An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

CEFUROXIME AXETIL: FORMULATION *IN VITRO- IN VIVO* EVALUATIONS AND ITS CORRELATION

Swapna .R[1], Basava Raju. D*[2] and Shailaja. P[3]

[1] Vagdevi College of Pharmacy, Gurazala, Andhra Pradesh, India
[*2]Shri Vishnu College of Pharmacy, Bhimavaram, Andhra Pradesh, India.
[3]Andhra University, Vishakapatnam, Andhra Pradesh, India

*Corresponding author E-mail**: director@svcp.edu.in**

ARTICLE INFO

Key Words

Cefuroxime Axetil, DCP, Lactose, Albizia gum, Dammar gum and Moi gum

ABSTRACT

Oral drug delivery system represents one of the frontier area of controlled drug delivery system. Floating drug delivery system belongs to oral controlled drug delivery system group, which is capable of floating in the stomach for prolong period of time. The objective of the present research work is to provide a gastroretentive system for sustained release of therapeutically active agent, cefuroxime axetil in upper part of gastro-intestinal tract in the form of floating tablet. Cefuroxime axetil, an oral prodrug shows a bioavailablity of 30% to 40% when taken on fasting and 5% to 60% when taken after food. The cefuroxim axetil esterase can hydrolyze cefuroximeaxetil to the nonabsorbable cefuroxim in the gut lumen and is therefore, suspected as a possible cause of incomplete bioavailability. Which suggests an absorption mechanism through the mucosa with limited capacity. Cefuroxime axetil had saturation kinetics that could be overcome by slow release of drug from the formulation, by incorporating cefuroxime axetil in sustained drug delivery system using Albizia gum, Dammar gum and Moi gum as polymers for controlling the drug release. Two types of diluents (Lactose and DCP) were used and the drug release was compared. Optimized formulation F4CADL was selected for *in vivo* studies by using albino rabbits. It was found that the tmax was extended for prolonged period of time.

INTRODUCTION

Due to non-invasive, non-complexity, safe, self administration, non-involvement of the physician oral route becomes the most acceptable and convenient route of drug administration. Generally, patients prefer to take drugs by oral route rather systemic routes of administration due to its non-invasive nature.The oral ingestion is the predominant and most preferable route for drug delivery. Time controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the

administration frequency leading to improved patient compliance[1]. Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size [2]. The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from the small intestine. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time. Cefuroxime Axetil is a second-generation cephalosporin, proven to be relatively safe. It can be given orally as well as parentrally[3]. Cefuroxime axetil is a prodrug of cefuroxime, which upon absorption undergoes immediate deesterification to free cefuroxime. Cefuroxime axetil has an *in vitro* antibacterial spectrum against many Gram-positive and Gram-negative organisms. Its beta-lactamase (b-lactam) stability makes it useful in treating a variety of infections caused by β-lactam-producing strains of *Haemophilusinfluenzae*, *Moraxella catarrhalis*and *Staphylococcus aureus*[4]. Chemically it is 5-Thia-1-azabicyclo [4.2.0] ct-2-ene-2-carboxylicacid, 3-[[(aminocarbonyl) oxy] methyl]-7-[[2-furanyl(methoxyimino)acetyl] amino]-8-oxo-, 1-(acetyloxy) ethylester, [6*R*-[6a7b (Z)]][5]. Mechanism of action of Cefuroxime is like the penicillins. It is a beta-lactam antibiotic. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins It is possible that Cefuroxime interferes with an autolysin inhibitor[6]. In conventional tablets or capsule drugs, the delivery pattern results in a transient overdose, followed by a long period of over dosing. So controlled release drug delivery system is preferred. Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs[7]. The objective of the present work is to prepare cefuroxime axetil floating tablets using natural gums and compare the release by using animal models.

MATERIALS AND METHODS: The drug Cefuroxime Axetil (CA) was received as a gift sample from Covalent Laboratories (Hyderabad, India). Albizia gum, Dammar gum and Moi gum were procured from Natural suppliers (Mumbai, India). Dicalciumphosphate (DCP), Lactose (LC), Sodium Bicarbonate (SBC), Magnesium Stearate (MGS), Talc (TC) were obtained from SD Fine chemicals Mumbai. Methanol and Conc. HCl is of analytical grade.

PREPARATION OF STANDARD PLOT OF CEFUROXIME AXETIL : The stock solution was freshly prepared by dissolving 100 mg of Cefuroxime Axetil in few ml of methanol (5ml) in a 100ml volumetric flask and then make up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/ml (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock 0.5,1.0, 1.5, 2.0, 2.5 ml, was taken separately and made up to 10ml with 0.1N HCl, to produce 5,10,15,20,25 µg/ml respectively. The absorbance was measured at 280 nm using a UV spectrophotometer (Systronic, Ahmedabad, India). The standard calibration curve of Cefuroxime Axetil in 0.1N HCl[8, 9] as shown in Fig. 1.

PREFORMULATION STUDIES OF CEFUROXIME AXETIL AND FORMULATIONS: The pure drug and excipients were evaluated for Angle of

Repose, Bulk Density, Tapped Density, Carr's index and Hausner's ratio as shown in tables 2, 3.

Angle of Repose: This is the maximum angle possible between the surface of a powder pile and the horizontal plane. It is the characteristic related to inter-particulate friction (or) resistance to movement between particles. Angle of repose was carried out by funnel method.[10, 11, and 12]

Where θ =angle of repose, h =the height of the pile, r= radius of the pile.

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Bulk Density: It is determined by pouring 20 gm of dry powder into 100 ml graduated cylinder and the volume (V) occupied is noted. Bulk density is calculated as

$$\text{Bulk density} = M/V$$

Tapped Density: Powder was passed into 100 ml graduated cylinder and was beaten for stipulated time, followed by the volume occupied (V) was calculated. Poured into 50 ml graduated cylinder and it was tapped for affixed time (around 100 taps).The minimum volume (V) occupied in the cylinder was measured. Tapped density was calculated by the formula

$$\text{Tapped density} = M/V$$

Where, m = initial weight of material in gm, V= volume of material after tapping. Generally replicate determinations are desirable for the determination of this property.

Compressibility Index: It is an indirect method for measurement of bulk density, size, shape, surface area and cohesiveness of the material. It is determined by Carr's compressibility index.

$$\text{Compressibility Index} = \frac{100\,(\text{Bulk density} - \text{Tapped density})}{\text{Bulk density}}$$

Hausner's Ratio*:* Hausner's ratio is a number that is correlated to flow ability of a powder. It is calculated by the formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

PREPARATION METHOD OF CEFUROXIME AXETIL FLOATING TABLETS: Cefuroxime Axetil (300 mg equivalent to 250 mg of cefuroxime base) was mixed with the required quantities of polymers (Albizia, Gum dammar and moi gum), sodium bicarbonate, lactose and dibasic calcium phosphate by geometric mixing. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmadabad, India) using a diameter of 12-mm standard flat-face punches [13, 14, and 15] as shown in table 1.

Evaluation Of Controlled Release Floating Matrix Tablets: Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Tablet thickness, Weight variation test, Hardness and Friability parameters were evaluated and shown in tables 4-8

Tablet Thickness: The thickness in millimeters (mm) was measured individually for 5 preweighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

Weight Variation: Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The Average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.[16, 17]

Tablet Hardness: Tablet hardness was measured using a Monsanto hardness tester. 5 tablets were taken whose total weight was predetermined. The hardness was reported in kg/cm^{2}The crushing strength of the 10 tablets with known weight and thickness of each was recorded

in kg/cm^2 and the average hardness and standard deviation was reported.

Friability: A batch containing 13 tablets were selected and weighed. The weighed tablets were taken and kept in a roche friabilator rotated at 25 rpm for a period of 4 minutes. The above tablets were taken and dedusted and again weighed in order to determine the decrease in weight. Friability was then calculated as percent weight loss from the original tablets.

Content Uniformity: The formulated Cefuroxime Axetil floating tablets were assayed for drug content. From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 5 ml of methanol was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 280 nm by using UV-Visible spectrophotometer.[18, 19]

Buoyancy / Floating Test:

The *in vitro* buoyancy was determined by floating lag time, as per the method described the tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT)[20,21].

Water Uptake Studies: The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at 37^o± 0.5^{o}c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake.[22]

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and WO is the initial weight of the tablet.

In-Vitro Drug Release: The tablet was placed inside the dissolution vessel. 5 ml of sample were withdrawn at time intervals of 60, 120 and 180, 240, 300, 360, 420, 480, 540,600, 660, and 720 minutes. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets and the mean values were plotted versus time. Each sample was analysed at 280 nm using double beam UV and Visible Spectrophotometer against the reagent blank. The drug concentration was calculated using standard calibration curve [23, 24, 25.] The data are given in tables 9-10 and shown in figures 6-7.

