F6 was in the range 21.65 ± 0.08^0 to 24.75 ± 0.09^0, indicating that the studied blends have excellent flow properties, because for a blend to have excellent flow properties, value of θ should be ≤ 25º.[8]

(ii) Bulk and tapped density

The BD and TD for the powder blend of various formulations F1 to F6 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/cm^3 to 0.3487±0.04 g/cm^3 and 0.3280±0.05 g/cm^3 to 0.4021±0.03 g/cm^3 respectively.

Table 3
Parameters evaluated for powder blend of Cefixime trihydrate

Formulation code	Angle of repose (θ) (n=3)	Bulk density (gm/cm^3) (n=3)	Tapped density (gm/cm^3) (n=3)	Carr's index (%) (n=3)	Hausner's ratio (H_R) (n=3)
F1	23.14 ± 0.02	0.3140±0.05	0.3659±0.04	14.35±3.81	1.1692±0.05
F2	21.65 ± 0.08	0.2883±0.05	0.3410±0.06	15.37±2.04	1.1820±0.03
F3	22.75 ± 0.05	0.2824±0.04	0.3280±0.05	13.95±0.85	1.1622±0.01
F4	23.64 ± 0.08	0.3199±0.06	0.3810±0.06	16.05±3.32	1.1924±0.05
F5	24.45 ± 0.03	0.3487±0.04	0.4021±0.03	13.52±5.32	1.1594±0.07

F6	24.75 ± 0.09	0.3219±0.06	0.3762±0.07	14.32±1.16	1.1672±0.02

(iii) Compressibility index

The compressibility indexes for the blend of various formulations F1 to F6 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 F6 was in the range of 13.52±5.32% to 16.05±3.32%, 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%.[16] 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 F6 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-F6 was in the range 1.1594±0.07 to 1.1924±0.05 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.[11]

B. Evaluation of physicochemical parameters

(i) Tablet Hardness:

Hardness of the developed formulations F1 to F6 varied from 6.2±0.04 to 7.2±0.08 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 is in the range of 0.62±0.08% to 0.92±0.04% (Table 4) in all the formulations F1-F6 and the friability value is less than 1% which ensures that formulated tablets are mechanically stable.[16]

(iii) Weight variation:

The maximum weight variation was found in the range of 499.33±4.04 to 501.33±3.51 (Table 4) from all the formulations. As none of the formulation showed a deviation of more than ±5% for any of the tablets tested, the prepared formulations comply with the weight variation test. Thus it fulfills the USP requirements. [16]

(iv) Tablet Thickness/ Diameter:

Thickness and diameter of the developed formulations F1 to F6 varied from 4.12±0.04 mm to 4.20±0.04 mm and 12.12±0.04 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.[16]

(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 shows the % swelling index

values of all the six formulations (F1-F6). It is evident that % swelling index values varies from 93.32±0.4% to 98.78±0.8% and also F1 has highest % swelling index value of 98.78±0.8%.

(vi) Floating or buoyancy test:

All formulations (F1- F6) 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 95.46 to 99.28 (Table 4) i.e within the permissible limits of IP.[17]

Table 4
Tablet formulations evaluated for different parameters

Parameters	F1	F2	F3	F4	F5	F6
Tablet wt. (mg) , n=3	500.00±4.36	501.33±3.51	500.33±4.51	501.33±3.06	501.33±3.06	499.33±4.04
Thickness (mm) , n=3	4.20±0.04	4.14±0.02	4.13±0.08	4.12±0.04	4.14±0.06	4.18±0.04
Diameter (mm) , n=3	12.12±0.08	12.12±0.06	12.12±0.04	12.16±0.04	12.14±0.02	12.12±0.06
Friability (%) , n=3	0.87±0.07	0.62±0.08	0.68±0.06	0.90±0.08	0.92±0.04	0.90±0.04
Hardness (Kg/cm^2), n=3	6.2±0.08	6.9±0.04	6.9±0.04	7.2±0.08	6.2±0.04	6.3±0.06
Drug content (%)	99.28	98.87	95.65	95.46	97.47	97.32
Floating lag time (min)	< 1	< 1	< 1	< 1	< 1	< 1
Floating duration (min)	> 720	> 720	> 720	> 640	> 640	> 640
Tablet integrity	Intact	Intact	Intact	Intact	Intact	Intact
Swelling index (%) , n=3	98.78±0.8	98.32±0.2	97.06±0.5	94.63±0.8	95.54±0.6	93.32±0.4

