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Formulation *in vitro* and *in vivo* evaluation of floating tablets of cephalexin using natural polymers

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Abstract
Floating tablets of cephalexin were prepared using Albizia gum, Dammar gum and Moi gum as polymers for controlling the drug release. Cephalexin is a semisynthetic antibiotic derived from cephalosporin C and is almost completely absorbed from the gastrointestinal tract with a bioavailability of 95%. Cephalexin has a half-life of around 1.1 hour. To maintain the therapeutic range, the drug should be administered three to four times a day. Addressing this problem, we attempted to formulate floating tablets of cephalexin, which can provide a constant effective drug level for 12 hours, based on calculations considering pharmacokinetic parameters. 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 increase the drug release channeling agents were introduced namely Lactose and DCP. Precompression parameters were performed to all the formulations and were found to be in the acceptable limit which ensures the good flow properties. Formulation F4CPDL containing gum dammar and lactose as channeling agent showed good results when compared to other formulations. The floating lag time of the optimized formulation was very short and the percentage of drug release at the end of 12hours was found to be high. The drug release kinetics revealed that formulation F4CPDL follows Zero order. *In vivo* studies were conducted on rabbit and pharmacokinetic parameters of the optimized formulation were evaluated using HPLC method. It was found that floating tablets showed increased t1/2 and decreased Kel. The design signified that the drug release rate from tablets was influenced by the small proportion of polymer mixture and it controlled medicament release upto 12 hrs effectively.

Keywords: cephalexin, Albizia gum, dammar gum, Moi gum, DCP, lactose

1. Introduction
Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Extended-release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance [1]. By incorporating the dose for 24 hrs into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented [2]. This helps to avoid the side-effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy. In biopharmaceutics, scientists generally are faced with an engineering problem; to develop drug delivery systems that hit a desired target. The target in pharmacokinetics is generally a plasma/blood drug concentration that lies between the minimum effect concentration (MEC) and minimum toxic concentration (MTC). Cephalexin is a semisynthetic antibiotic derived from cephalosporin C and is almost completely absorbed from the gastrointestinal tract with a bioavailability of 95%. Cephalexin has a half-life of around 1.1 h [3-5]. To maintain the therapeutic range, the drug should be administered three to four times a day, which leads to saw tooth kinetics resulting in ineffective therapy [6]. Addressing this problem, we attempted to formulate extended- release floating tablets of cephalexin, which can provide a constant effective drug level for 12 hours.

Table 1: Standard curve for Cephalexin Floating Tablets

S. No.	Concentration	Absorbance
1	0.000	-0.000
2	5.000	0.190
3	10.000	0.375
4	15.000	0.585
5	20.000	0.765
6	25.000	0.958

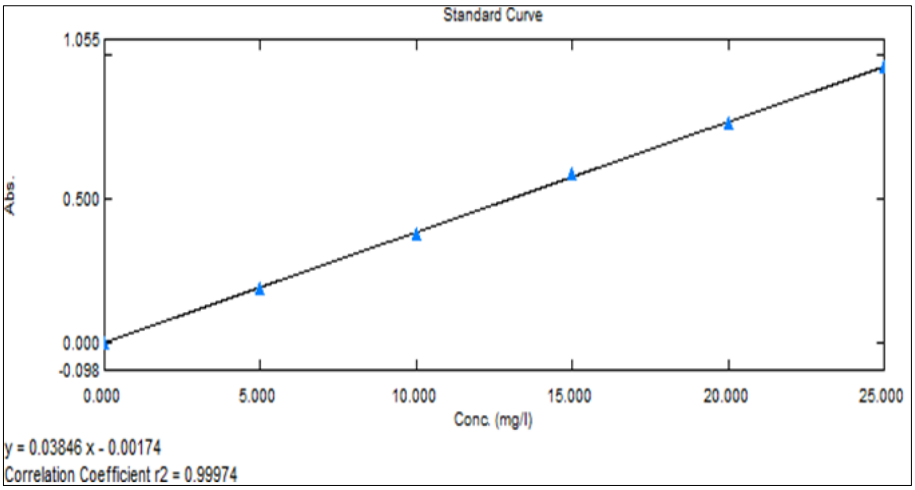

Fig 1: Standard plot of Cephalexin

2. Preformulation studies of cephalexin floating tablets the pure drug and excipients were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio [7, 8, 9].

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.

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

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

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

Bulk density=M/V

Tapped Density: Pure drug were poured into 100ml 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.

Tapped density= M/V

Where, M = initial weight of material in gm, V= volume of material after tapping.

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.

$$\text{Compressibility index} = \frac{100 \text{ x (Bulk density} - \text{Tapped density)}}{\text{Bulk density}}$$

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

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

2. Preparation of cephalexin floating tablets

Cephalexin 500mg was mixed with the required quantities of natual gums (Albizia, Gum dammar and moi), sodium bicarbonate, lactose and 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, Ahmedabad, India) using a diameter of 12-mm standard flat-face punches [10, 11, 12].

3. Evaluation of floating tablets

Evaluation was performed to assess the physicochemical properties [13, 14] and release characteristics of the developed formulations. Tablet thickness, Weight variation, Hardness and Friability parameters were evaluated.

Tablet thickness

The thickness in millimeters (mm) was measured individually for 5 pre weighed 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.

