ORIGINAL ARTICLE

Design and *in vitro* Evaluation of Gastroretentive Drug Delivery System of Cefixime Trihydrate

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Abstract

Aim: The present investigation concerns with the developments of hydrodynamically balanced tablets of cefixime trihydrate were designed to prolong the gastric residence time after oral administration and thereby increasing drug bioavailability. **Materials and Methods:** Floating tablets of cefixime trihydrate were prepared by direct compression using hydrophilic rate controlling polymers such as different grades of hydroxypropyl methylcellulose (HPMC) (k100 and 15M), xanthan gum, and ethyl cellulose. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid and along with the binder and diluents. **Results and Discussion:** The kinetic study results suggested that the drug was released by Fickian diffusion mechanism for the developed floating matrix tablet formulations of cefixime trihydrate. The optimized formulation composed of 15% w/w xanthan gum exhibited 98.71±0.2% drug release within 12 h and the tablets remain floated for <12 h. Fourier transform infrared and differential scanning calorimetry studies were performed for pure drug and its physical mixture with polymer blends showed that no polymeric change interaction was occurred during manufacturing of tablet, and there is no significant change in *in vitro* dissolution pattern after storage at 40°C/75% R.H for 3 months for their stability studies.

Key words: Cefixime trihydrate, floating tablets, hydroxypropyl methylcellulose, xanthan gum

INTRODUCTION

Oral dosage forms have been developed from the past four decades, due to their significant therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation.[1] The importance of controlled drug delivery systems that release drug over an extended period has long been recognized in the pharmaceutical field. Gastroretentive technology is an alternative to overcome this problem. Through this technology, the dosage form can be able to remain in the gastric region for several hours and hence significantly prolonging 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.[2] Application of such controlled release technology to oral drug delivery system, however, has been limited because the actual time for effective drug delivery is restricted by gastrointestinal transit time. Gastric retention devices are designed to prolong the gastric residence time of oral controlled release dosage forms. They, thus result in increased contact time for drugs that act locally, increased absorption of drugs that have absorption windows in upper part of gastrointestinal tract, and better absorption for drugs less soluble in the intestinal fluid.[3] Several approaches have been developed to achieve extended gastric residence time of the oral drug delivery systems such as bioadhesive system, swelling and expanding systems, floating systems, and delayed gastric emptying devices. Among these methods, floating drug delivery system is preferred one that offers a simple and practical approach to achieve gastro retention.[4] Floating dosage forms have a bulk density lower than that of gastric fluids, and therefore, remain buoyant on the stomach contents to prolong the gastric retention time.[5-9]

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The aim or objective of this study was to prepare a sustained release floating drug delivery system of cefixime trihydrate were prepared by direct compression using rate-controlling polymers such as different grades of hydroxypropyl methylcellulose (HPMC) (k100 and 15M) and xanthan gum, ethyl cellulose was incorporated as coating polymer. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid and along with binders and diluents. Cefixime trihydrate, 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 3-4 h, activity against the 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 with 400 mg dose.[10] Therefore, in the light of above background, it was decided to develop gastro retentive floating matrix tablets of cefixime trihydrate.

MATERIALS AND METHODS

Materials used in the development of cefixime trihydrate tablets. Cefixime trihydrate and xanthan gum were obtained as a gift sample from Dr. Reddy's lab Ltd., Hyderabad. HPMC (K10M, 15M), ethylcellulose, magnesium stearate, sodium alginate, and sodium carboxymethylcellulose was obtained from Colorcon Asia Pvt., Ltd., Mumbai. Sodium bicarbonate and citric acid were obtained from Qualigens Fine Chem., Mumbai. All other materials used were of pharmacopoeial grade.

Saturated solubility studies

Saturated solubility studies of cefixime trihydrate were performed in different dissolution media. 10 mg of cefixime trihydrate was weighed and transferred into different conical flasks. 10 ml of different dissolution media were transferred into individual conical flasks. All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37 ± 1°C for 24 h. Then, the conical flasks were removed from the incubator shaker, and the samples were filtered using Whatman filter paper. The clear filtrate was suitably diluted with appropriate dissolution media, and the absorbance values were noted at 289 nm using corresponding dissolution media as blank solutions.