Mechanism Of In Vitro Drug Release:

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data was fitted in zero-order, first order, Higuchi, and Korsmeyer-Peppas release model [26, 27, 28].

Zero Order Release Rate Kinetics: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$\mathbf{F = K_o.t}$$

Where 'F' is the drug release, 'K' is the release rate constant and't' is the release time. The plot of % drug release versus time is linear.

First Order Release Rate Kinetics: The release rate data are fitted to the following equation

$$\mathbf{\ln(1-Q) = -k_1 t}$$

A plot of log % drug release versus time is linear.

Higuchi Release Model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$Q = k_2 t^{½}$$

Where 'k' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus the square root of time is linear.

Korsmeyer And Peppas Release Model

The release rate data were fitted to the following equation,

$$M_t / M_\infty = K.t^n$$

'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or nonfickian diffusion (Swellable& Cylindrical Matrix).In this model, a plot of log (M_t/M_∞) versus log (time) is linear. The data is shown in table 11 and figures in 8- 11.

STABILITY TESTING PROCEDURE[29]:

Any dosage form, apart from other requirements, should be stable with respect to drug release characteristics. The optimized formulations of effervescent floating tablets F4CADL (cefuroxime axetil) was evaluated for accelerated stability testing as per ICH guidelines. The formulations were placed in HDPE (High-density polyethylene) containers at 40±2°C/75±5%RH and 25±2°C/60±5% RH (Relative humidity) in stability chamber for a period of 6 months. After storing for 6 months, the products were tested for appearance, uniformity of weight, hardness, friability, drug content, floating characteristics and drug release.

***In vivo* studies[30]**

In the present study *in vivo* clinical study of Cefuroxime Axetil was performed in healthy rabbits (New Zealand, White) of either sex weighing (2.5-3.5 kg) were divided into 2 groups, each consisting of 6 animals. In case of Cefuroxime Axetil first group received pure drug. Second group received the in-house floating formulation (F4CADL). Food was withdrawn from the rabbits 12 hrs before drug administration and until 24 hrs post dosing. All rabbits had free access to water throughout the study. The data was mentioned in tables 12, 13. The Institutional Animal Ethical Committee approved the protocol for this *in vivo* animal study bearing register no: HCOP/IAEC/PR-2-2018**.**

STUDY OF *IN VITRO-IN VIVO* CORRELATION OF CEFUROXIME AXETIL FLOATING TABLETS[31]:

Drug dissolution is the rate-limiting step in absorption for controlled release formulations. Therefore, *in vitro* dissolution of the drug correlates with its *in vivo* absorption. To predict *in vivo* input rate, the dissolution method should discriminate between the variables of drug substance, product and/or manufacturing method that affect the rate and extent of drug release and dissolution. In the most successful case, in vitro dissolution conditions that mimic in vivo dissolution may be found. For reasons of clarity, three levels A, B and C have been defined for IVIVC (FDA175guidance, 1997). Level A is the highest level correlation; it represents a point-to-point relationship between in vitro dissolution and in vivo input rate. Only in the case of level A correlation can in vitro dissolution be used as a surrogate for in vivo bioequivalence studies, i.e., the level A model and dissolution method can be used in bio waivers. Level B and C models have ess predictive power than level A model, lbecause C_{max}, t_{max} or MRT values can be the same for different formulations. Level B, is based on statistical moment analysis. MRT or mean dissolution time in vivo (MDT in vivo) is compared to the mean dissolution time in vitro (MDT in vitro). Level C represents single-point correlation between one dissolution time point and one pharmacokinetic parameter. The development of IVIVC models, includes the establish conditions for dissolution tests, which can be used as surrogates for relative bioavailability or bioequivalence studies.

Several bioavailability and bioequivalence studies were conducted during the development process of a new drug product. Different types of formulations can have the same AUC, C_{max} or T_{max} values. Thus, level B or C models can't be used to replace relative bioavailability or bioequivalence studies. Correlations between in vitro and in vivo data (IVIVC) are often used during pharmaceutical dosage development in order to reduce formulation development time and optimize the formulation. A good correlation is a tool for predicting in vivo results based on in vitro data. IVIVC allows dosage form optimization with the fewest possible trials in man, fixes dissolution acceptance criteria, and can be used as a surrogate for further bioequivalence studies; it is also recommended by regulatory authorities. Five correlation levels have been defined in the IVIVC-FDA guidelines. The concept of correlation level is based up on the ability of the correlation to reflect the complete plasma drug level-time profile which result from administration of the given dosage form. Level A correlation represents a point to point relationship between in vitro dissolution rate and in vivo input rate of the drug from the dosage form. The Wagner – Nelson method was used to determine the fractional oral absorption at each sampling time. The fraction of drug absorbed was calculated by using the following formula.

F(t) = Fraction of drug absorbed

$$F(t) = \frac{C(t) + K_{el} * AUC_{0-t}}{(K_{el} * AUC_{0-\infty})}$$

Where, C (t) = Plasma drug concentration at't' time, K_{el}= Elimination rate constant, AUC_{0-t}= Area under the curve from '0' time to't', $AUC_{0-\infty}$ = Area under the curve from '0' time to't' and '∞' time.

DISCUSSION

Cefuroxime axetil pure drug and their optimized floating tablet formulation F4CADL were subjected to FTIR spectroscopic analysis, to ascertain whether there was any interaction between the drug and the polymers used. The obtained spectra are given in following Figures 2-3. Characteristic peaks of Cefuroxime axetil of pure drugs were compared with the peaks obtained for their matrix tablet formulation F4CADL.The characteristic bands of cefuroxime axetil were identifiable and there was no major shift in them when combined with polymers used in the preparation of matrix tablet. This indicated that the drug was intact and had not reacted with the excipients used in the formulations and hence, they were compatible. Studies were carried out for cefuroxime axetil pure drug and optimized formulation F4CADL and the thermo grams obtained were presented in following Figures 4-5. Graphs obtained for pure drug showed a sharp peak at 181.58^{o}C for cefuroxime axetil which corresponds to their melting point. Tablet acting at particular location F4CADL showed endothermic peak at 181.58^{o}C which is similar to the melting point of the drug. From the thermo grams, it was evident that the melting point of cefuroxime axetil has not changed after it was formulated as floating tablets. The intact drug, polymers, excipients and powder blends were subjected to evaluation of flow properties before compression and the results were given in Tables 2 and 3. The angle of repose values of all the prepared powder blends of natural gums was in the range of (25.57-28.45°) indicating their suitability for direct compression. The quality control tests such as uniformity of weight variation, hardness, friability and drug content for all the formulations were calculated and the results were given in Table 4. All the formulations complied with compendia standards of IP. The weight variation of the tablets was within the IP limits. (Not more than two of the individual weights deviate from the average weight by more than 5% and none deviates by more than 10%). The

hardness for all the formulations was found to be in the range of 4-5 Kg/ cm^2 and was satisfactory. Weight loss in the friability test was found to be less than 1%. The drug content in all the matrix tablets were found in the acceptable range of 85.61–99.94%. Thus the formulated matrix tablets were of good quality, fulfilling the official requirements of the tablets. Further, the formulated tablets on immersion in 0.1N HCl media they remain buoyant for 12 hrs with lag time of 111 to 138 seconds. Sodium bicarbonate was added as a gas-generating agent. This helps in keeping the tablets buoyant by decreasing its density less than 1. The reason for the buoyancy was due to the generation of carbon dioxide gas that was present in the formed matrix tablet and aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced CO_2 that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. Results are shown above. All the batches showed good *in vitro* buoyancy. The percentage swelling obtained from the water uptake studies of the formulations are shown in Tables 6-8. The formulations with albizia gum, gum dammar and moi gum showed the swelling and tablet integrity. The change in sodium bicarbonate concentration did not show any effect on swelling of the tablet. Complete swelling was achieved at the end of 8 hours, then followed by diffusion and erosion takes place. The formulation containing albizia gum with DCP shows the higher swelling compared to that of the formulations containing gum dammar and moi gum. The swelling index of the tablets increases by increasing the polymer concentration. *In-vitro* dissolution study of formulations F1CAAL, F2CAAL and F3CAAL were prepared with albizia gum with lactose. The percent of drug release from formulations F1CAAL, F2CAAL and F3CAAL was 95.2%, 99.2% and 99.6%, respectively, formulations F2CAAL and F3CAAL, unable to sustain the drug release for desired period of time (12 hrs) but in case of formulation F1CAAL 95.2% of the drug was released at 12 hrs. All these three formulations floated more than12 hrs. Formulations F2CAAL and F3CAAL were failed to drug release profile. *In vitro* dissolution study of formulations F4CADL, F5CADL and F6CADL formulations were prepared with gum dammar with lactose and the percent of drug release from formulations F4CADL, F5CADL and F6CADL was 99.2%, 99.5%, and 99.9% respectively. The results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly. Formulation F5CADL and F6CADL were unable to sustain the drug release for desired period of time, but in case of formulation F4CADL, 99.2% of the drug was released at 12 hrs, this was considered due to different polymer concentrations in all the three formulations. All these three formulations floated for more than 12 hrs. Formulations F5CADL and F6CADL failed to produce desired drug release profile Formulation F4CADL obtained the desired drug release profile and floated with a lag time of 138 Seconds, for these reasons, it was considered as best formulation among all the four formulations. *In vitro* dissolution study of formulations F7CAML, F8CAML and F9CAML formulations were prepared with moi gum with lactose and the percent of drug release from formulations F7CAML, F8CAML and F9CAML was 89.2%, 92.5% and 99.7%, respectively. The results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly. Formulation F8CAML and F9CAML were unable to sustain the drug release for desired period of time, but in case of formulation F7CAML, 89.2% of the drug was released at 12 hrs, this was considered due to different polymer concentrations in all the three formulations. All these

