International Journal of Drug Delivery 5 (2013) 63-72

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Development, intra-gastric performance and pharmacokinetic study of gastroretentive drug delivery system for cefdinir in human volunteers

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Abstract

The objective of this study was to develop sustained-release floating tablets of cefdinir (CFDN) using effervescent technique to prolong gastric residence time (GRT) and compare their pharmacokinetics with immediate release (IR) and conventional sustained release (SR) tablets. The tablets were designed using $CaCO_3$ as gas-former and three grades of polyethylene oxide as release-retardants and further were evaluated for their physical characters, *in vitro* drug release and buoyancy studies. The optimized formulation (F3) was found to be physically stable when stored at 40 ^oC/75% RH for 3 months. *In vivo* radiographic imaging of F3 revealed a mean GRT of 4.83 ± 0.57 h (n=3). Comparative pharmacokinetic study was performed for F3, IR and SR tablets of CFDN in humans. Based on *in vivo* performance, the difference between t_{max}, AUC_{0-}, $t_{1/2}$ and MRT of F3, IR and SR tablets were found to be statistically significant ($p < 0.05$). The difference between C_{max} of F3 and IR tablet was statistically significant, but the C_{max} of F3 and SR tablet was not statistically significant. The relative bioavailability of F3 was 1.71 fold to IR and 1.24 fold to SR. This improved bioavailability is due to the combined effect of sustained release and increased GRT.

Keywords: Cefdinir, Gastroretentive floating tablets, Polyethylene oxide, Radiographic imaging, Pharmacokinetic study.

Introduction

The oral route remains the preferred route for the administration of therapeutic agents Due to the low cost of therapy and ease of administration there by leading to patient compliance. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate [1]. An important requisite for the successful performance of an oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT) to ensure continuous absorption of the released drug [2]. A major limitation in the oral controlled drug delivery is that not all drug candidates get uniformly absorbed throughout the GIT.

Dosage forms that can be retained in the stomach are called as gastroretentive drug delivery systems (GRDDS) [3]. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability [4]. Garg et al., 2008 [5] classified the GRDDS into four main classes: (i) floating systems [6], (ii) expandable systems [7], (iii) bioadhesive systems [8] and (iv) high density systems [9]. Floating systems are of two types: (A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and (B) non-effervescent systems. The latter systems can be further divided into four sub-types, including hydrodynamically balanced systems [10], microporous compartment systems [11], alginate beads [12] and hollow microspheres/microballons [13]. In addition, super-porous hydrogels [14] and magnetic systems [15] were described.

As reported [4], the floating drug delivery is of particular interest for drugs which: (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment. Cefdinir (CFDN) is a semi-synthetic, third-generation broad-spectrum oral cephalosporin antibiotic, which is active against both Gram positive and negative bacteria. It is widely used to treat acute and chronic bronchitis, rhinosinusitis and pharyngitis. It is approved by U.S Food and Drug Administration in 1997. It has a biological half life of 1.6 h with 21–25% of oral bioavailability [16]. Further, the drug has poor aqueous solubility and is soluble in dilute hydrochloric acid [17]. Therefore, due to above characters, it becomes a good candidate for the development of GRDDS.

The gastroretentive tablets of CFDN were not reported until now. The present investigation involved the preparation and in vitro/in

vivo evaluation of CFDN floating tablets by effervescent technique using a release retarding polymer, polyethylene oxide and a gas former, calcium carbonate ($CaCO_3$). The optimized formulation exhibited excellent floating behaviour, sustained drug release and good physical stability when stored at 40 ºC/75% RH for 3 months. Further, *in vivo* investigations were also conducted to determine mean gastric residence time and bioavailability in healthy human volunteers.

Material and Methods

Materials

Cefdinir (CFDN) and Polyox WSR 1105 were received as generous gift samples from M/s Orchid Pharma Ltd., Chennai, India. Polyethylene oxide (PEO) polymers available commercially under the trade name of Polyox WSR (water soluble resins), are novel materials with unique properties. Cefadroxil was a generous gift sample from M/s Aurobindo Pharma. Ltd., Hyderabad, India. Polyox WSR 205 and Polyox WSR 303 were purchased from Colorcon Asia Pvt., Ltd, India. Calcium carbonate, microcrystalline cellulose (Avicel PH102), magnesium stearate and talc were purchased from S.D. Fine-Chem. Ltd., Mumbai, India. Acetonitrile, methanol and dichloromethane (DCM) HPLC grade were purchased from Merck Ltd., Mumbai, India. All other solvents and reagents used were of analytical grade.