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 (K15M and K100M), xanthan gum, and ethyl cellulose were chosen as hydrophilic polymeric matrix materials. Lactose was selected as tablet diluent for increasing the compressibility and flow ability 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 the liberation of CO_2 when the tablets come in contact with dissolution medium which entrapped in the matrix. Microcrystalline cellulose was used as filler. Sodium alginate was used as gel-forming agent. Citric acid was used as acid source. Magnesium stearate was employed as a lubricant and sodium CMC was incorporated as a swelling agent. To make powder blended, all the formulate agents were thoroughly blended for 10 min. This powder blend was then lubricated with 1% talc and magnesium stearate using clit -10 station mini press. The detailed compositions of the prepared matrix tablets formulations are given in Table 1.

Characterization of cefixime trihydrate floating tablets

Various formulations before compression were evaluated for their flow properties in terms of following parameters such as angle of repose and Carr's index, Hauser's ratio. The prepared tablets were evaluated for quality control tests such as hardness, friability, weight variation, swelling index, floating or buoyancy test, drug content uniformity, and *in vitro* dissolution studies. The drug-excipients interaction of optimized floating tablets was evaluated by Fourier transform-infrared (FT-IR) and differential scanning calorimetry (DSC) studies.

In vitro dissolution studies

Dissolution studies on each formulation were performed with (USP apparatus II method) employing 900 ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 75 rpm and the temperature was maintained at 37 ± 0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 24 h and replaced with equal volume of same dissolution medium to maintain the sink condition. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium, and the amount of drug released was estimated by ELICO double beam spectrophotometer at 289 nm. The dissolution studies on each formulation were conducted in triplicate. The release values and dissolution profiles for all the formulations were shown in Figure 1.

Accelerated stability studies

It is imperative that the final product is sufficiently rugged for marketing worldwide under various climate conditions

Table 1: Composition of various cefixime trihydrate controlled release floating matrix formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cefixime trihydrate (mg)	200	200	200	200	200	200	200	200	200	200	200	200
HPMCK100M (mg)	75	100	125	-	-	-	-	-	-	-	-	-
HPMCK15M (mg)	-	-	-	75	100	125	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-	75	100	125	-	-	-
Ethyl cellulose	-	-	-	-	-	-	-	-	-	75	100	125
Sodium bicarbonate	75	75	75	75	75	75	75	75	75	75	75	75
Micro crystalline cellulose (mg)	25	25	25	25	25	25	25	25	25	25	25	25
Sodium carboxymethyl cellulose (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Citric acid (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Sodium alginate (mg)	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate (mg)	10	10	10	10	10	10	10	10	10	10	10	10
Lactose (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	500	500	500	500	500	500	500	500	500	500	500	500