three formulations floated for more than 12 hrs. Formulations F8CAML and F9CAML failed to drug release profile. Formulation F7CAML obtained the desired drug release profile and floated with a lag time of 136 sec, for these reasons, it was considered as best formulation among all the three formulations. *In vitro* dissolution study of formulationsF10CAADCP, F11CAADCP and F12CAADCP prepared with albizia gum with diluent DCP and the percent of drug release from formulations was 54.3%, 63.5% and 70.3% in 12 hrs respectively. Formulations F10CAADCP, F11CAADCP and F12CAADCP failed to meet the desired drug release profile. *In vitro* dissolution study of formulations F13CADDCP, F14CADDCP and F15CADDCP were prepared with gum dammar with DCP as diluent and the percent of drug release from formulations F13CADDCP, F14CADDCP and F15CADDCP was 63.4%, 73.2% and 75.6% respectively, The results indicated that by increasing the grade of polymer concentrations, drug release was retarded greatly. *In vitro* dissolution study of formulations F16CAMDCP, F17CAMDCP and F18CAMDCP were prepared with moi gum with DCP and the percent of drug release from formulations F16CAMDCP, F17CAMDCP and F18CAMDCP was 53.4%, 63.2% and 69.6% respectively. The results indicated that by increasing the grade of polymer concentrations drug release was retard greatly. Comparing the three different grades of the gums (albizia gum, gum dammar and moi gum), it was found that gum dammar with diluent lactose that is F4CADL provided better-sustained release characteristics with excellent drug release and *in vitro* buoyancy. The variation in the change of filler on the drug release was minimized by keeping the different fillers in formulations. Formulation F1CAAL to F9CAML was made with lactose as filler. After incorporation of lactose, the drug release pattern was good and was considered due to the capillary action of lactose, as this facilitated higher drug release without affecting the matrix. In formulations F10CAADCP to F18CAMDCP was made with DCP as filler. The results showed that there is a decrease in the drug release when the DCP was used as filler. The results showed that there is a decrease in the drug release when the DCP was used as filler due to its hydrophobic nature. The mechanism of release for the optimized formulations was determined by finding the R value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the R value of Korsmeyer-Peppas, zero-order and Higuchi model is very near to 1 than the R values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas, zero-order and Higuchi model mechanism. Therefore the most probable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion. The optimized formulation F4CADL was administered after reduced to the rabbit dose as SF4CADL. Pharmacokinetic parameters were calculated using non-compartmental model. The plots of the mean plasma concentration of the cefuroxime axetil in both test (SF4CADL) and reference (Pure drug) were shown in Figures 12-13 and comparative mean plasma concentration-time profiles are show in Figure 14. The mean peak plasma concentration of test (T) formulation C_{max} 4302.1ng/ mL was gradually reached in 3 hrs. In case of Pure drug (R) the C_{max} was 4658.3 ng/ mL which was reached in 2 hrs. The C_{max} of the test formulation (T) was less when compared with reference (R) formulation. The increase in T_{max} was clearly indicating the drug availability for prolonged period.

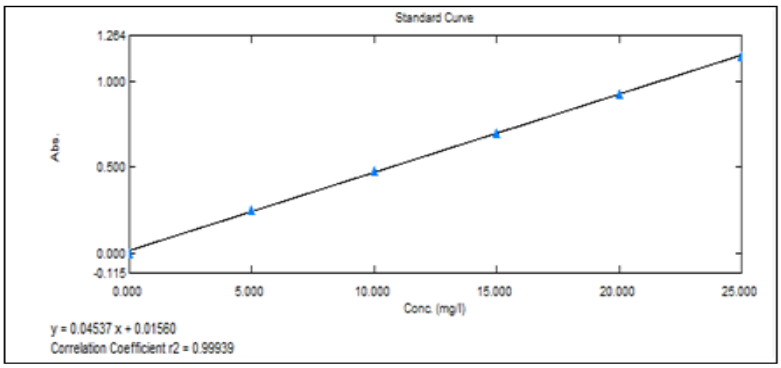

Figure 1: ***Standard plot of Cefuroxime Axetil***

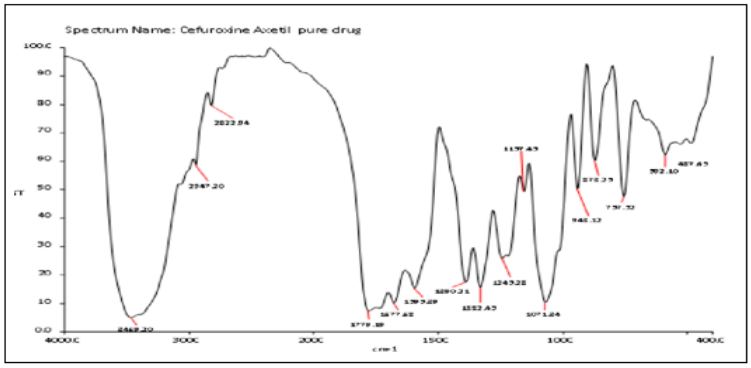

Figure 2: ***FTIR of Pure Cefuroxime axetil***

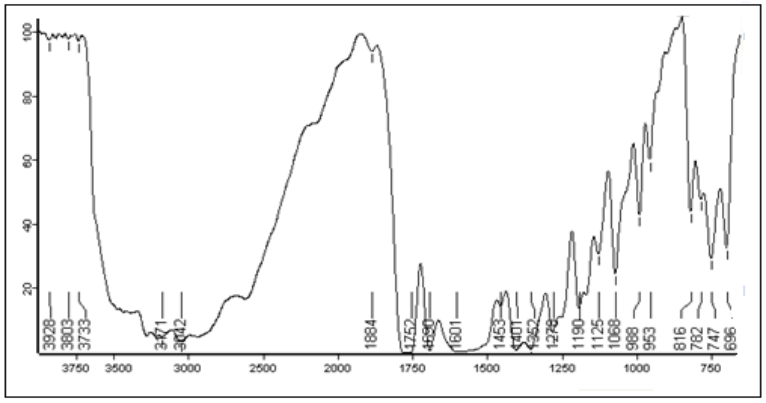

Figure 3: ***FTIR of Physical mixture of optimized formulation***

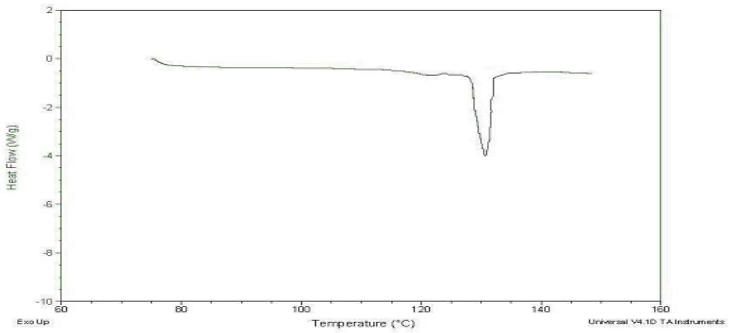

Figure 4- ***DSC of Pure Cefuroxime axetil***

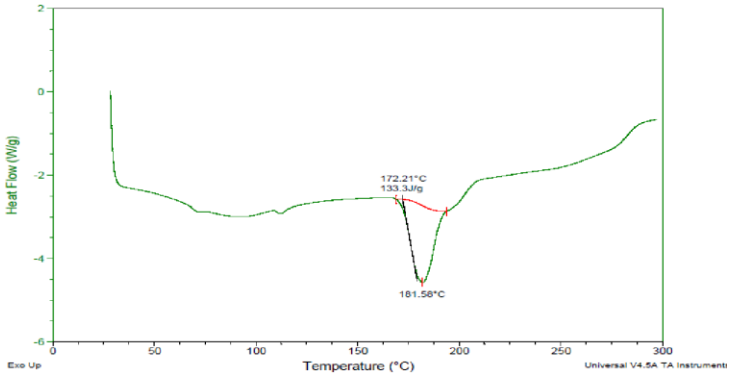

Figure 5- ***DSC of Physical mixture of optimized formulation***

Table 1- ***Formulation composition of gastroretentive tablets of cefuroxime axetil***

