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FORMULATION *IN VITRO* AND *IN VIVO* EVALUATION OF CEFUROXIME AXETIL FLOATING TABLETS USING NATURAL GUMS

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ABSTRACT

Floating tablets of Cefuroxime Axetil were prepared using Albizia gum, Dammar gum and Moi gum as polymers for controlling the drug release. Cefuroxime Axetil is a poorly water-soluble drug (second-generation cephalosporin) and its bioavailability is very low. The rate of absorption and the extent of bioavailability for such insoluble drug are controlled by the rate of dissolution in the gastrointestinal fluids. Two types of diluents were used and the drug release was compared. Pure drug and optimized formulation were subjected to the drug excipient compatibility studies using FTIR and DSC. The studies revealed that there was no interaction between the drug and excipients. In order to increase the drug release, channeling agents were introduced namely Lactose and DCP. Lactose is water soluble diluent and DCP is water insoluble diluent. All the formulations were taken and studied for the precompression parameters and found that they were within the limits. Precompression parameters were performed to all the formulations and were found to be in the acceptable limit which ensures the good flow properties. Formulation F4CADL containing gum dammar and lactose as channeling agent showed good results when compared with other formulations. The floating lag time of the optimized formulation was very short and the percentage of drug release at the end of 12 hours was found to be high. The drug release kinetics revealed that F4CADL follows Korsmeyer-Peppas and the mechanism was non-fickian diffusion. Optimized formulation was selected for *in vivo* studies by using albino rabbits. It was found that the tmax was extended for prolonged period of time.

KEY WORDS: ***Cefuroxime Axetil, DCP, Lactose, Albizia gum, Dammar gum and Moi gum***

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INTRODUCTION

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 *Haemophilus influenzae*, *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 ml, was taken separately and made up to 10ml with 0.1N HCl, to produce 5,10,15,20, 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[10, 11 and 12].

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

The flow properties of powders were determined by the angle of repose technique. Fixed funnel method was used to determine the angle of repose. In this method a powder funnel was fixed to a stand at a constant height (h) above the graph paper placed on a flat horizontal surface. The gum powder was carefully poured through the powder funnel until the

apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the pile was determined and the angle of repose (θ) was calculated by the following equation.

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

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

Bulk Density

20g of dry powder (M) was weighed and transferred into 100 mL measuring cylinder. The powder was carefully levelled without compaction and initial volume (V_O) was noted. The bulk density was calculated in grams per mL using the equation.

$$\text{Bulk Density} = M/V_o$$

Tapped Density

The required quantity of powder was weighed and transferred to the graduate measuring cylinder. Initial volume was noted and then the cylinder was tapped for about 100 times per minute from a height of 3 mm. The volume of powder was measured after each of the 100 drops until the difference between last two volume measurements is zero and the volume was noted as tapped volume (V_t). Tapped density was calculated by the following.

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

Where, M = Total mass of the powder and V_t = Tapped Volume

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 Axetilfloating tablets:

Cefuroxime Axetil (300 mg equivalent to 250 mg of cefuroxime base) was mixed with the required quantities of polymer (Albizia, Gum dammar and moi gum), sodium bicarbonate, lactose or dicalcium 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

The prepared floating tablets were evaluated for floating lag time and floating time, swelling index, uniformity of weight, hardness, thickness, friability, estimation of drug content and *in-vitro* drug release.

Tablet thickness

The average thickness and standard deviation were reported. The thickness of five randomly selected tablets from each formulation was measured individually by using vernier calipers.

Weight variation

According to IP, 20 tablets were taken randomly, weighed together and then individually for the determination of uniformity of weight of the tablets. The mean and standard deviation were determined[16, 17].