(viii) In vitro dissolution studies

From *in vitro* drug dissolution data (table 5) of Cefixime trihydrate matrix tablet formulations (F1-F6), it was found that more than 20% drug was released till 1h from all cases. Also, after 8 h more than 70% of the drug was released from all the six formulations. However, it has been observed that in case of formulations (F4-F6) having Xanthan gum in different concentration exhibited maximum drug release at 10h while formulations (F1-F3) developed using HPMC K4M, showed maximum drug release at 12h. Therefore, it

is evident that hydrophilic matrices developed using HPMC K4M are able to retain in the stomach for sufficient long time enabling the drug to absorb effectively from stomach mucosa. It was observed that formulations (F1,F4) having drug is to polymer ratio 40:15% w/w/tablet showed high drug release rates 94.71±0.20% and 91.21±0.88% respectively whereas formulations (F2,F5 and F3,F6) having comparatively higher concentration of polymers exhibited less release i.e. 90.33±0.88%, 88.19±0.22% and 88.30±1.32%, 86.54±0.26% respectively. Hence, it can be concluded that as the concentration of polymer, HPMC or Xanthan gum is increased, the release of drug tends to become slower. This 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 caused by more intimate contact between the particles of HPMC or Xanthan gum results in decreased mobility of insoluble drug particles in swollen matrices, which leads to decreased release rate.[18]

Table 5 enlists the dissolution parameters of all the six formulations developed in the current investigation and Fig.1 portrays their corresponding drug release profiles.

Table 5
In vitro drug release study: % drug released

Time (h)	F1 (%)± SD	F2 (%)± SD	F3 (%)± SD	F4 (%)± SD	F5 (%)± SD	F6 (%)± SD
1	31.33±0.09	25.74±0.54	23.36±0.13	28.64±0.19	20.20±0.91	21.82±0.17
2	38.80±0.04	31.91±0.54	30.85±0.13	36.46±0.26	25.72±0.67	29.74±0.13
3	45.39±0.09	40.05±1.07	38.78±0.12	42.58±0.36	35.30±0.15	37.41±0.36
4	52.99±0.02	47.60±0.09	45.39±0.13	50.61±0.18	42.78±0.18	45.62±0.22
5	58.60±0.04	54.66±0.10	52.90±0.11	59.52±0.35	49.97±0.07	51.87±0.18
6	64.32±0.05	58.35±0.36	57.29±0.05	65.69±0.30	56.02±0.18	59.67±0.36
7	71.10±0.54	63.01±0.10	63.46±0.14	71.96±0.35	64.82±0.14	66.11±0.72
8	77.56±0.04	70.51±0.09	70.52±0.11	79.33±0.26	71.96±0.15	71.86±0.18
9	82.88±0.04	76.23±0.10	75.79±0.12	84.38±0.28	79.98±0.62	79.91±0.25
10	87.98±0.42	82.85±0.09	81.10±0.12	91.21±0.88	88.19±0.22	86.54±0.26
12	94.71±0.20	90.33±0.88	88.30±1.32	90.33±0.88	87.42±0.77	85.34±0.81
16	92.30±0.44	88.93±0.18	86.70±0.78	88.82±0.71	85.09±0.45	83.59±0.26
20	90.77±0.64	86.09±0.42	84.94±1.28	86.45±1.85	83.44±0.31	81.78±0.22
24	88.71±0.20	84.44±0.62	82.66±4.30	84.06±1.04	81.27±0.22	79.89±0.18