Methods

Preparation of CFDN floating tablets

Accurately weighed quantities (Table I) of CFDN, Polyox WSR 205/WSR 1105/WSR 303, calcium carbonate and Avicel PH102 were passed through a sieve no. 40 to get uniform sized particles, then they were taken in a mortar and triturated with the help of a pestle for 10 min. Then the mixture was transferred into a polyethylene bag and further mixed for 5 min to ensure a homogeneous mass. To the mixture, magnesium stearate and talc were added and continued the mixing for another 2 min. Finally, about 600 mg of each mixture was weighed and fed manually into the die of a 16 station punching machine (Riddhi, RDD3 Ahmedabad, India) to produce the desired tablets using 13 mm flat- faced round punches.

Table 1. Composition (in mg) of CFDN floating tablets.

Ingredients	Formulation code										
	F1	F2	F3*	F4	F5	F6	F7	F8	F9	F10	F11
Cefdinir	300	300	300	300	300	300	300	300	300	300	300
Polyox WSR 303	120	100	90	80	-	-	-	-	-	-	-
Polyox WSR 205	-	-	-	-	100	120	140	160	-	-	-
Polyox WSR 1105	-	-	-	-	-	-	-	-	100	120	130
Calcium carbonate	60	60	60	60	60	60	70	70	60	60	60
Avicel PH 102	108	128	138	148	128	108	78	58	128	108	98
Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6	6
Total tablet weight	600	600	600	600	600	600	600	600	600	600	600

*Lead formulation used in pharmacokinetic studies.

Preparation of immediate and conventional sustained release tablets of CFDN

The conventional sustained release (SR) tablets of CFDN were prepared using CFDN 300 mg, Polyox WSR 80 mg, Avicel PH 102 208mg, magnesium stearate 6 mg and talc 6 mg per tablet. CFDN immediate release (IR) tablets were prepared using 300 mg of CFDN, 288 mg of Avicel PH 102, 6 mg of magnesium stearate and 6 mg of talc in each tablet. The tablets were prepared by direct compression using 13 mm flat- faced round punches.

In vitro evaluation of the prepared tablets

The prepared tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester) using 6 tablets, thickness (Vernier caliperse) using 6 tablets, friability (Roche friabilator) using 10 tablets, drug content using 10 tablets, *in vitro* buoyancy using 3 tablets and in vitro dissolution studies using 3 tablets. The results were expressed as mean ± S.D.

Floating lag time and total floating time

Floating characteristics of tablets were determined in a United States Pharmacopeia (USP) dissolution apparatus II (Electrolab, TDT-06T, Mumbai, India) in 900 ml of 0.1 N HCl at 37±0.5 C and 50 rpm [18]. The floating lag time (FLT) as well as total floating time (TFT) were determined visually. The time required for the

tablet to rise to the surface of the dissolution medium and the total duration of floating were noted as FLT and TFT, respectively.

Drug release studies

The release of CFDN from the prepared tablets was studied using USP dissolution apparatus II (Electrolab, TDT-06T, Mumbai, India). The dissolution medium was 900 ml of 0.1 N HCl (pH1.2). The temperature was maintained at 37±0.5 ^{o}C. The rotation speed was 50 rpm. Five ml of aliquot was withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10 and 12 h. The medium was replenished with 5ml of fresh medium each time. Samples were filtered through a membrane filter (0.45 µm) and analyzed by using UV-Visible spectroscopy (Elico, SL 159, India) at λ_{max} 280 nm.

Kinetic modelling of drug release profiles

The profiles of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of CFDN from the floating tablets. The model with the highest correlation coefficient (R^2) was considered to be the best fitting one. In the present study, the *in vitro* drug release profiles were fitted to zero-order [19], first-order [20], Higuchi [21] and Korsmeyer-Peppas kinetic models [22].

Zero-order: $Q_t = Q_0 + k_0 t$ (1)

First order: $\log C = \log C_0 - k_1 t/2.303$ (2)

Higuchi: $Q_t = k_2 t^{1/2}$ (3)

$Q_t/Q = kt^n$ (4)

Where Q_0, Q_t and Q are the amounts of drug dissolved at zero time, at time t and at time. C_0 and C are the concentrations of the drug at zero time and at time t, and k_0, k_1, k_2 and k refer to the rate constants obtained from the linear curves of the respective models, and n refers to the release exponent indicative of the mechanism of drug release. If the value of n is 0.5 or less, the release mechanism follows Fickian diffusion, while the higher values ($0.5 < n < 1$) indicates a non- Fickian model (anomalous transport). The non-Fickian model corresponds to coupled diffusion/polymer relaxation. If the n-value is 1, the drug release follows zero order and case II transport. The Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain. However, the mechanism of drug release is regarded as super case-II transport if n-values are higher than 1. This mechanism could result from increased plasticization at the relaxing boundary, i.e., gel layer [23].