Tablet hardness

Tablet hardness was measured using a Monsanto hardness

tester. The crushing strength of the 5 tablets with known weight and thickness of each was recorded in kg/cm2 and the average hardness and standard deviation was reported.

Friability
Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

Content uniformity [15, 16]
The formulated cephalexin 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 278 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating Test
The *in vitro* buoyancy was determined by floating lag time, as per the method described. Here, 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) [17, 18].

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 37o $\pm$ 0.5oc, 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 (%WU).

$$\%WU = (W_t - W_o) * 100 / W_o$$

Where W_t is the weight of the swollen tablet and W_o is the initial weight of the tablet.

4. 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 [21, 22, 23].

- **Zero order release rate kinetics:** To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F= K_o.t$$

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

$$Log (100-F) = kt$$

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,

$$F = k\ t1/2$$

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,

$$M_t / M_\square = K.tn$$

'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 ($M_t/M_\square$) versus log (time) is linear.

5. *In vitro* drug release studies
The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 60, 120 and 180, 240, 300, 360, 420, 480, 540,600, 660, and 720minutes. 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, & the mean values were plotted versus time. Each sample was analyzed at 256 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve [24, 25, 26].

6. *In vivo* evaluation of cephalexin floating tablets
Bio analytical method was developed for the estimation of cephalexin in rabbit plasma by RP-HPLC. The same method was used for the estimation of cephalexin in the present work with some slight modifications[27]. RP-HPLC (Shimadzu model SPD-M20A 230V) system composed of a LC-20AD pump, a SPD-M20A UV detector, an ODS C-18 column (150 mmx4.6 mm I.D., 5µm particle size) 25µL Hamilton injection syringe was used. The mobile phase consisted of phosphate buffer: acetonitrile (60:40 v/v, pH 4.0 was adjusted by using 0.1% orthophosphoric acid). ODS C-18 (150 mm X 4.6 mm I.D., 5 µm particle size) column was used for analysis and mobile phase was pumped with a flow rate of 1.2 mL/min. Detection was carried out by using UV detector at a wavelength of 256 nm. 500 µl of mobile phase were used for the preparation of each sample and vortexed for 30 sec; and then 20 µl of it was injected into the HPLC system. Calibration curve was plotted by using a concentration range of 50-3000 ng/ml of cephalexin; and showed linearity in between the concentration of cephalexin and its peak area (R=0.992).The optimized floating tablets were further evaluated for their pharmacokinetic parameters. The pharmacokinetic study protocol was approved by the 1263/CO/HCOP/S/014/CPCSEA.

Six male adult rabbits weighing about 2.5 to 3.5 kg range were selected for the study. Food was withdrawn from the rabbits 12 hrs before drug administration and until 12 hrs post dosing, but they had free access to water throughout the study. The study was conducted as parallel design in which a single dose was administered to rabbits orally. The animals were divided into 2 groups containing 3 animals in each. For one group pure cephalexin was given with water and for another group matrix tablet was given. at 1.0, 1.5, 2.5, 3, 3.5, 4, 6, 8, 10 and 12hrs, blood samples were collected from the marginal ear vein of rabbit by syringe; and then the collected samples were centrifuged for 10 minutes at 2500-3500 rpm using Micro centrifuge (Remi Equipment, Mumbai, India). Immediately after centrifugation, samples were stored in refrigeration condition until the analysis was performed. Safety aspects were evaluated by monitoring adverse effects and vital symptoms and through physical examination.

7. Results and Discussion

The study started with calibration curve of cephalexin. The λ_{max} of Cephalexin in 0.1N HCl was scanned and found to have the maximum absorbance at 256 nm. Standard graph of cephalexin in 0.1N HCl was plotted by taking concentration ranging from 5 to 25 µg/ml and a good correlation was obtained with R2 value of 0.99974.

Table 2: Formulation composition of gastro retentive tablets of cephalexin

CODE	CP	SBC	A	D	M	MGS	L	DCP	TC
F1CPAL	500	60	80	-	-	5	50	-	5
F2CPAL	500	60	55	-	-	5	75	-	5
F3CPAL	500	60	30	-	-	5	100	-	5
F4CPDL	500	60	-	80	-	5	50	-	5
F5CPDL	500	60	-	55	-	5	75	-	5
F6CPDL	500	60	-	30	-	5	100	-	5
F7CPML	500	60	-	-	80	5	50	-	5
F8CPML	500	60	-	-	55	5	75	-	5
F9CPML	500	60	-	-	30	5	100	-	5
F10CPADCP	500	60	80	-	-	5	-	50	5
F11CPADCP	500	60	55	-	-	5	-	75	5
F12CPADCP	500	60	30	-	-	5	-	100	5
F13CPDDCP	500	60	-	80	-	5	-	50	5
F14CPDDCP	500	60	-	55	-	5	-	75	5
F15CPDDCP	500	60	-	30	-	5	-	100	5
F16CPMDCP	500	60	-	-	80	5	-	50	5
F17CPMDCP	500	60	-	-	55	5	-	75	5
F18CPMDCP	500	60	-	-	30	5	-	100	5

Note: CP=Cephalexin; A=Albizia gum; D=Dammar gum; M=Moi gum; L=Lactose; DCP=Dibasic calcium phosphate; MGS=Magnesium stearate; SBC=Sodoum bicarbonate; T=Talc

