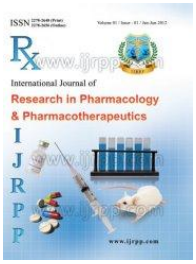
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.6 | Issue 2 | Apr - Jun - 2017***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Formulation and *in vitro, in vivo* evaluation of Cefixime controlled Gastroretentive floating drug delivery system

E. Sathish Reddy[*,], Meesala. Srinivasa Rao[*,**] and Mohammed Ibrahim[*,**]**

**Department of pharmaceutics and Pharmaceutical Bio technology, Prathap Narender Reddy College of Pharmacy, Peddashapur (V), Shamshabad (M), Ranga Reddy Dist.*
***Asian Institute of Advance Research, Hyderabad d-500 058, Telangana State, India.*

***Corresponding author: E. Sathish Reddy**

ABSTRACT

The aim of the present work was to develop and optimize gastroretentive floating system of cefixime (CF) for the effective treatment. The present study was carried out with an objective of preparation and in vivo evaluation of floating tablets of using cefixime as a model drug using Eudragit polymers (Eudragit-S100, Eudragit-RLPO & Eudragit-RSPO) to improve oral bioavailability of cefixime floating tablets by increasing gastric residence time. The tablets were prepared by direct compression method. The effect of polymers concentration and viscosity grades of Eudragit on drug release profile was evaluated. The result of in vitro dissolution study showed that the drug release profile could be controlled by increasing the concentration of Eudragit-RLPO. The optimized formulation (F18) containing Eudragit-RLPO showed 99.24% drug release at the end of 24h. Changing the viscosity grade of Eudragit-RLPO had no significant effect on drug release profile. The optimized formulations (F18) containing sodium bicarbonate 40mg per tablet showed desired buoyancy (floating lag time of about 20 min and total floating time of >24hr). Optimized formulation (F18) followed diffusion controlled zero order kinetics and fickian transport of the drug. FTIR and DSC studies revealed the absence of any chemical interaction between drug and polymers used. The best formulation (F18) was selected based on in vitro characteristics and was used in vivo radiographic studies by incorporating BaSO4. These studies revealed that the tablets remained in the stomach for 24hrs in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. Studies to evaluate the pharmacokinetics in vivo showed better bioavailability, area under the concentration time curve, elimination rate constant and half-life than marketed product.

Keywords: Cefixime, Eudragit-S100, Eudragit-RLPO, Eudragit-RSPO, Sodium alginate, PVP K30, Magnesium stearate and micro crystalline cellulose, Radiographic studies.

INTRODUCTION

In the past few decades, significant medical advances have been made in the area of drug delivery with the development of novel dosage forms. The area of sustained drug delivery has graduated from being merely a research item to result in full-fledged commercial products. An appropriately designed sustained release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery. The term "optimization "is often used in pharmacy relative to formulation and to processing, and one will find it in the literature referring to any study of the formula. Drug products are often developed by an effective compromise between competing characteristics to achieve the best formulation and process within a given set of restrictions. Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. A gastric floating drug delivery system (GFDDS) is particularly useful for drugs that have an absorption window in a particular region of the gastrointestinal tract that is in the duodenum and upper jejunum segments. This system prolongs the retention time of the oral dosage form in the stomach thereby improving the oral bioavailability of the drug, prolong dosing intervals and increase patient compliance. Such retention systems are useful for those drug that get degraded in the intestine like antacids, certain antibiotics and enzymes that act locally in the stomach etc.[1,2]

Cefixime is a broad spectrum cephalosporin antibiotic and is commonly used to treat bacterial infections such as bronchitis (infection of the airway tubes leading to the lungs); gonorrhea (a sexually transmitted disease); and infections of the ears, throat, tonsils, and urinary tract. Cefixime is in a class of medications called cephalosporin antibiotics. It works by killing bacteria.

Pharmacokinetic parameters of cefixime such as absorption from the gastrointestinal tract 50% protein binding 21%-29%, low pKa help the drug remain unionized in stomach for better absorption. Cefixime is a pro drug and de-esterified to cefpodoxime (active), half-life is 2.09 to 2.84 hour and about 29% to 33% of the absorbed dose is excreted unchanged in the urine in 12 h. [3,4] Some drug degrades in alkaline pH, to prevent this, gastro retentive dosage forms can be formulated using hydrophilic polymer that slowly forms thick gel, which retains integrity of the formulation and promotes drug release through thick gel and controls the burst release. The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier.

MATERIALS AND METHODS

Cefixime was obtained from Sun global formulations, Hyderabad. Eudragit-S100, Eudragit-RLPO and Eudragit-RSPO were gifted by Evonik pharma Pvt Ltd. Sodium CMC was obtained from Mylan Chem Mumbai. Sodium bicarbonate and Citric acid were obtained from Sisco research laboratories Pvt. Ltd Mumbai. Microcrystalline Cellulose, Magnesium stearate, Aerosil & PVP-K 30 were obtained from S.D Fine-Chem. LTD, Mumbai. Sodium alginate was obtained from Vijayalakshmi chemicals, Hyderabad. Talc was obtained from Swastik pharmaceutical, Bombay. And Conc. HCL was obtained from Spectrum reagents and chemicals Pvt. Ltd, Cochin. All the Chemicals were used as received.

Preparation of Cefixime floating tablets

Floating tablets of Cefixime was prepared by direct compression. The compositions of the formulations were made using different swellable polymers like Eudragit-S100, Eudragit-RLPO and Eudragit-RSPO to get a floating time of more than 12hr. All the ingredients except Magnesium stearate were blended in a glass mortar uniformly and passed through sieve no.80 to get fine particles. To this, Magnesium stearate was added and further mixed for additional 2-3 min. The resultant mix was compressed into tablets on a 10 station single punch rotary tablet compression machine (Rimek). A flat-faced punch 10 mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 5-6 kg/cm2 for different batches. All the formulations F1 – F21 containing 500 mg of the drug were prepared and each tablet weighing approximately 1000 mg was punched. The Composition of cefixime floating tablets were shown in Table 1.