Physical stability studies

Physical stability studies were conducted according to International Conference on Harmonization (ICH) guidelines [24]. One of the optimized formulations F3 was enclosed in polyethylene bottle and placed in a desiccator containing saturated sodium chloride solution (75% RH) [25]. The desiccator was stored at 40 ^{o}C for 3 months. At predetermined time intervals, the tablets were examined for hardness, FLT, TFT, drug content and drug release. Finally, the tablets were tested for any statistical difference using the Students paired t-test, the differences were considered to be significant at $p < 0.05$.

Preparation of tablets for in vivo radiographic studies

To make the tablet of optimized formulation (F3) x-ray opaque, 85 mg of the drug was replaced with barium sulphate ($BaSO_4$) and all other ingredients were kept constant so that the tablet weight remained same. This amount was determined experimentally to allow x-ray visibility but not to hinder tablet buoyancy. The prepared tablets were characterized for their hardness, thickness, weight variation, friability, FLT and TFT.

In-vivo evaluation of gastric residence time in healthy volunteers

To determine the *in vivo* residence time of a GRDDS, a variety of techniques were used like x-ray, endoscopy, ϒ-scintigraphy [26]. In this study, x-ray technique was used to determine the gastric residence time of CFDN floating tablets. The protocol of radiographic studies on healthy human volunteers was approved by the Institutional Ethics Committee, University College of Pharmaceutical Sciences, Kakatiya University, India. In this study, three healthy male volunteers participated after giving informed written consent. The subjects weighed in between 60–73 kg (67±6.5 kg), in height from 170-176 cm (173.3±3.0 cm) and in the age group of 24-25 years (24.3±0.5 years). The study was conducted under the guidance of an expert radiologist. After overnight fasting, the volunteers were fed with low calorie food (100 g of bread). Half an hour later, a $BaSO_4$-loaded floating tablet was given to every volunteer with a glass of water. During the study, the subjects were not allowed to eat but water was made available *ad libitum*. At different time intervals like, 0.5, 2.5, 4.5 and 5.5 h, the volunteers were exposed to abdominal x-ray imaging in a standing position. The distance between source of x-rays and the subject was kept constant for all images. Thus, the observation of the tablet movements could be easily noticed [27]. The mean gastric residence time was calculated.

Comparative bioavailability studies

The bioavailability study protocol was approved by the Institutional Ethics Committee, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India. Nine healthy male volunteers participated in the study after giving the informed written consent. The mean age of volunteers was 24±1 years, mean height was 170.5±6.5 cm and the mean body weight was 67.2±10.6 kg. They were judged to be healthy based on medical history, physical examination, haematological and biochemical laboratory tests. The subjects were instructed to take no medicine for at least one week before and during the study period.

A single dose, randomized, three-way cross-over study was designed with nine subjects in each treatment group. A one week washout period existed between treatments of the study. After

overnight fasting, in three study periods for each subject the assigned formulation (300 mg of Floating F3/IR/conventional SR) was administered orally with 240 ml of water. Blood samples (5 ml) were obtained from forearm vein using sterile disposable needle and collected into 10 ml sterile test tubes. The blood samples were collected at predetermined time intervals such as 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Subjects received standard, uniform meals after 5 h of tablet administration. The samples were centrifuged immediately at 4000 rpm for 15 min and the separated serum was transferred into 2.5 ml of Eppendorf tubes and stored at 80 ^{o}C till the time of analysis.

CFDN-serum concentrations were determined by reversed phase high performance liquid chromatography (R-HPLC) equipped with a pump model, Shimadzu, LC-10AT and an SPD-10A detector. Mobile phase used was 12:88 v/v of acetonitrile: 0.015M potassium dihydrogen phosphate (pH 3.8 adjusted with orthophosphoric acid) and pumped isocratically at 1 ml/min through a Hibar, Lichrospher (5 µm, 250 4.6 mm) column. The UV-Visible detector was adjusted to 280 nm. The serum samples were extracted by liquid-liquid extraction method. To 300 µl of serum, 600 µl ml of cold methanol, 100 µl of internal standard (Cefadroxil, 30 µg/ml) was added and vortexed for 3 min in an Eppendorf tube [28]. After mixing well, centrifuged for 15 min at 4000 rpm. Supernatant was collected and transferred into test tube. To this 2 ml of dichloromethane was added and vortexed for 3 min, then centrifuged at 7000 rpm for 15 min. About 20 µl of supernatant was injected into the HPLC system (Shimadzu, LC-10AT).

Pharmacokinetic analysis

The pharmacokinetic studies were carried out in healthy human volunteers for optimized floating (F3), IR and conventional SR tablets. The elimination rate constant (kE) was obtained from the least square fitted terminal log-linear portion of the plasma concentration-time profile curve. The peak plasma concentration (Cmax) and corresponding time to peak (tmax) were obtained directly from the observed individual drug serum concentration-time profiles. The area under the curve to the last measurable concentration (AUC0-t) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity (AUC0-) was calculated by equation [5].

$$AUC_{0-} = AUC_{0-t} + Ct/kE \quad (5)$$

Where Ct is the last measured concentration. The mean residence time (MRT) of the drug and relative bioavailability (BA) of the formulations were calculated by the following equations. MRT = $AUMC_{0-} / AUC_{0-}$. (6)

Relative BA = AUC0- of test/AUC0- of reference (7)

Where, AUMC is the area under the first moment of the concentration-time curve [29].