Table 3: Preformulation results of cephalxein floating tablets

Ingredients	Bulk density (gm/ml) ± SD*	Tapped density (gm/ml) ± SD*	Compressibility index (%)± SD*	Hausner's ratio± SD*	Angle of repose (°) ± SD*
Cephalexin	0.426±0.23	0.624±0.19	17.84±0.13	1.16±0.15	27.46±0.15
Lactose	0.741±0.45	0.888±0.54	13.22±0.14	1.14±0.01	16.32±0.29
Dicalcium 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	24.57±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

Angle of repose for all formulations were examined. The values were found to be within the range from 20.27±0.34 to 27.15±0.14. Angle of repose 25-30o shows good flow property. Tapped density values were found to be within the range from 0.46±0.21 to 0.67±0.12 respectively. Compressibility index shows the values between 10.15±0.12 to 14.33±0.13this indicates that the Compressibility index in the range 12-16 shows good flow property. The Hauser's ratio values were found to be within the range from 1.02±0.03 to 1.14±0.03.This indicated that powder blend having free flow property.

Table 4: Pre compression parameters of the cephalaxein 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*
F1CPAL	0.54±0.33	0.62±0.15	11.33±0.14	1.10±0.08	23.20±0.54
F2CPAL	0.58±0.12	0.67±0.12	10.88±0.12	1.12±0.02	22.12±0.35
F3CPAL	0.50±0.16	0.61±0.19	12.25±0.16	1.14±0.04	27.15±0.14
F4CPDL	0.46±0.11	0.54±0.21	13.16±0.13	1.05±0.05	24.21±0.72
F5CPDL	0.48±0.14	0.52±0.15	12.27±0.15	1.04±0.02	20.27±0.34
F6CPDL	0.44±0.11	0.50±0.24	12.20±0.17	1.12±0.04	21.31±0.13
F7CPML	0.52±0.15	0.56±0.14	13.51±0.14	1.10±0.02	25.26±0.11
F8CPML	0.50±0.11	0.54±0.17	12.24±0.16	1.12±0.04	22.28±0.16
F9CPML	0.46±0.04	0.50±0.19	11.54±0.15	1.04±0.06	21.17±0.36
F10CPADCP	0.47±0.25	0.51±0.37	11.22±0.13	1.05±0.06	24.22±0.33
F11CPADCP	0.48±0.28	0.54±0.14	13.25±0.18	1.12±0.02	21.36±0.25
F12CPADCP	0.44±0.36	0.52±0.35	12.44±0.17	1.13±0.03	21.32±0.58
F13CPDDCP	0.43±0.23	0.51±0.15	10.15±0.12	1.14±0.03	22.47±0.47
F14CPDDCP	0.43±0.16	0.52±0.16	13.52±0.15	1.10±0.05	21.37±0.59
F15CPDDCP	0.40± 0.12	0.46±0.21	12.11±0.19	1.12±0.07	22.24±0.32
F16CPMDCP	0.54±0.19	0.61±0.22	14.33±0.13	1.09±0.02	22.22±0.12
F17CPMDCP	0.43±0.16	0.52±0.15	12.17±0.16	1.05±0.05	21.33±0.34
F18CPMDCP	0.46±0.12	0.54±0.30	13.24±0.12	1.02±0.03	22.15±0.22

Table 5: Post compression parameters of gas generating tablets of cephalexin

Formulation Code	Weight(mg)±SD*(n=20)	Friability(%)±SD* (n=20)	Hardness(Kg/Cm2) ±SD*(n=5)	Thickness(mm) ±SD*(n=5)	Drugcontent(%) ±SD* (n=10)
F1CPAL	700.0± 1.42	0.48± 0.16	4.50 ± 0.14	4.6± 0.52	96.73 ± 0.05
F2CPAL	701.0± 0.68	0.32 ± 0.02	5.20 ± 0.30	4.6± 0.37	95.53 ± 0.08
F3CPAL	700.0± 1.02	0.47±0.12	4.90 ± 0.19	4.9± 0.58	95.12 ± 0.13
F4CPDL	700.0± 1.18	0.22±0.06	5.00 ± 0.33	4.7± 0.52	96.01 ± 0.07
F5CPDL	699.0± 0.79	0.49±0.14	4.50 ± 0.21	4.8± 0.57	96.33 ± 0.11
F6CPDL	698.0± 0.63	0.49±0.25	5.10 ± 0.15	4.7± 0.85	95.79 ± 0.13
F7CPML	698.0± 0.49	0.51±0.13	5.00 ± 0.34	4.8± 0.19	98.34 ± 0.35
F8CPML	699.0± 0.33	0.17±0.08	5.00 ± 0.27	4.7± 0.22	96.45 ± 0.55
F9CPML	700.0± 0.60	0.63±0.07	4.50 ± 0.18	4.8± 0.54	97.76 ± 0.02
F10CPADCP	700.0± 0.81	0.33±0.16	4.65 ± 0.43	4.7± 0.52	93.34 ± 0.23
F11CPADCP	699.0± 0.45	0.45±0.11	4.50 ± 0.47	4.9± 0.59	96.28 ± 0.08
F12CPADCP	698.0± 1.33	0.25±0.16	4.50 ± 0.34	4.8± 0.61	95.37 ± 0.15
F13CPDDCP	699.0± 0.59	0.35±0.13	4.32 ± 0.61	4.6± 0.52	92.61 ± 0.23
F14CPDDCP	700.0± 0.75	0.73±0.54	4.21 ± 0.22	4.8± 0.47	93.35 ± 0.35
F15CPDDCP	700.0± 0.12	0.33±0.19	4.49 ± 0.27	4.9± 0.20	96.27 ± 0.41
F16CPMDCP	700.0± 0.45	0.17±0.03	5.21 ± 0.44	4.9± 0.25	91.25 ± 0.09
F17CPMDCP	699.0± 0.89	0.51±0.05	4.81 ± 0.47	4.7± 0.52	93.48 ± 0.34
F18CPMDCP	701.0± 0.33	0.50±0.11	4.36 ± 0.22	4.8± 0.25	95.77 ± 0.15

