INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
3(1): Jan.-March.: (2013), 541-348
ISSN: 2231-6078

Research Article

Formulation, Evaluation and Study of Effect of Hydrophilic Polymers on Release Rate of Cephalexin Floating Tablets

Ravi Kumar Zinka *, Snehalatha, T.S. Nagaraja, R. Yogananda

Dept. of Pharmaceutics, SJM College of Pharmacy, JMIT Campus, Chitradurga, Karnataka -577502

Abstract

In the present investigation effervescent floating matrix tablets of Cephalexin are formulated to achieve gastric retention for a period of 8 to 12 hrs. Cephalexin is first generation cephalosporin antibiotic used to treat infections caused by bacteria, including upper respiratory infections, ear infections, skin infections, and urinary tract infections. Cephalexin has well absorbed & short biological half life of 0.5-1.2 hrs. This favors development of sustained release dosage form by increasing gastric residence time. In this study polymers like HPMC K4M, Xanthan gum, Carbopol used in different ratios individually and combindlly. Sodium bicarbonate used as gas generating agent. The prepared formulations were evaluated for different physical and chemical evaluation parameters, *in vitro* drug release, swelling index, *in vitro* buoyancy studies. From the results of *in vitro* drug release the formulation F10 containing Xanthan gum noted as best formulation showed more sustain action than others and the kinetics of drug release was best explained by Peppas kinetic and the mechanism of the drug release was found to be diffusion controlled process. By observing the results it can be concluded that the anti microbial activity of the Cephalexin may be increased in the stomach due to increase in the retention time and absorption by using the natural polymer Xanthan gum than the synthetic polymers like HPMC K4M and Carbopol.

Keywords: Gastroretentive, Floating, Effervescent, Cephalexin, Xanthan gum, HPMC K4M, Carbopol, peppas.

Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[1]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations.[2, 3]

*** Corresponding Author**
E.mail: ravik.zinka@gmail.com
Mob. No. +918880512625

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[4]

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[5] A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.[6]

Conventional oral controlled dosage forms suffer from mainly two adversities.[7]The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. These problems can be overwhelmed by altering the gastric emptying. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.[8,9]

Cephalexin is in a group of drugs called cephalosporin antibiotics and is used to fight bacteria in the body. [10, 11, 12] It works by interfering with the bacteria's cell wall formation, causing it to rupture, and killing the bacteria. It's have good absorption in GIT, low pKa, which remained unionized in the stomach for better absorption and it's have half life 0.5-1.2 hours.[13] Cephalexin is used to treat infections caused by bacteria, including upper respiratory infections, ear infections, skin infections, and urinary tract infections.[14, 15]

The aim of the present study was not only preparing a cephalexin floating system but also to release the drug in the controller manner, therefore the maximum drug release is maintained at desired site. The effect of different polymers and the effect of amount of polymers was investigated in the formulation to monitor the sustained release effect respectively.

MATERIAL AND METHOD

Materials:

Cephalexin was obtained as gift sample from orchid chemicals & pharmaceutics ltd., Chennai. HPMC K4M, Xanthan gum, Carbopol and other excipients are obtained from yarrow chem. Products, Mumbai. The polymers were used in different ratios individually and combindlly.

Method of preparation:

Preparation of floating tablets of Cephalexin[16,17]

Floating effervescent tablets of cephalexin were prepared by direct compression method. The powder mixture contains drug, controlled release polymers as for the formulae and MCC was used as the diluent, sodium bicarbonate added as effervescent agent. The blend was lubricated with magnesium stearate for 3-5 mins and talc was added as glidant. Then the mixed blend was then compressed into tablets by direct compression method using 12.5 mm punches on a ten station rotary tablet punching machine.

Formulation:

Method:

The composition of different formulations of cephalexin floating tablets was shown in the table no. Different formulations were prepared by direct compression method. All the powders passed through 40/60 mesh sieve. Add talc and mg. stearate then compressed into tablets.