Results and discussion

Physicochemical characteristics of prepared tablets

The physicochemical characteristics of the tablets are summarized in Table II. The hardness of all tablet batches ranged from 5.12 ± 0.40 to 5.28 ± 0.30 kg/cm^2 and that of thickness from 4.13 ± 0.022 to 4.17 ± 0.027 mm. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability [30]. The weight of the tablets ranged from 598.3 ± 7.80 to 601.7 ± 8.34 mg. Drug content results were found to be good among different batches; the percentage of drug content ranged from 98.29 ± 1.18 to 101.39 ± 1.61. The percentage friability for all formulations was less than 1%, indicating good mechanical resistance.

Floating lag time and total floating time

In this study, calcium carbonate was used as a gas-generating agent in order to aid floating of tablets. The *in vitro* testing revealed the ability of most formulations to maintain buoyant for more than 10 h. This suggested that the gel layers formed by the investigated polymers enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it to float on the test medium (0.1 N HCl) for extended period of time. The calcium carbonate induced CO_2 generation in the presence of dissolution medium. The generated gas was entrapped and protected within the gel formed by hydration of the polymer. This, decreased the density of the tablet below 1 gm/ml, and the tablet became buoyant [4]. As shown in Table II, all the formulations floated with a lag time of less than 1 min. The FLT of the formulations F1-F4, prepared with different concentrations of Polyox WSR 303 with constant calcium carbonate ratio (10% w/w), ranged from 12 ± 2 to 15.67 ± 2.52 s and that of formulations F5-F8, prepared with Polyox WSR 205, ranged from 13.3 ± 3.0 to 23.0 ± 6.2 s had no significant effect. The FLT of formulations F9-F11, prepared with Polyox WSR 1105 (100, 120 and 130 mg/tablet), showed in the range of 8 ± 2 to 12.3 ± 2.5 s. In all the formulations, as the concentration of polymer increased, the FLT was decreased and TFT increased, but the difference in FLT was not statistically significant.

Table 2. Physicochemical characters of CFDN floating tablets.

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Tablet weight (mg)	Friability (%)	Floating lag time (s)	Floating duration (h)	Drug content (%)
F1	5.18±0.29	4.14±0.042	598.30±7.80	0.32	15.67±2.52	>12	98.29±1.18
F2	5.14±0.24	4.16±0.042	599.90±7.77	0.37	14.33±2.08	>12	99.65±1.68
F3	5.18±0.35	4.17±0.027	601.00±5.72	0.41	12.33±2.52	>12	100.51±1.38
F4	5.24±0.40	4.15±0.035	601.70±8.34	0.43	12.00±2.00	10	99.82±1.26
F5	5.22±0.29	4.15±0.035	599.70±6.75	0.45	13.33±3.06	6	99.48±1.21
F6	5.18±0.23	4.14±0.042	600.80±5.87	0.39	14.67±2.52	8	99.65±1.04
F7	5.28±0.30	4.14±0.044	600.80±6.86	0.34	17.67±2.53	10	99.65±1.26
F8	5.20±0.32	4.13±0.027	599.60±5.91	0.32	23.00±6.24	>12	101.39±1.61
F9	5.14±0.36	4.13±0.029	600.40±6.52	0.36	8.00±2.00	8	99.65±1.24
F10	5.12±0.40	4.13±0.022	599.50±7.03	0.33	9.00±3.00	10	101.36±1.32
F11	5.14±0.39	4.13±0.024	600.90±6.49	0.32	12.33±2.52	>12	99.31±2.17

Drug release studies

Initially, we calculated the theoretical drug release profile of a CFDN floating tablets for 12 h [31]. The calculation was based on the pharmacokinetic parameters of the drug. It was expected that the developed formulation should have the theoretical drug release profile as 16% in 1h, 23% in 2 h, 31% in 3 h, 39% in 4 h, 54% in 6 h, 69% in 8 h, 87% in 10 h and 100% in 12 h. *In vitro* dissolution studies of all the formulations of CFDN tablets were carried out in 0.1 N HCl (pH 1.2). The study was performed for 12 h and cumulative drug release was calculated. The drug release profiles of the formulations, F1-F4 prepared with Polyox WSR 303 are shown in Figure 1. It was observed that the polymer Polyox WSR 303 had a sustaining effect on the release of drug from the floating matrix tablets of CFDN. The effect of Polyox WSR 303 concentration (120 mg, 100 mg, 90 mg and 80 mg/tablet) on drug release was evaluated. As the concentration of Polyox WSR 303 was decreased, the drug release from the floating tablets was significantly increased. The maximum drug released from the formulations F1-F3 was 80.49 ± 1.08%, 88.06 ± 0.93% and 101.23 ± 1.27% in 12 h respectively. The maximum drug released from the formulation F4 was 98.11 ± 1.64% in 10 h and it was unable to sustain the drug release for desired period of time. The differences in the release might be due to the amount of gel layer formed on the surface of the tablets. Formulation F3 was considered as best formulation among all the four formulations as it showed good sustained release very near to theoretical release profile.