* All values are expressed as Mean±SD

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 701.0± 0.68 to 698.0±0.49. The % deviation was coming within 5 % range. For 700mg tablet the accepted % deviation should be 5 %. F1CPAL-F18CPMDCP batches came within limit and passed the test.

Hardness of the tablet was fixed 4-5 kg/cm2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because; the effect of polymer concentration is the only area of interest. The hardness of the prepared tablets was ranged from 4.21 ± 0.22 to 5.21 ± 0.44.

Friability values were ranged from 0.17 ± 0.03 to 0.73± 0.54 which fallen within the limit of standard (0.1 to 0.9%). Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion.

Drug content of tablets was ranged from 91.25 ± 0.09 to 98.34 ± 0.35. F7CPML showed maximum drug content. Thickness of tablets was uniform and values are ranged from 4.6± 0.37 to 4.9± 0.59.

Table 6: Floating properties of cephalexin tablets

Formulation Code	Floating lag time (Sec)	Duration of floating (hrs)
F1CPAL	140±0.23	>12±0.05
F2CPAL	129±0.65	>12±0.25
F3CPAL	127±0.33	>12±0.53
F4CPDL	136±0.37	>12±0.45
F5CPDL	130±0.48	>12±0.73
F6CPDL	127±0.46	>12±0.25
F7CPML	135±0.42	>12±0.41
F8CPML	124±0.56	>12±0.65
F9CPML	125±0.69	>12±0.33
F10CPADCP	122±0.25	>12±0.24
F11CPADCP	118±0.35	>12±0.49
F12CPADCP	116±0.51	>12±0.65
F13CPDDCP	119±0.45	>12±0.29
F14CPDDCP	118±0.33	>12±0.33
F15CPDDCP	116±0.49	>12±0.16
F16CPMDCP	123±0.56	>12±0.29
F17CPMDCP	112±0.64	>12±0.36
F18CPMDCP	113±0.55	>12±0.45

Further, the formulated tablets on immersion in 0.1N Hydrochloric acid media they remain buoyant for 12 h with lag time of 112 to 140 seconds. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized 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. All the batches showed good *in vitro* buoyancy.

Table 7: Swelling index of formulations F1CAPL – F6CPDL

Time (hrs)	%swelling index ±SD*					
	F1CPAL	F2CPAL	F3CPAL	F4CPDL	F5CPDL	F6CPDL
	Lactose			Lactose		
1	10.37±0.52	10.21±0.64	9.35±0.25	6.27±0.34	6.59±0.55	5.31±0.23
2	16.23±0.11	15.30±0.66	14.23±0.67	9.56±0.44	9.81±0.57	7.41±0.16
3	21.27±0.84	20.25±0.55	19.23±0.11	14.71±0.52	14.67±0.50	12.41±0.91
4	26.28±0.25	25.29±0.31	23.20±0.56	20.23±0.37	19.44±0.63	17.32±0.64
5	32.15±0.33	29.23±0.63	28.16±0.41	23.53±0.70	22.36±0.51	20.54±0.35
6	38.33±0.29	36.20±0.15	33.72±0.25	26.39±0.25	25.84±0.76	23.52±0.63
7	42.17±0.23	40.22±0.10	37.22±0.19	29.44±0.41	28.75±0.89	26.50±0.57
8	49.86±0.54	48.17±0.38	42.69±0.16	34.51±0.30	33.59±0.45	30.68±0.70
9	58.13±0.36	53.10±0.16	47.44±0.13	39.44±0.56	38.90±0.64	33.49±0.66
10	63.64±0.26	61.20±0.23	53.21±0.29	43.27±0.53	42.42±0.59	37.76±0.43
11	67.10±0.17	65.22±0.31	61.03±0.36	47.13±0.55	46.53±0.74	41.65±0.79
12	72.22±0.46	70.21±0.14	67.2±0.46	54.21±0.56	50.1±0.23	45.23±0.20

*represents mean±SD (n=3)