Table1: Formulation of gastro retentive drug delivery systems of cefixime

Formulation code	Cefixime (mg)	Eudrait S100 (mg)	Eudrait RSPO (mg)	Eudrait RLPO (mg)	Sodium Alginate (mg)	Mg Stearate (mg)	PVPK30 (mg)	Aerosil (mg)	$NaHO_3$ (mg)	Citric acid (mg)	MCC (mg)	Total (mg)
F1	500	50	-	-	25	10	25	7.5	50	50	382.5	1000
F2	500	100	-	-	25	10	25	7.5	50	50	332.5	1000
F3	500	150	-	-	25	10	25	7.5	50	50	282.5	1000
F4	500	200	-	-	25	10	25	7.5	50	50	232.5	1000
F5	500	250	-	-	25	10	25	7.5	50	50	132.5	1000
F6	500	300	-	-	25	10	25	7.5	50	50	32.5	1000
F7	500	-	50	-	25	10	25	7.5	50	50	382.5	1000
F8	500	-	100	-	25	10	25	7.5	50	50	332.5	1000
F9	500	-	150	-	25	10	25	7.5	50	50	282.5	1000
F10	500	-	200	-	25	10	25	7.5	50	50	232.5	1000
F11	500	-	250	-	25	10	25	7.5	50	50	132.5	1000
F12	500	-	300	-	25	10	25	7.5	50	50	32.5	1000
F13	500	-	-	50	25	10	25	7.5	50	50	382.5	1000
F14	500	-	-	100	25	10	25	7.5	50	50	332.5	1000
F15	500	-	-	150	25	10	25	7.5	50	50	282.5	1000
F16	500	-	-	200	25	10	25	7.5	50	50	232.5	1000
F17	500	-	-	250	25	10	25	7.5	50	50	132.5	1000
F18	500	-	-	300	25	10	25	7.5	50	50	32.5	1000
F19	500	150	150		25	10	25	7.5	50	50	32.5	1000
F20	500		150	150	25	10	25	7.5	50	50	32.5	1000
F21	500	150		150	25	10	25	7.5	50	50	32.5	1000

Buoyancy lag time determination & total floating time

The in vitro buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation [5].

In vitro dissolution studies

In vitro drug release studies for the prepared immediate release tablets were conducted for a period of 24h using USP type-II (Paddle) dissolution apparatus at 37±0.5oC at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed for cefixime by UV/Visible spectrophotometer Shimadzu 1800 at 231 nm.

Kinetic modeling of drug release

The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi and Peppas equations [6,7].

$Mt = M0 + k0t$ (1)

$\ln Mt = \ln M0 + k1t$ (2)

$Mt = M0 – kHt1/2$ (3)

$Mt/M\alpha = Ktn$ (4)

In these equations, Mt is the cumulative amount of drug released at any specified time (t) and M0 is the dose of the drug incorporated in the delivery system and $Mt/M\alpha$ is a fraction of drug released at time (t). k0, k1, kH and K are rate constants for zero order, first order, Higuchi and Korsmeyer model respectively, n is the release exponent. The n value is used to characterize different release mechanisms for cylindrical shaped matrices.

The dissolution data were also fitted according to the well-known exponential Zero Order equation,

which is often used to describe drug release behavior from polymeric systems. The best fit with higher correlation (r2 > 98) was found with Higuchi's equation for all the formulations.

DRUG EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for cefixime, Eudragit and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer (PERKIN ELMER BX1) samples were prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. The samples were scanned from 4000 to 400/cm-1

Stability studies

The stability studies were carried out as per ICH guidelines. The best formulation F18 was subjected to accelerated stability test by storing at 40±20C/75±5% relative humidity in an accelerated stability chamber (Remi, Mumbai). After specified period of time (1, 2 & 3 months) samples were withdrawn and floating lag time, total floating time and in vitro dissolution studies were conducted [8].

Radiographic studies

The radiographic and In-vivo bioavailability study was carried according to the guidelines of the Institutional Human Ethics Committee (IHEC).

Determination of In vivo gastric residence time

For this study, the tablets are prepared by replacing half the amount of drug with barium sulphate. After overnight fasting, the volunteers were fed with a low calorie food. After half an hour, a barium sulphate labelled tablet was given to every subject with 200ml of water. The volunteers were asked to take 200ml water after every 1h. At different time intervals (1, 8, 12, 22 and 23h post administration of tablets), the volunteers were exposed to abdominal X-ray imaging in standing position. The distance between the source of X-rays and the subject was kept constant for all images. Thus, the observation of the floating tablet movements could be easily noticed [9]. The mean gastric retention period was estimated.

In vivo bioavailability studies of cefixime: [10]

Six healthy male subjects with a mean age of 28.83 ± 3.60 years (ranging from 24 to 34 years), mean weight 69.33 ± 7.61Kg (ranging from 61 to 79 Kg) and a mean height of 173.17 ± 10.46cm (ranging from 157 to 182cm) participated in this study. Informed and signed consent and approval of the Human Ethical Committee were obtained. The volunteers were judged healthy on the basis of their previous medical history, physical examination and routine laboratory tests. None of the subjects used alcohol or tobacco. All subjects were free from drugs 15 days before and during the study.

They were randomly divided into 2 groups of 6 subjects each. The subjects were fasted over night at least 10hr prior to dose. After collecting the zero hour blood sample (blank). A standardized high fat-breakfast approximately 900KCal was given in the morning halfan- hour before administration. Group A received Formulated cefixime and group-B received commercial formulation was administered with 200ml of water. All the subjects were given a glass of water for every 2hrs (approximately 200 ml). Standardized lunch, snacks and dinner was provided to all the subjects respectively at 4, 8 and 12h after the administration of formulations, Blood samples (2ml) were collected by the intravenous route using heparinized disposable syringes at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 20 and 24 hrs. The blood samples were collected in vacutainers containing EDTA as anticoagulant and immediately centrifuged at 3000rpm for 15min. The separated plasma samples were stored at -20^{0}C until analyzed.