CODE	CA	SBC	AG	GD	MG	MGS	LC	DCP	TC
F1CAAL	300	40	112.5	-	-	5	37.5	-	5
F2CAAL	300	40	75	-	-	5	75	-	5
F3CAAL	300	40	37.5	-	-	5	112.5	-	5
F4CADL	300	40	-	112.5	-	5	37.5	-	5
F5CADL	300	40	-	75	-	5	75	-	5
F6CADL	300	40	-	37.5	-	5	112.5	-	5
F7CAML	300	40	-	-	112.5	5	37.5	-	5
F8CAML	300	40	-	-	75	5	75	-	5
sF9CAML	300	40	-	-	37.5	5	112.5	-	5
F10CAADCP	300	40	112.5	-	-	5	-	37.5	5
F11CAADCP	300	40	75	-	-	5	-	75	5
F12CAADCP	300	40	37.5	-	-	5	-	112.5	5
F13CADDCP	300	40	-	112.5	-	5	-	37.5	5
F14CADDCP	300	40	-	75	-	5	-	75	5
F15CADDCP	300	40	-	37.5	-	5	-	112.5	5
F16CAMDCP	300	40	-	-	112.5	5	-	37.5	5
F17CAMDCP	300	40	-	-	75	5	-	75	5
F18CAMDCP	300	40	-	-	37.5	5	-	112.5	5

CA=Cefuroxime axetil; SBC= Sodium bicarbonate; DCP=Dicalcium Phosphate; LC=Lactose; MGS= magnesium stearate; AG= Albizia gum; DG= Dammar gum; MG= Moi gum; TC=Talc.

Table 2: ***Pre formulation results of cefuroxime axetil***

Ingredients	Bulk Density (gm/cc) ± SD*	Tapped Density (gm/cc) ± SD*	Compressibility Index (%)± SD*	Hausner's Ratio ± SD*	Angle Of Repose (°) ± SD*
Cefuroxime Axetil	0.499±0.23	0.541±0.09	12.57±0.11	1.08±0.04	26.14±0.16
Lactose	0.741±0.45	0.888±0.54	13.22±0.14	1.14±0.01	26.32±0.29
Dibasic calcium Phosphate	0.435±0.14	0.458±0.34	14.55±0.13	1.05±0.04	26.56±0.21
Albizia Gum	0.632±0.39	0.702±0.16	15.31±0.12	1.11±0.06	28.45±0.15
Dammar Gum	0.712±0.22	0.698±0.15	14.45±0.17	1.12±0.03	26.25±0.85
Moi Gum	0.699±0.11	0.559±0.19	13.22±0.12	1.05±0.01	25.57±0.47
Magnesium Stearate	0.456±0.36	0.651±0.12	15.23±0.17	1.17±0.07	26.21±0.23

**** (n=3) Mean±SD, P<0.2 when compared with control***

Table 3: ***Pre compression parameters of the cefuroxime auxetil gas generating floating formulations***

Formulation	Bulk density(gm/cc) ± SD*	Tapped density(gm/cc) ± SD*	Compressibility index (%)± SD*	Hausner's ratio± SD*	Angle of repose (°) ± SD*
F1CAAL	0.56±0.23	0.63±0.28	12.63±0.16	1.12±0.06	24.60±0.36
F2CAAL	0.59±0.49	0.68±0.19	11.92±0.14	1.15±0.03	22.34±0.21
F3CAAL	0.51±0.12	0.62±0.36	13.31±0.13	1.18±0.02	29.23±0.52
F4CADL	0.48±0.18	0.56±0.39	15.87±0.14	1.16±0.06	26.40±0.39
F5CADL	0.49±0.22	0.53±0.18	14.85±0.13	1.08±0.03	23.42±0.54
F6CADL	0.47±0.19	0.52±0.16	13.43±0.15	1.10±0.04	22.43±0.81
F7CAML	0.53±0.21	0.59±0.26	12.23±0.14	1.11±0.04	26.41±0.33
F8CAML	0.51±0.39	0.58±0.39	14.36±0.16	1.13±0.02	23.35±0.73
F9CAML	0.49±0.14	0.52±0.21	13.33±0.13	1.06±0.07	22.43±0.14
F10CAADCP	0.48±0.15	0.52±0.14	12.01±0.18	1.08±0.05	25.35±0.47
F11CAADCP	0.49±0.06	0.55±0.28	14.32±0.12	1.12±0.02	22.42±0.35
F12CAADCP	0.45±0.11	0.53±0.17	13.85±0.11	1.17±0.03	22.24±0.24
F13CADDCP	0.46±0.12	0.53±0.12	11.62±0.16	1.15±0.06	23.55±0.29
F14CADDCP	0.49±0.15	0.55±0.28	15.10±0.12	1.12±0.05	22.64±0.11
F15CADDCP	0.42±0.37	0.48±0.13	13.04±0.17	1.14±0.08	23.35±0.54
F16CAMDCP	0.59±0.32	0.64±0.21	15.69±0.14	1.08±0.03	23.46±0.24
F17CAMDCP	0.46±0.36	0.53±0.25	14.32±0.12	1.15±0.06	22.64±0.25
F18CAMDCP	0.48±0.17	0.56±0.29	14.54±0.11	1.16±0.02	23.24±0.29

**** represents Mean±SD (n=3), P<0.1 when compared with control***

Table 4- ***Post compression parameters of gas generating floating tablets of cefuroxime axetil***

Formulation Code	Uniformity Of Weight (mg)±SD* (n=20)	Friability (%)±SD* (n=10)	Hardness (Kg/cm^2)±SD* (n=3)	Thickness (mm) ±SD* (n=3)	Drug Content (%) ±SD* (n=10)
F1CAAL	500±0.19	0.12 ± 0.01	4.20 ± 0.74	4.5± 0.03	89.90 ± 0.34
F2CAAL	499±0.42	0.14± 0.33	4.7 ± 0.28	4.4± 0.02	85.61 ± 0.70
F3CAAL	500±0.27	0.19 ± 0.22	4.60 ± 0.45	4.4± 0.01	97.22 ± 0.66
F4CADL	499±0.91	0.10 ± 0.14	4.29 ± 0.54	4.5± 0.04	97.33 ± 0.65
F5CADL	501±0.22	0.15 ± 0.12	4.40 ± 0.52	4.4± 0.02	99.41 ± 0.36
F6CADL	499±0.67	0.14 ± 0.03	4.35 ± 0.15	4.5± 0.04	98.14 ± 0.23
F7CAML	500±0.21	0.11 ± 0.14	4.74 ± 0.57	4.5± 0.02	96.27 ± 0.81
F8CAML	501±0.19	0.11 ± 0.34	4.25 ± 0.28	4.4± 0.03	98.25 ± 0.37
F9CAML	500±0.45	0.18 ± 0.12	4.88 ± 0.15	4.5± 0.01	99.94 ± 0.41
F10CAADCP	498±0.63	0.11 ± 0.56	4.13 ± 0.41	4.4± 0.05	97.02 ± 0.33
F11CAADCP	500±0.39	0.13 ± 0.22	4.20 ± 0.18	4.3± 0.02	95.27 ± 0.35
F12CAADCP	501±0.27	0.15 ± 0.13	4.27 ± 0.37	4.5± 0.06	98.14 ± 0.54
F13CADDCP	501±0.42	0.13 ± 0.18	4.09 ± 0.17	4.5± 0.02	98.25 ± 0.75
F14CADDCP	499±0.38	0.12 ± 0.24	4.46 ± 0.19	4.4± 0.03	96.25 ± 0.33
F15CADDCP	498±0.23	0.14 ± 0.28	4.19 ± 0.31	4.5± 0.01	97.22 ± 0.37
F16CAMDCP	499±0.39	0.12 ± 0.32	5.21 ± 0.19	4.5± 0.04	96.13 ± 0.91
F17CAMDCP	499±0.22	0.16 ± 0.18	4.02 ± 0.14	4.5± 0.02	99.46 ± 0.33
F18CAMDCP	500±0.08	0.13 ± 0.11	4.12 ± 0.18	4.4± 0.03	95.55 ± 0.18