Table 8: Swelling index of formulations F7CPML – F12 CPADCP

Time (hrs)	%swelling index±SD*					
	F7CPML	F8CPML	F9CPML	F10CPADCP	F11CPADCP	F12CPADCP
	Lactose			DCP		
1	6.41±0.51	5.33±0.44	4.22±0.17	12.15±0.33	11.55±0.64	11.23±0.43
2	10.30±0.20	10.15±0.34	8.32±0.25	18.55±0.12	17.33±0.54	16.53±0.15
3	14.23±0.36	13.24±0.34	12.54±0.17	25.31±0.33	22.71±0.18	21.19±0.52
4	21.23±0.55	17.42±0.34	18.20±0.22	30.18±0.27	29.16±0.60	26.23±0.33
5	24.20±0.30	22.24±0.25	21.45±0.16	35.17±0.16	32.48±0.25	31.47±0.29
6	26.14±0.58	25.11±0.27	24.21±0.51	40.11±0.37	38.27±0.41	36.51±0.15
7	29.67±0.88	28.54±0.55	26.55±0.34	44.33±0.52	43.50±0.37	40.27±0.24
8	34.35±0.33	32.41±0.44	31.74±0.53	51.14±0.31	48.17±0.19	46.29±0.33
9	38.45±0.65	35.57±0.55	33.52±0.34	59.21±0.61	56.39±0.48	54.19±0.29
10	42.27±0.52	41.56±0.24	36.22±0.35	64.25±0.37	62.17±0.33	59.25±0.24
11	46.18±0.86	45.86±0.54	42.74±0.22	69.13±0.16	67.15±0.22	64.33±0.15
12	51.9±0.71	49.55±0.67	44.25±0.36	79.23±0.22	75.0±0.19	73.2±0.33

*represents mean±SD (n=3)

Table 9: Swelling index of formulations F13CPDDCP – F18CPMDCP

Time (hrs)	%swelling index±SD*					
	F13CPDDCP	F14CPDDCP	F15CPDDCP	F16CPMDCP	F17CPMDCP	F18CPMDCP
	DCP			DCP		
1	7.15±0.15	6.33±0.14	5.33±0.42	7.35±0.34	6.17±0.32	5.15±0.26
2	9.52±0.34	9.17±0.16	9.64±0.25	9.51±0.22	9.36±0.19	11.37±0.35
3	16.19±0.41	14.13±0.23	12.15±0.12	16.21±0.37	14.65±0.69	15.29±0.22
4	20.33±0.31	19.54±0.25	18.23±0.14	21.32±0.15	19.57±0.35	19.31±0.20
5	24.55±0.57	22.16±0.47	21.58±0.31	24.40±0.33	22.19±0.37	21.33±0.15
6	28.39±0.12	25.57±0.35	24.34±0.88	27.17±0.91	26.27±0.14	25.23±0.20
7	29.14±0.23	28.55±0.17	27.17±0.13	29.57±0.16	29.65±0.18	28.32±0.26
8	34.33±0.20	33.19±0.54	32.12±0.52	36.53±0.32	34.67±0.88	33.21±0.50
9	40.57±0.48	38.24±0.73	35.32±0.18	42.14±0.24	37.55±0.64	36.31±0.36
10	45.16±0.22	42.16±0.27	39.66±0.77	45.55±0.25	41.58±0.58	39.61±0.71
11	49.45±0.31	46.35±0.35	43.54±0.20	49.47±0.33	45.57±0.23	43.21±0.25
12	54.22±0.33	52.0±0.47	47.26±0.54	53.11±0.14	51.0±0.37	45.27±0.54

*represents mean±SD (n=3)

The percentage swelling obtained from the water uptake studies of the formulations is 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 hrs, then diffusion and erosion takes place. The formulation F10CPADCP containing albizia gum with DCP shows the higher swelling 79.23±0.22 compared to that of the formulations containing gum dammar and moi gum. The swelling index of the tablets increases with by increasing the polymer concentration.

***In vitro* drug release study of formulated floating controlled release**

The release of cephalexin was studied using USP dissolution apparatus II. The dissolution media were 900 ml 0.1 N HCl maintained at 37 ± 0.50C 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 256 nm. The results are expressed as mean±S.D (n=3).

The *in-vitro* dissolution study of formulations F1CPAL, F2CPAL and F3CPAL were prepared with albizia gum with lactose. The percent of drug release from formulations F1CPAL, F2CPAL and F3CPAL was 99.2%, 99.4% and 99.9% respectively. Formulations F2CPAL and F3CPAL, were unable to sustain the drug release for the desired period of time 12 hrs. All these three formulations floated for 12 hrs. Formulations F2CPAL and F3CPAL failed in drug release profile.

In vitro dissolution study of formulations F4CPDL, F5CPDL and F6CPDL were prepared with dammar gum with lactose and the percent of drug release from formulations F4CPDL, F5CPDL and F6CPDL were 99.3%, 99.5%, and 99.9% respectively. The results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly, formulations F5CPDL and F6CPDL were unable to sustain the drug release for desired period of time 12 hrs but in case of formulation F4CPDL, 99.3% 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 more than12 hrs. Formulations F5CPDL and F6CPDL failed in drug release profile. Formulation F4CPDL 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 four formulations.

In vitro dissolution study of formulations F7CPML, F8CPML and F9CPML were prepared with moi gum with lactose and the percent of drug release from formulations F7CPML, F8CPML and F9CPML were 91.3%, 95.6% and 99.6% respectively. The results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly. Formulation F8CPML and F9CPML were unable to sustain the drug release for desired period of time 12 hrs but in case of formulation F7CPML, 91.3% of the drug was released in 12 hrs. This was considered to be due to different polymer concentrations in all the three formulations. All these three formulations floated for 12 hrs. Formulations F8CPML and F9CPML failed in drug release profile. Formulation F7CPML obtained the desired drug release profile and floated with a lag time of 135 sec., for these reasons, it was considered to be the best formulation among all the three formulations. *In vitro* dissolution study of formulations F10CPADCP, F11CPADCP and F12CPADCP prepared with albizia gum with diluent DCP were done in 0.1N HCl and the percent of drug release from formulations was 55.4, 65.3 and 72.31 in 12 hrs respectively. Formulations failed to F10CPADCP, F11CPADCP and F12CPADCP meet the desired drug release profile.

