International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.3, pp 986-993, July-Sept 2012

Formulation and Evaluation of Floating Capsules of 3rd Generation Cephalosporin

Darshan Patel*, S. Shivakumar

Department of Pharmaceutics, National College of Pharmacy, Balraj URS road, Shimoga, India-577201.

***Corres. Author: bhagwati13@yahoo.in**
Cell: 09586917919

Abstract : The objective of the present study was to develop a Hydrodynamically Balanced System for 3rd generation cephalosporin as single unit floating capsule. Floating study of different polymers was studied. The formulation blends were prepared by physical blending of drug and polymer in varying concentration. Drug compatibility with polymer was confirmed by FT-IR study. The bulk density and other flowability parameters of powder blend were determined. Prepared HBS capsules were also evaluated for % drug content and weight variation. The formulation was optimized on the basis of *in vitro* buoyancy and *in vitro* drug release in 0.1N HCl pH 1.2. The drug release pattern varied significantly with increased in polymer concentration in the formulations. The release rate can be effectively modified by using hydrophobic and hydrophilic release modifiers. The effect of formulation processing parameter was also studied by preparing powder and granule filled capsule. All the HBS capsules of Cefixime trihydrate were prolonged drug release compared to capsule contains only pure drug. The release data was best fit to zero-order kinetics and follows super case type II release. The optimized HBS capsule of Cefixime trihydrate was found to be stable at 40ºC and 75% RH for 1 month.

Keywords: Cefixime trihydrate, Hydrodynamically Balanced System, Floating Capsule, Bulk density, HPMC, *in vitro* buoyancy, *in vitro* drug release study.

INTRODUCTION

Gastro retentive drug delivery system (GDDS) is prolonged the gastric retention time of dosage forms in absorption window. It may lead to improves bioavability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment, suitable for narrow absorption window drugs, for local and systemic action to the stomach and proximal small intestine. GDDS is classified into two types based on mechanism of floatation: 1) Effervescent floating drug delivery system and 2) Non-effervescent drug delivery system (HBS).[1]

The hydrodynamically balanced system is designed to prolong the gastric residence time of the dosage forms. It can be formulate by one or more low density gel-forming hydrophilic polymers. The HBS capsule is comply with to form a cohesive gel barrier structure and attain a density less than that of gastric fluids after administration. It should dissolve slowly enough to serve as a "reservoir" for the delivery system.[3]

Cefixime trihydrate is mainly used as an antibacterial agent. It is insoluble in water and stable at acidic pH. It has 40-50% bioavailability and 3-4 h elimination half life.[4]

The objective of the present study was to develop a hydrodynamically balanced system for Cefixime trihydrate as single-unit floating capsules with the help of low density polymer and also tried to study the different release modifier effect. We had tried to prolong the drug release and increase gastric residence time, to increase therapeutic efficacy of the drug compared to multiple conventional dosage forms.

MATERIALS AND METHODS

Materials

Cefixime trihydrate (CFT) was obtained as a gift sample from Bharat Parenterals Ltd, Baroda, India. HPMC K4M by Colorcon Asia Pvt. Ltd.,Goa; Ethyl cellulose by Loba chemie Pvt. Ltd., Mumbai.; PEG 6000 by Sd fine Chem Ltd, Mumbai; hard gelatin capsule shell (#00) by Prakash Pharmaceutical, Shimoga. All other reagents used were of AR grades.

Flotation behavior study of different polymers

Accurately weighed 200 mg of different low density hydrophilic polymers were added in appropriate size of empty hard gelatin capsule shell (size# 0), which upon administration would attain a density of less than that of gastric fluids and therefore would float. The polymer that shows maximum floating time was selected for further studies (Figure 1).

Formulation of HBS Capsules

Single-unit floating capsules were formulated using low density hydrophilic polymer, which upon administration swells and would attain a density less than that of gastric fluids and floats. Accurately 224 mg of Cefixime trihydrate was weighed and physically blended with polymer using mortar and pestle for 15 min and filled into hard gelatin capsule (size #00) manually. The polymer concentration was selected as 10, 20, 40 and 50 percent of the drug in the formulations. The composition of the HBS capsule is given in the Table 1.

