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FORMULATION AND *IN VITRO, IN VIVO* EVALUATION OF CEFADROXIL CONTROLLED GASTRORETENTIVE DRUG DELIVERY SYSTEM

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Abstract:

Introduction: *Cefadroxil is a first-generation cephalosporin and is very effective against Gram positive and Gram negative infections. Cefadroxil is an antibiotic agent which has high absorption in the upper part of the gastrointestinal tract (GIT). Conventional Cefadroxil tablets produce rapid and relatively high peak blood level and require frequent administration to keep the plasma drug level at an effective range. The present study was carried out with an objective of preparation and in vivo evaluation of floating tablets of using Cefadroxil as a model drug using Eudragit polymers to improve oral bioavailability of Cefadroxil floating tablets by increasing gastric residence time.*

Methodology: *Floating controlled-release cefadroxil tablets were prepared by direct compression method. Tablets were formulated using Eudragit polymers (Eudragit-RLPO & Eudragit-RSPO), with Sodium alginate (SA) and Carbomer (CP) as release-retarding polymers, sodium bicarbonate (NaHCO3) as the effervescent agent. Floating behavior, in vitro drug release, and swelling index studies were conducted. Initial and total drug release duration was compared with a commercial tablet in 0.1 N HCl (pH 1.2) at 37 ± 0.5°C for 24 hours. Tablets were then evaluated for various physical parameters, including weight variation, thickness, hardness, friability, and drug content etc. Consequently, 6 months of physical stability studies and in vitro-in vivo gastro-retentive studies were conducted.*

Results and Discussion: *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 (F20) containing Eudragit-RLPO showed 99.17% 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 (F20) containing sodium bicarbonate 40mg per tablet showed desired buoyancy (floating lag time of about 20 min and total floating time of >24h). Optimized formulation (F20) 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 (F20) 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 24h 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.*

Conclusion: *In conclusion, in order to suggest a better drug delivery system with constant favorable release, resulting in optimized absorption and less side effects, formulated Eudragit based cefadroxil floating controlled-release tablets can be a promising improves candidate therapy.*

Keywords*: Cefadroxil, Eudragit RLPO, Eudragit RSPO, sodium alginate, PVP K30, magnesium stearate and micro crystalline cellulose, Radiographic studies.*

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INTRODUCTION:

Gastroretentive Delivery Systems (GRDS) have been designed for achieving therapeutic benefit for drugs that are preferentially absorbed from the proximal part of the Gastrointestinal Tract (GIT) or that are less soluble in or degraded by the alkaline pH they encounter at the lower part of GIT [1-3]. These systems offer various pharmacokinetic advantages specifically for β-lactam antibiotics with reduction of blood level fluctuations when compared to that observed from conventional forms [4].

Gastroretention depends on various factors such as density and size of dosage form, fasting/fed condition, posture, complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach etc. Various approaches like floating, swellable, muco adhesive and high-density formulations have been studied to achieve gastroretention by formulating various dosage forms like microparticles, pellets, tablets, capsules, etc. [5-11].

Cefadroxil (CD) is a broad-spectrum cephalosporin antibiotic commonly prescribed in the treatment of respiratory tract, urinary tract and skin and soft tissue infections with usual dosage of 1 or 2 g daily in a single or divided doses [12]. It exhibits short elimination halflife of 1.2 h with primary excretion via renal pathway (88 to 93% of the administered dose within 24 h). Thus, the short half-life and very high urinary excretion makes it undesirable to maintain the plasma levels of Cefadroxil in the therapeutic range for prolonged time, providing a strong rationale for development of sustained release (SR) formulation of Cefadroxil. Cefadroxil has good solubility and stability in acidic pH and decreases with increasing pH [4]. Thus, the present work includes development of Gastroretentive Control Release (GRCR) formulation of Cefadroxil and evaluation of floating properties *in vitro* and *in vivo*.

Various approaches for evaluation of *in vivo* gastroretention of the formulation in experimental animals as well as in human volunteers have been studied. Some of the well-known techniques are gamma scintigraphy, use of radiopaque materials, etc. The gamma scintigraphy technique has been successfully explored in experimental animals [13,14] as well as in Human subjects [15,16] as reported in some of the literature data. The use of radiopaque materials in the experimentalproduct with evaluation of the subject using X-ray technique post administration has also been studied in experimental animals [17- 21]. The technique however has been used in animal models with the results predicted for humans. The X-ray technique is comparatively less complicated still provides accurate evaluation of the gastroretentive system *in vivo*.

The aim of the study was to evaluate the developed GRCR formulation of CFD in human subjects using the X-ray technique for *in vivo* gastroretention.