In vitro dissolution study of formulations F13CPDDCP, F14CPDDCP and F15CADDCP were also done in 0.1N HCl and the percent drug released was calculated. These three formulations prepared with gum dammar with DCP as diluent and the percent of drug release from formulations F13CPDDCP, F14CPDDCP and F15CPDDCP was 65.3, 75.12 and 78.16 respectively, The results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly.

In vitro dissolution study of formulations F16CPMDCP, F17CPMDCP and F18CPMDCP were also done in 0.1N HCl and the percent drug released was calculated. These three formulations prepared with moi gum with DCP and the percent of drug release from formulations F16CPMDCP, F17CPMDCP and F18CPMDCP Was 54.3, 64.12 and 71.24 respectively, the results indicated that by increasing the grade of polymer concentrations drug release was retarded greatly. Comparing the three different grades of gums (albizia gum, gum dammar and moi gum), it was found that gum dammar with diluents lactose that is F4CPDL 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 the formulations. Formulation F1CPAL to F9CPML 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 F10CPADCP to F18CPMDCP 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.

Table 10: Cumulative drug release profiles of F1CPAL- F9CPML FORMULATIONS

Time	F1CPAL	F2CPAL	F3CPAL	F4CPDL	F5CPDL	F6CPDL	F7CPML	F8CPML	F9CPML
1	7.06±0.15	8.03±0.27	9.12±0.96	7.6±0.14	08.51±0.46	10.6±0.80	7.6±0.23	9.5±0.17	14.16±0.33
2	16.4±0.45	17.02±0.13	18.01±0.23	27.3±0.16	25.3±0.12	25.7±0.42	11.5±0.32	17.19±0.24	19.53±0.22
3	22.03±0.86	28.06±0.33	33.06±0.74	30.61±0.49	32.4±0.93	37.21±0.62	22.6±0.66	25.3±0.12	30.12±0.52
4	38.63±0.11	44.60±0.75	46.65±0.90	44.0±0.24	43.06±0.13	55.3±0.84	32.15±0.27	34.9±0.33	37.2±0.57
5	51.54±0.53	54.31±0.63	58.79±0.19	51.7±0.82	52.9±0.56	63.52±0.65	41.17±0.11	42.19±0.30	44.51±0.63
6	67.62±0.96	69.66±0.13	77.02±0.63	60.8±0.12	64.70±0.63	75.13±0.27	51.61±0.12	53.17±0.27	56.30±0.40
7	72.4±0.33	78.05±0.14	84.6±0.19	74.13±0.28	73.51±0.23	82.31±0.18	60.13±0.11	63.15±0.39	77.51±0.23
8	79.01±0.14	88.25±0.66	90.45±0.48	79.8±0.36	82.5±0.06	87.5±0.96	69.4±0.29	79.13±0.12	84.5±0.71
9	88.27±0.45	97.02±0.12	99.3±0.24	88.3±0.44	89.3±0.35	99.3±0.12	78.17±0.18	90.51±0.21	99.6±0.51
10	92.13±0.52	99.4±0.35	-	95.2±0.04	99.5±0.73		86.12±0.44	95.6±0.13	-
11	93.3±0.65	-	-	96.5±0.10	-		88.52±0.02	-	-
12	95.2±0.30	-	-	99.3±0.61	-		91.3±0.12	-	-