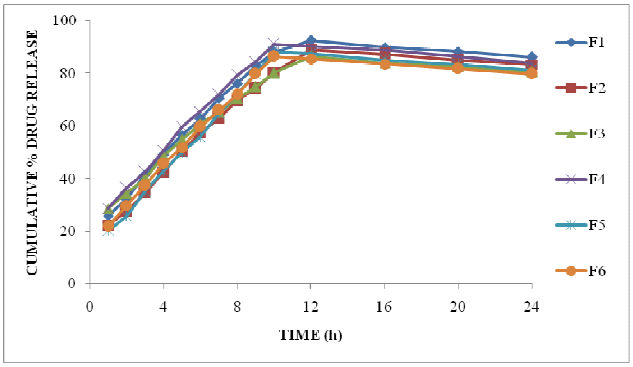

Figure 1
In vitro drug release profiles of floating matrix tablet formulations (F1-F6) of Cefixime trihydrate

Formulation F1 containing 15% of HPMC K4M exhibited short buoyancy lag time, floated for more than 12 h, and showed maximum swelling index (98.78± 0.8). It 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 F1 was selected as the optimized 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.[19]

Kinetic analysis of dissolution data

The *in vitro* drug release data of all the six formulations (F1 to F6) were fitted into 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 (F1) are given in Fig.2 to 5. 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 F6) ranges from 0.3842 to 0.5048, suggesting that the drug was released by Fickian diffusion in all the cases.

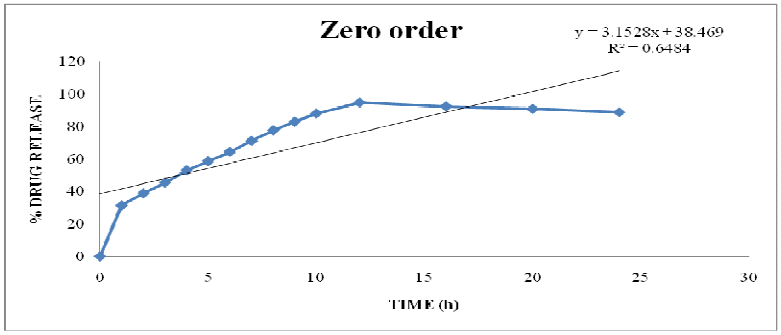

Figure 2
% Drug release vs time plot of F1 showing zero order kinetics.

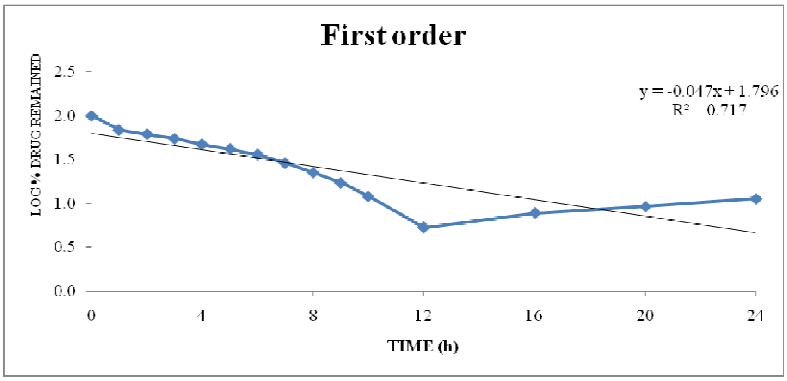

Figure. 3

Log % drug remained vs time plot of F1 showing first order kinetics.