Evaluations of powder blend formulations (Micromeritic properties) [6]

Bulk density and tapped density

Both bulk density (BD) and tapped density (TD) were determined. A known quantity of powder from each formula was transferred into a 10 ml of measuring cylinder. The initial volume was observed and tapped volume was measured till standard tapping. BD and TD were calculated using the following formula:

BD = weight of the powder / volume of the untapped powder ------ (1)

TD = weight of the powder / volume of the tapped powder ------ (2)

Compressibility index (CI)

The compressibility index of the powder formulation was determined by Carr's compressibility index:

Carr's index (%) = [(TD-BD)*100]/TD ------ (3)

Hausner's ratio

The hausner's ratio was determined using BD and TD of the powder blend formulations:

H = TD/BD ------ (4)

Table 1: Composition of HBS Capsule Formulation

Formulation code	Cefixime trihydrate (mg)	HPMC K4M (%)	Ethyl cellulose (% w/w)	PEG 6000 (% w/w)
F1	224	10%	-	-
F2	224	20%	-	-
F3	224	40%	-	-
F4	224	50%	-	-
F5	224	20%	5%	-
F6	224	20%	-	5%
F7*	224	40%	-	-
FP	224	-	-	-

*Granules filled capsules (Granules were prepared using Isopropyl alcohol as granulating agent and pass through sieve no. 22).

Evaluation of HBS capsules formulations

Weight variation

10 capsules were weighed individually and the average weight was determined. Test was performed according to the official method.

Drug content

The HBS capsules contain was dissolved methanol and make up volume upto 100 ml with 0.1 N HCl pH 1.2 solution (SGF) and filter. The absorbance was measured at 288 nm after suitable dilution by UV-Visible spectrophotometer (Shimadzu UV-1601, Japan).

***In vitro* buoyancy studies**

The capsules were immersed in 900 ml of 0.1 N HCl pH 1.2 solutions, in USP type II paddle apparatus at 50 rpm at 37±0.5 ºC. The time for which remained buoyant was observed and taken as floating time.

***In vitro* drug release studies**

The *in vitro* drug release studies of HBS capsules were conducted in 900 ml of 0.1N HCl pH 1.2 solution (SGF) using a USP type II paddle apparatus at 50 rpm at 37±0.5 ºC. A series of triplicate samples were withdrawn at predetermined time intervals for 9 h and replaced with fresh SGF. The absorbance was measured at 288 nm after suitable dilution by UV-Visible spectrophotometer.

Effect of release modifiers

The ethyl cellulose (EC) and polyethylene glycol 6000 (PEG 6000) were used at 5% concentration in the formulation to study their effect on the *in vitro* drug release study (Table 1). The release modifiers were added to the powder blend, physically blended in mortar and pestle for 15 min and filled into hard gelatin capsule (size #00) manually.

Kinetic analysis of dissolution data [7,8]

To analyze the mechanism of drug release from the HBS capsules the *in vitro* dissolution data were fitted to different model dependent kinetics and model independent approaches like zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer-Peppas model.

Stability studies

Stability studies were carried out according to ICH guidelines by storing the optimised formulation (F3) at 40 ºC/75±5% RH for a period of 1 month using an automated stability testing chamber (Remi Lab, Mumbai). The samples were withdrawn at 0 and 1st month and analyze for the % drug content, *in vitro* buoyancy and drug release studies; measured at 288 nm by UV-visible spectrophotometer to assess the stability of the formulation.[9]

All the readings are average of three trials ± SD in this research work.