**** represents Mean±SD, P<0.2 when compared with control***

Table 5- ***Buoyancy and floating time of gas generating floating tablets of cefuroxime axetil***

Formulation Code	Floating lag time (Sec))±SD*	Duration of floating (hrs))±SD*
F1CAAL	138±0.02	12±0.22
F2CAAL	131±0.39	12±0.16
F3CAAL	128±0.68	12±0.18
F4CADL	138±0.57	12±0.71
F5CADL	129±0.91	12±0.39
F6CADL	125±0.29	12±0.14
F7CAML	136±0.33	12±0.26
F8CAML	124±0.51	12±0.47
F9CAML	122±0.24	12±.015
F10CAADCP	122±0.16	12±0.98
F11CAADCP	120±0.79	12±0.31
F12CAADCP	116±0.51	12±0.69
F13CADDCP	118±0.39	12±0.45
F14CADDCP	116±0.17	12±0.39
F15CADDCP	115±0.11	12±0.21
F16CAMDCP	119±0.36	12±0.15
F17CAMDCP	113±0.48	12±0.69
F18CAMDCP	111±0.59	12±0.31

**** represents Mean±SD, P<0.5 when compared with control***

Table 6- ***Swelling index of formulations F1CAAL – F6CADL***

Time (hrs)	% Swelling index ± SD*					
	F1CAAL	F2CAAL	F3CAAL	F4CADL	F5CADL	F6CADL
	Albizia gussm with Lactose			Gum dammar with Lactose		
1	8±0.31	7.3±0.37	6.3±0.23	6.8.±0.22	6.2±0.41	5.1±0.14
2	15.1±0.25	13.3±0.24	11.02±0.65	10.2±0.30	9.5±0.36	9.31±0.20
3	21.3±0.31	19.2±0.47	15.5±0.33	17.60±0.12	15.13±0.16	13.3±0.53
4	24.7±0.42	22.8±1.2	19.1±0.37	21.2±0.36	18.17±0.33	17.20±0.24
5	28.1±0.36	26.5±0.54	23.6±0.48	25.6±0.17	23.4±0.27	21.1±0.42
6	33.6±0.33	29.3±0.17	27.1±0.46	29.5±0.28	26.1±0.38	25.3±0.20
7	38.1±0.29	35.7±0.15	32.5±0.42	36.31±0.17	34.1±0.29	30.22±0.31
8	46.7±0.30	40.8±0.49	36.0±0.56	43.2±0.13	39.1±0.42	34.3±0.21
9	51.9±0.55	45.4±0.65	41.3±0.69	46.06±0.24	41.2±0.19	37.9±0.09
10	57.6±0.85	49.1±0.05	46.7±0.25	49.22±0.19	45.6±0.31	42.3±0.30
11	61.1 ±0.41	55.3±0.54	51.0±0.35	54.11±0.33	51.2±0.42	47.11±0.41
12	73.5±0.63	68.3±0.75	65.5±0.51	58.20±0.63	55.1±0.53	52.09±0.31

* Represents Mean±SD (n=3), P<0.2 when compared with control

Table 7- Swelling index of formulations F7CAML– F12CAADCP

Time (hrs)	%Swelling index± SD*					
	F7CAML	F8CAML	F9CAML	F10CAADCP	F11CAADCP	F12CAADCP
	Moi gum with Lactose			Albizia Gum with DCP		
1	6.1±0.22	5.9±0.63	4.2±0.32	8.64±0.36	7.35±0.45	6.21±0.42
2	10.01±0.63	9.21±0.18	8.59±0.31	15.30±0.24	13.51±0.12	12.30±0.33
3	13.3±0.23	14.59±0.31	12.9±0.21	22.41±0.15	21.1±0.41	16.2±0.69
4	17.5±0.43	19.36±0.07	17.33±0.19	25.1±0.30	24.5±0.22	21.3±0.71
5	21.1±0.36	21.5±0.12	22.23±0.24	29.3±0.54	27.3±0.48	25.2±0.53
6	25.7±0.25	25.2±0.32	24.3±0.12	34.5±0.41	30.2±0.62	29.7±0.22
7	30.4±0.53	32.5±0.17	29.43±0.31	39.2±0.58	36.2±0.30	33.6±1.3
8	34.0±0.53	38.2±0.36	32.5±0.16	47.1±0.40	41.2±0.04	38.3±0.66
9	39.5±0.55	40.2±0.24	36.9±0.12	52.3±0.61	46.2±0.53	43.3±0.12
10	45.3±0.25	47.4±0.16	44.1±0.24	58.1±0.72	51.3±0.81	48.1±0.51
11	49.9±0.52	53.43±0.42	49.42±0.41	65.1±0.53	56.2±0.63	53.3±0.95
12	64.9±0.42	57.53±0.58	51.22±0.55	75.3±0.73	71.0±0.53	70.3±0.49

* represents Mean±SD (n=3), P<0.2 when compared with control

Table 8- Swelling index of formulations F13CADDCP – F18CAMDCP

Time (hrs)	%swelling index± SD*					
	F13CAD DCP	F14CAD DCP	F15CAD DCP	F16CAM DCP	F17CAM DCP	F18CAM DCP
	Gum dammar with DCP			Moi gum with DCP		
1	7.1±0.02	6.15±0.34	5.11±0.36	7.0±0.51	6.2±0.21	4.9±0.91
2	11.2±0.31	10.12±0.50	9.14±0.32	11.12±0.46	10.00±0.39	8.99±0.17
3	17.33±0.30	14.9±0.22	12.90±0.31	16.9±0.42	15.5±0.16	13.02±0.42
4	22.12±0.61	18.15±0.37	17.3±0.11	23.25±0.15	19.3±0.14	18.0±0.55
5	26.12±0.27	24.5±0.14	22.3±0.14	27.35±0.12	24.7±0.27	22.7±0.34
6	30.7±0.19	29.15±0.19	26.5±0.31	31.4±0.15	30.5±0.09	27.5±0.15
7	37.12±0.27	34.9±0.67	30.7±0.14	36.42±0.18	36.3±0.42	31.5±0.17
8	43.9±0.33	40.4±0.8	35.5±0.21	42.9±0.23	39.74±0.18	34.7±0.35
9	46.45±0.09	41.5±0.11	39.3±0.53	45.15±0.17	43.46±0.35	40.2±0.53
10	48.1±0.72	45.74±0.63	44.22±0.37	49.74±0.25	49.43±0.26	43.17±0.46
11	55.45±0.09	53.35±0.55	48.13±0.12	53.32±0.04	52.01±0.22	47.34±0.12
12	61.23±0.33	59.0±0.43	55.09±0.42	61.21±0.02	59.9±0.38	49.45±0.23

**** represents mean± SD (n=3), P<0.2 when compared with control***

Table 9 - ***Cumulative drug release profiles of F1CAAL- F9CAML formulations***

	Cumulati ve % drug release±SD*								
Time (hrs)	**F1CAAL**	**F2CAAL**	**F3CAAL**	**F4CADL**	**F5CADL**	**F6CADL**	**F7CAML**	**F8CAML**	**F9CAML**
1	9.6±0.11	10.3±0.21	11.21±0.3	9.6±0.03	10.5±0.04	12.6±0.34	6.6±0.12	10.5±0.16	12.6±0.12
2	18.6±0.27	19.2±0.68	20.1±0.21	20.7±0.14	23.9±0.16	27.5±0.18	10.7±0.48	11.9±0.23	17.5±0.29
3	24.3±0.19	30.6±0.49	35.6±0.25	29.6±0.05	31.2±0.33	39.2±0.13	19.6±0.31	23.2±0.54	29.2±0.81
4	40.6±0.31	46.6±0.26	48.6±0.49	40.5±0.23	42.6±0.41	51.6±0.87	30.5±0.16	32.6±0.62	35.6±0.47
5	53.6±0.43	56.1±0.15	60.8±0.11	49.7±0.31	50.9±0.48	62.5±0.61	39.7±0.31	40.9±0.11	42.5±0.19
6	69.6±0.51	71.6±0.47	79.2±0.25	58.6±0.05	61.7±0.57	74.3±0.55	48.6±0.24	51.7±0.37	54.3±0.15
7	74.2±0.87	80.5±0.21	86.4±0.16	69.3±0.16	72.5±0.99	80.3±0.39	59.3±0.36	62.5±0.65	66.3±0.50
8	76.1±0.93	90.2±0.13	92.6±0.78	78.9±0.74	80.5±0.01	86.5±0.57	68.9±0.48	77.5±0.69	89.5±0.32
9	81.3±0.37	95.1±0.81	99.6±0.43	87.3±0.26	88.3±0.10	93.7±0.48	77.3±0.60	87.5±0.03	99.7±0.25
10	86.3±0.41	99.2±0.21	-	94.2±0.31	97.5±0.14	99.9±0.51	84.2±0.72	92.5±0.55	-
11	90.1±0.65	-	-	96.5±0.45	99.5±0.43	-	86.5±0.25	-	-
12	95.2±0.52	-	-	99.2±0.16	-	-	89.2±0.31	-	-