The drug release profiles of the formulations F5-F8, prepared with Polyox WSR 205 are shown in Figure 2. Formulations F5-F7 sustained the drug release for only 6, 8 and 10 h respectively. This is because a sufficient polymer concentration in the hydrophilic matrix system is required to form a uniform gel barrier around the tablet upon hydration.

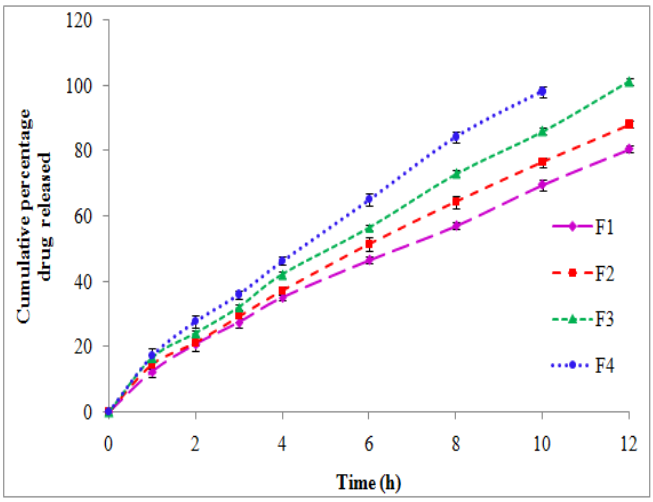

Figure 1. Drug release profiles of cefdinir floating tablets prepared with Polyox WSR 303 (n = 3). Standard deviation bars are not visible (< 3%).

This barrier is expected to prevent the drug from immediate release into the dissolution medium. If the polymer concentration is too low, a complete gel layer may not form resulting in a significant amount of drug being released too quickly or in the worst case, tablet disintegrate [32]. Figure 2 shows that an increased PEO level in the formulation resulted in a decreased drug release rate. Maximum drug released from formulations F5, F6, F7 and F8 were found to be 97.92 ± 1.54%, 99.24 ± 1.36%, 100.42 ± 1.39% and 99.69 ± 1.54% in 6, 8, 10 and 12 hours respectively. Formulation F8 sustained the drug release for desired period of time and matched with the theoretical release profile.

The results of the *in vitro* dissolution studies of the formulations F9-F11, prepared with Polyox WSR 1105 are shown in Figure 3.

Maximum drug released from formulations F9, F10 and F11 were 97.15 ± 1.7%, 96.30 ± 1.32% and 99.61 ± 1.43% in 8, 10 and 12 h respectively. When the Polyox WSR 1105 was less than 120 mg/tablet, the CFDN floating tablets could not retain the physical integrity for desired period of time. Formulations F9 and F10 were unable to sustain the drug release for the desired time. Formulation F11 was able to sustain the drug release for desired period and followed the theoretical release profile

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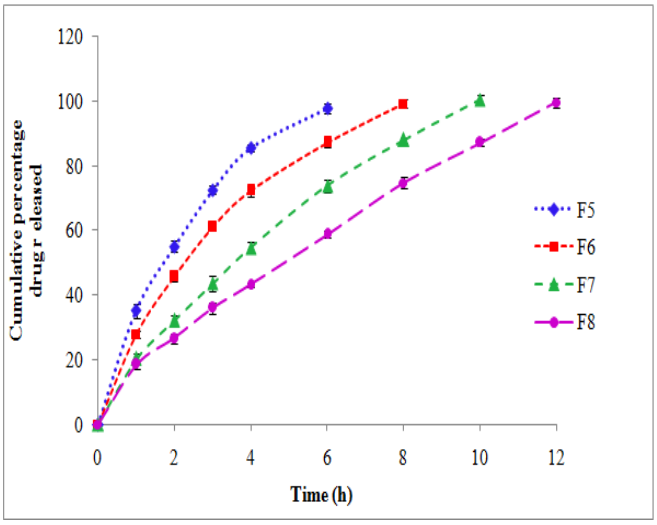

Figure 2. Drug release profiles of cefdinir floating tablets prepared with Polyox WSR 205 (n = 3). Standard deviation bars are not visible (< 3%).