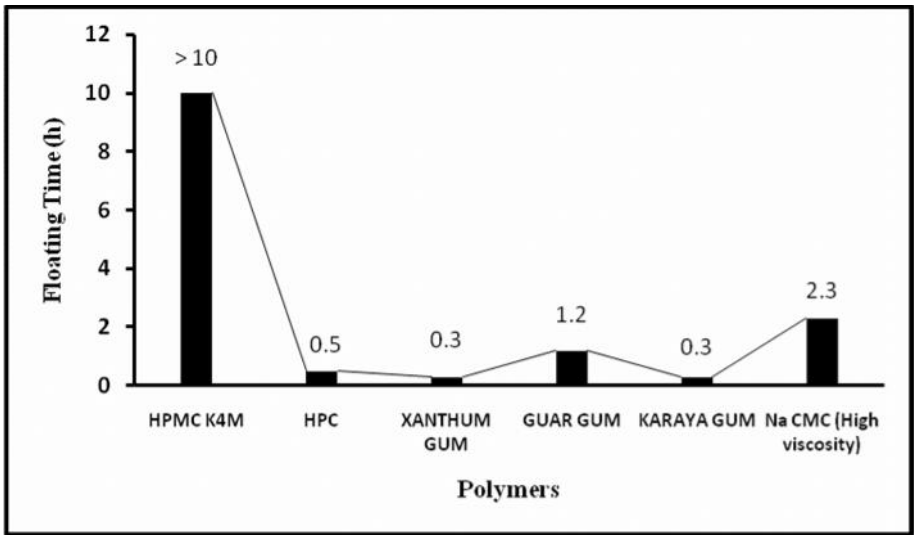

Figure 1: Floating behavior of various polymers

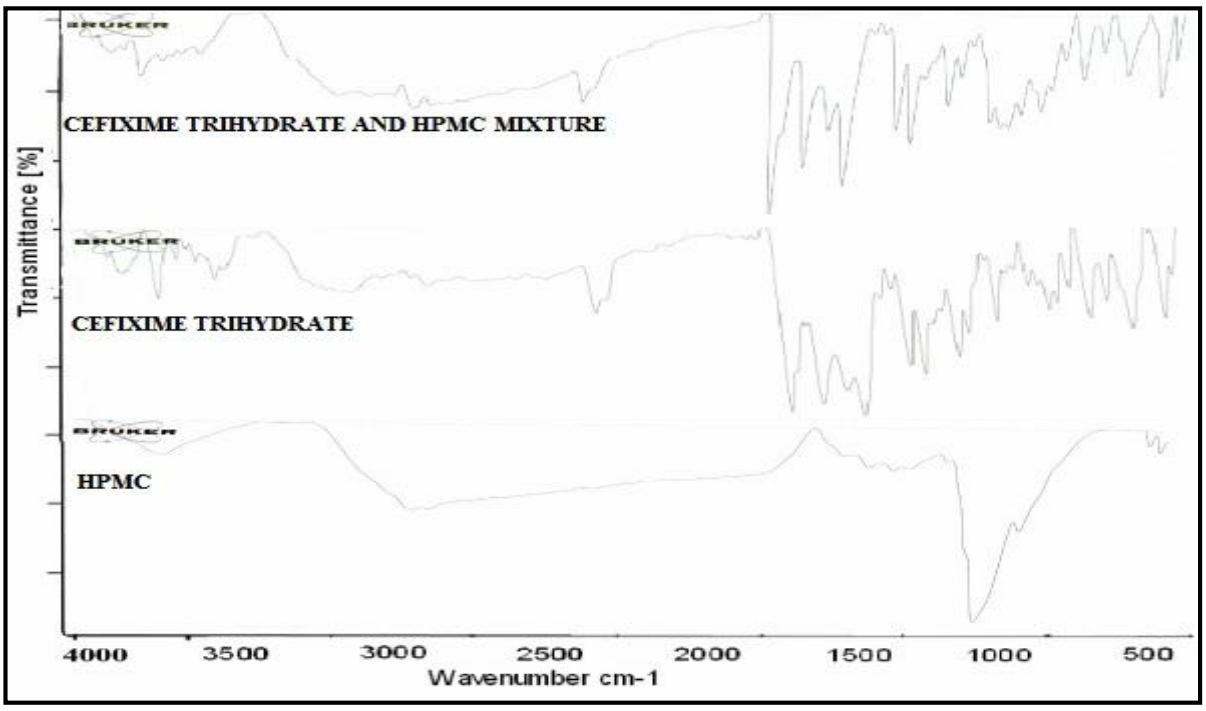

Figure 2: FT-IR spectra of Drug, Polymer and Drug-Polymer mixture

Table 2: Micromeritic Properties of Powder Blend Formulations

F.N. Code	Bulk density (g/cc)	Tapped density (g/cc)	% Carr's index	Hausner's ratio
F1	0.2873	0.3112	7.69	1.0833
F2	0.2660	0.3007	11.53	1.1304
F3	0.2420	0.2702	10.44	1.1166
F4	0.2343	0.2678	12.50	1.1428
F5	0.2342	0.2523	7.14	1.0769
F6	0.2375	0.2601	8.69	1.0952
F7*	0.2452	0.2791	12.12	1.1379
FP	0.2924	0.3045	3.96	1.0413