Determination of Cefixime in Human plasma by HPLC method [11]

Determination of Cefixime using internal standard lamotrogine by high performance liquid chromatography with a RPC18 chromatographic column, Phenomenex Kinetex (150 mm × 4.6 mm i.d) and a mobile phase consisting of 0.1% ortho phosphoric acid with tri-ethyl amine as modifier buffer: acetonitrile (50:50 % v/v) at a flow rate 0.6ml/min and the wavelength detection was 294 nm.

Preparation of Plasma Samples for HPLC Analysis

Human plasma (0.5ml) was prepared for chromatography by precipitating proteins with 2.5ml of ice-cold absolute ethanol for each 0.5ml of plasma.

After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1min. After centrifugation (5000 – 6000 rpm for 10min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200µl of 50% of acetonitrile and 50% 0.1% ortho-phosphoric acid was injected for HPLC analysis.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (Cmax) and time to reach peak concentration (tmax) were directly obtained from concentration time data. In the present study, AUC0-t refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and AUC0-α refers to the AUC from time at zero hours to infinity. Calculated using the formula AUC0-t + [Clast/K] where C last is the concentration in µg/ml at the last time point and K is the elimination rate constant. Various pharmacokinetic parameters like area under the curve [AUC], elimination half life (t½). Volume of distribution (Vd), total clearance (ClT) and mean residence time for each subject using a non compartmental pharmacokinetic program. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using oneway analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

RESULT AND DISCUSSION

Twenty one formulations were prepared and evaluated for in vitro buoyancy lag time and total floating time. The time required for the tablet to rise to the surface (when the tablets were placed in a beaker containing 0.1 N HCl) for floating was described as the buoyancy lag time. NaHCO3 induces CO2 generation in the presence of HCl. All the formulations had buoyancy lag time in the range of 32 to 45 sec. The total floating time was found to be more than 24 hrs, which indicates a stable gel layer formation by all polymers and that NaHCO3 remains for a longer time. The results of floating lag time and total floating time was depicted in Table 2 & Figure 1.

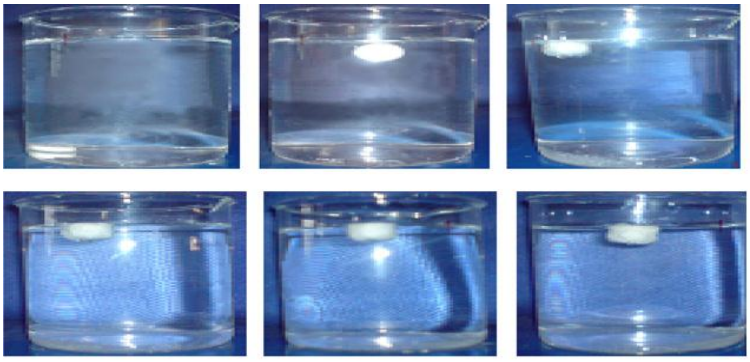


Figure 1: *In vitro* buoyancy lag time of the optimized formulation (F18)

Table 2: Buoyancy lag time and total floating period of cefixime floating tablets

Formula Code	Buoyancy lag time in min	Total floating time(Hrs)
F1	10	>24
F2	18	>24
F3	16	>24
F4	13	>24
F5	18	>24
F6	20	>24

F7	15	>24
F8	12	>24
F9	13	>24
F10	14	>24
F11	15	>24
F12	17	>24
F13	10	>24
F14	12	>24
F15	14	>24
F16	16	>24
F17	18	>24
F18	20	>24
F19	22	>24
F20	24	>24
F21	16	>24

All the formulations (F1-F21) were prepared with different grades of polymer like Eudragit with different grades. F1to F6 are having cefiexime, Eudragit-S100 in different proportions shown the drug release was 96.6% (8hr),98.94% (10hr),99.17% (12hr),95.22% (14hr),96.17% (16hr) and 95%(18hr) respectively. The formulations F7 to F12 were developed using Eudragit-RSPO and the % of drug release was 98.24% (10hr), 98.45% (14hr), 98.56% (16hr),98.45% (16hr),98.18% (18hr) and 99.10% (22hr) respectively indicating comparatively better release rates than formulations F1to F6 (Table 3 & Figure 2).

The formulations F13 to F18 were developed using Eudragit-RLPO and the % of drug release was 98.27%(12hr), 98.56%(14hr), 98.18% (16hr),97.22% (18hr),98.56% (20hr) and 99.24% (24hr) respectively indicating comparatively better release rates than formulations F1to F13. The formulation F19 was developed using Eudragit-S100 & Eudragit-RSPO and the %drug release was 97.28% (18hr). The formulation F20 was developed using Eudragit-RSPO & Eudragit-RLPO and the %drug release was 98.68% (22hr). F21 was developed using Eudragit-S100 & Eudragit-RLPO and the %drug release was 98.26% (20hr) respectively. The results are summarized in Table 4& Figure 3. Formulation F18 selected as optimized formulation based on the better drug release, lag time and total floating time.