Characterization of Cephalexin Description:

The pure drug cephalexin was analyzed for colour, odour and taste.

Melting point

The melting point of drug was determined by open capillary method.

Standard curve

Standard curve of cephalexin was estimated by UV spectrophotometric method.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed on drug, excipient and the optimized formulation using FTIR. The sample were analysed between wave numbers 4000 and 400 cm-1.

Evaluation of granules: [18, 19, 20]

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula.

$$\Theta = \tan^{-1} (h/r)$$

Bulk density

Apparent bulk density (p_b) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.

$$p_b = M/ V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (ρ_t) was calculated using formula.

$$\rho_t = M/ V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I)was calculated as follows.

$$I = V0 - V_t /V_0 100$$

Where, V_0 is the bulk volume and V_t is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method

$$\text{Hausner ratio} = \rho_t /\rho_d$$

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Evaluation Of Tablets: [21,22]

Characterization of tablets for physiochemical parameters

The prepared Cephalexin floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

***In vitro* floating lag time**

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37^{o}C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

***In vitro* floating duration time**

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid i.e. 0.1N HCl. The time interval between introduction of the tablet into the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

***In vitro* drug release**

The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5^{o}C temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbance value of the diluted sample was measured at 257nm for Cephalexin by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

Characterization of drug in Floating tablets

FTIR studies were conducted for characterization of drug in tablets. The floating tablets were compressed and

powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Cephalexin and pelletized powder of tablets were taken, interpreted and compared with each other.

Determination Of Swelling Index: [23]

From each formulation, one tablet was weighed and placed in a beaker containing 200ml of 0.1N HCl buffer solution. After each hour the tablet was removed from beaker and weighed. The percentage weight gain by the tablet was calculated by using the formula.

$$\% SI = \frac{W_t - W_0}{W_0} X\ 100$$

S.I = Swelling index
Wt = Weight of tablet at time t
W0 = Weight of tablet before immersion

Result and Conclusion

The drug sample of Cephalexin was off white or almost white coloured, crystalline powder and have characteristic odour. The melting point value was observed in the range of 326^0C. The absorption maximum was found to be 257 nm when scanned between 200 to 400 nm in 0.1 N HCl by the UV-Visible spectrophotometer. FTIR spectra revealed that there was no interaction between the drug and the polymers i.e. the drug is compatible with the polymers.

The Preformulation studies were performed and the results were shown in the following table 2. Bulk density was found in the range of 0.62-0.68 g/cm^3 and the tapped density between 0.75-0.82 g/cm^3. Using these two density data compressibility index was calculated. The compressibility index was found between 16.45 and 20.02 and the compressibility- flowability correlation data indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 27.31^0 – 29.13^o), which is below 40^o indicating good flowability.

The mean thickness values were found in the range from 2.74±0.12 to 2.86±0.12 mm, the hardness of formulated tablets was found to be 4.52 to 5.40 kg/cm^3. The loss in friability was ranged from 0.31±0.08 to 0.64±0.16. These values were represented in Table 3. The floating lag time was ranged from 18 to 56 sec and all the formulations showed good floating buoyancy time i.e. ≥12 hrs (except F4) so the formulations remained in the stomach for long time thus the bioavailability of the dosage form was increased. F4 formulation did not float may be due to high density so the formulations F5, F6, F7 were prepared by mixing Carbopol and HPMC K4M 1:1 ratio then these formulations were floated in the medium.

The FTIR spectrum of formulated blend showed characteristic peaks of drug which indicatedthat the compatibility of the drug with the excipients used. The spectrum was shown in Figure 1.

The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. And the dissolution profile was represented in the below figure 2-4.

Swelling index:

The swelling index values were determined and the results were shown in the below figure 5-6.

From the results of %drug release of the tablet dosage form it was observed that all the formulations shows the drug release in the controlled manner and the formulation F9 showed 59.064% drug release at the end of 12 hrs. Thus the biological half life of the drug was increased.