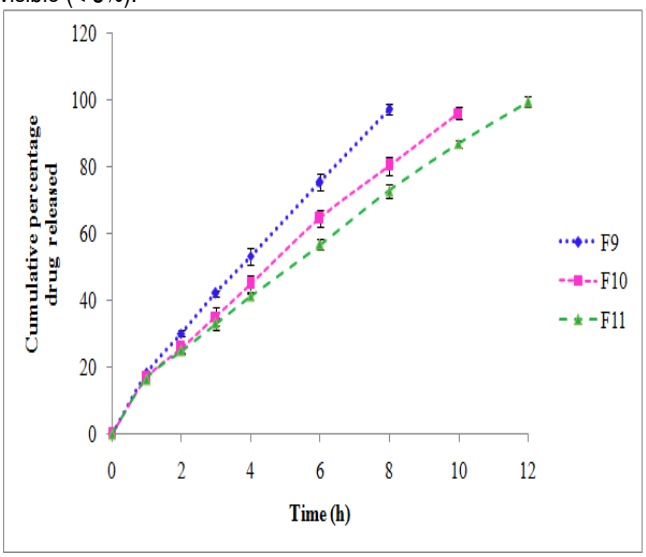

Figure 3. Drug release profiles of cefdinir floating tablets prepared with Polyox WSR 1105 (n = 3). Standard deviation bars are not visible (< 3%).

Kinetic modeling of drug release profiles

The dissolution profiles of all the formulations of CFDN were fitted to different kinetic equations. The values of n with corresponding correlation coefficients (R^2) for all the formulations are shown in Table III. Formulations F5 and F6 followed the Higuchi model due to highest regression coefficient value, R^2 = 0.991 and 0.992 respectively. Formulations F1-F4 and F7-F11 followed the Peppas model and R^2 values were ranged from 0.986-0.999. The optimized formulation F3 with highest regression coefficient values (R^2) was predicted by Peppas model (0.995), when compared to zero (0.992), first order (0.528), and Higuchi models (0.954). The value of release exponent n for all the formulations ranged from 0.588 to 0.805 and that of optimized formulation was 0.750. All the formulations have n values between 0.5 and 1, indicating anomalous transport (non-Fickian). The relative complexity of the prepared formulations indicated that the drug release was controlled by more than one process i.e., a coupling of diffusion and erosion. In controlled or sustained release formulations, diffusion, swelling, and erosion are the three most important rate controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion and is best described by Fickian diffusion. However, in the case of formulations containing swelling polymers, other processes in addition to diffusion play an important role in exploring the drug release mechanisms. The release rate constants (k) of all the formulations were significantly different. The value of k for formulations F1-F4, prepared with Polyox WSR 303, was ranged from 5.97-6.74, formulations F5-F11, prepared with Polyox WSR 205, was ranged from 2.69-5.78 and that of formulations F9-F11, prepared with Polyox WSR 1105 was ranged from 5.47-6.42. Higher k values meant higher quantities of drug released.

Physical stability studies

The prepared CFDN floating tablets containing Polyox WSR 303 (F3) was selected for stability study based on physical characters and *in vitro* drug release. The stability study was conducted for 3 months. Before and after conducting the stability studies for 3 months, the results were analysed statistically by using Student's paired t-test. No significant difference ($p > 0.05$) was observed in the tablet hardness, FLT, TFT, drug content or *in vitro* dissolution (Table IV). The FLT was slightly increased from 12.33 ± 2.51 s to 15 ± 2.64 s after storage for 3 months at 40 °C under 75% RH.
But the difference was not statistically significant ($p > 0.05$). Thus, the F3 floating tablets of CFDN were stable for at least 3 months under these storage conditions.

Table 3. Mathematical models and release kinetics of CFDN floating tablets.

Formulation Code	Zero order		First order		Higuchi		Korsmeyer-Peppas		
	R^2	k_0	R^2	k_1	R^2	k_2	R^2	k	n
F1	0.988	19.21	0.535	0.294	0.963	71.42	0.999	6.60	0.753
F2	0.990	21.25	0.532	0.299	0.960	78.81	0.996	6.57	0.750
F3	0.992	24.29	0.528	0.304	0.954	89.72	0.995	6.74	0.750
F4	0.991	28.73	0.534	0.382	0.951	95.67	0.996	5.97	0.768
F5	0.905	15.82	0.516	0.725	0.991	41.66	0.986	2.69	0.588
F6	0.917	35.21	0.473	0.490	0.992	109.2	0.989	3.37	0.613
F7	0.971	29.15	0.499	0.389	0.976	99.3	0.998	5.00	0.710
F8	0.984	23.73	0.502	0.297	0.969	88.65	0.995	5.78	0.696
F9	0.994	11.80	0.558	0.513	0.942	34.31	0.998	5.47	0.805
F10	0.991	09.36	0.538	0.382	0.951	31.15	0.996	6.08	0.774
F11	0.990	08.00	0.521	0.301	0.959	29.65	0.995	6.42	0.737

k_0, k_1, k_2 and k refer to the rate constants of the respective models, and n refers to the release exponent.