Tablet hardness

Tablet hardness has been defined as the force required in breaking a tablet in a diametric compression test. Five tablets were selected at random and the hardness of each tablet was measured on the Monsanto hardness tester

Friability

Tablets equivalent to the weight of 6.5 g were selected randomly from a batch and initial weight (w_0) was noted. They were placed in a Roche friabilator. The chamber was allowed to rotate 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were collected from the chamber, dedusted and weighed them (w). The loss in weight indicates the friability. Prepared tablets complies the test if the percentage of friability is within the pharmacopeia limit (< 1%).

$$f\ (\%) = \left(1 - \frac{w}{w_0}\right) \times 100$$

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 100 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 $37^{o}\pm 0.5^{o}$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 analyzed at 280 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve. [23, 24, 25] The data is 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 analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into 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.

$$F = K_0.t$$

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

$$\text{Log (100-F)} = kt$$

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,

$$F = k\,t^{1/2}$$

Where 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus 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_α) versus log (time) is linear. The data is shown in table 11 and figured in 8, 9, 10, and 11.

In vivo studies[29]

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 (SF4CADL). 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: 1263/CO/HCOP/S/014/CPCSEA.

STATISTICAL ANALYSIS

The data obtained were analyzed using Sigma Stat software (version 2.0). Student's (paired) t test was used for analysis of comparison. The data was presented as mean ± standard deviation (SD). Probability value (P) of less than 0.5 was considered significant.