Table 3: Cumulative percent drug release of formulations F1-F12

Parameter	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11(%)	F12(%)
1 hr	58.24	52.34	48.25	43.96	38.25	36.22	52.62	48.17	44.10	34.32	33.36	35.26
2 hr	63.63	56.25	56.62	48.24	45.09	42.14	57.94	54.92	56.17	47.55	44.48	37.94
4 hr	72.21	73.64	68.55	54.17	56.10	49.71	64.63	62.17	63.15	56.24	57.62	46.55
6 hr	82.65	82.93	75.14	63.24	63.21	51.22	77.21	75.22	69.36	64.36	66.35	52.17
8 hr	96.64	86.25	82.36	72.55	74.55	56.14	96.56	87.14	78.66	73.26	75.17	58.27
10 hr		93.94	88.47	84.32	81.62	65.55	98.24	93.33	86.14	86.24	86.21	64.33
12 hr			99.17	89.17	86.17	70.01		96.22	92.63	88.22	89.88	72.22
14 hr				95.22	92.22	79.33		98.45	95.24	93.63	92.27	85.17
16 hr					96.17	86.07			98.56	98.45	94.61	88.16
18 hr						95.00					98.18	93.24
20 hr												96.18
22 hr												99.10
24 hr												

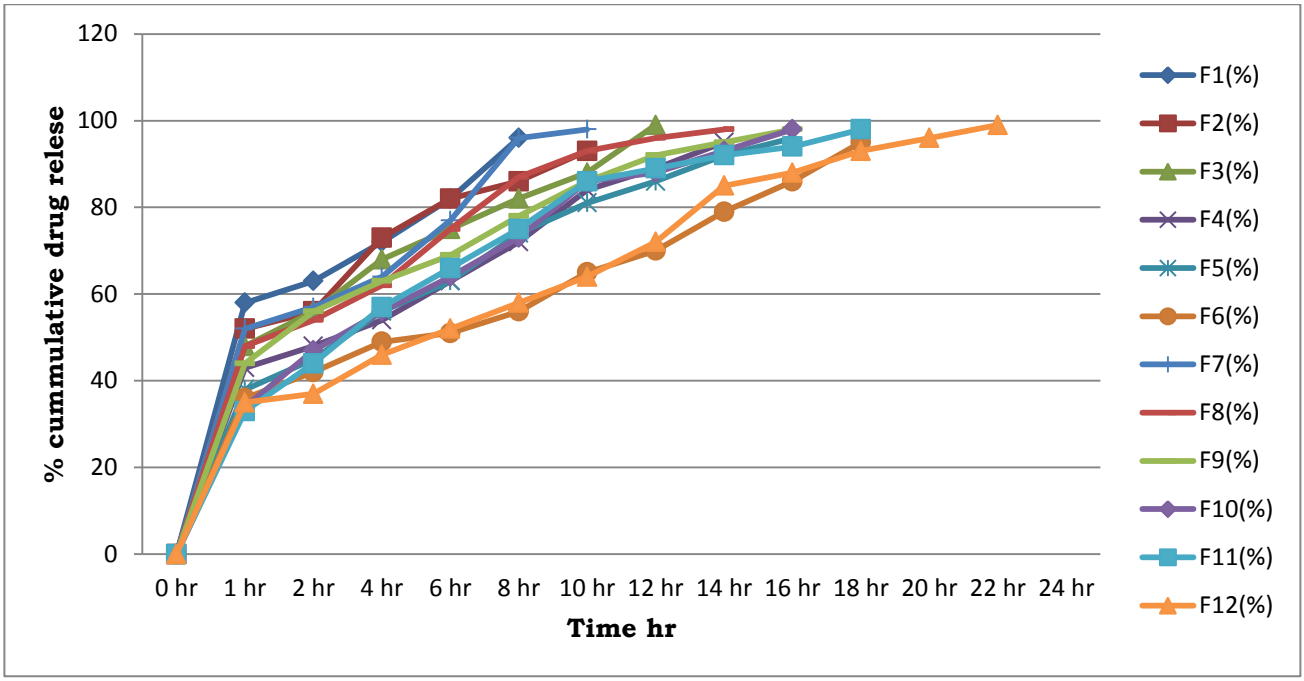


Figure 2: Drug release profile from formulations F1- F12

Table 4: Cumulative percent drug release of formulations F13-F21

Parameter	F13(%)	F14(%)	F15(%)	F16(%)	F17(%)	F18(%)	F19(%)	F20(%)	F21(%)
1 hr	47.21	46.14	40.34	37.22	27.17	18.27	38.88	28.18	32.18
2 hr	54.22	55.26	46.18	44.37	38.64	27.48	47.64	36.18	39.63
4 hr	63.63	64.61	54.17	53.61	48.26	39.22	55.49	45.34	43.22
6 hr	74.51	68.27	63.66	65.23	55.78	48.28	64.24	55.10	52.47
8 hr	85.14	74.10	68.19	67.57	64.94	56.54	72.76	66.25	58.24
10 hr	93.23	86.19	82.16	82.19	78.64	63.39	75.22	72.14	63.95
12 hr	98.27	93.47	87.14	88.95	83.22	70.67	83.36	78.33	74.66
14 hr		98.56	93.56	94.64	87.18	75.29	87.41	83.27	82.25
16 hr			98.18	96.37	91.26	82.17	93.27	88.94	87.65
18 hr				97.22	95.27	88.89	97.23	92.73	95.55
20 hr					98.56	92.36		93.45	98.26
22 hr						95.28		98.63	
24 hr						99.24			