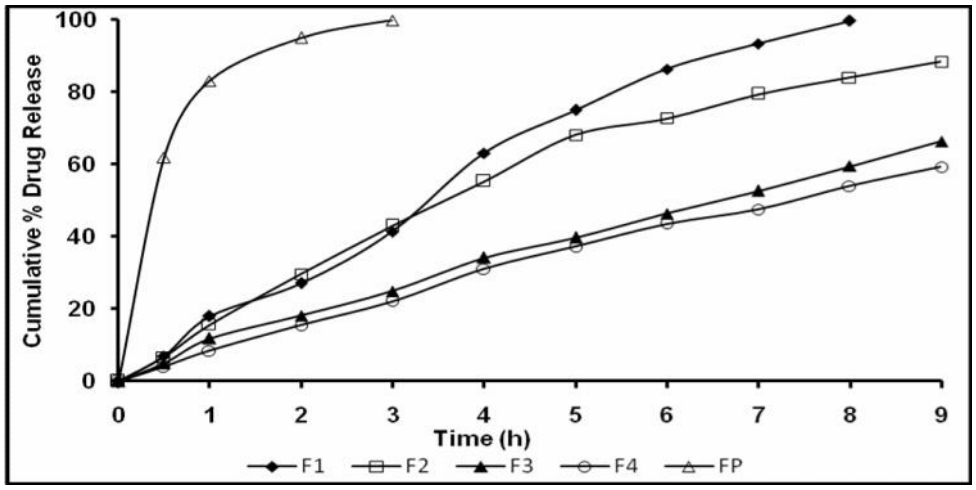

Figure 3: *In vitro* drug release profile of F1 to F4, FP formulations

RESULTS AND DISCUSSIONS

The HPMC K4M shows that it has maximum floating time compare to other hydrophilic polymers. So, HPMC K4M was selected for further studies and formulations (Figure 1).

FT-IR studies, Cefixime trihydrate and HPMC K4M exhibited characteristic absorption peaks are respectively 3295 cm^{-1} (-NH_2 stretch), 2946 cm^{-1} (β-lactam ring and –CH2 aliphatic stretch), 1766 cm^{-1} (C=O stretching of amide, carbamate), 1591 cm^{-1} (oxime C=N stretch), 1336 cm^{-1} (carbamate –NH2 stretch), 1095 cm^{-1} (C-O stretch in CH3O) and (C-S stretch) and 3700 cm^{-1} (O-H stretching), 2880 cm^{-1} (aliphatic C-H stretching), 1450 cm^{-1} (O-CH stretching), 1051 cm^{-1} (C-O stretch) and 943 cm^{-1} (CH2 rocking). Similarly all the characteristics peaks are observed in drug-polymer mixture. This reveled that there was no chemical interaction between drug and the polymer (Figure 2).

The BD and TD of the powder blend and granules of the formulations were range respectively from 0.2342 g/cc to 0.2924 g/cc and 0.2523 g/cc to 0.3112 g/cc which indicated that the formulation has lesser density than the gastric fluid (1.004 g/cc). While % carr's compressibility index and Hausner's ratio were determined to be less than 15% and < 1.18 respectively, which indicates the good flow property of prepared powder blend and granules formulations (Table 2).

The average percent deviation and % drug content of all the HBS capsule formulations was found to be within the official limit > 1% and 90-110% respectively(Table 3). All the prepared formulations were buoyant instantaneously without any lag time. The duration of floating time was more than 9 h. This indicated a good buoyancy property of the prepared formulations.

F1 and F4 formulations were showed the highest (99.64%) and lowest (59.64%) *in vitro* drug release with in 8 h and 9 h respectively (Figure 3). Drug release was retard due to the formation of gel layer of the hydrophilic polymer incorporated in the formulations. Formation of gel matrix plays a very important role in controlling the drug release. The concentration of HPMC was increased in the formulations also increased strength of the cohesive gel structure and increases the diffusion path length for the drug to come out from matrix gel. Because of increase in the concentration of HPMC K4M in the formulation as the drug release was decrease.

In vitro buoyancy and *in vitro* drug release studies reveled that all the HBS formulations were controlled as well as prolonged the drug release for 9 h. It was better compared to capsule contains only pure drug; it showed the drug release with in 3 h (Figure 3). The formulation F2, F3 and F5 showed good dissolution profile to prolong the drug release and buoyancy upto 12 h and selected as optimized formulations.