Table 4. Stability studies of CFDN floating tablets

Characteristic	0 day	15^{th} day	30^{th} day	60^{th} day	90^{th} day
Hardness (kg/cm^2)	5.20±0.275	5.18±0.312	5.21±0.306	5.23±0.314	5.20±0.340
Floating lag time (s)	12.33±2.51	12.66±3.05	13.66±2.51	14.66±0.31	15.0±2.64
Duration of floating (h)	>12	>12	>12	>12	>12
Drug content (%)	99.66±1.85	99.41±1.73	99.32±1.64	99.29±1.75	99.15±1.63
Drug released at 12 h	99.64±2.51	99.52±1.35	99.27±1.22	99.35±1.31	99.17±1.58

In-vivo evaluation of gastric residence time in healthy volunteers

The floating tablets (F3) prepared for radiological studies were characterized for hardness (5.16 ± 0.33 kg/cm^2), thickness (3.94 ± 0.055 mm), weight variation (599.0 ± 8.54 mg), friability (0.37%), FLT (133.6 ± 7.77 sec) and TFT was greater than 12 h. The increased lag time of $BaSO_4$-loaded CFDN floating tablets, compared to the original formulation F3 (12 ± 2 s) was expected because of high density of $BaSO_4$ (4.5 g/cm^3). Figure 4 shows the radiographic images taken at different periods after administration of $BaSO_4$-loaded CFDN floating tablet in one volunteer. The first radiographic image was taken at 0.5 h post-administration of tablet and the tablet was observed in the stomach. The next pictures were taken at 2.5, 4.5 and 5.5 h; the tablet had altered its position, yet remained within the stomach till the end of 5.5 h. The mean gastric residence time was found to be 4.83 ± 0.57 h (n=3).

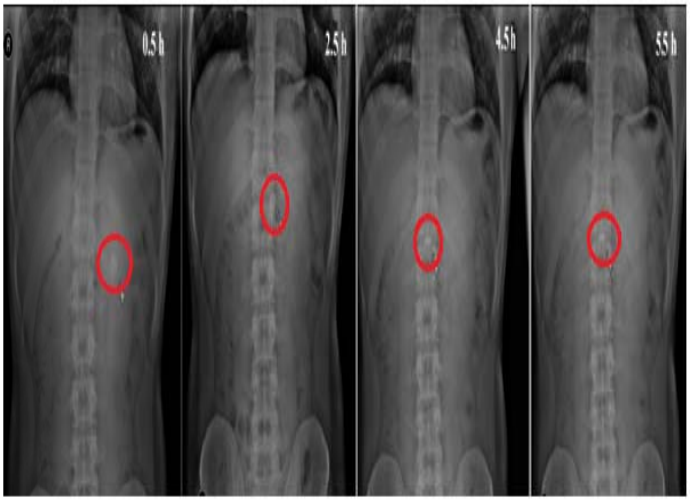

Figure 4. Radiographic images showing the presence of BaSO4-oaded floating tablets of CFDN in the stomach at different time points (the location of the tablet is indicated with an oval shape).

Pharmacokinetic analysis

In this study, the pharmacokinetics of CFDN floating tablets were compared with IR and conventional SR tablets. The bioavailability study was conducted according to the protocol. The drug was well tolerated with no other symptoms or disturbances during the three study periods. The plasma samples were analyzed by HPLC method. The retention time of internal standard cefadroxil and drug was 3.8 and 8.8 min respectively. The mean serum concentration-time curves of the three CFDN formulations are shown in Figure 5. The pharmacokinetic parameters of the three formulations are summarized in Table V. The significance of the difference between the treatments was evaluated by one-way analysis of variance (ANOVA) using GraphPad Prism (version 5.04, 2010) by Dunnett's Multiple Comparison Test. The differences between formulations were considered to be significant at $p < 0.05$ with 95% confidence intervals.

Table 5. Pharmacokinetic parameters of three formulations of CFDN (300 mg, single dose) (n = 9).

Pharmacokinetic parameter	CFDN conventional IR tablets Mean ± SD	CFDN conventional SR tablets Mean ± SD	CFDN floating tablets Mean ± SD
C_{max} (µg ml^{-1})	2.05 ± 0.31*	1.54 ± 0.15**	1.48 ± 0.15**
t_{max} (h)	2.66 ± 0.50*	3.44 ± 0.52*	4.22 ± 0.66*
AUC_{0-t} (µg ml^{-1} h)	9.39 ± 1.12*	13.48 ± 1.23*	16.51 ± 1.41*
$AUC_{0-\infty}$ (µg ml^{-1} h)	9.95 ± 1.11*	13.67 ± 1.25*	17.08 ± 1.57*
$t_{1/2}$ (h)	2.30 ± 0.17*	3.43 ± 0.28*	4.21 ± 0.56*
MRT (h)	5.11 ± 0.26*	7.25 ± 0.40*	8.78 ± 0.61*

* Statistically significant ($p < 0.05$).
** Statistically not significant ($p > 0.05$).