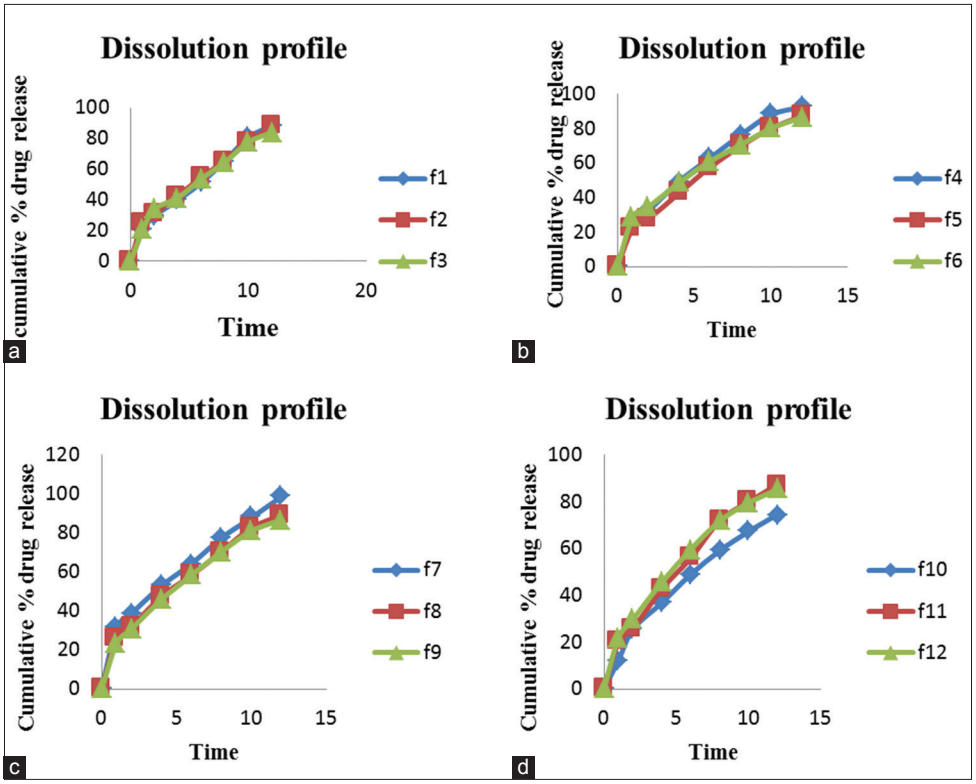

Figure 1: (a-d) Cefixime trihydrate release profiles from various controlled release floating matrix tablet formulations

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)[11] to ascertain the product stability for a longer period in a shorter period. The most satisfactory formulation sealed in aluminum packing and kept in humidity chamber maintained at 40°C/75% RH for 3 months. At the end of studies, samples were analyzed for color, *in vitro* drug release, % friability, hardness, and % drug content.

RESULTS AND DISCUSSION

The spectrophotometric method used for the estimation of cefixime trihydrate in the dissolution medium was found to be linear and reproducible. The standard calibration curve yields a straight line, which shows that the drug Obeys Beer's law. Thus, the method was found to be suitable for the estimation of cefixime trihydrate dissolution medium. Cefixime trihydrate stability in 0.1N HCl was performed for 24 h. The values obtained at various time intervals were

found to be linear. This shows that the drug remains stable in 0.1 N HCl over a period of 24 h. The absorbance values obtained were highly reproducible and were within the beers law limitations. The pre-formulation studies thus indicated that there were no drug and excipients incompatibilities. Based on these studies suitable excipients were selected and cefixime trihydrate controlled release floating matrix tablets were formulated. All the matrix tablet formulations were prepared by direct compression method using CLIT 10 station mini press. The powder blends were evaluated for flow properties such as angle of repose, Carr's index, and Hauser's ratio. The flow property values obtained for various powder blends were in the range and showed good flow characteristics. Thus, all the powder blends were found to be stable and suitable for compression as matrix tablets. The compressed matrix tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability, and drug content. These studies revealed that all the tablet formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability, and drug content. The hardness of all the tablet formulations was in the range of 5.5-6.0 kg/cm^2, weight uniformity of all the tablet formulations was in the range of 500 ± 3, friability loss of the tablet formulations was negligible and was in the range of 0.1-0.2%, and drug content estimated for all the tablet formulations was highly uniform with <3% variation. Thus, all the batches of tablet formulations were found to be stable and suitable for further studies.

Swelling index characteristics were performed on floating matrix tablet formulations. 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. It is evident that % swelling index values varies from 93.05 ± 0.6% to 99.78 ± 0.8% and also F7 have the highest % swelling index value of 99.78 ± 0.8%. All formulations (F1-F12) show the floating lag time <1 min and good floating time of more than 12 h. Different stages of floating matrix tablet of cefixime trihydrate formulation F7 was shown in Figure 2.

Dissolution studies were performed on all the tablet formulations using USP paddle (Apparatus II) method. It was observed that formulation with the drug polymer ratio 40:15% w/w/tablet (F1, F4, F7, and F10) showed high drug release rates in the range of 88.13 ± 0.20%, 92.53 ± 0.20%, 98.71 ± 0.20%, and 74.58 ± 0.18%, respectively. When compared to 40:20% w/w/tablet (F2, F5, F8, and F11) which showed a drug release rates from 87.60 ± 0.88%, 87.30 ± 0.32%, 88.93 ± 0.25%, and 87.42 ± 0.30%, respectively, and those of 40:25% w/w/tablet (F3, F6, F9, and F12) which showed a drug release rates in the range of 83.30 ± 1.32%, 86.48 ± 0.20%, 86.70 ± 0.20%, and 85.34 ± 0.15%, respectively, over a period of 12 h. The order of drug release from the selected