Data obtained from the *in vitro* release studies were fitted to various kinetic models such as zero order, first order, Higuchi and korsmeyer-peppas model and the results are shown in the table 4 and the figure 7 below.

It was found that all the formulations were shown Peppas as te best fit model except F7, F8 and they were fitted into matrix and first order model respectively. When the release data's were analyzed as per peppas equation, the release exponent 'n' was found to be in the range of 0.5178 to 0.7073 indicating non-fickian diffusion mechanism.

Conclusion:

The effervescent-based floating drug delivery is a promising approach to achieve in vitro buoyancy. The addition of gel forming layer and gas generating agent was essential to achieve in vitro buoyancy. By observing the dissolution profile of the formulation it can be concluded that the anti microbial activity of the Cephalexin may be increased in the stomach due to increase in the retention time and absorption by using the natural polymer Xanthan gum than the synthetic polymers like HPMC K4M and Carbopol. F10 formulation showed controlled drug release and adequate floating properties. The kinetics of drug release was best explained by Peppas kinetic and the mechanism of the drug release was found to be diffusion controlled process.

References

1) Robinson JR, Lee VHL. Controlled drug delivery: fundamentals and pplications, 2nd ed. New York : Marcel Dekker; 1978.
2) Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise. 1st ed. New Delhi : Vallabh Prakashan; 1995.
3) Chein YW. Novel drug delivery systems. 2nd ed. New York : Marcel Dekker; 1992.
4) Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. The Eastern Pharmacist 1991; 45 : 25-28.

5) Gennaro RA. Remington: The Science and Practice of Pharmacy. 20th ed. New York : Lippincott Williams; 2000.
6) Banker GS, Rhodes CT. Modern Pharmaceutics. 3rd ed. New York : Marcel Dekker; 1996.
7) Hoffmann A. Pharmacodynamic aspects of sustained release preparations. Adv. Drug. Deliv. Rev 1998; 33 : 185-99.
8) Stanley SD, Lisbeth I. Drug delivery systems for challenging molecules. Int. J. Pharm. 1998; 176 : 1-8.
9) Natasha Sharma, Dilip Agarwal, M.K. Gupta and Mahaveer Pr. Khinchi. A Comprehensive Review on Floating Drug Delivery System. *Int. J. Res. Pharm. Biomed. Sci.* Vol. 2 (2) Apr – Jun 2011.
10) Good man and gilman's The pharmacological basis of therapeutics. 11th edition. Medical publication division. 1095-154
11) URL:http://www.drugbank.com/generic/view/
12) British Pharmacopoeia. Her Majesty's Stationery Office. London: 2005, 3, 1609.
13) http://en.wikipedia.org/wiki/Cephalexin
14) http://membrana.com/polymers/products/product_mp.htm accessed on Jul 2012
15) KD Tripathi. Essentials of medical pharmacology. 6th ed. Jaypee brothers medical publishers. 667-94.
16) Kavita.K, Sudhir K. Yadav,Tamizhamani T. Formulation and Evaluation of Floating Tablets of RHCL Using Natural and Synthetic Polymers. *Int. J. Pharm Tech Res.* 2010;2(2): 1513-19.
17) Sharad N, Satej S, Shekhar B, Maesh R, Kamla K. Development and evaluation of floating tablets of salbutamol sulphate. *Int J Pharm Res Dev* 2101 july;2(5):1-7.
18) Gangadharappa HV, Balamuralidhara V, Pramod Kumar TM. Formulation and *in vitro* evaluation of gastric floating tablets of Atenolol. *J Pharm Res* 2010;3(6):1450-5.
19) Shoufeng Li,Senshang Lin, Bruce P , Daggy BP, Michandani H L and Chein Y.W.Drug.Dev.Ind Pharm.28(7),783-793, 2002
20) Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets-formulation and *in vitro* evaluation. *Drug Dev Ind Pharm* 2005;31(4):367-74.
21) Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm*. 2000; 195 : 125 -35.
22) Karthikeyan D, Karthikeyan M, Ramasamy C. Development of floating microsphere to improve oral bioavalibilty of cefpodoxime proxetil. *Acta pharmaceutical sciencia* 2010; 52: 101-104.
23) J. A. Ravala, J. K. Patela, Naihong Lib, M. M. Patela. Ranitidine hydrochloride fl oating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release. *Asian Journal of Pharmaceutical Sciences* 2007, 2 (4): 130-142.