From the release data of formulation F5 containing HPMC K4M and hydrophobic release modifier ethyl cellulose at 5% w/w drug show the drug release 72.10% at the end of 9^{th} h and F6 containing HPMC K4M and hydrophilic release modifiers PEG 6000 at 5% w/w shows the drug release 98.83% at the end of 9^{th} h when compared with F2 formulation with drug release 88.83% at the end of 9^{th} h (Figure 4). Formulation containing hydrophilic polymer as release modifier will increase the drug mobility in the gel matrix. PEG 6000 soluble in the dissolution media at pH 1.2 (SGF) making more pores resulting increase in the drug release, when compared with F5 containing hydrophobic release modifier, which retards the drug release.

Table 3: % Drug Content and Average Weight Variation of HBS Capsule Formulations

F.N. Code	Average weight variation (mg)	% Drug content
F1	340.6 ± 1.01	100.16 ± 0.11
F2	392.0 ± 1.73	99.58 ± 0.45
F3	441.0 ± 1.73	99.26 ± 0.16
F4	482.6 ± 0.57	99.50 ± 0.57
F5	448.0 ± 1.00	99.59 ± 0.32
F6	447.2 ± 1.92	98.52 ± 0.41
F7*	444.0 ± 1.00	98.44 ± 0.16
FP	308.6 ± 1.52	100.00 ± 0.00
1 month (F3)	440.1 ± 1.54	99.83 ± 0.58

Table 4: Release Kinetic Data

F.N. Code	r^2 value			K-Peppas model		Hixson-Crowell cube root	
	Zero Order	First Order	Higuchi Eq.	r^2 value	*n* value	r^2 value	*n* value
F1	0.9827	0.7817	0.9456	0.9880	1.0309	0.9499	-0.4513
F2	0.9944	0.9594	0.9723	0.9838	0.8950	0.9970	-0.2695
F3	0.9952	0.9885	0.9554	0.9931	0.9108	0.9960	-0.1507
F4	0.9968	0.9937	0.9537	0.9978	0.9390	0.9989	-0.1328
F5	0.9983	0.9576	0.9095	0.9986	1.1544	0.9780	-0.1732
F6	0.9470	0.9237	0.9423	0.9738	1.1519	0.9885	-0.3990
F7*	0.9905	0.9804	0.9676	0.9687	0.9316	0.9926	-0.0942
FP	0.6809	0.9562	0.9168	0.9400	0.2641	0.9601	-1.2717

The drug release profile of formulations F1 (powder filled capsule) and F7* (granule filled capsule) were compared in order to assess the effect of processing method on the drug release. From the powder filled and granule filled capsules 66.33% and 50.14% of drug were released respectively at the end of 9th h. the observed change in the profile of the drug release pattern could be related to surface area of the particle exposed to dissolution fluid (Figure 5).

The *in vitro* dissolution data were fitted to kinetic models to analyze the kinetics and mechanism of drug release. It was observed that R^2 values of zero order release kinetics was higher as compared to first order release, indicated that *in vitro* drug release follows the zero order kinetics. The dissolution data were also plotted in accordance with the Hixson-Crowell cube root law. The R^2 value of all the formulation was closer to 1. It indicated that a change in surface area and diameter of the capsule with progressive dissolution of the matrix as a function of time. The *n* value of K-Peppas model was > 0.89, indicated that the release mechanism was super case II type of release (Table 4).

Stability sample showed that there was no significant change *in vitro* drug release, % drug content and floating behaviour from the F3 HBS capsule formulation kept for 1 month stability studies (Figure 6).