RESULTS AND DISCUSSION

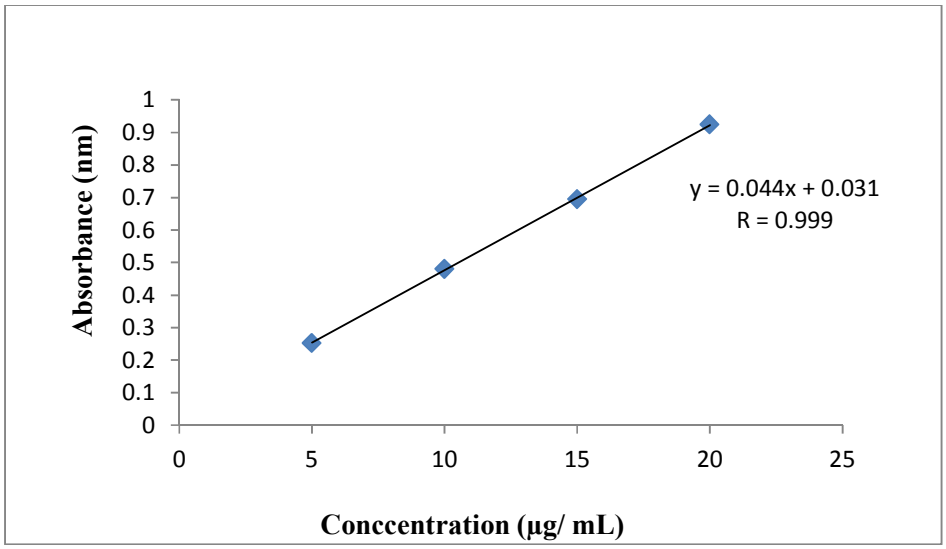

Figure 1
Standard plot of Cefuroxime Axetil

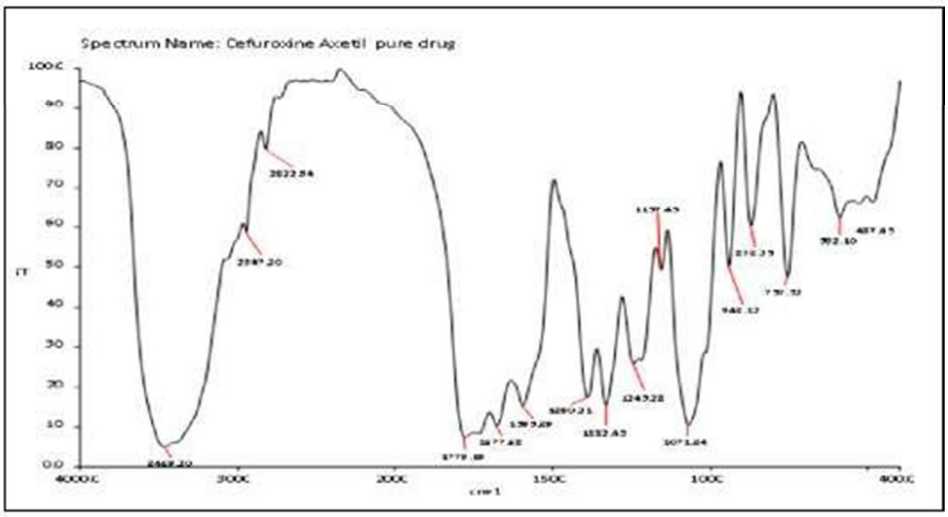

Figure 2
FTIR of Pure Cefuroxime axetil

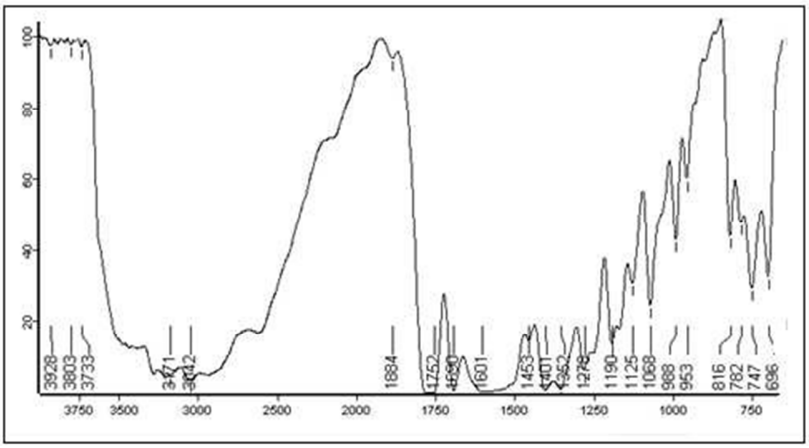

Figure 3
FTIR of Physical mixture of optimized formulation

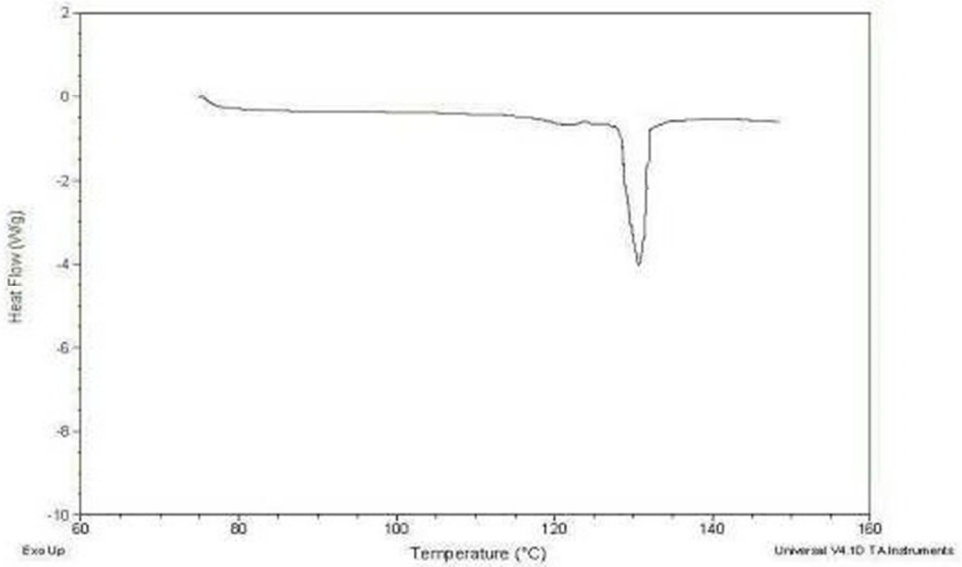

Figure 4
DSC of Pure Cefuroxime axetil

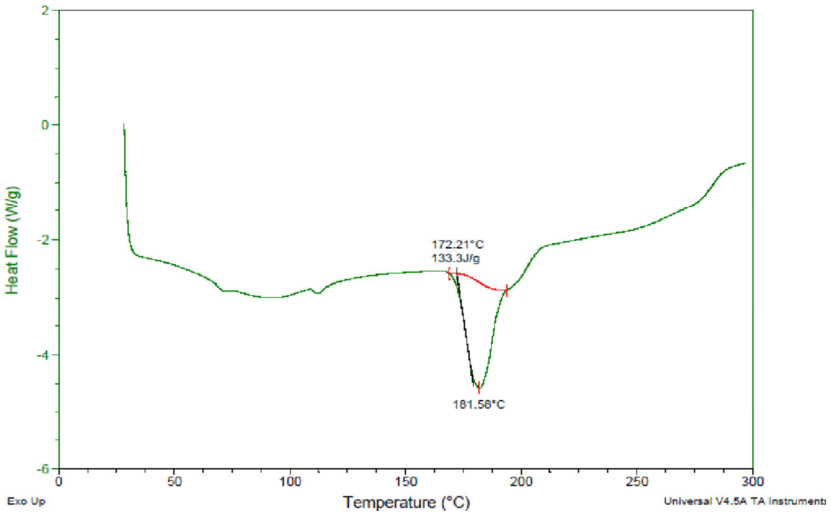

Figure 5
DSC of Physical mixture of optimized formulation

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
F9CAML	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: Dibasic calcium Phosphate; LC: Lactose; MGS= magnesium stearate; AG= Albizia gum; DG= Dammar gum; MG= Moigum; TC=Talc