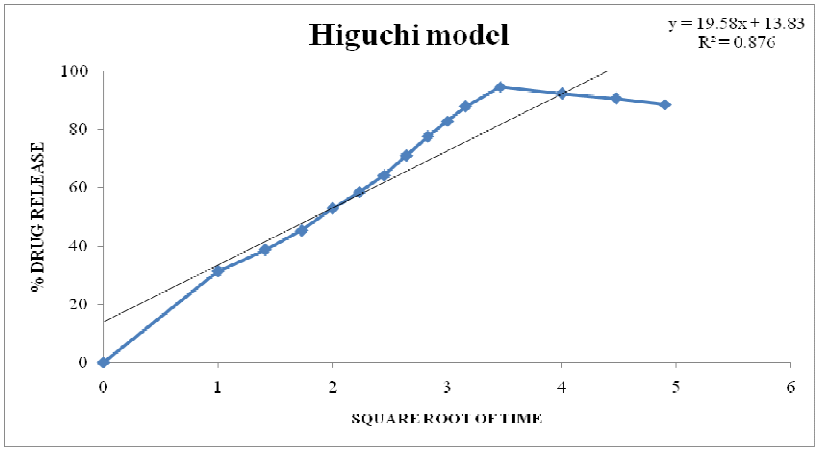

Figure 4

% Drug release vs square root of time plot of F1 showing Higuchi's model

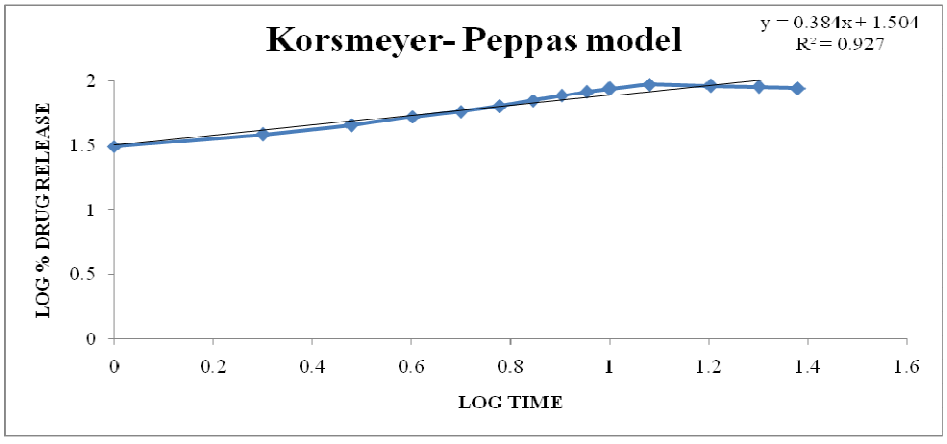

Figure 5
Log % drug release vs time plot of F1 showing Korsemeyer-peppas model

Table 6
Modeling of dissolution data of all formulations (F1-F6)

Model	Parameters	F1	F2	F3	F4	F5	F6
Zero order	Slope (K)	3.1528	3.1684	3.1414	2.999	3.2246	3.0182
	Intercept	38.469	33.221	32.205	38.611	30.842	33.189
	r^2	0.6484	0.6825	0.6795	0.591	0.6349	0.6197
First order	Slope (K/2.303)	-0.0472	-0.0397	-0.0371	-0.0387	-0.0364	-0.0333
	K	-0.108 241	-0.089 817	-0.085 211	-0.087 514	-0.082 908	-0.075 999
	Intercept	1.7964	1.8352	1.838	1.7621	1.8295	1.8094
	r^2	0.7177	0.7449	0.7512	0.6202	0.6544	0.6489
Higuchi model	Slope (K)	19.588	19.35	19.2	19.012	19.792	18.817
	Intercept	13.838	9.3445	8.4954	14.816	6.2854	9.4394
	r^2	0.8766	0.8915	0.8889	0.8319	0.8495	0.8435
Korsemeyer-Peppas model	Slope (n)	0.3842	0.4364	0.4556	0.3991	0.5048	0.4664
	Intercept (log K)	1.5047	1.4202	1.3932	1.4824	1.3307	1.3818
	K	31.37	62.38	23.66	28.64	20.20	21.82
	r^2	0.9273	0.9328	0.931	0.8902	0.9002	0.8975

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 C-H stretching appears in the region 1540-1600 cm^{-1}. FT-IR spectrum of formulation (Fig.7) does 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.