MATERIALS AND METHODS:

Cefadroxil was obtained from Sun global formulations, Hyderabad. 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 and PVP K 30 were obtained from S.d Fine-Chem. LTD, Mumbai. Sodium alginate was obtained from Vijayalakshmichemicals, Hyderabad. Talc was obtained from Swastic pharmaceutical, Bombay. And Conc. HCL was obtained from Spectrum reagents and chemicals Pvt. Ltd, Cochin. All the Chemicals were used as received.

Preparation of Cefadroxil floating tablets:

Floating tablets of Cefadroxil was prepared by direct compression. The compositions of the formulations were made using different swellable polymers like Eudragit RLPO and Eudragit RSPO to get a floating time of more than 24 h. 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 – F20 containing 500 mg of the drug were prepared and each tablet weighing approximately 1000 mg was punched. The Composition of Cefadroxil floating tablets were shown in Table 1.

Table1: Formulation of gastro retentive drug delivery systems of Cefadroxil

Formulation code	Cefixime (mg)	NaCMC (mg)	Eudrait RSPO (mg)	Eudrait RLPO (mg)	Na Alginate (mg)	Mg Stearate (mg)	PVPK 30 (mg)	Aerosil (mg)	$NaHO_3$ (mg)	Citric acid (mg)	MCC (mg)	Total (mg)
F1	500	20	50	-	30	10	25	7.5	60	60	237.5	1000
F2	500	20	75	-	30	10	25	7.5	60	60	212.5	1000
F3	500	20	100	-	30	10	25	7.5	60	60	187.5	1000
F4	500	20	125	-	30	10	25	7.5	60	60	162.5	1000
F5	500	20	150	-	30	10	25	7.5	60	60	137.5	1000
F6	500	20	175	-	30	10	25	7.5	60	60	112.5	1000
F7	500	20	200	-	30	10	25	7.5	60	60	87.5	1000
F8	500	20	225	-	30	10	25	7.5	60	60	62.5	1000
F9	500	20	250	-	30	10	25	7.5	60	60	37.5	1000
F10	500	20	275	-	30	10	25	7.5	60	60	12.5	1000
F11	500	20	-	50	30	10	25	7.5	60	60	237.5	1000
F12	500	20	-	75	30	10	25	7.5	60	60	212.5	1000
F13	500	20	-	100	30	10	25	7.5	60	60	187.5	1000
F14	500	20	-	125	30	10	25	7.5	60	60	162.5	1000
F15	500	20	-	150	30	10	25	7.5	60	60	137.5	1000
F16	500	20	-	175	30	10	25	7.5	60	60	112.5	1000
F17	500	20	-	200	30	10	25	7.5	60	60	87.5	1000
F18	500	20	-	225	30	10	25	7.5	60	60	62.5	1000
F19	500	20	-	250	30	10	25	7.5	60	60	37.5	1000
F20	500	20	-	275	30	10	25	7.5	60	60	12.5	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 [22].

***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 Cefadroxil 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 [23,24].

$Mt = M0 + k0t$ (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 Cefadroxil, 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 [25].

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 sulfate. After overnight fasting, the volunteers were fed with a low calorie food. After half an hour, a barium sulfatelabeled 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 [26]. The mean gastric retention period was estimated.

***In vivo* bioavailability studies of Cefadroxil: *In vivo* study protocol [27]**

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 10h 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 Cefadroxil and group-B received commercial formulation was administered with 200ml of water. All the subjects were given a glass of water for every 2h (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 Cefadroxil in Human plasma by HPLC method[28]

Determination of Cefadroxil 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 triethyl 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 resuspended 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% orthophosphoric 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-□ 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 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.

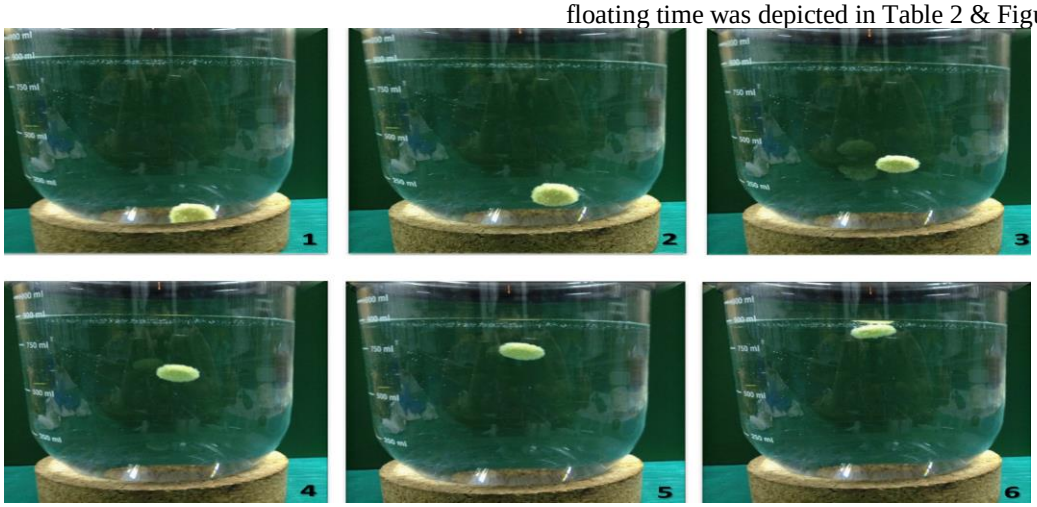


Fig 1: *In vitro* buoyancy lag time of the optimized formulation (F20)