**** represents mean± SD (n=3), P<0.1when compared with control***

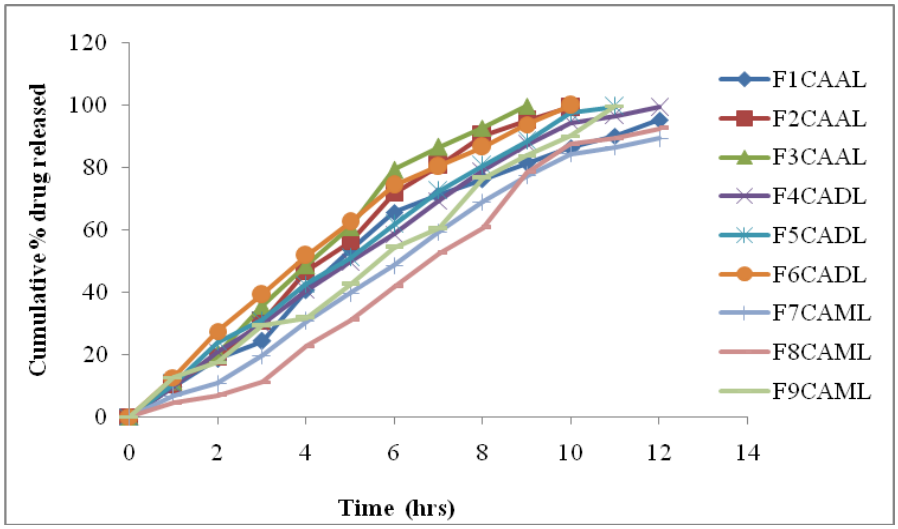

Figure 6- ***Drug release profiles of F1CAAL- F9CAML formulations***

Table 10- ***Cumulative drug release profiles of F10CAADCP- F18CAMDCP***

	Cumulative % drug release± SD*								
Time (hrs)	F10CA ADCP	F11CA ADCP	F12CA ADCP	F13CA DDCP	F14CA DDCP	F15CA DDCP	F16CA MDCP	F17CA MDCP	F18CA MDCP
1	2.3±0.012	3.6±0.21	4.7±0.22	4.3±0.25	3.8±0.12	4.5±0.11	3.7±0.06	2.8±0.14	2.5±0.31
2	5.9±0.36	7.4±0.15	9.5±0.34	7.9±0.36	7.1±0.16	9.7±0.23	7.9±0.31	6.9±0.29	10.7±0.42
3	11.2±0.41	11.9±0.25	15.6±0.46	14.2±0.13	11.2±0.54	15.9±0.3	10.2±0.13	11.7±0.40	17.9±0.53
4	15.6±0.99	15.8±0.23	21.9±0.57	19.6±0.41	15±0.36	21.6±0.17	15.6±0.52	14.9±0.53	20.6±0.21
5	20.9±0.31	23.5±0.37	26.8±0.68	26.9±0.33	23.1±0.39	26.2±0.33	18.9±0.16	17.1±0.61	25.2±0.68
6	25.1±0.57	29.1±0.19	33.2±0.13	31.1±0.58	29.6±0.57	33.8±0.29	21.1±0.32	23.6±0.73	31.8±0.31
7	30.5±0.19	36.8±0.05	39.5±0.57	36.5±0.24	37.2±0.19	39.1±0.1	26.5±0.27	27.2±0.81	37.1±0.25
8	35.8±0.21	43±0.21	47.1±0.38	41.8±0.16	43.5±0.15	47.5±0.38	31.8±0.65	33.5±0.93	42.5±0.41
9	41.7±0.13	50.2±0.65	54.2±0.19	48.7±0.13	56.9±0.25	54.8±0.29	38.7±0.21	46.9±0.87	50.8±0.35
10	47.3±0.57	56.9±0.39	62.8±0.17	54.3±0.51	64.5±0.31	62.2±0.11	44.3±0.61	54.5±0.91	58.2±0.22
11	50.9±0.51	60.2±0.38	66.2±0.13	58.6±0.49	68.6±0.68	69.4±0.39	49.2±0.75	59.2±0.28	62.5±0.45
12	54.3±0.44	63.5±0.23	70.3±0.1	63.4±0.58	73.2±0.39	75.6±0.12	53.4±0.32	63.2±0.90	69.6±0.51

**** represents mean± SD (n=3), P<0.1when compared with control***

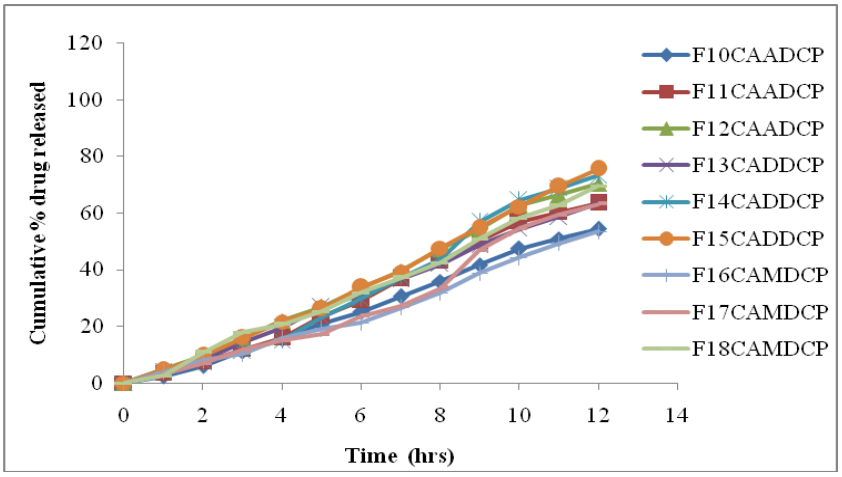

Figure 7- ***Drug release profiles of F10CAADCP- F18CAMDCP formulations***

Table 11- ***Release kinetics of optimized formulations***

S. No.	Formulation	Zero order	First order	Higuchi	Peppas
1	F4CADL	0.984	0.868	0.946	0.994

Figure 8- ***Graph showing Zero Order Drug Release***

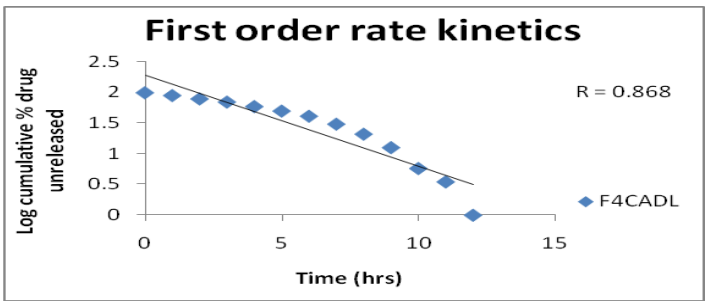

Figure 9- ***Graph showing First Order Drug Release***

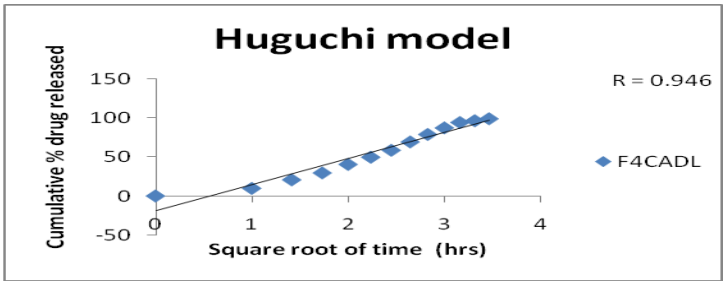

Figure 10- ***Graph showing Higuchi model***

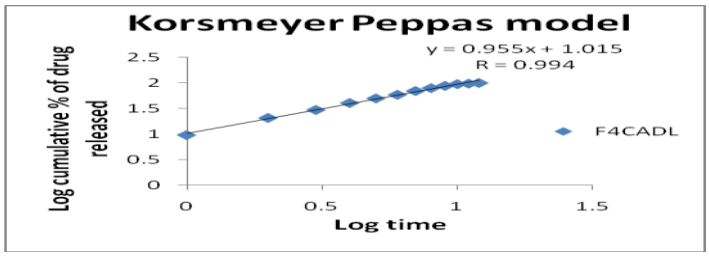

Figure 11- ***Graph showing Peppas model***

Table 12

Time	Mean plasma drug concentration (ng/ml) ±SD [n=6] P<0.1 when compared with control	
	F4CADL	PURE DRUG
1	2020.3±8.32	2253.6±0.36
1.5	3003.9±3.6	3160.1±0.96
2	3574.8±5.27	4658.3±1.23
2.5	3995.9±0.16	3568.8±0.33
3	4302.1±1.23	2215.6±0.33
3.5	2078.8±0.12	2068.8±0.13
4	1423.3±4.56	1986.2±0.16
6	611.7±0.69	1452.3±0.11
8	533.35±0.17	366.2±0.25
10	206.1±0.75	-
12	26.3±0.22	-