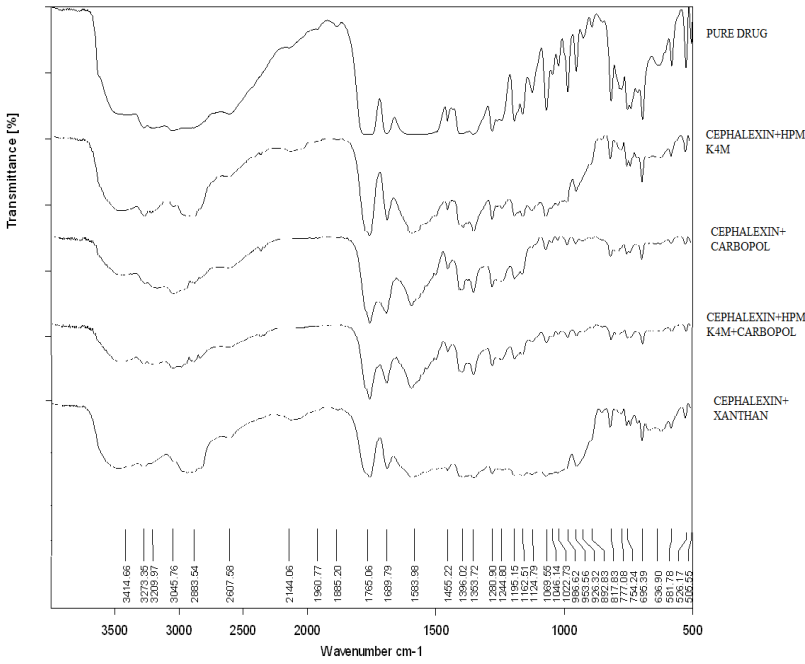

Figure: 1: FTIR Spectra of Cephalexin by Polymers

Figure: 2: Dissolution profile of Cephalexin with HPMC K4 M

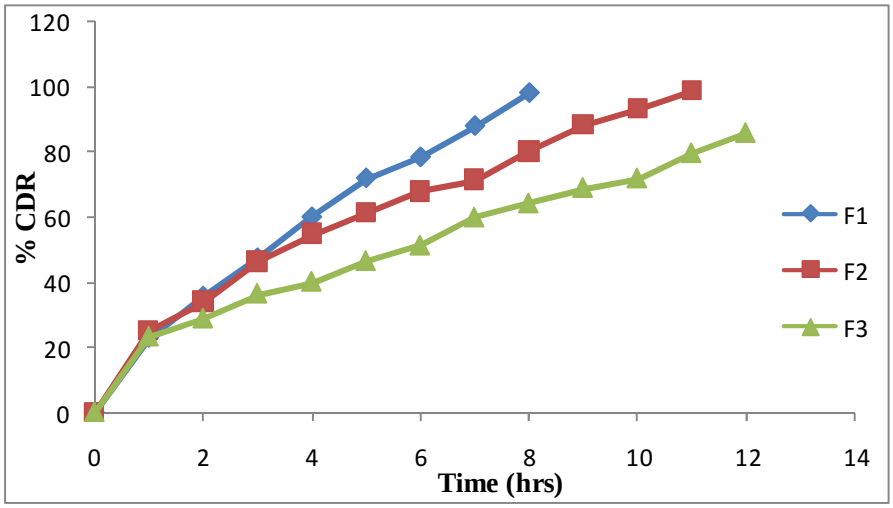

Figure: 3: Dissolution profile of Cephalexin with Carbopol, Carbopol+ HPMC K4M

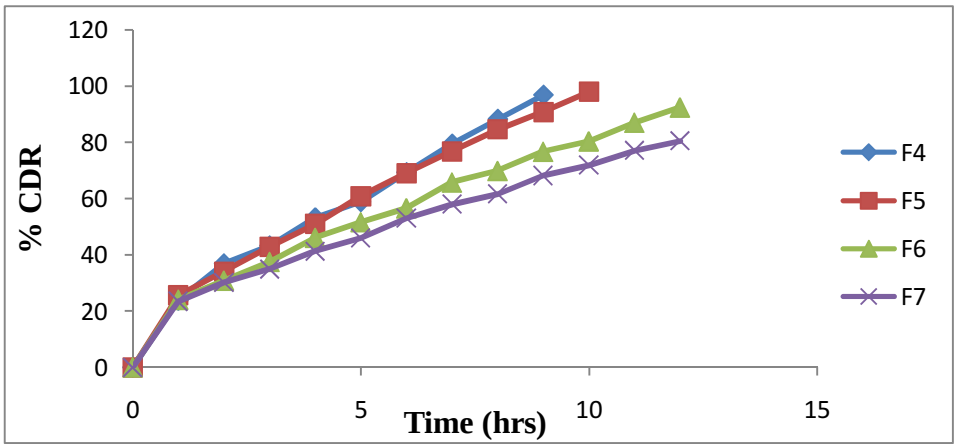

Figure: 4: Dissolution profile of Cephalexin with Xanthan gum

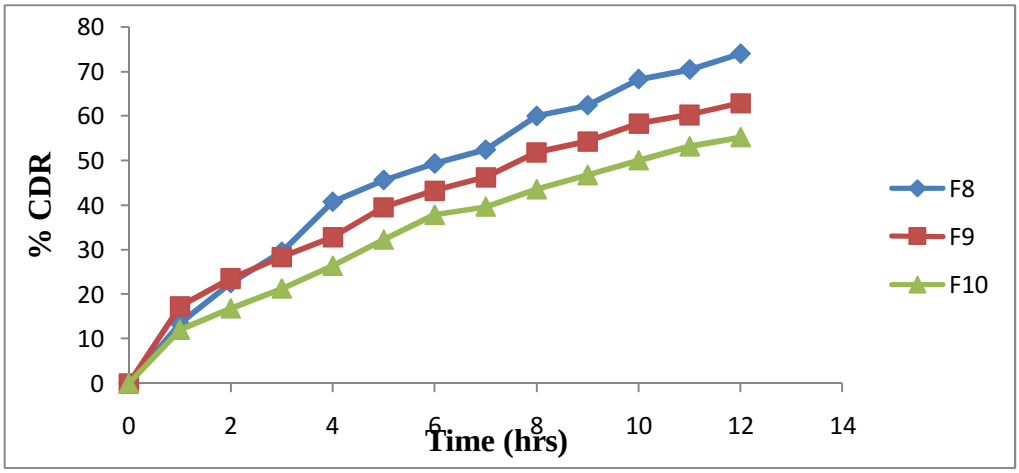