Table 2: Buoyancy lag time and total floating period of Cefadroxil 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

All the formulations (F1-F20) were prepared with different grades of polymer like Eudragit with different grades. F1to F10 are having Cefadroxil, Eudragit RSPO in different proportions shown the drug release was 94.78%(4hrs), 96.19%(6hrs),93.16%(8hrs),97.24%(10hrs),96.98%(12hrs),96.2%(14hrs),98.24%(16hrs),98.18%(18hrs),98.55%(20hrs)and 96.11%(22hrs) respectively. The formulations F11 to F20 were developed using Eudragit RSPO and % of drug release was 96.36%(6hrs), 98.56%(10hrs), 92.65%(10hrs), 97.36%(12hrs), 98.36%(14hrs),98.78%(16hrs),98.27%(18hrs),98.20 % (20hrs),96.36% (20hrs) and 99.17% (24hrs) respectively indicating comparatively better release rates than formulations F1to F10 (Table 3 & Figure 2) respectively. The results are summarized in Table 4& Figure 3. Formulation F20 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-F10

Formulation code/Parameter → Time ↓	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)
1 hr	49.28	45.62	37.55	33.28	30.28	32.54	30.63	28.42	27.66	27.61
2 hr	63.15	67.34	53.17	54.64	44.25	47.37	55.55	36.55	34.37	32.95
4 hr	94.78	77.38	67.52	63.25	57.64	56.18	67.53	47.45	41.22	38.63
6 hr		96.19	78.37	77.37	68.27	79.67	74.61	53.69	49.13	46.18
8 hr			93.16	83.28	74.38	83.14	79.66	74.34	58.15	51.34
10 hr				97.24	88.47	89.96	86.73	82.28	63.67	55.69
12 hr					96.98	94.56	92.77	86.51	69.24	60.24
14 hr						96.62	96.95	91.60	77.69	65.21
16 hr							98.24	96.53	89.34	68.35
18 hr								98.18	92.25	76.85
20 hr									98.55	85.96
22 hr										96.11
24 hr										

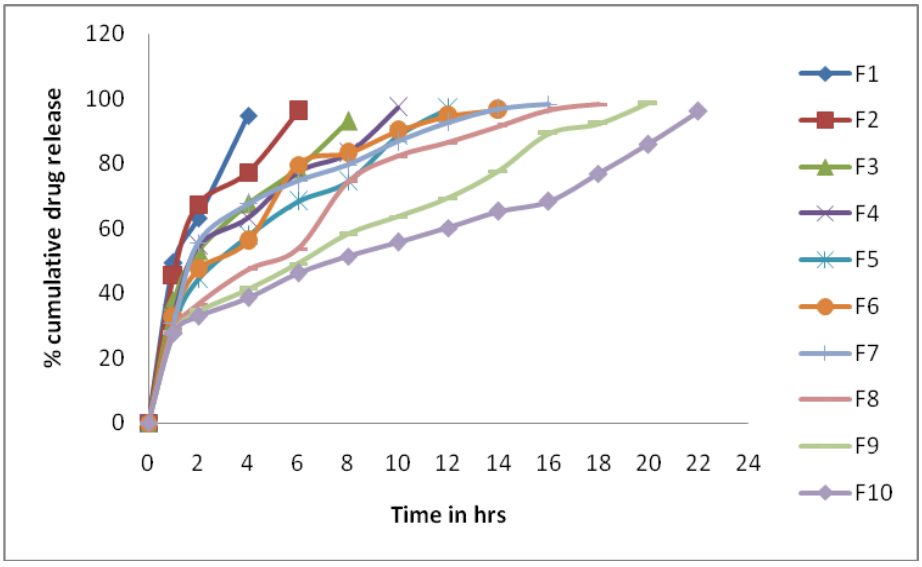


Fig 2: Drug release profile from formulations F1- F10

Table 4: Cumulative percent drug release of formulations F11-F20

Formulation code/Parameter → Time ↓	F11 (%)	F12 (%)	F13 (%)	F14 (%)	F15 (%)	F16 (%)	F17 (%)	F18 (%)	F19 (%)	F20 (%)
1 hr	58.17	55.24	47.22	43.56	44.18	42.15	36.54	33.21	32.63	24.84
2 hr	65.38	68.62	56.54	55.24	58.16	56.78	43.62	38.50	38.54	32.62
4 hr	73.14	77.37	63.29	66.87	66.21	61.36	57.18	46.43	46.76	44.36
6 hr	96.36	93.25	74.55	73.55	72.20	68.54	65.34	52.39	52.54	53.17
8 hr		98.56	85.26	87.25	86.39	75.12	72.66	64.67	58.15	61.52
10 hr			92.65	93.21	95.54	86.39	83.34	76.26	66.65	68.98
12 hr				97.36	98.23	93.65	89.62	83.81	72.23	74.45
14 hr					98.36	96.21	94.87	88.54	83.69	79.87
16 hr						98.78	96.96	92.33	88.45	84.63
18 hr							98.27	95.86	92.16	89.18
20 hr								98.20	96.36	94.63
22 hr										98.54
24 hr										99.17