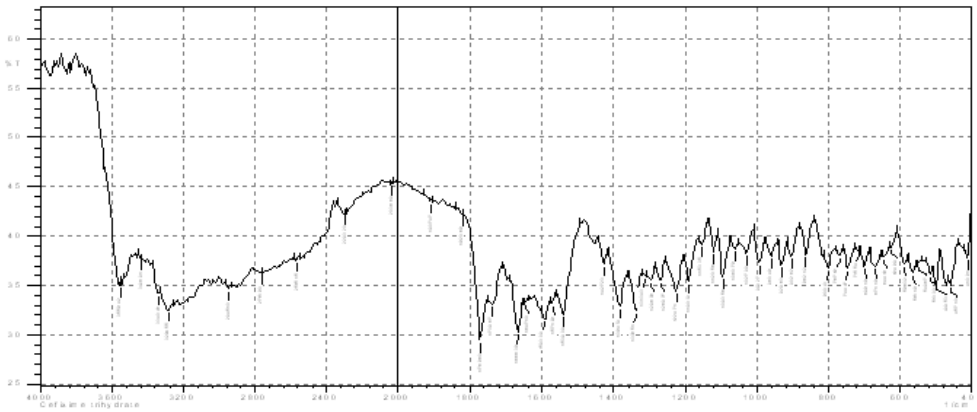

Figure 6
FTIR Spectra of pure drug Cefixime trihydrate

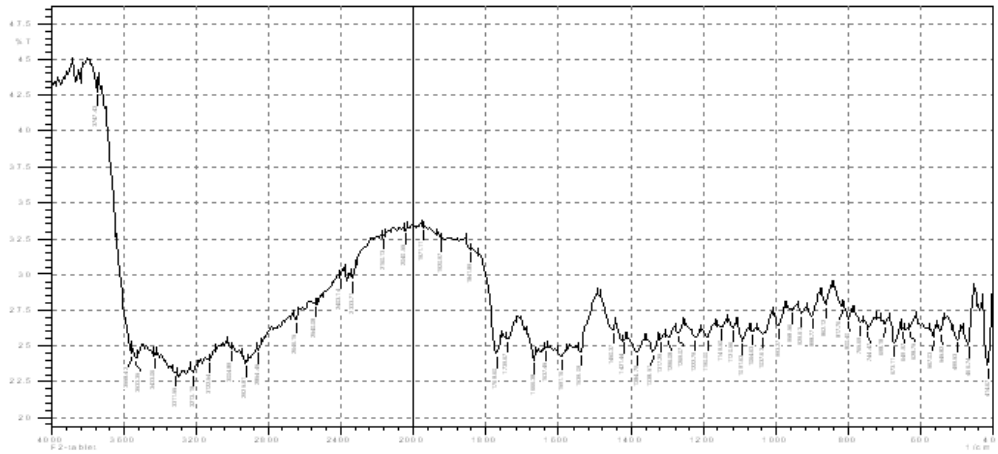

Figure 7
FTIR Spectra of formulation 1

Accelerated stability study of floating matrix tablets of Cefixime trihydrate

Formulation F1 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 and remained 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. So, it can be concluded that floating matrix tablet formulation of Cefixime trihydrate (F1) developed during the current investigation is stable.

Table 7

Parameters of the selected formulation (F1) 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	40ºC/75%RH	Light Yellow	94.71±0.20	0.87±0.07	6.2±0.08	98.28
1	40ºC/75%RH	Light Yellow	94.08±0.04	0.85±0.03	6.1±0.02	97.85
2	40ºC/75%RH	Light Yellow	93.05±0.03	0.86±0.02	6.4±0.04	97.25
3	40ºC/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 HPMC K4M and Xanthan gum. The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel forming polymer (methocel and Xanthan gum) and gas generating agent sodium bicarbonate along with citric acid was essential to achieve *in vitro* buoyancy. All the formulations had desired floating lag time (<1 minute) regardless of viscosity and content of polymeric matrices. All the tablet formulations get swelled while coming in contact with aqueous medium and 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 depended on viscosity and concentrations of the polymers used. It was found that as the concentration of polymer increased, the drug release rate decreased. Formulations developed using HPMC K4M exhibited extended drug release till 12 h vis à vis formulations developed using Xanthan gum that showed maximum drug release till 10 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 F1 was found to be optimum because it had shown most consistent (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 F1 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.