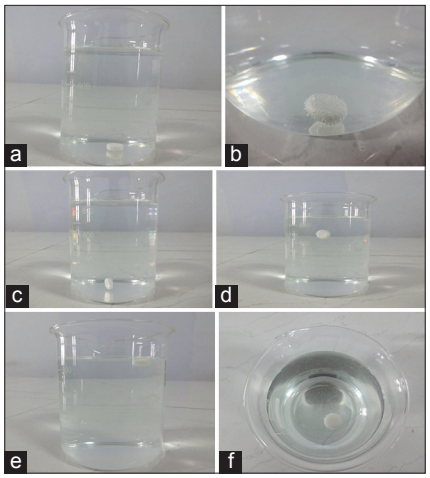

Figure 2: (a-f) Different stages of floating matrix tablet of cefixime trihydrate formulation F7

polymers was found to decrease in the following order ethyl cellulose>HPMC K15M > HPMC K100M>xanthan gum.

From the dissolution data of cefixime trihydrate matrix tablet formulations F1-F12, it has been observed that when the viscosity and content of HPMC are increased, the release of drug tends to become slower. Increase in polymer level from 15% to 20% and to 25% further reduces the release of cefixime trihydrate from matrix tablets. Formulation F7 containing 15% of xanthan gum exhibited short buoyancy lag time, floated for more than 12 h, showed maximum swelling index (99.78 ± 0.8%), and released its maximum drug content (98.71 ± 0.2%) up to 12 h in a controlled manner without changing the physical integrity of tablets in the dissolution medium. Hence, formulation F7 was selected as the best formulation for the development of controlled release matrix tablets of cefixime trihydrate. The dissolution profile of various formulations was shown in Figure 1.

The *in vitro* drug release data of all the formulations (F1-F12) were fitted into zero order, first order, Higuchi's model and Korsmeyer-Peppas model and the values of slope, intercept and R^2 were calculated in each case. On the basis of kinetic analysis, it can be concluded that the drug release from the studied formulation followed Korsmeyer-Peppas model as it has the highest value 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-F12) ranges from 0.3870 to 0.5038, suggesting that the drug was released by Fickian diffusion in all the cases. The optimized formulation F7 was subjected to accelerated stability studies and then evaluated for physical parameters, for *in vitro* drug release and further characterized by FT-IR and DSC studies.

FT-IR studies of cefixime trihydrate and optimized formulations were carried out to study the interaction

between the drug and excipients used. C=O stretching, OH stretching, S-H stretching, CH stretching of pure cefixime trihydrate, and the optimized formulations were almost in the same region of wave number ranging from 2980.28 cm^{-1} to 1747.92 cm^{-1}. In FT-IR studies, the groups in pure cefixime trihydrate and optimized formulation were having similar fundamental peaks and pattern. This indicates that there were no drug-excipients interactions in the formulations. The IR spectra of pure drug cefixime trihydrate, xanthan gum, and F7 formulation were shown in Figure 3.

DSC analysis was performed for the cefixime trihydrate, xanthan gum, and F7 prepared by direct compression method. The DSC results reveal that a sharp endothermic peak for cefixime trihydrate was observed at 276.7°C. An endothermic peak for Xanthan gum and F7 formulation were observed at