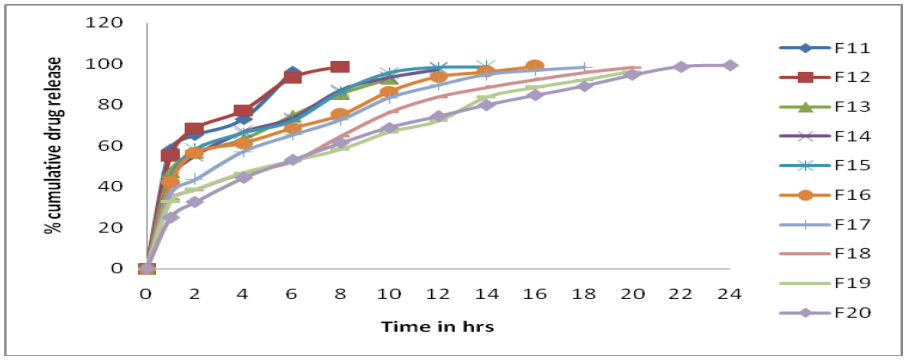


Fig 3: Drug release profile from formulations F11- F20

Comparison among formulations shown drug release for extended periods (F9, F10, F19, F20) was done and it was shown in Figure 4. The extended drug release for 24 hrs in F20 formulation may due to the presence of optimum levels of Eudragit RLPO, sodium alginate, sodium bi carbonate and citric acid.

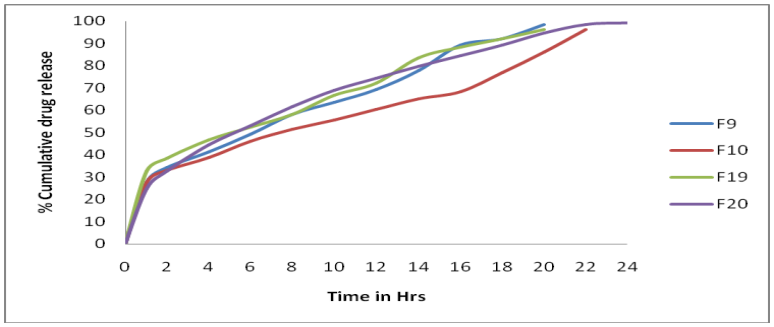


Fig 4: Comparison among formulations drug release profile from formulations (F9, F10, F19 and F20)

Table 5: Release order kinetics of optimized formulation (F20)

Formulation code	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F20	0.9708	3.7574	0.9091	0.1582	0.9734	23.753	0.900	0.57

Mathematical modeling of floating tablets

To explore the mechanism of drug release from Cefadroxil 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 (F20) was shown in Table 5.

The in vitro drug release data of all the formulations (F1-F20) 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 Cefadroxil formulations. From the Korsmeyer-Peppas plots, it has been observed that regression value (n-value) of all the formulations (F1-F20) ranges from 0.3870 to 0.57, suggesting that the drug was released by Fickian diffusion in all the cases. The optimized formulation F20 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.

Drug - excipient compatibility studies:

The FT-IR spectra of pure drug Cefadroxil (Figure 5) and optimized formulation F20 (Figure 6) 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 Cefadroxil suggesting that there was no interaction between the drug and polymer.