Mean plasma drug concentration (±S. D., n=6) profile of CA in Optimized formulations

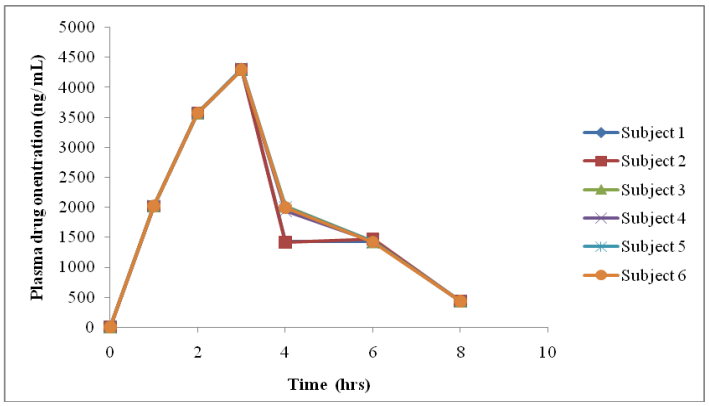

Figure 12 -Plasma profiles of pure drug cefuroxime axetil (R) from different subjects

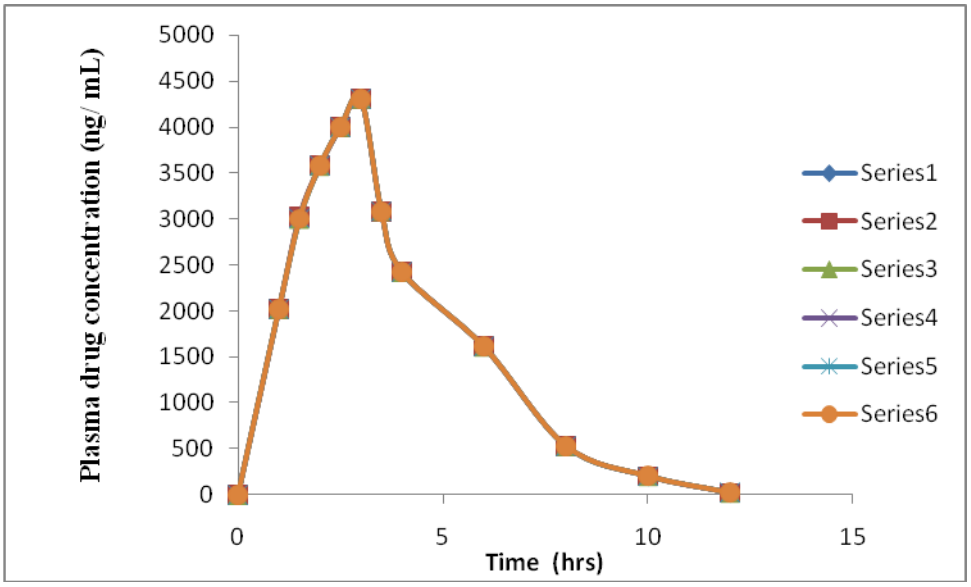

Figure -13: Plasma profiles of cefuroxime axetil SF4CADL (T) from different subject

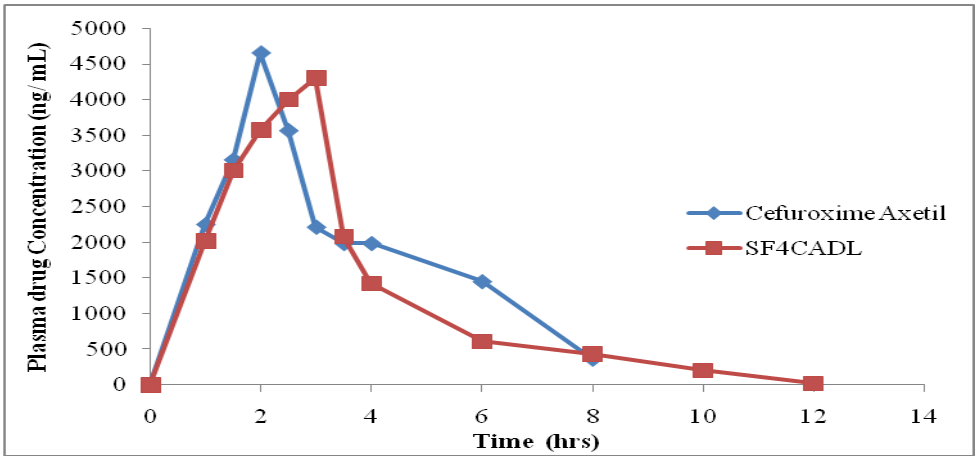

Figure -14: Comparative plasma profiles of cefuroxime axetil pure drug (R) with SF4CADL (T)

Table 13
Pharmacokinetic data of cefuroxime axetil Pure drug (R) and SF4CADL (T)

Pharmacokinetic Parameters	PURE DRUG	SF4CADL
tmax(h)	2±0	3±0
Cmax(ng/mL)	4658.3±1.23	4302.1±1.23
AUC_{0-t}(ng/mL.hr)	15270.55±14.5	14301.045±11.57
$AUC_{0-\infty}$(ng/mL.hr)	16564.542±15.3	14477.55±0.88
K_{el}(hr^{-}1)	0.239±0.66	0.149±0.61
$t_{1/2}$(hrs)	2.89±0.94	4.65±0.33

Table 14: Level A correlation for CA in SF4CADL

Time (hr)	Fraction of drug dissolved	Fraction of drug absorbed
1	0.088	0.507
2	0.215	0.870
3	0.312	0. 998
4	0.415	0.657
6	0.593	0.575
8	0.795	0.227
10	0.952	0.080
12	0.998	0.018

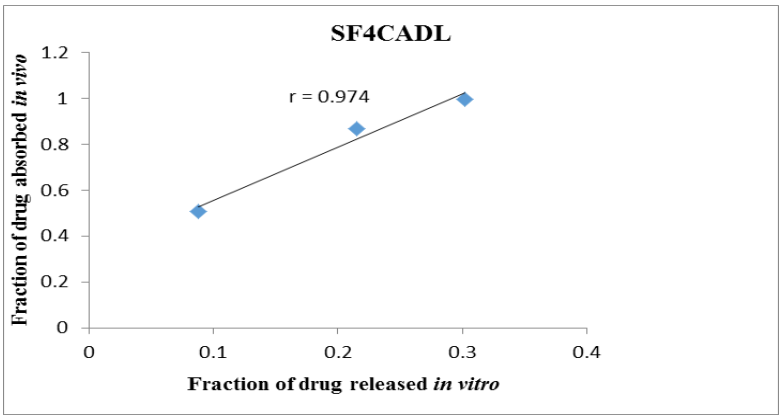

Figure 15- Plot of Fraction of drug released *in vitro* and Fraction of drug absorbed *In vivo* SF4CADL

Tables 13 show the kinetic data of cefuroxime axetil pure drug (R) and In-house formulation SF4CADL (T) respectively. The reference (R) reached the T_{max} in about 2 hrs. After reaching the T_{max} the drug starts elimination and the plasma concentration gradually decreased. In case of test (T) formulation the T_{max} achieved slowly and the drug availability was found for long time. The AUC_{0-t}, of the reference (R) was found to be 15270.55 ng.hrs/ mL. The increase in AUC_{0-t} was observed in the test (T) formulation, which were around 14301.045 ng.hrs/ mL. This clearly indicates the drug availability for long duration. Decrease in elimination rate constant (K_{el}) from 0.239 hrs^{-1} (R) to 0.149 hrs^{-1} (T) indicates the slow release rate of the drug in the body. There was a difference in T_{max} and C_{max} was observed when compared among individual subjects which may be due to the subjective variability. This was observed in both test and reference formulation it shows that SF4CADL good *in vivo* properties. It can be concluded from the above results that SF4CADL could achieve the required level A correlation. The data for linear correlation plot for Fraction of drug released *in vitro* and Fraction of drug absorbed *in vivo* at different time intervals is given in Table - 14 and plots are shown in Figure-15. An acceptable correlation was obtained with a good linear-fitting with correlation coefficients of 0.974 for SF4CADL. This kind of level A correlation is quite important since it represents a point-to-point relationship between *in vitro* dissolution and the *in vivo* input rate of the drug from the dosage form. Thus, an *in vitro* dissolution curve can serve as surrogate for *in vivo* performance. *In vitro* drug release studies of the optimized formulation F4CADL reveals that the drug release was showed up to 12 hours with zero order kinetics. For *in vivo* studies the tablets size was reduced to rabbit's dose. Drug release from the matrix tablets SF4CADL was higher when compared with the pure drug in healthy rabbits indicated by maintaining drug-plasma levels up to 12 hours. There was difference in AUC values for optimized formulations and pure drugs indicating significant difference in absorption. Thus indicating the drug release from matrix tablets was prolonged for 12 hours, therefore dammar gum can be used as rate controlling matrix polymer for cefuroxime axetil. A high IVIVC of level A observed supported the