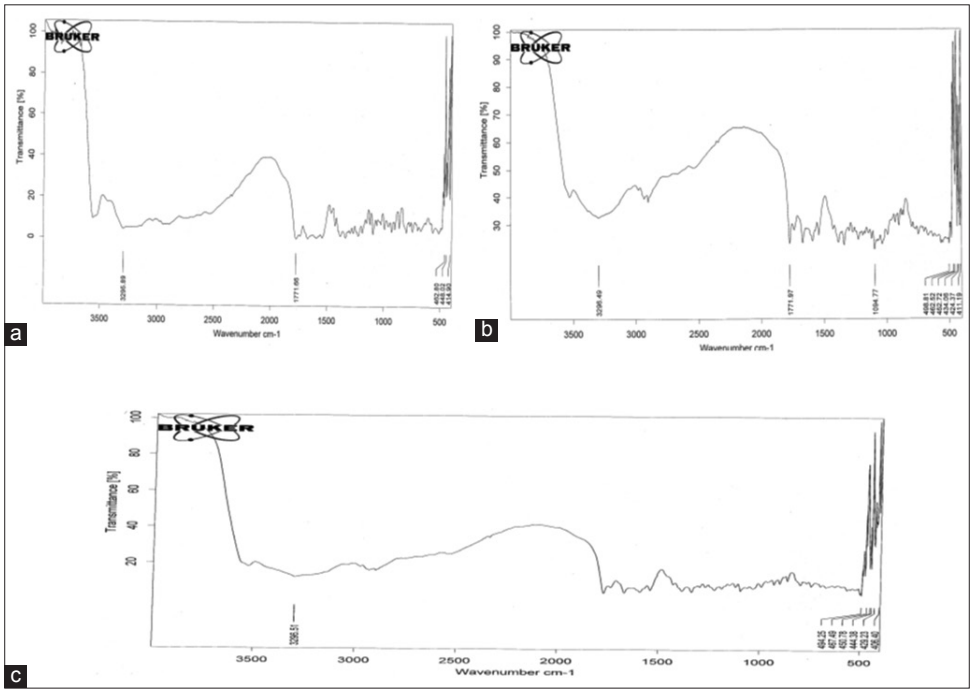

Figure 3: (a) Fourier transform infrared of cefixime trihydrate, (b) Fourier transform infrared of xanthan gum, and (c) F7 formulation

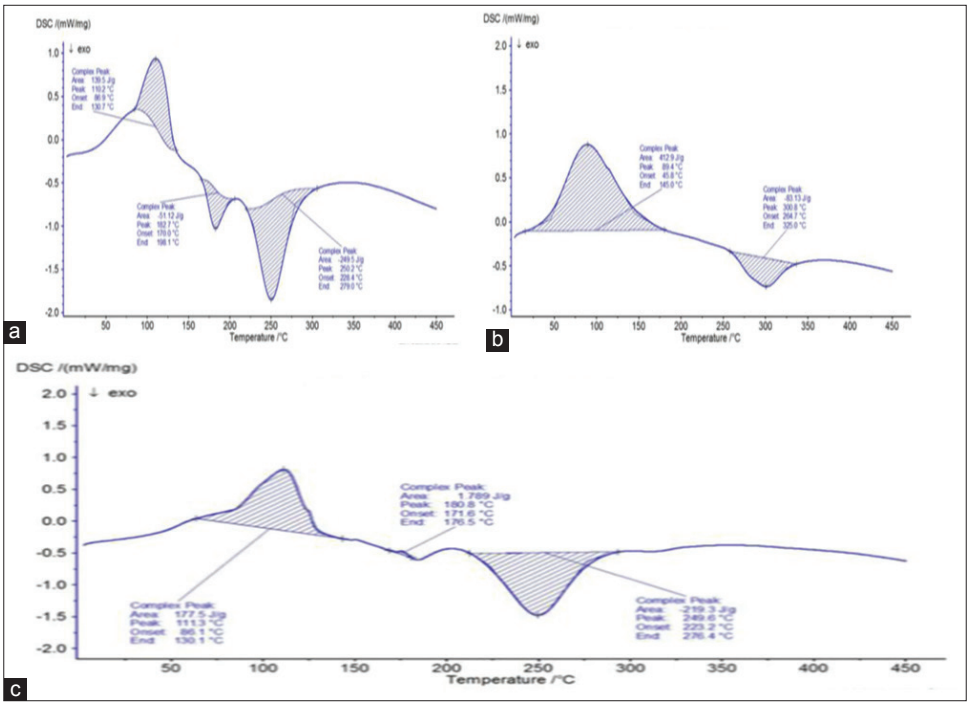

Figure 4: (a) Differential scanning calorimetry of pure drug, (b) differential scanning calorimetry of xanthan gum, and (c) F7 formulation

363.2°C and 277.4°C, respectively. The DSC thermograms were shown Figure 4. It indicated that there was no drug and polymer interaction.

CONCLUSION

The present investigation concerns the developments of hydrodynamically balanced tablets of cefixime trihydrate are designed to prolong the gastric residence time after oral administration and thereby increasing drug bioavailability. Floating tablets of cefixime trihydrate were prepared by direct compression using polymers such as different grades of HPMC (k100 and 15M), xanthan gum, and ethyl cellulose were incorporated for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid and along with the binder and diluents. It was concluded that the rate of drug release from all formulations was depended on viscosity and concentrations of polymers used. It was found that as the viscosity and concentration of polymer increased, the drug release rate decreased. 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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