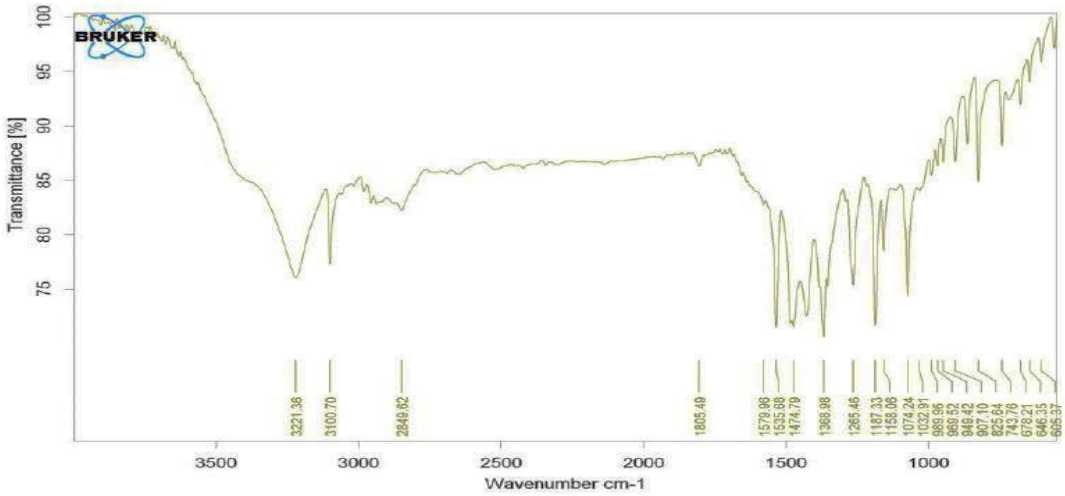


Fig 5: FTIR spectrum pure drug Cefadroxil

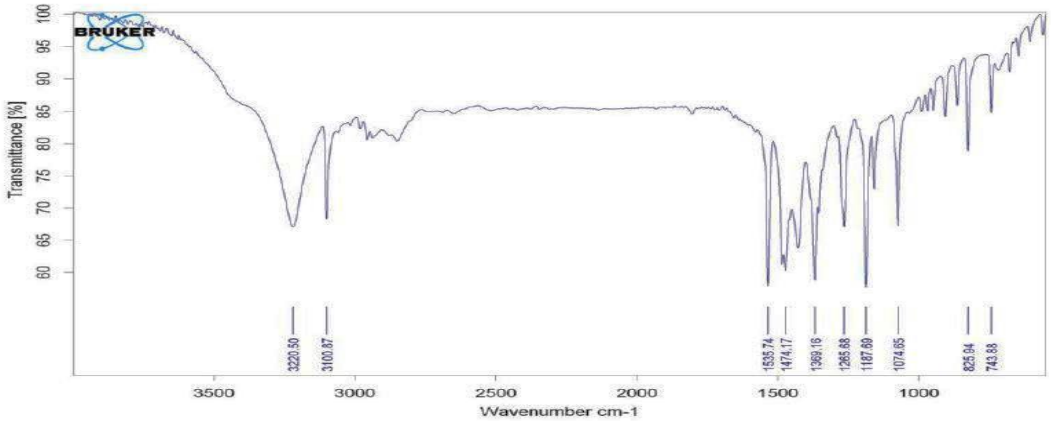
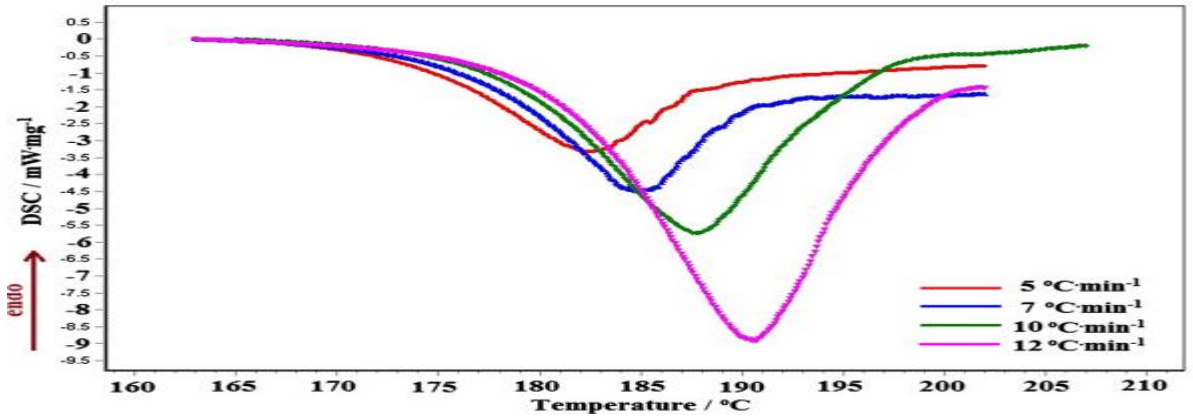


Fig 6: FTIR spectrum optimized formulation (F20)

DSC analysis was performed for the Cefadroxil and F20 prepared by direct compression method. The DSC results reveal that a sharp endothermic peak for Cefadroxil was observed at 276.7°C. An endothermic peak for F18 formulation was observed at277.4°C, respectively. The DSC thermograms were shown Figure 7 A,B. It indicated that there was no drug and polymer interaction.