ACKNOWLEDGEMENTS

The authors are thankful to the management of Lord Shiva College of Pharmacy, Sirsa (Haryana), India for providing requisite facilities for this research work. Vital inputs provided by Dr. Preeti Wasil, Associate Professor, Lord Shiva College of Pharmacy, Sirsa and Mr Mukesh Kumar, Production Chemist, Macleods, Baddi (HP) in compiling the current manuscript is gratefully acknowledged.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using gastroretentive technologies. Cur. Opi. Pharmaco.2006;6:501-508.
2. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Exp. Opi. Dru. Del.2006;3(2):217-33.
3. Ponchel G and Irache JM. Specific and nonspecific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv. Drug Del. Rev. 1998; 34: 191-219.
4. Deshpande AA, Rhodes CT, Shah NH and Malick AW. Controlled-release drug delivery systems forprolonged gastric residence: an overview. Drug Dev.Ind. Pharm.1996;22: 531-539.
5. Garg S, Sharma S. Gastroretentive drug delivery systems. Drug Delivery Tech.2003;161-66.
6. Singh BN, Kim KH. Floating drug delivery system: an approach to oral controlled drug delivery via gastric retention. J. Cont. Release.2000;63:235-59.
7. Raghavendra RNG, Ram P, Bussetti SS. Formulation and evaluation of gas powered systems of Cefixime tablets for controlled release. Int. J. Pharm Bio Sci.2010;1(2):1-15.
8. Caroter SJ. Tutorial pharmacy. 1st edition. 1986. Chapter 19. Power flow and compaction, CBS publishers and distributors, New Delhi, India; p.211–233.
9. Subrahmanyam CVS. Laboratory manual of physical pharmaceutics. Experiment-7 Porosity-powders. 1st edition 2002. Published by Vallabh Parkashan; p.46-53.
10. Sharma S, Gupta GD. Formulation & characterization of fast dissolving tablets containing promethzine theoclate solid dispersion with PEG 4000. The Pharma Review. 2008.
11. The United States Pharmacopoeia XX/ National Formulary XV. 15th edition 1980. US Pharmacopoeial Convention, Rockville, MD; p. 958-990.
12. Rajput GC, Majumdar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB. Stomach Specific Mucoadhesive Tablets as Controlled Drug Delivery System-A Review Work. Int. J. Pharma. & Bio. Res.2010;1(1):30-41.
13. Varelas CG, Dixon DG, Steiner C. Zero-order release from biphasic polymer hydrogels. J. Control. Rel.1995;34:185–192.
14. Mulye NV, Turco SJ. A simple model based on first order kinetics to explain release of highly water soluble drugs from porous dicalcium phosphate dihydrate matrices. Drug Dev. Ind. Pharm.1995;21:943–953.
15. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm.1983;15:25–35.
16. Banker GS, Anderson NR. In: Lachman L, Lieberman HA, Kanig J. 3rd edition. 1987. The theory and practice of industrial pharmacy. Chapter 11. Tablets. Published by Verghese publishing house; p.293-345.
17. The Indian pharmacopoeia. Vol II 6th edition. 2010. Controller of Publications, Ministry of health and family welfare.

Published by The Indian pharmacopoeia commission, Ghaziabad. p.1012-1014.
18. Patel VF, Patel NM. Statistical evaluation of influence of viscosity and content of polymer on Dipyridamole release from floating matrix tablets: A technical note. Aaps Pharm.SciTech.2007;8(3):E1- E5.
19. Ulla SN, Roy AK, Kulkarni M, Vinod KSM. Formulation and evaluation of sustained release matrix tablets of lornoxicam. Int. J. Drug Dev. Res.2011;3(1):31-44.