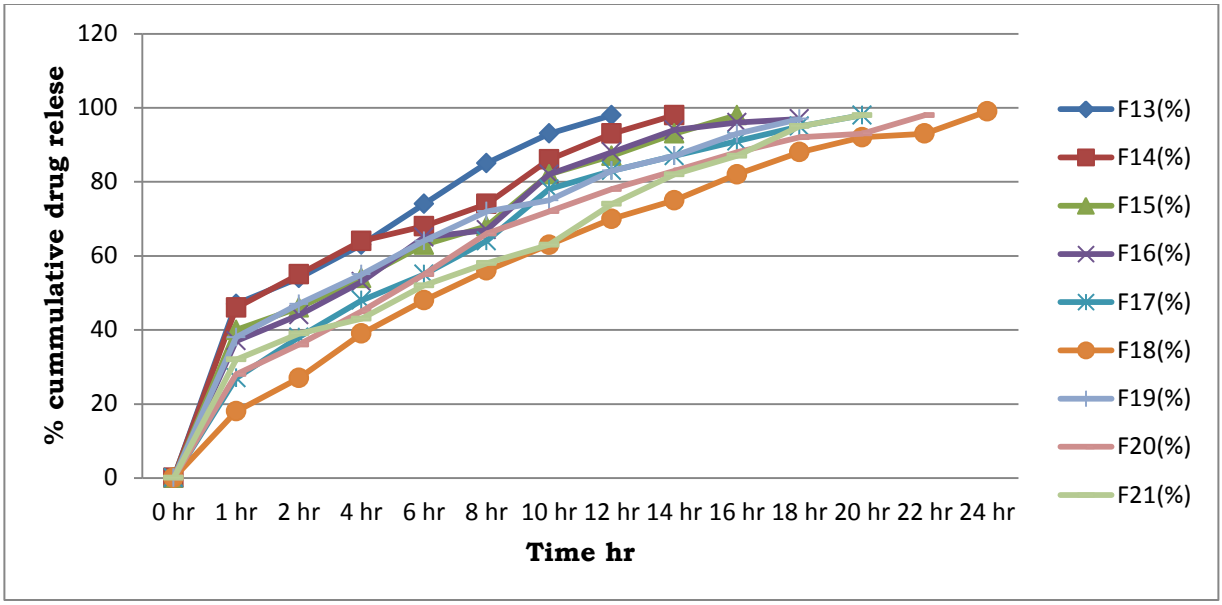


Figure 3: Drug release profile from formulations F13- F21

Mathematical modeling of floating tablets

To explore the mechanism of drug release from CF (Cefixime) floating tablets, various kinetic models like zero order, first order, Higuchi and Korsmeyer-Peppas equations were applied to the different formulations. The release order kinetics of optimized formulation (F18) was shown in Table 5.

The in vitro drug release data of all the formulations (F1-F21) 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 formulations. From the Korsmeyer-Peppas plots, it has been observed that regression value (n-value) of all the formulations (F1-F21) ranges from 0.3870 to 0.5038, suggesting that the drug was released by Fickian diffusion in all the cases. The optimized formulation F18 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.

Table 5: Release order kinetics of optimized formulation (F18)

Formulation code	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F18	3.1528	0.6484	0.7177	0.0472	0.8766	19.588	0.9273	0.3842

Drug - excipient compatibility studies

The FT-IR spectra of pure drug cefixime (Figure 4) and optimized formulation F18 (Figure 5) were found to be identical. The FTIR spectra of the optimized formulation displayed the characteristic peaks of both drug and polymers. Overall there was no alteration in the characteristic peaks of cefixime suggesting that there was no interaction between the drug and polymer.