Table 2
Preformulation results of cefuroxime axetil

Ingredients	Bulk density(gm/ml) ± SD*	Tapped density(gm/ml) ± 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 axetil gas generating floating formulations

Formulation	Bulk density(gm/ml) ± SD*	Tapped density(gm/ml) ± 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	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 gum 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	10.1±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	45.5±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±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*					
	F13CADDCP	F14CADDCP	F15CADDCP	F16CAMDCP	F17CAMDCP	F18CAMDCP
	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

	Cumulative % drug release±SD*								
Time	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***

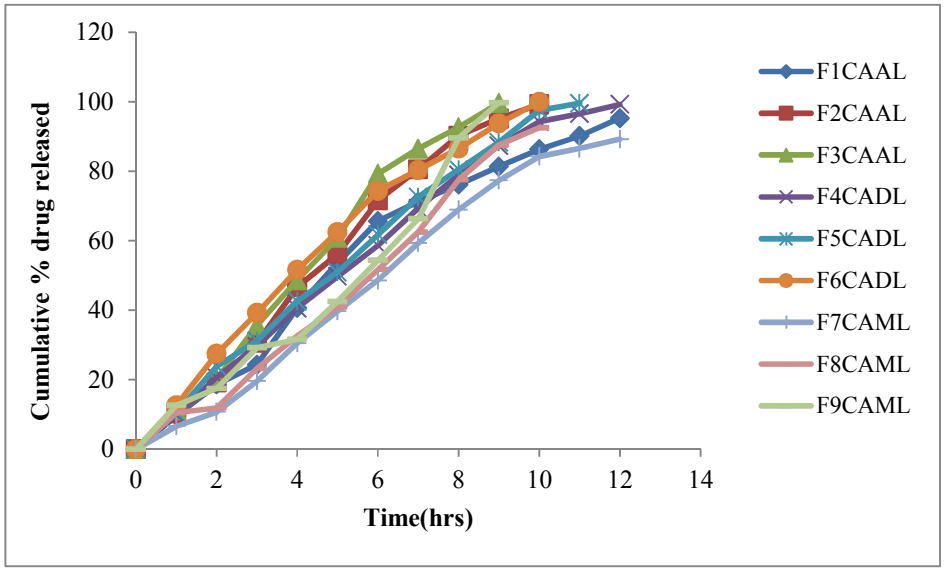

Figure 6
Drug release profiles of F1CAAL- F9CAML formulations

Table 10
Cumulative drug release profiles of F10CAADCP- F18CAMDCP

	Cumulative % drug release±SD*								
TIME (hrs)	**F10CAA DCP**	**F11CAA DCP**	**F12CAA DCP**	**F13CAD DCP**	**F14CAD DCP**	**F15CAD DP**	**F16CAM DCP**	**F17CAM DCP**	**F18CAM DCP**
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***