Mean±s.d.n=3

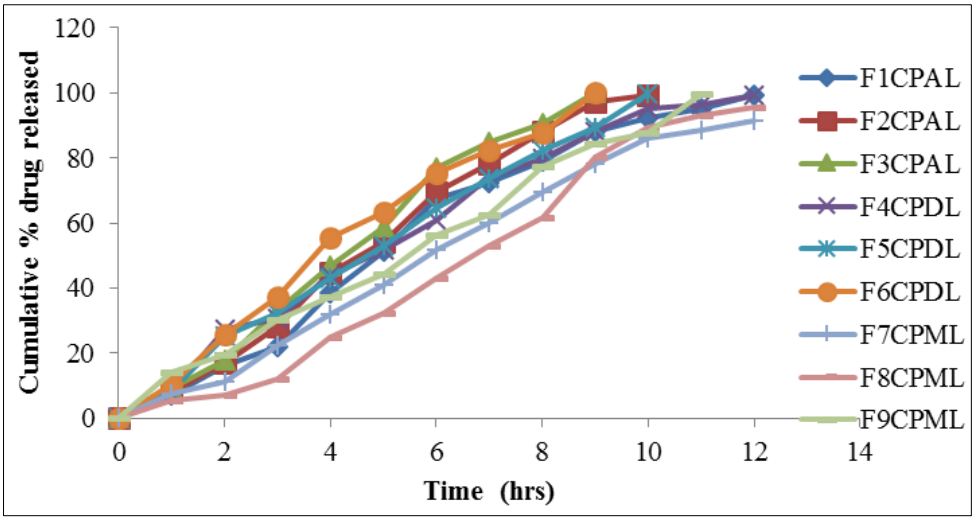

Fig 2: Drug release profiles of F1CPAL- F9CPML formulations

Table 11: Cumulative drug release profiles of F10CPADCP- F18CPMDCP formulations

Time	F10CPADCP	F11CPADCP	F12CPADCP	F13CPDDCP	F14CPDDCP	F15CPDDCP	F16CPMDCP	F17CPMDCP	F18CPMDCP
1	3.1±0.52	3.9±0.93	7.2±0.94	5.31±0.32	4.8±0.53	5.5±0.71	4.17±0.21	3.81±0.23	3.6±0.23
2	6.5±0.37	7.8±0.21	9.7±0.45	8.9±0.21	8.1±0.82	10.7±0.31	8.10±0.75	7.33±0.17	11.17±0.38
3	12.21±0.51	13.09±0.92	16.5±0.96	15.2±0.63	12.1±0.13	16.7±0.12	12.1±0.65	13.17±0.60	19.6±0.34
4	16.5±0.32	18.5±2.02	22.1±0.25	20.06±0.21	17.0±0.22	23.06±0.83	16.5±0.92	16.3±0.73	22.62±0.93
5	21.23±0.65	25.3±0.36	28.6±0.96	27.19±0.61	25.1±0.16	27.12±0.59	19.8±0.12	18.52±0.63	27.20±0.39
6	26.11±0.70	29.14±0.10	34.12±0.22	32.11±0.03	30.16±0.94	34.18±0.21	23.14±0.84	25.41±0.25	32.80±0.56
7	31.52±0.82	38.6±0.53	39.51±0.24	37.8±0.93	39.7±0.45	40.51±0.84	27.53±0.75	28.32±0.49	39.5±0.42
8	38.81±0.94	43.05±0.36	48.14±0.07	42.82±0.52	44.6±0.32	48.77±0.13	32.7±0.25	34.6±0.33	44.51±0.65
9	42.72±0.52	52.12±0.18	56.42±0.51	50.17±0.14	57.19±0.12	56.18±0.83	39.17±0.39	48.09±.27	52.81±0.19
10	49.03±0.02	58.9±0.50	63.8±0.84	56.96±0.63	67.15±0.27	64.23±0.13	46.39±0.47	55.4±0.59	60.12±0.36
11	51.9±0.63	62.2±0.03	68.2±0.52	59.61±0.13	69.6±0.96	70.14±0.21	51.27±0.19	61.12±0.29	64.5±0.69
12	55.4±0.02	65.3±0.51	72.31±0.25	65.3±0.12	75.12±0.12	78.16±0.53	54.3±0.15	64.12±0.27	71.24±0.25

Mean±s.d.n=3

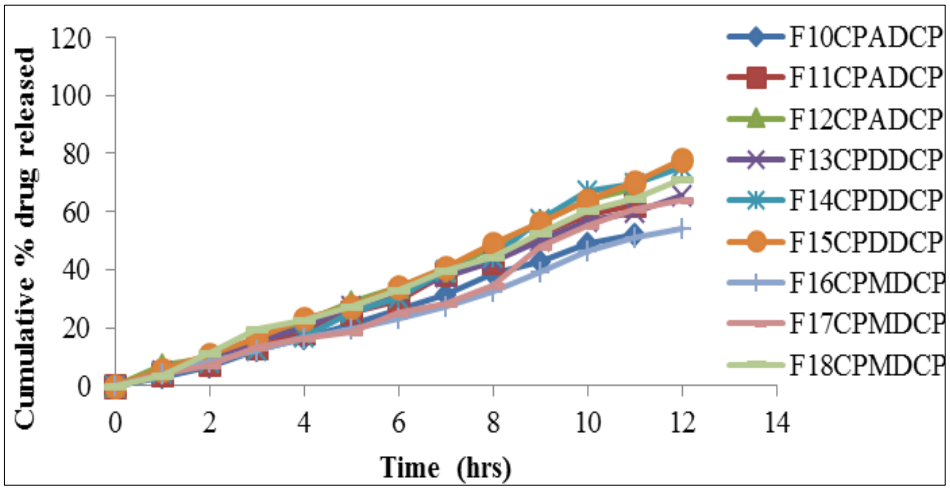

Fig 3: Drug release profiles of F10CPADCP- F18CPMDCP formulations

The mechanism of release for the optimized formulations was determined by finding the R2 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 R2 value of zero-order model and Korsmeyer-Peppas model is very near to 1 than the R2 values of other kinetic models. Thus it can be said that the drug release follows zero- order model korsymeyer and peppas and Higuchi model. Based on that we confirmed that the optimized formulation followed zero order release.