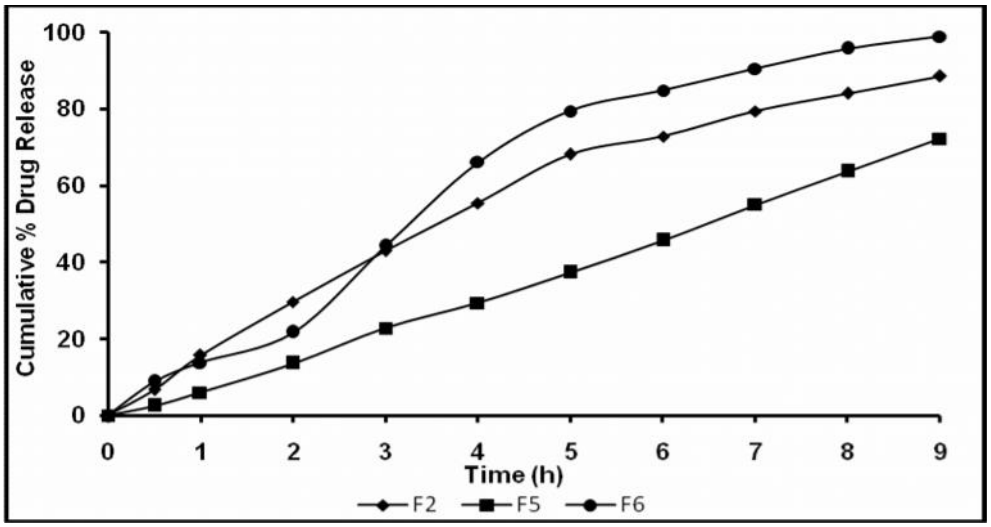

Fig. 4: *In vitro* drug release profile of F2, F5 and F6 formulations

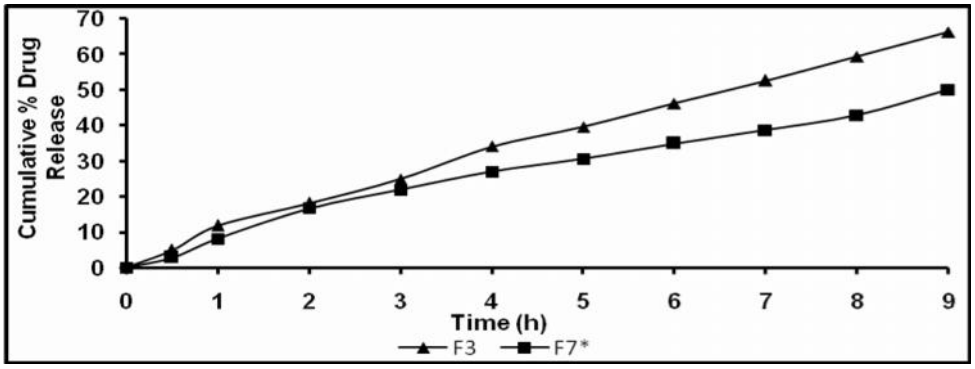

Figure 5: *In vitro* drug release profile of F3 and F7* formulations

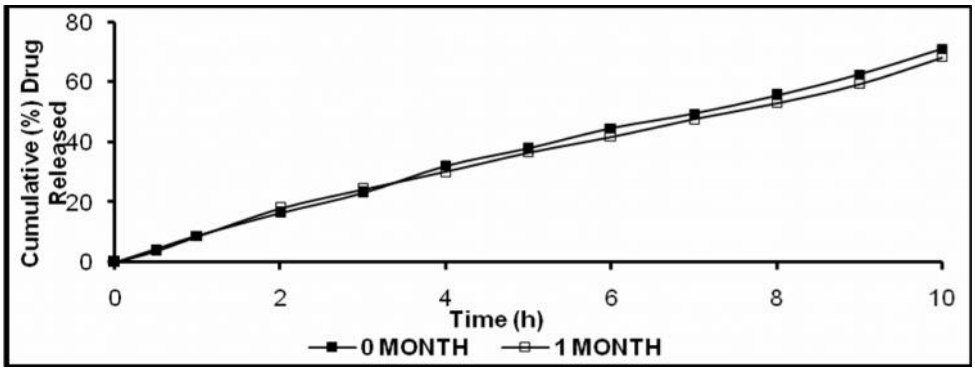

Figure 6: *In vitro* drug release profile of F3 formulation at 0 and 1st month stability study

CONCLUSION

It was concluded that, on the basis of *in vitro* buoyancy and *in vitro* drug release profiles that the formulations F3 and F6 showed good dissolution profile to control the drug release upto 12 h as compared to capsules contains only pure drug. So, it was better compared to uncontrolled fluctuation observed in multiple conventional dosage forms are administered in patient. The polymer concentration was increased in the formulations, as decreased in the drug release rate. The effect of hydrophobic and hydrophilic release modifiers was also studied. FT-IR studied reveled that there was no any chemical interaction between drug and polymer. The drug release was followed by zero order kinetics; it was confirmed by zero order kinetics and K-Peppas model. The prepared HBS capsules of Cefixime trihydrate were found to be stable at 40 ºC and 75% RH for 1 month.

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