A) Differential scanning calorimetry of pure drug



B) Differential scanning calorimetry of F20 formulation

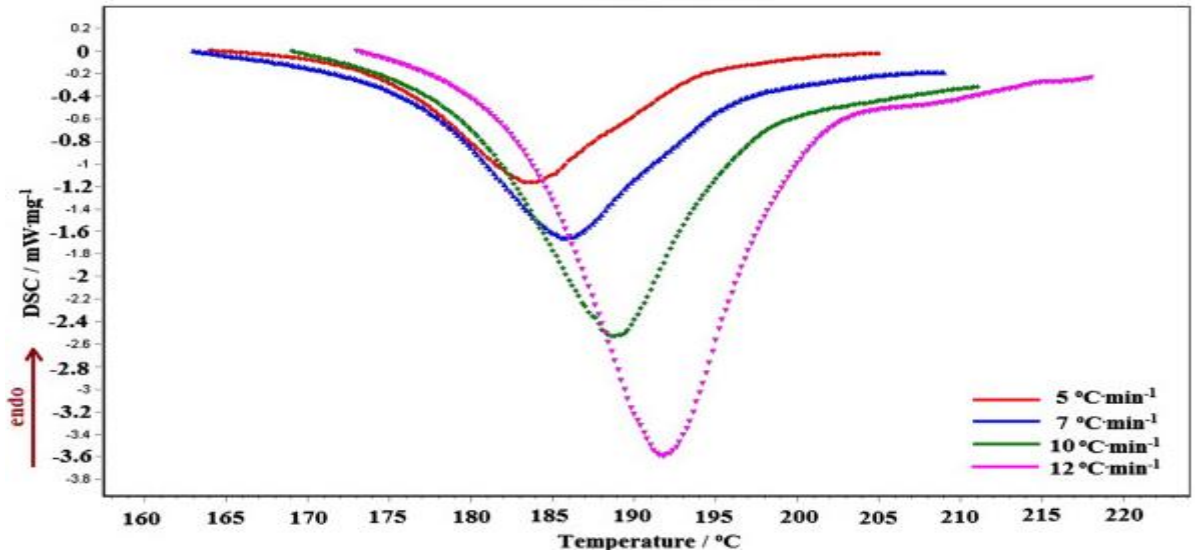


Fig 7: (a) Differential scanning calorimetry of pure drug (b) differential scanning calorimetry of F20 formulation

Stability studies

The stability of optimized formulation (F20) of Cefadroxil 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 Cefadroxil release rate (Table 6) from the floating tablets (F20) 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 (F20) stored at 40 ±2ºC /75 ±5%RH for 90 days

Stability condition	Sampling (days)	Cefadroxil Drug content release profile (%)
40°C/75% RH	0	99.72± 1.2
	7	99.68±2.4
	15	99.36±1.8
	30	98.29±2.6
	60	98.49±1.9
	90	97.98±1.4

Intragastric behavior of Cefadroxil 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 Cefadroxil optimized formulation (F20) at different time intervals (1 hr, 8 hrs, 12 hrs, 23 hrs and 24hrs) were shown in Fig. no. 8. The tablet remained buoyant for 23 hrs. (Fig.no. E) 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.