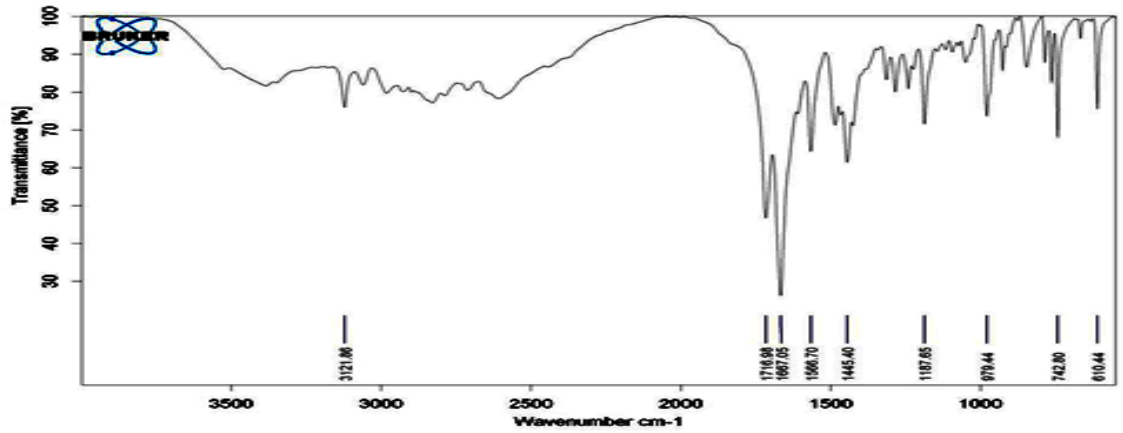


Figure 4: FTIR spectrum pure drug cefixime

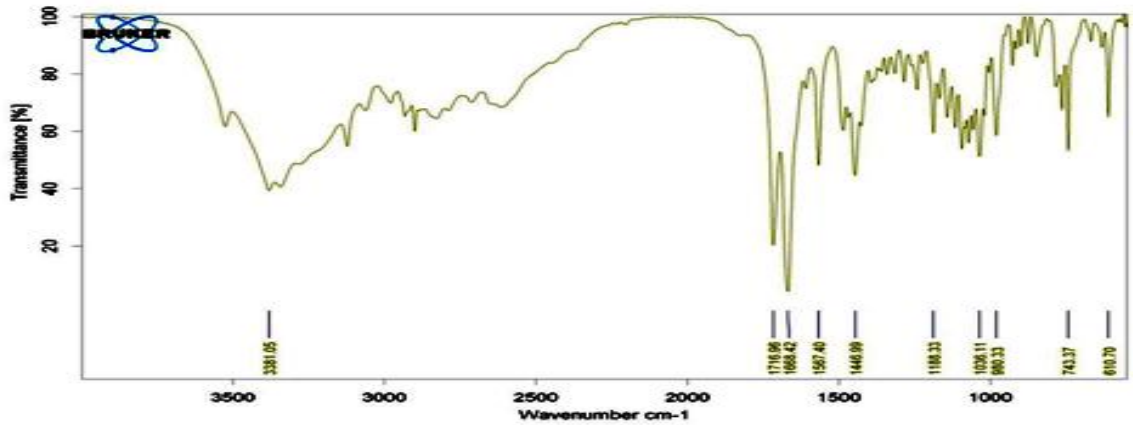
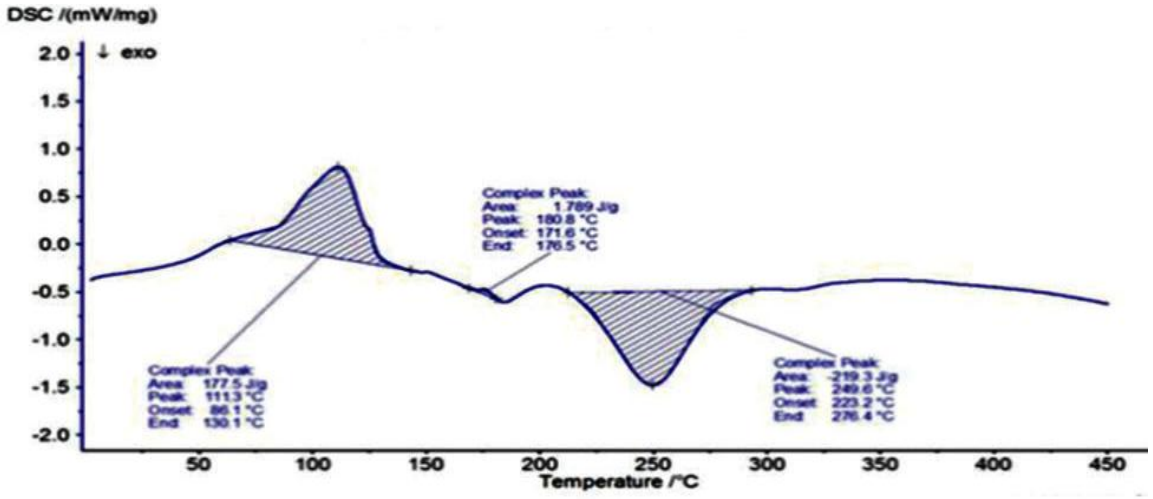


Figure 5: FTIR spectrum optimized formulation (F18)

DSC analysis was performed for the cefixime and F18 prepared by direct compression method. The DSC results reveal that a sharp endothermic peak for cefixime was observed at 276.7°C. An endothermic peak for F18 formulation was observed at277.4°C, respectively. The DSC thermograms were shown Figure 6 A,B. It indicated that there was no drug and polymer interaction.

Differential scanning calorimetry of pure drug



Differential scanning calorimetry of F18 formulation

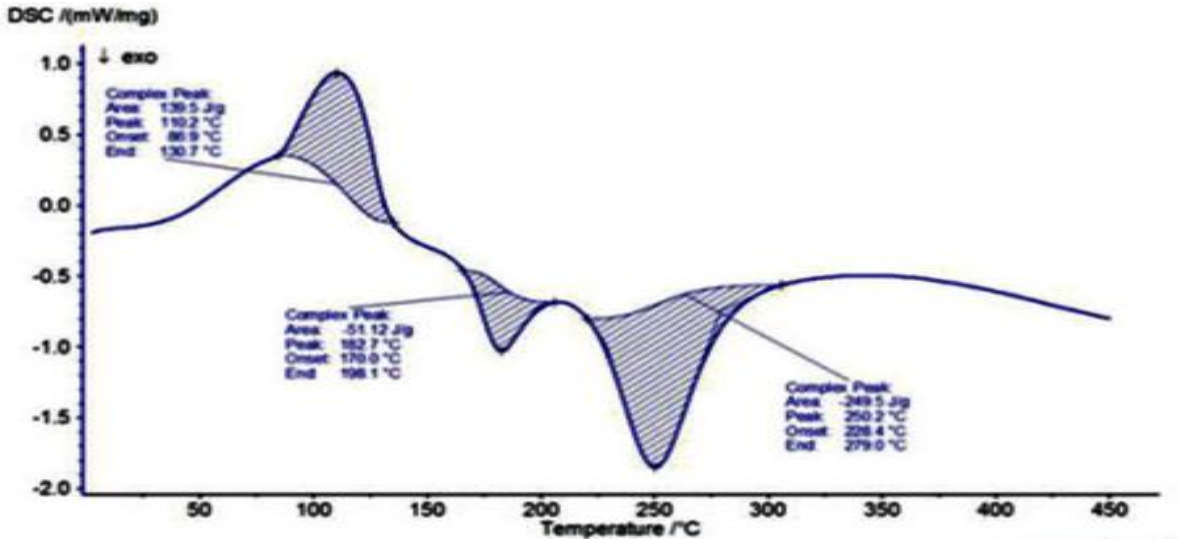


Figure 6: (a) Differential scanning calorimetry of pure drug (b) differential scanning calorimetry of F18 formulation

Stability studies

The stability of optimized formulation (F18) of Cefixime floating tablets were tested for stability at 40°C/75%RH in properly closed HDPE bottles along with 1 gm desiccant for 3 months. The Cefixime release rate (Table 6) from the floating tablets (F18) showed no significant change during storage for 3 months, there is no significant change in floating lag time, total floating time and also in vitro drug release profile. The formulation stored in both conditions for 3 months floated on the surface of the media (0.1NHCl) for 24h.

Table 6: Physico-chemical characteristics of optimized formulation (F18) stored at 40 ±2ºC /75 ±5%RH for 90 days

Stability condition	Sampling (days)	Cefixime Drug content release profile (%)
40°C/75% RH	0	99.98± 2.5
	7	99.90±1.2
	15	99.74±2.6
	30	98.23±3.1
	60	97.17±2.2
	90	96.95±1.2

Intragastricbehavior of Cefixime floating tablets

The *in vivo* floating study was aimed to examine whether the floating tablet system could float and retained in the stomach. A radiological method was adopted to monitor the system in the gastricregion of humans. The X-ray photographs The radiographic images were taken at different periods post administration of the barium sulfate-loaded tablet in human volunteers after administration of cefixime optimized formulation (F18) at different time intervals (1 hr, 8 hrs, 12 hrs, 23 hrs and 24hrs) were shown in Fig. no. 7. The tablet remained buoyant for 23 hrs. (Fig.no.7E) on gastric content under fasted state in the human volunteer participated in the study. No floating tablet observed after 24 hrs of administration. The increased gastric residence time favours increase in the bioavailability of drugs.