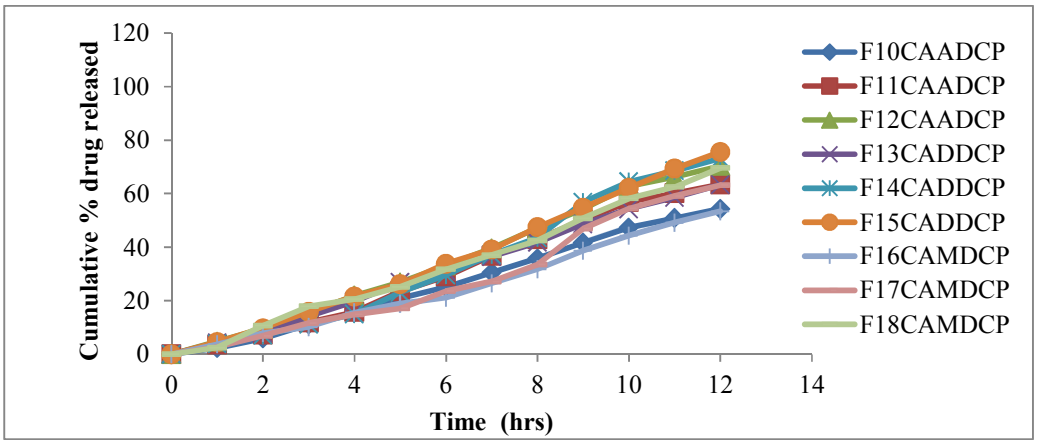

Figure 7
Drug release profiles of F10CAADCP- F18CAMDCP formulations

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

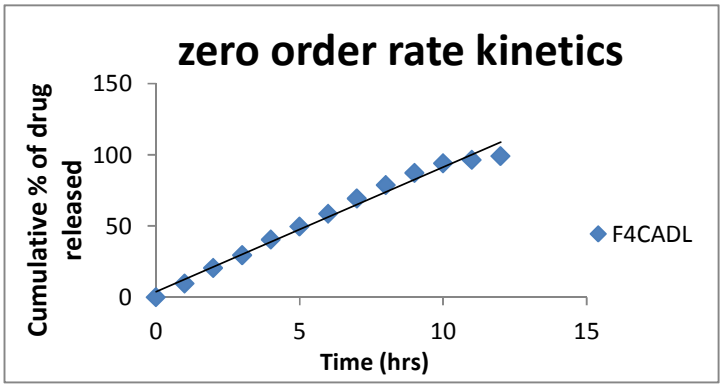

Figure 8
Graph showing Zero Order Drug Release

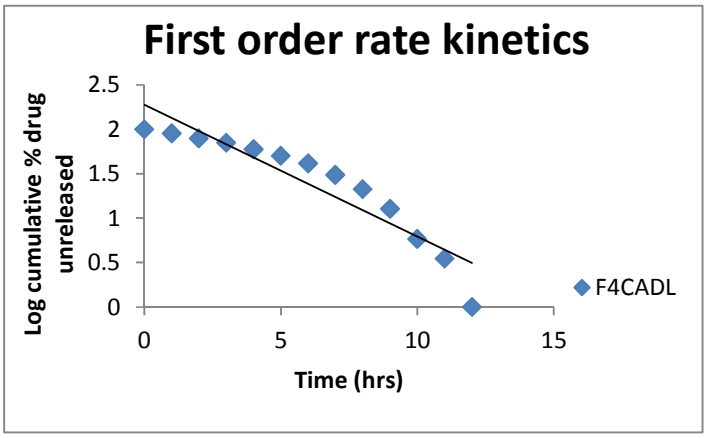

Figure 9
Graph showing First Order Drug Release

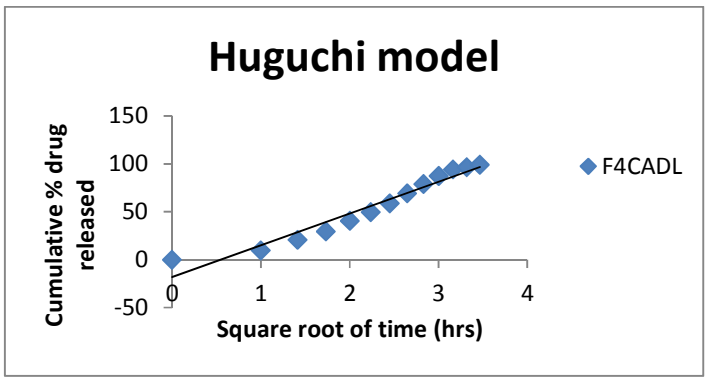

Figure 10
Graph showing Higuchi model

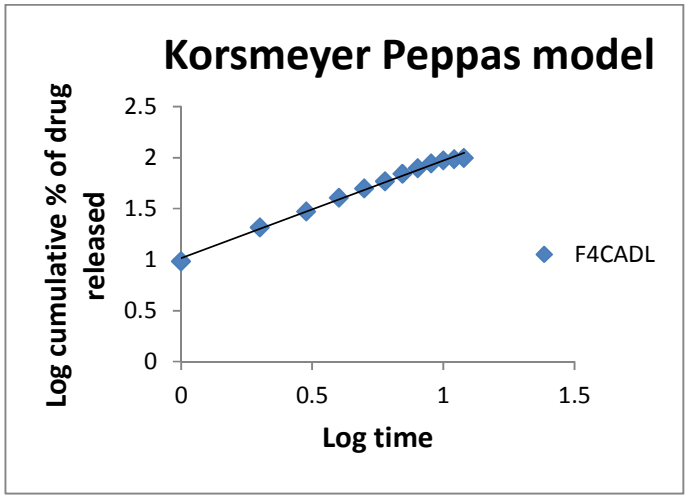

Figure 11
Graph showing Peppas model

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	3078.8±0.12	2068.8±0.13
4	2423.3±4.56	1986.2±0.16
6	1611.7±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

Table 13

Pharmacokinetic Parameters	PURE DRUG	SF4CADL
Tmax(hrs)	2±0	3±0
Cmax(ng/mL)	4658.3±1.23	4302.1±1.23
AUC_{0-t}(ng.hrs/mL)	15270.55±14.5	18820.39±11.57
$AUC_{0-\infty}$(ng.hrs/mL)	16802.767±15.3	18932.305±0.88
$K_{el}(hrs^{-1})$	0.283±0.66	0.235±0.61
$t_{1/2}$(hrs)	2.44±0.94	2.95±0.33