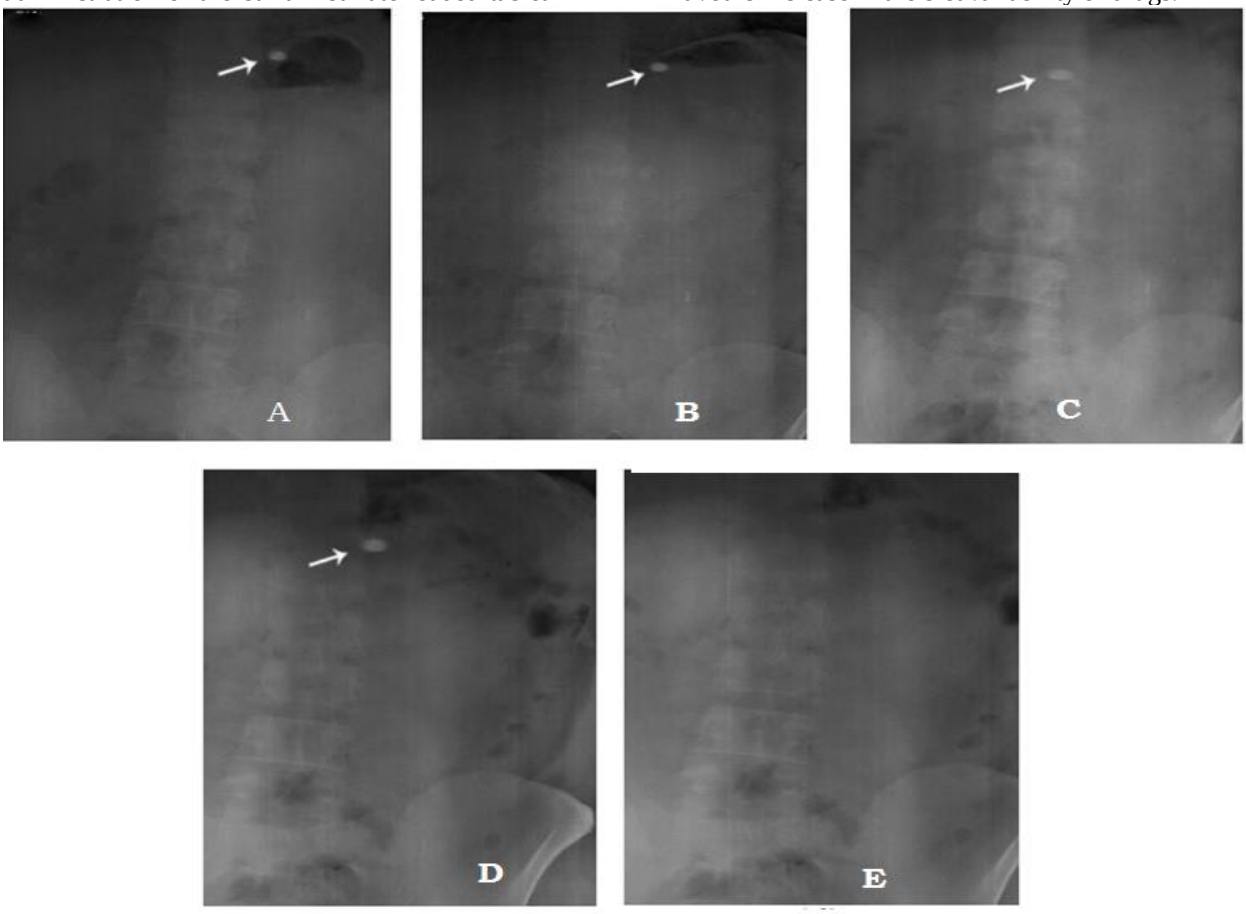


Fig 8: Radiographic images of optimized Cefadroxil floating tablet (F20) in the stomach at different time intervals:

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

Parameters	Optimized formulation (F20)	Marketed Product
Cmax (ng/ml)	15460.0±0.1	14530.0±0.6
AUC0-t(ng. h/ml)	31040.1±0.6	30028.6±1.7
AUC0-∞ (ng. h/ml)	32740.4±0.3	31996.2±1.2
Tmax (h)	1.5±0.0	1.2±1.0
$t_{1/2}$ (h)	1.8±0.2	1.5±1.6
Kel (h-1)	0.46 ±0.3	0.24 ±1.5

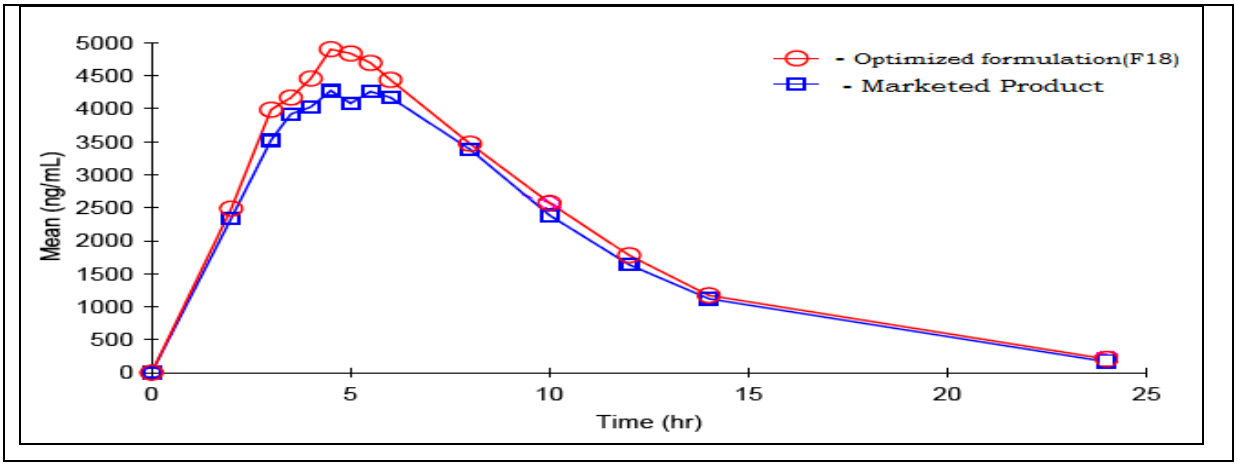


Fig 9: Plasma concentrations at different time intervals for Cefadroxil optimized formulation and Marketed Product