Fig: 5: Swelling Index of formulations F1 to F7

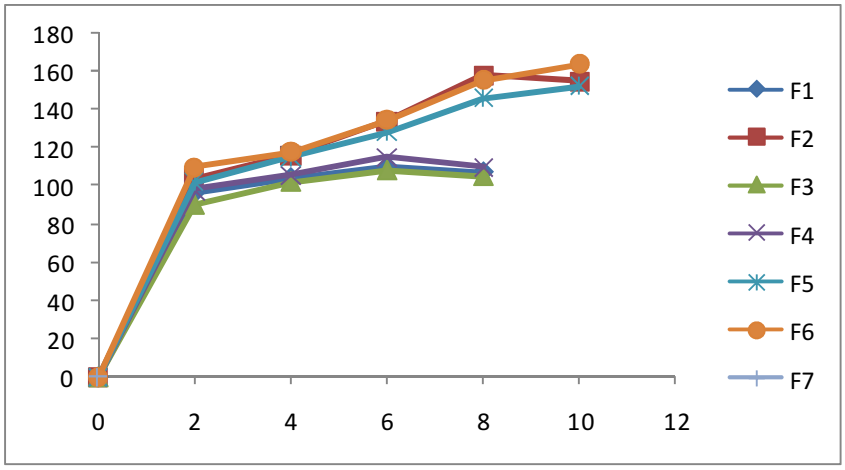

Fig: 6: Swelling Index of formulations F8, F9, F10

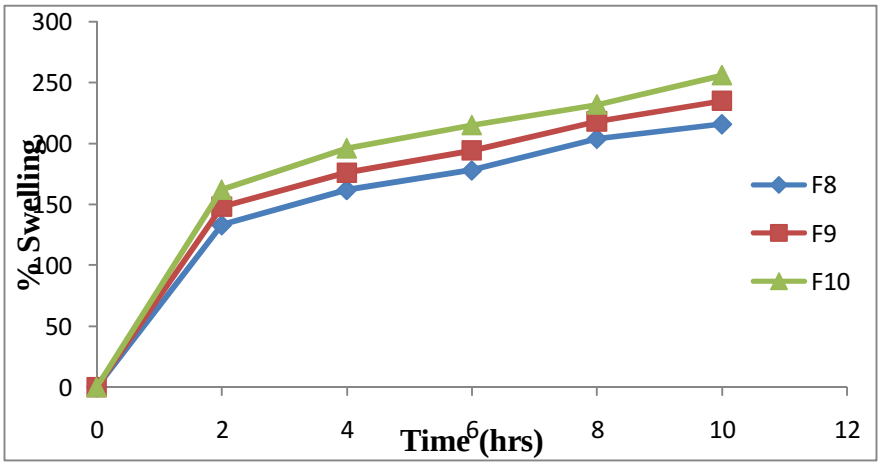

Fig: 7: Graphical representation of *in vitro* drug release kinetics for F10

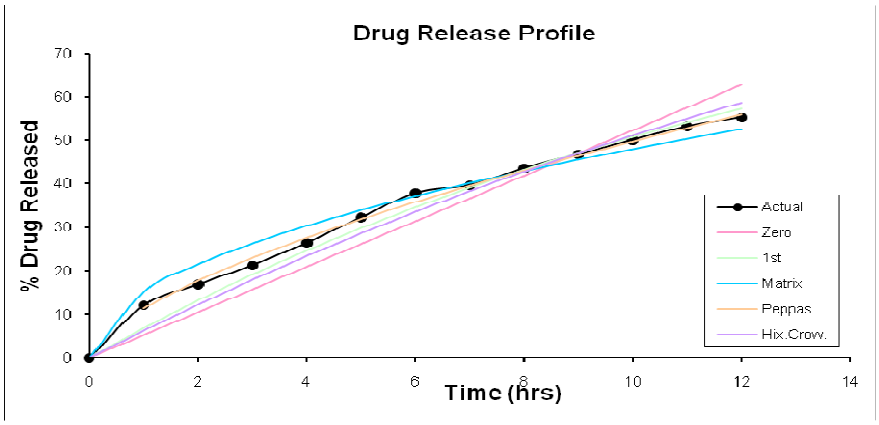

Table: 1: Composition of floating tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	250	250	250	250	250	250	250	250	250	250
HPMC K 4M	80	140	190	-	40	70	95	-	-	-
Carbopol	-	-	-	80	40	70	95	-	-	-
Xanthangum	-	-	-	-	-	-	-	80	140	190
$NaHCo_3$	55	55	55	55	55	55	55	55	55	55
MCC	140	80	30	140	140	80	30	140	80	30
Talc	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mg.stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Total weight	550	550	550	550	550	550	550	550	550	550