DISCUSSION

The IR spectra of pure drug (Cefuroxime axetil) showed the characteristic absorption peaks at 1677 cm^{-1} indicates the presence of C=O. Strong absorption band at 3469cm^{-1} belonging to the amine group (N-H) characteristic band at 2947cm^{-1} (C-H) . The IR spectra of physical mixture of optimized formulation also showed the above mentioned bands of Cefuroxime Axetil. So it was concluded that there was no interaction. DSC studies were also performed for pure drug and optimized formulation and found that there were no changes produced in the exothermic and endothermic curves as shown in Figs. 2,3,4,5. The precompression parameters were done by the procedure .The results were illustrated in the table 3. Angle of repose values were found to be within the range from 22.24±0.24 to 29.23±0.52. This indicated that powder blend had good flow property. The bulk density values were in the range 0.42±0.37 to 0.59±0.49. Tapped density values were found to be within the range from 0.52±0.14 to 0.68±0.19 respectively. Compressibility index shows the values between 11.62±0.16 to 15.87±0.14. This indicates that the Compressibility index in the range 12-16 shows good flow property. The Hausner's ratio values were found to be within the range from 1.08±0.03 to 1.18±0.02. This indicated that Hausner's ratio index between the range 1 to1.2 shows powder blend having good flow property. The formulated floating tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 498±0.23 to 501±0.42. The % deviation was within 5 % range this is due to the presence of difference in quantity of polymer. The hardness of the prepared tablets was ranged from 4.02 ± 0.14 to 5.21 ± 0.19, friability values were ranged from 0.11± 0.14 to 0.19 ± 0.22 which fallen within the limit of standard (0.1 to 0.9%). Drug content of tablets was ranged from 85.61 ± 0.70 to 99.94 ± 0.41, F15CADDCP showed maximum drug content. Thickness of tablets was uniform and values are ranged from 4.3± 0.02 to 4.5± 0.04. Further, the formulated tablets on immersion in 0.1N Hydrochloric acid 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 carbondioxide 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. 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 hour, 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. The *in vitro* dissolution testing was performed and the results of the formulations were expressed. The release of Cefuroxime Axetil as studied using USP dissolution apparatus II. The dissolution media were 900 ml 0.1 N HCl maintained at 37 ± 0.5^0C with rotation speed of 50 rpm. Aliquots of 5 ml was collected at predetermined time intervals and replenished with equivalent volume of fresh medium. The samples were diluted to a suitable concentration with 0.1N HCl and were analyzed by using UV/VIS double beam spectrophotometer at 280 nm. The results are expressed as mean±S.D(n=3). In *in-vitro* dissolution study of formulations F1CAAL, F2CAAL and F3CAAL, prepared with ALBIZIA GUM with LACTOSE were done in 0.1 N HCl and the 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 h) but in case of formulation F1CAAL 95.2% of the drug was released in 12 hrs. All these three formulations floated for 12 hrs. Formulations F2CAAL and F3CAAL were failed to drug release profile. *In vitro* dissolution study of formulations F4CADL, F5CADL and F6CADL were also done in 0.1N HCl and the drug released was calculated. These three formulations prepared with GUM DAMMAR with lactose and the 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 in 12 hrs, this was considered due to different polymer concentrations in all the three formulations. All these three formulations floated for 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 sec, for these reasons, it was considered as best formulation among all the four formulations. *In vitro* dissolution study of formulations F7CAML, F8CAML and F9CAML were also done in 0.1N HCl and the percent drug released was calculated. These three formulations prepared with MOI GUM with lactose and the 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 in 12 hrs, this was considered due to different polymer concentrations in all the three formulations. All these three formulations floated for 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 formulations F10CAADCP, F11CAADCP and F12CAADCP prepared with ALBIZIA GUM with diluents DCP were done in 0.1N HCl and the 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 also done in 0.1N HCl and the percent drug released was calculated. The formulations prepared with GUM DAMMAR with DCP as diluent, and the 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 also done in 0.1N HCl and the drug released was calculated. These three formulations 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 gums (ALBIZIA GUM, GUM DAMMAR and MOI GUM) with diluents 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 filler 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 decrease in the drug release when the DCP was used as filler. The results showed that there is 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 mean peak plasma concentration of test (T) formulation C_{max} 4302.1 ng/ml^{-1} 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. 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 was around 18820.39 ng.hrs/mL. This clearly indicates the drug availability for long duration. Decrease in elimination rate constant (K_{el}) from 0.283 hrs^{-1} (R) to 0.235 hrs^{-1} (T) indicates the slow release rate of the drug in the body. The plasma elimination half -life ($t_{1/2}$) of the reference (R) and test (T) formulations were 2.44 hrs and 2.95 hrs respectively, which were significantly different. Thus the prolonged $t_{1/2}$ is another indication on the *in-vivo* performance of the floating tablets.

There is 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 formulations. The overall C_{max}, T_{max}, AUC_{0-t}, K_{el} and $t_{1/2}$ were completely different between both test and reference formulation. Therefore the prepared formulation was releasing the drug for a prolonged period of time. From this, best formulation from the each polymer (ALBIZIA GUM, GUM DAMMAR and MOI GUM) was found to be F4CADL respectively.

CONCLUSION

Floating tablets were successfully prepared using different gums in various ratios by direct compression method. Among all the formulations, F4CADL was considered to be most promising for controlled release of Cefuroxime Axetil up to 12 hours when compared with other formulations.

AUTHORS CONTRIBUTION STATEMENT

All authors contributed equally in conceiving the presented idea, investigated and supervised the finding of the work. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST

With the findings of the present investigation, it is possible to transfer the utilized technology to commercial scale by: Scaling up the formula according to the industrial needs and performing clinical trials to demonstrate their safety and efficacy.

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