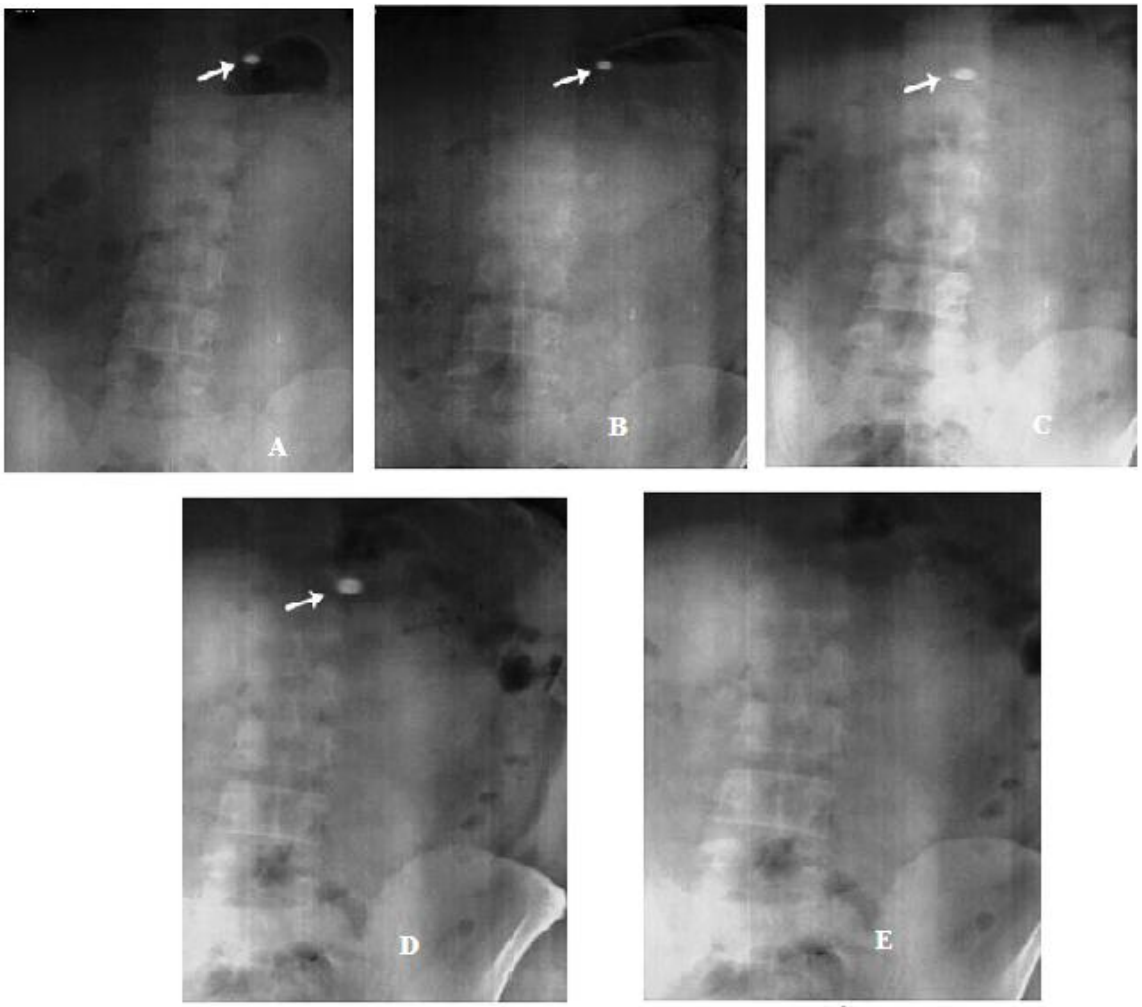


Figure 7: Radiographic images of optimized Cefixime floating tablet (F18) in the stomach at different time intervals

Table 7: Comparison of pharmacokinetic parameters of Cefixime optimized formulation and Marketed Product

Parameters	Optimized formulation (F18)	Marketed Product
Cmax (ng/ml)	5447.79±1226.34	488210±1460.89
AUC0-t(ng. h/ml)	47120.63±15465.78	43071±17248.64
AUC0-∞ (ng. h/ml)	48999.85±16178.48	45331.92±17622.62
Tmax (h)	6.23±1.62	4.98±1.26
$t_{1/2}$ (h)	3.99±1.08	3.56±1.38
Kel (h-1)	0.195±0.92	0.174±0.86