Note: All ingredients are mentioned the above table is in mg/tab

Table: 2: Flow properties of Cephalexin powder blend:

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
F1	29.13 ± 0.04	0.64 ± 0.02	0.80±0.02	20.02 ±0.04	1.25 ± 0.02
F2	27.31 ± 0.03	0.65 ± 0.02	0.78±0.03	16.66 ±0.02	1.20 ± 0.01
F3	28.26 ± 0.01	0.64 ± 0.01	0.78±0.02	17.94 ±0.04	1.21 ± 0.04
F4	28.28 ± 1.50	0.63± 0.08	0.77 ± 0.05	18.18 ± 0.02	1.22 ± 0.05
F5	29.01 ± 1.04	0.68± 0.04	0.82 ± 0.03	17.07 ± 0.04	1.21 ± 0.02
F6	26.87 ± 2.0	0.64± 0.03	0.79 ± 0.02	18.98 ± 0.01	1.234 ± 0.03
F7	27.48 ± 1.05	0.63± 0.05	0.78 ± 0.07	19.23 ± 0.08	1.238 ± 0.04
F8	28.15 ± 1.53	0.67± 0.08	0.81 ± 0.02	17.28 ± 0.05	1.20 ± 0.07
F9	28.44 ± 1.25	0.66± 0.02	0.79 ± 0.06	16.45 ± 0.03	1.19 ± 0.04
F10	27.57 ± 0.82	0.62± 0.06	0.75 ± 0.08	17.33 ± 0.06	1.20 ± 0.06

All values are expressed as mean ± SD, n=3

Table: 3: Evaluation of physical parameters of Cephalexin floating tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Average weight (mg)	Friability (%)	Drug content (%)	Floating lag time (sec)	Total floating time (h)
F1	2.86±0.12	4.52	552	0.41±0.05	99.81 ± 1.4	18	>24
F2	2.82± 0.16	5.20	550	0.31±0.08	99.67 ± 1.7	13	>24
F3	2.85± 0.14	4.55	549	0.36±0.03	98.75 ± 0.5	20	>24
F4	2.83±0.75	5.40	550	0.64± 0.16	97.53 ± 1.3	No floating	-
F5	2.85±0.62	5.25	551	0.39± 0.94	99.18 ± 0.6	52	>10
F6	2.81±0.84	5.25	552	0.53± 0.62	100.65 ± 0.4	56	>12
F7	2.82±0.15	5.30	549	0.47± 0.16	100.82 ± 0.3	48	>12
F8	2.76±0.09	4.85	551	0.48± 0.08	98.63 ± 1.2	35	>24
F9	2.74±0.12	4.85	549	0.62± 0.14	99.67 ± 0.5	33	>24
F10	2.79±0.1	4.80	552	0.40± 0.06	100.26 ± 0.8	32	>24

Table: 4: Regression coefficient fits to different drug release kinetics models

Formulation code	**r^2**					**Best fit model**
	Zero order	**First order**	**Higuchi's model**	**Korsmeyer Peppas**	**N**	
F1	0.9757	0.8900	0.9803	0.9991	0.7073	Peppas
F2	0.9323	0.9021	0.9935	0.9975	0.5782	Peppas
F3	0.935	0.9783	0.9892	0.9892	0.5413	Peppas
F4	0.9660	0.8958	0.9797	0.9897	0.6058	Peppas
F5	0.9579	0.9056	0.9868	0.9943	0.6053	Peppas
F6	0.9398	0.9677	0.9905	0.9933	0.5638	Peppas
F7	0.9164	0.9914	0.9945	0.9920	0.5178	Matrix
F8	0.9447	0.9968	0.9873	0.9958	0.6836	1st order
F9	0.9908	0.9826	0.9968	0.9972	0.5395	Peppas
F10	0.9534	0.9915	0.9862	0.9966	0.6438	Peppas