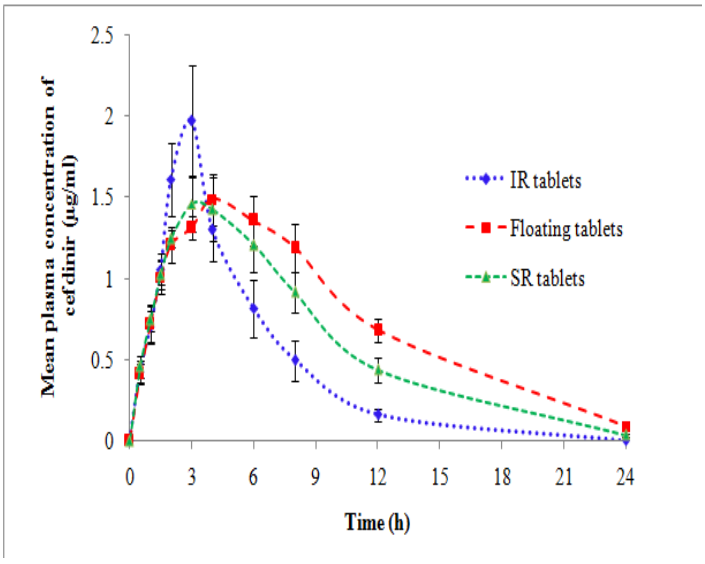

Figure 5. Plasma concentration-time profiles of IR, conventional SR and floating tablets of CFDN (n = 9).

The results showed that the difference between all pharmacokinetic parameters of IR and floating tablets of CFDN were statistically significant ($p < 0.05$). The peak plasma concentration (C_{max}) of IR tablets was 2.05 ± 0.31µg ml^{-1} and that of floating tablets 1.48 ± 0.15 µg/ml. The t_{max} of floating tablets (4.22 ± 0.66 h) was significantly delayed when compared with the IR tablets (2.66 ± 0.50 h), indicating the better sustained release character of floating tablets. The $AUC_{0-\infty}$ of the IR and floating tablets were found to be 9.95 ± 1.11 µg h ml^{-1} and 17.08 ± 1.57 µg h ml^{-1} respectively. The higher $AUC_{0-\infty}$ of CFDN floating formulation may be due to slower release rate or the prolonged gastric residence time. The IR tablets exhibited shorter $t_{1/2}$ (2.30 ± 0.17 h) than floating tablets (4.21 ± 0.56 h). MRT values for IR and floating formulations were 5.11 ± 0.26 and 8.78 ± 0.61 h respectively. Similarly, the difference between all pharmacokinetic parameters of conventional SR and floating tablets of CFDN were statistically analysed and the results showed that the C_{max} of conventional SR tablets (1.54 ± 0.15 µg ml^{-1}) was slightly greater than that of floating tablets (1.48 ± 0.15 µg ml^{-1}) of CFDN, but the difference was not statistically significant. And the difference between t_{max}, $AUC_{0-\infty}$, $t_{½}$ and MRT were found to be statistically significant ($p < 0.05$). The relative bioavailability was found to be 1.71 times to that of IR tablets and is significant, but not very significant when compared to SR tablets as it was 1.24 times. This improved bioavailability is due to the combined effect of sustained release and increased GRT of CFDN floating tablets.

Conclusions

The floating tablets of CFDN were successfully developed using Polyox WSR 303, Polyox WSR 205 and Polyox WSR 1105 by effervescent floating technique. The optimized formulation (F3) showed satisfactory results with respect to FLT, TFT and sustained drug release, and was physically stable during 3 months period. The non-Fickian diffusion was the release mechanism from all the prepared tablets. The *in vivo* radiographic studies showed that the $BaSO_4$-loaded floating tablets were retained in the stomach for 4.83 ± 0.57 h (n=3). Formulation F3 increased the bioavailability when compared to IR and conventional SR formulations of CFDN. The increased relative bioavailability was 1.71 fold to IR and 1.24 fold to conventional SR tablets. This improved bioavailability is due to the combined effect of sustained release and increased GRT of CFDN floating tablets.

Acknowledgements

The authors acknowledge M/s Orchid Pharma Ltd., Chennai, India for providing drug and polymer as gift samples. The authors also acknowledge M/s Aurobindo Pharma. Ltd., Hyderabad, India for providing cefadroxil as gift sample.

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