CONCLUSION

In vitro drug release studies of the optimized formulation F4CADL reveals that the drug release was showed up to 12 hours with zero order kinetics. For *in vivo* studies the tablets size was reduced to rabbit's dose. Drug release from the matrix tablets SF4CADL were higher when compared with the pure drug in healthy rabbits indicated by maintaining drug-plasma levels up to 12 hours. There was difference in AUC values for optimized formulation and pure drug indicating significant difference in absorption. Thus indicating the drug release from matrix tablets was prolonged for 12 hours, therefore dammar gum can be used as rate controlling matrix polymer for cefuroxime axetil. A high IVIVC of level A observed supported the same.

Authors Contribution Statement: Authors are thankful for the laboratory facilities extended by shri Vishnu College of pharmacy, as well as college of pharmacy, Andhra University and Vagdevi college of pharmacy.

REFERENCES:

1. Streubel a, siepmann j, bodmeier r. Drug delivery to the upper small intestine window using gastroretentive technologies. Curr

Opin Pharmacol. 2006; 6(5):501–8. DOI: 10.1016/j.coph.2006.04.007

2. Patent Briefing. Drug Deliv. 2003; 10(3):221–2. DOI: 10.1080/713840405
3. Ridgway E, Stewart K, Rai G, Kelsey MC, Bielawska C. The phannacokinetics of cefuroxime axetil in the sick elderly patient. J Antimicrob Chemother. 1991; 27(5):663–8. DOI: 10.1093/jac/27.5.663
4. Marx MA, Fant WK. Cefuroxime Axetil. Drug Intell Clin Pharm. 1988; 22(9):651–8. DOI: 10.1177/106002808802200901
5. Sommers DK, Wyk M, Moncrieff J, Schoeman HS. Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil. Br J Clin Pharmacol. 1984;18(4):535–9. DOI: 10.1111/j.1365-2125.1984.tb02501.x
6. GK M. Cephalosporins: cefuroxime sodium and cefuroxime axetil. Bethesda, MD. Am Soc Hosp Pharm Inc. 2003; 11:152–9.
7. Finn A, Straughn A, Meyer M, Chubb J. Effect of dose and food on the bioavailability of cefuroxime axetil. Biopharm Drug Dispos. 1987; 8(6):519–26. DOI: 10.1002/bdd.2510080604
8. D. K. Formulation and evaluation of floating tablet of cefuroxime axetil. Int J Pharm Res Bio Sci. 2012; 1(5):184–92. Available from: http://www.ijprbs.com/issuedocs/2012/10/9-13-7-IJPRBS-159.11.pdf
9. Gudigennavar S. Development and evaluation of gastro-retentive drug delivery systems of cefuroxime axetil. African J Pharm Pharmacol. 2013; 7(20):1332–8. DOI: 10.5897/ajpp12.1211
10. Washington c. Pharmaceutical Dosage Forms: Parenteral Medications Volume 1, 2nd Edition: Edited by Kenneth E. Avis, Herbert A. Lieberman and; Leon Lachman. J Pharm Pharmacol. 1993; 45(3):240. DOI: 10.1111/j.2042-7158.1993.tb05544.x
11. Lachman L LH. The Theory and Practice of Industrial Pharmacy 3rd Edition. Varghese Publishing house; 1987. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jps.2600760125
12. United States Pharmacopoeia and National Formulary (2002). United States Pharmacopoeia, XXIII. Rockville: U.S.P Convention Inc
13. Patel K PK. Enhancement of Dissolution Rate of Domperidone Using Melt Granulation Technique. Sch Res Libr. 2011; 3(2):25–33. Available from: https://pdfs.semanticscholar.org/5bec/292cd2d7515ccf82a7e780755b631fd94e0b.pdf
14. Mohapatra S, KumarKar R, Mohapatra DK, Sahoo SK, Barik BB. Cefuroxime axetil loaded gastroretentive floating tabletsbased on hydrophilic polymers: preparation and in vitro evaluation. Brazilian Arch Biol Technol. 2012; 55(2):269–75. DOI: 10.1590/s1516-89132012000200013
15. Shende M. A ASC. Formulation and in-vitro evaluation of sustained release delivery of diltiazem hydrochloride through wax matrices. Int J Chem Tech Res. 2009; 1(4):889–97. Available from: https://www.semanticscholar.org/paper/Formulation-and-In-vitro-Evaluation-of-Sustained-of-AkareS.CBooruguR/14939d0ce34ad3dc1f2483678b05a3dcdf8faeb1
16. Abolfazal A JH. Formulation, Characterization and Physicochemical Evaluation of

Ranitidine Effervescent Tablets. Adv Pharm Bull. 2013; 3(2):315–22.

17. Ravi kumar M AW. Formulation and Evaluation of Sustained Release Matrix Tablet of a Model Drug. Asian J Chem Pharm Res. 2013; 1(1):1–12.
18. Martin A. Micromeretics, In: Martin A, Physical Pharmacy. Baltimores. Wilkins MdlW and, editor. 2001, 423-454 p. Available from: http://www.worldcat.org/title/martins-physical-pharmacy-and-pharmaceutical-sciences-physical-chemical-and-biopharmaceutical-principles-in-the-pharmaceutical-sciences/oclc/463631927
19. The United States Pharmacopoeia. Asian edit. 2004, 1359-1360 p. Available from: https://www.worldcat.org/title/united-states-pharmacopeia/oclc/779529991
20. Srinivas S.A. GA. Formulation and evaluation of Ondansetron HCL, directly compression mouth disintegrating tablets. IndianDrugs. 2006; 42(1):35–8.
21. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and in vitro evaluation. AAPS PharmSciTech. 2004; 5(2):77–82.
22. Patel VF, Patel NM. Statistical Evaluation of Influence of Xanthan Gum and Guar Gum Blends on Dipyridamole Release from Floating Matrix Tablets. Drug Dev Ind Pharm. 2007; 33(3):327–34.
23. Negi J, Kasliwal N, Jugran V. Development of non-effervescent floating matrix tablets based on Euryale ferox seeds. Asian J Pharm. 2011; 5(2):93. DOI: 10.4103/0973-8398.84549
24. Getyala A, Gangadharappa H, Prasad M, Reddy M, Kumar T. Formulation and Evaluation of Non-Effervescent Floating Tablets of Losartan Potassium. Curr Drug Deliv 2013; 10(5):620–9. DOI: 10.2174/1567201811310050013
25. Shende A AS. Formulation and in-vitro Evaluation of Sustained Release Delivery of Diltiazem Hydrochloride through Wax Matrices. Int J Chem Tech Res. 2009; 1(4):88-997. Availablefrom:https://www.researchgate.net/publication/288795164
26. Umasankar M SM. Formulation and evaluation of floating tablets of cefuroxime axetil. Int JPharm PharmSci .2013; 5(4):15661. Availablefrom:https://innovareacademics.in/journal/ijpps/Vol5Suppl4/7771.pdf
27. MadhusudanRao Y SKG. Formulation and Evaluation of Gastroretentive Floating Tablets of Cefuroxime Axetil. Int J Res Pharm Biomed Sci. 2012; 3(1):187–95.
28. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release. 1987; 5(1):37
29. Carstense JT. Drug stability: principle and practices, second edition. Marcel Dekker, New York, 1995, 538-550.
30. Sruti Jammula, Ch.Niranjan Patra, Suryakanta Swain, Kanhu Charan Panigrahi, Sabita Nayak, Subas Chandra Dinda & Muddana Eswara Bhanoji Rao (2015) Design and characterization of cefuroxime axetil biphasic floating minitablets, Drug Delivery. 2015; 22(1):125-135.
31. J-M. Cardotl, E. Beyssac and M.Alric. *In Vitro– In Vivo* Correlation: Importance Of Dissolution In IVIVC. Dissolution Technologies. 2007, 15-19.