Table 12: Release kinetics of optimized formulations

S. No.	Formulation	Zero order	First order	Higuchi	Korsmeyer&Peppas
1	F4CPDL	0.974	0.842	0.953	0.961

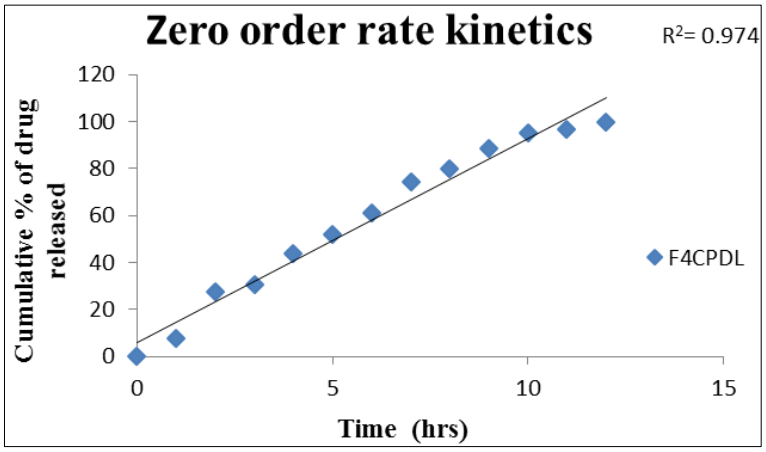

Fig 4: Zero order drug release of optimized formulation

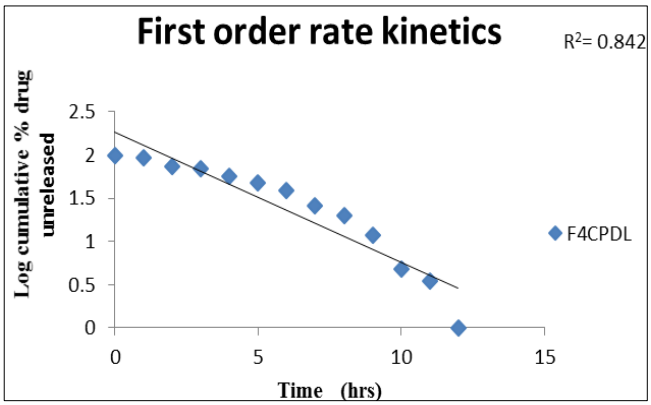

Fig 5: First order drug release of optimized formulation

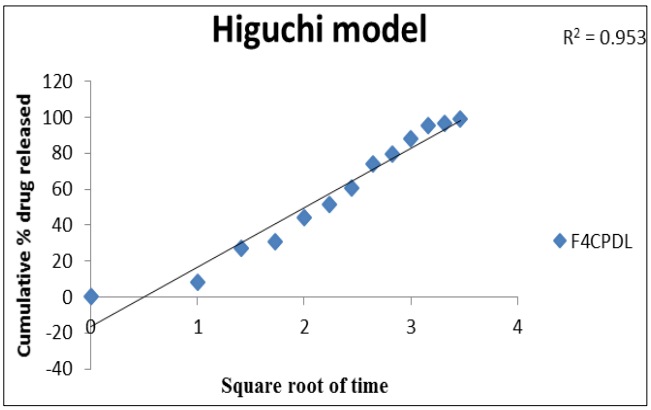

Fig 6: Higuchi model of optimized formulation

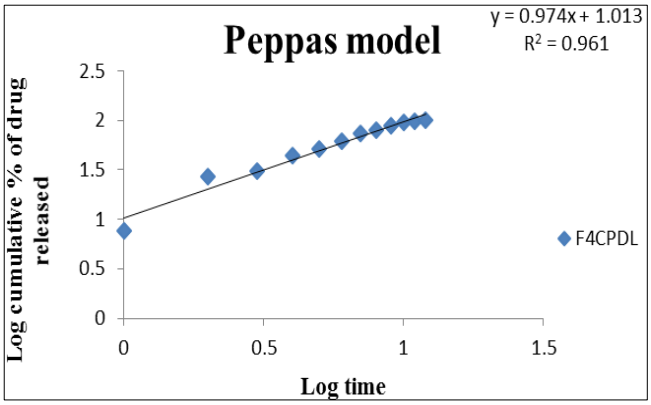

Fig 7: Peppas model of optimized formulation

Table 13: Pharmacokinetic parameters of cephalexin

Parameters	Pure cephalexin (R)	Floating tablets (T) SF4CPDL
Kel (hr^{-1})	0.204±0.12	0.138±0.91
t1/2 (hrs)	3.39±0.55	5.02±0.14
Tmax (hrs)	2±0.32	4±0.32
Cmax (ng/ml^{-1})	1817.9±0.06	1731.4±0.61
AUC0- t (ng.hr mL^{-1})	5465.15±2.30	13899.87±0.12
AUC0-∞ (ng.hr mL^{-1})	7096.42±1.32	15597.14±0.81

The mean peak plasma concentration of test (T) formulation C_{max} 1731.4 ng/ mL was gradually reached in 4 hrs. In case of pure drug (R) the C_{max} was 1817.9 ng/ mL which was reached in 2 hrs. The C_{max} of the test formulation SF4CPDL (T) was less when compared with reference (R) formulation. The increase in T_{max} was clearly indicating the drug availability for prolonged period. Table 13 show the kinetic data of cephalexin pure drug (R) & In-house formulation (T) respectively. The reference (R) formulation reached the T_{max} in about 2hrs. 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 7947.65 ng.hr/ mL. The increase in AUC_{0-t} was observed in the test (T) formulation, which was around 8488.8 ng.hr/ mL. This clearly indicates the drug availability for long duration.

Decrease in elimination rate constant (K_{el}) from 0.209 hr^{-1} (R) to 0.204 hr^{-1} (T) indicates the slow release rate of the drug in the body. 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}, and K_{el} were completely different between both test and reference formulation. Therefore the prepared formulation was releasing the drug for a prolonged period of time. From the results discussed above it was found that the in house formulation prepared with Dammar gum. Thus the formulation has good potential to liberate cephalexin.

8. Conclusion

Floating tablets of drug cephalexin were successfully prepared using different gums in various ratios by direct compression method. Among all the formulations, F4CPDL was considered to be most promising for controlled release of Cephalexin upto 12 hours when compared with other formulations.

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