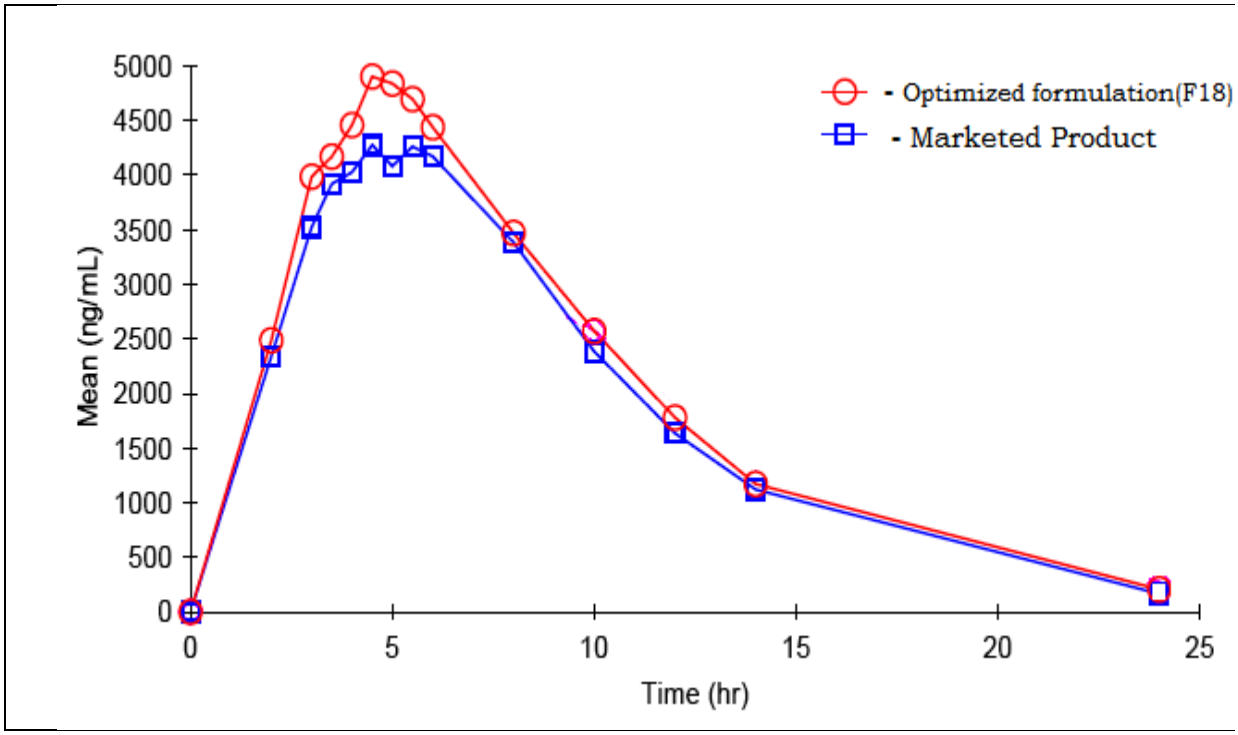


Figure 8: Plasma concentrations at different time intervals for Cefixime optimized formulation and Marketed Product

Bioavailability parameters

Mean plasma concentration profiles of prepared cefixime optimized formulation and marketed product are presented in Figure 8. cefixime optimized formulation exhibited as controlled release *in vivo* when compared with marketed tablet. All the pharmacokinetics parameters displayed in Table 7. In this study in human subjects, prolonged drug absorption was achieved with the test formulation. The average peak concentration of the test formulation was significantly higher than that of the reference (5447.79±1226.34 ng/ml for the test formulation versus 488210±1460.89 ng/ml for the reference). In order to estimate the amount of drug absorbed from the test formulation, the relative bioavailability was calculated from the AUC of the reference and test formulations (45331.92±17622.62 ng. h/ml for the reference product versus 48999.85±16178.48 ng.h/ml for the test formulation). The results indicated that the test formulation could increase the bioavailability of cefixime in humans effectively. In this study, the cefixime floating tablet produce higher bioavailability than that of a marketed product, this overall increase in bioavailability and increased gastric residence time, caused by flotation of dosage form in the stomach.

SUMMARY AND CONCLUSION

Present study aims in design of controlled release floating formulations of cefixime using different polymers like Eudragit-S100, Eudragit-RLPO, Eudragit-RSPO polymers to control the drug release and a lipid excipient to decrease the gastric irritation and to enhance the penetration of drug. Based on the evaluation parameters for F18 was found to be optimized formulation upon its floating lag time, buoyancy period and in vitro drug release was better than other formulations. The kinetic data revealed that the regression coefficient value of optimized formulation F18 closer to unity in case of zero order plot i.e. 3.1528indicates that the drug release follows a zero order mechanism. The mass transfer with respect to square root of time has been plotted, revealed a linear graph with regression value close to one i.e. 0.8766 stating that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.3842 suggest that the drug release from floating tablet was anomalous fickiandiffusion. The comparison plot of the In-vitro drug release profiles of optimized formulation and innovator indicating the better drug release in F18 than innovator. The drug excipient

compatibility studies were carried out to rule out any interactions between the drug and the polymers/excipients by FTIR and differential scanning calorimetric analysis. From the above results can conclude that the drug release from the optimized formulation F18 was in controlled manner for 24h by increasing the gastric residence time. The best formulation (F18) was selected based on in vitro characteristics and was used in vivo radiographic studies by incorporating BaSO4. These studies revealed that the tablets remained in the stomach for 22h in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. Studies to evaluate the pharmacokinetics in vivo showed better bioavailability, area under the concentration–time curve, elimination rate constant and half-life than marketed product.

REFERENCES

[1]. Moes J. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst, 10, 1993, 143-59.
[2]. Deshpande A, Shah N, Rhodes C, Malick W. Development of a novel controlled release system for gastric retention. Pharm Res., 14, 1997, 815-9.
[3]. Tripathi KD. Essentials of medical pharmacology. New delhi: jaypee brothers medical publishers (p) LTD, 6, 2008, 254.
[4]. www.Drug Bank (CefpodoximeProxitel).
[5]. Tadros M. Eur J of Pharma and Biopharma. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitroin vivo evaluation in healthy human volunteers. 74, 2010, 332–339.
[6]. Higuchi T, Mechanism of sustained action medication theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci, 50, 1961, 874-875.
[7]. Siepmann J, Peppas N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Delivery Reviews. 48, 2001, 139-157.
[8]. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Trop J of Pharm Res. 7(3), 2008, 1055-1066.
[9]. Anand Patel. Development and *In Vivo* Floating Behavior of Verapamil HClIntragastric Floating Tablets. AAPSPharmSciTech. 10(1), 2009, 310-315.
[10]. PrasannaKumari J, Ramarao T, Jayaveera K N, Bhikshapathi D V R N, MadhusudanRao Y. Design and *In vivo* evaluation of Metoprolol Tartrate bilayer floating tablets in healthy human volunteers. Int J of Drug Delivery. 6, 2014, 14-23.
[11]. Kiran B. V, SreenivasRao B, Somshankar D. Validation of drugs in Pharmaceutical Dosage by Reverse-Phase HPLC with Internal Standard Method, J of Chemistry. 2013; Article ID 578537.