Bioavailability parameters

Mean plasma concentration profiles of prepared Cefadroxil optimized formulation and marketed product are presented in Figure 9. Cefadroxil 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 (15460.0±0.1ng/ml for the test formulation versus 14530.0±0.6 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 (31996.2±1.2 ng. h/ml for the reference product versus 32740.4±0.3 ng. h/ml for the test formulation). The results indicated that the test formulation could increase the bioavailability of Cefadroxil in humans effectively. In this study, the Cefadroxil 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 Cefadroxil using different polymers like 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 F20 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 F20 closer to unity in case of zero order plot i.e. 0.9708 indicates 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. 0.9734 stating that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.57 suggest that the drug release from floating tablet was anomalous fickiandiffusion. The comparison plot of the In vitro drug release profiles ofoptimized formulation and innovator indicating the better drug release in F20 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 F20 was in controlled manner for 24h by increasing the gastric residence time. The best formulation (F20) 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.Deshpande AA, Rhodes CT, Shah NH, Malick AW Controlled-release drug delivery systems for

prolonged gastric residence: an overview. Drug Dev Ind Pharm,1996; 22: 531-539.
2.Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release,2000; 63: 235-259.
3.Talukder R, Fassihi R. Gastroretentive delivery systems: a mini review. Drug Dev Ind Pharm,2004; 30: 1019-1028.
4.Kulkarni AR, Soppimatha KS, Aminabhavia TM, Rudzinski WE. *In-vitro* release kinetics of cefadroxil-loaded sodium alginate interpenetrating network beads. Eur J Pharm Biopharm ,2001;51: 127-133
5.Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm,2003; 253: 13-22.
6.Chueh HR, Zia H, Rhodes CT.Optimization of sotalol floating and bioadhesive extended release tablet formulations. Drug Dev Ind Pharm,1995; 21: 1725-1747.
7.Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. AAPS Pharm Sci Tech, 2000; 1: 62-70.
8.El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm ,2001;220: 13-21.
9.Adebisi A, Conway B. Gastroretentive microparticles for drug delivery applications. J Microencapsul,2011; 28: 689-708.
10.Awasthi R, Kulkarni GT. Decades of research in drug targeting to the upper gastrointestinal tract using gastroretention technologies: where do we stand. Drug De,2016;l 23: 378-394.
11.Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their *in vivo* success: A recent update. Asian J Pharm Sci,2016; 11: 575-584.
12.Buck RE, Price KE. Cefadroxil, a new broad-spectrum cephalosporin. Drugs,1977; 11: 324-330.
13.Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, et al. Formulation and development of hydrodynamically balanced system for metformin: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm,2007; 67: 196-201.
14.Guan J, Zhou L, Nie S, Yan T, Tang X, et al. A novel gastric-resident osmotic pump tablet: *in vitro* and *in vivo* evaluation. Int J Pharm,2010; 383: 30-36.
15.Sugihara H, Matsui Y, Takeuchi H, Wilding I, Connor A, et al. Development of a gastric retentive system as a sustained-release formulation of pranlukast hydrate and its subsequent *in vivo* verification in human studies. Eur J Pharm Sci,2014; 53: 62-68.
16.Yao H, Yao H, Zhu J, Yu J, Zhang L . Preparation and evaluation of a novel gastric floating alginate/poloxamer inner-porous beads using foam solution. Int J Pharm ,2012;422: 211-219.
17.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: 125-135.
18.Diós P, Nagy S, Pál S, Pernecker T, Kocsis B, et al. Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of *Helicobacter pylori*. Eur J Pharm Biopharm,2015; 96: 196-206.
19.Zhang C, Xu M, Tao X, Tang J, Liu Z, et al. A floating multiparticulate system for ofloxacin based on a multilayer structure: *In vitro* and *in vivo* evaluation. Int J Pharm,2012; 430: 141-150.
20.Malakar J, Datta PK, Purakayastha SD, Dey S, Nayak AK .Floating capsules containing alginate-based beads of salbutamol sulfate: *In vitro-in vivo* evaluations. Int J Biol Macromol,2014; 64: 181-189.
21.Liu Y, Chen L, Zhou C, Yang J . Development and evaluation of alginatechitosan gastric floating beads loading with oxymatrine solid dispersion. Drug Dev Ind Pharm,2016; 42: 456-463.
22.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.2010; 74: 332–339.
23.Higuchi T, Mechanism of sustained action medication theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci, 1961; 50, 874-875.
24.Siepmann J, Peppas N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Delivery Reviews. 2001; 48: 139-157.
25.Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Trop J of Pharm Res. 2008; 7 (3): 1055-1066.
26.Anand Patel. Development and *In Vivo* Floating Behavior of Verapamil HCl Intragastric Floating Tablets. AAPS PharmSciTech. 2009; 10(1): 310-315.
27.Prasanna Kumari J, Ramarao T, Jayaveera K N, Bhikshapathi D V R N, Madhusudan Rao Y. Design and *In vivo* evaluation of Metoprolol Tartrate bilayer floating tablets in healthy human volunteers. Int J of Drug Delivery. 2014; 6: 14-23.
28.Kiran B. V, Sreenivas Rao B, Somshankar D. Validation of drugs in Pharmaceutical Dosage by Reverse-Phase HPLC with Internal Standard Method, J of Chemistry. 2013; Article ID 578537.