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Research Article

FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE FLOATING TABLET OF CEPHALEXIN USING HYDROPHILIC POLYMERS

ANILKUMAR J. SHINDE[1*], ARUN N. WAGHULE[1], MANOJ B. PAITHANE,[1] HARINATH N. MORE[1]

[*1] **Department of Pharmaceutics, Bharati Vidhyapeeth College of Pharmacy, Near chitranagri, Kolhapur, Masharashtra**

Email: ajshinde07@rediffmail.com

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ABSTRACT

The purpose of this investigation was to prepared a gastroretentive floating drug delivery system (GFDDS) of cephalexin(CFL). Sustained release of floating tablets of cephalexin were formulated employing the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. A 3^2 factorial design was applied systematically; the amount of citric acid (X1) and amount of HPMC K100M (X2) were selected as independent variables. The time required for 50% drug release ($t_{50\%}$), percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) were selected as dependent variables. The results of factorial design indicated that high level of HPMC K100M and citric acid favors preparation of floating sustained release tablet of cephalexin. The granules were prepared by wet granulation method and evaluated for their granules properties. Tablets were compressed by Minipress rotary tablet machine and evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, in vitro buoyancy study, swelling characteristics, scanning electron microscopy, kinetic release data. Hardness was found to being the range of 13 ± 0.23 to 13 ± 0.40 kg/cm2, the percent friability was in the range of 0.0010 ± 0.02 to 0.0027 ± 0.01, and tablets showed 99.63 ± 0.12 to 115.73 ± 0.13 of the labeled amount of cephalexin indicating uniformity content. The tablets containing CFL released 72.28 to 99.461 % of drug at the end of 12 hrs by in vitro release study. The drug release from the tablets was sufficiently sustained followed the Korsmeyer and Peppas model controlled mechanism of cephalexin tablet

Keywords: Factorial design, floating drug delivery, in vitro Buoyancy, Cephalexin, HPMC

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 etc. From immediate release to site specific delivery, oral dosage forms have really progressed. A gastric floating drug delivery system (GFDDS) [1,2,3] can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.

Gastroretentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance.[4,5] Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach. This systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract, thus ensuring optimal bioavailability.[6,7] Various gastroretentive techniques were used, including floating,[8] swelling,[9] high density and bioadhesive system,[10] have been explored to increase the gastroretention of dosage forms. Floating systems having low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduces fluctuation in plasma drug concentration.

Formulation of floating tablet containing cephalexin as a drug candidate, which would remain in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site. Cephalexin having good absorption in GIT, low pKa, which remain unionized in stomach for better absorption. Cephalexin is a semisynthetic cephalosporin β lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections.[11] Pharmacokinetic parameters of cephalexin such as absorption from the gastrointestinal tract, protein binding 14 %, and metabolism 90% excreted unchanged in the urine, half-life is 1 hour.[12] It degraded in alkaline pH, so as to prevent degradation, gastro retentive dosage forms can help in preventing degradation, which degrades in small intestine. Low viscosity hydrophilic polymers HPMC K100 were found to be more beneficial to improving floating properties. Hydrophilic polymer slowly forms thick gel, which retains integrity of the formulation and promotes drug release through thick gel and controls the burst release.

The objective of this study was to develop an optimized GFDDS containing Cephalexin as a model drug a peroral intragastric floating dosage form having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents. To investigate the effect of amount of citric acid and hydroxylpropylmethyl cellulose K100M on the formulation to monitor the sustained release effect respectively. Both the drug and polymer fulfills the above characteristics, which indicate its suitability for fabrication into the floating drug delivery system.

MATERIALS AND METHODS

Cephalexin was received as a gift sample from Orchid Chemicals and Pharmaceutical (Chennai, India), Okasa Pharma, Satara and Aurobindo Pharma, hydrabad. Hydroxy propyl methylcellulose K-100M (HPMC- K100M) was obtained from Colorcon Asia Pvt Ltd (Goa, India) and Microcrystalline cellulose was received as a gift sample from Maple Biotech Pvt Ltd (Pune, India). Sodium bicarbonate, citric acid, magnesium stearate, talc were purchased from Loba chemie, Mumbai. Gamma scintigraphy study was conducted under medical supervision in the Spect Lab nuclear medicine services, Pune. This laboratory is approved by human ethical committee. All other ingredients were of analytical grade.

EXPERIMENTAL

Characterization of Cephalexin

The sample of cephalexin was analyzed for its nature, color and taste. Cephalexin was estimated by UV Spectrophotometry method. Infrared spectrum of Cephalexin was determined on Fourier Transform Infrared Spectrophotometer (FTIR-4100s) using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run. The Differential Scanning Calorimetric analysis was carried out using SDT 2960 TA Instrument, USA, for differential scanning calorimeter, samples were placed in a platinum

crucible and the DSC thermograms were recorded at a heating rate of 10ºC/min in the rage 20 ºC to 350 ºC, at a nitrogen flow of 20 ml/min.

Preparation of floating tablet of Cephalexin

Each floating tablets containing 500mg cephalexin were prepared by a conventional wet granulation method, employing sodium bicarbonate, citric acid as gas generating agent and water soluble polymer (HPMC K100M) as hydrophilic matrix in each formulation (Table No.1). The concentration of gas generating agent (sodium bicarbonate) was developed as optimal concentration under experimental formulae and condition of preparation. All the ingredients were mixed thoroughly except magnesium stearate and talc. Granules were prepared manually with a solution of the Polyvinyl pyrrolidone (PVP K30) in sufficient quantity of isopropyl alcohol as binder. The wet mass was passed through a 16 mesh sieve no. and the wet granules produced were dried in hot air oven for 35 min at 60°C. The dried granules mixed with magnesium stearate as lubricant, talc as glidant and compressed into tablet on a Minipress rotary tablet machine. Prior to compression, granules were evaluated for their flow and compressibility characteristics.[13-18]

Table 1: Composition of floating tablets of Cephalexin

Ingredient (mg)	CET1	CET2	CET3	CET4	CET5	CET6	CET7	CET8	CET9
Cephalexin	500	500	500	500	500	500	500	500	500
HPMC K100M	100	125	150	100	125	150	100	125	150
Sodium bicarbonate	150	150	150	150	150	150	150	150	150
Citric acid	15	15	15	20	20	20	25	25	25
Microcrystalline cellulose	50	50	50	50	50	50	50	50	50
PVK-K30	40	40	40	40	40	40	40	40	40
Magnesium stearate	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Total weight of tablets	880	905	930	885	910	935	890	915	940
Floating lag time in sec.	45	45	60	50	45	40	60	50	55

Full Factorial Design

A 3^2 randomized full factorial design was used, in this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of citric acid (X_1) and amount of HPMC (X_2) were selected as independent variables. The time required for 50% drug dissolution ($t_{50\%}$), percentage drug release at 12 hours (Q_{12}) and percentage release at 6 hours (Q_6) were selected as dependent variables.[19-21]

Evaluations of granules properties

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.[22-24]

Evaluation of tablet properties

The prepared cephalexin floating tablets were evaluated for thickness, diameter, hardness, friability, uniformity of weight and drug content. The thickness and diameter of tablets were measured by vernier caliper. Hardness of tablets was tested using Monsanto hardness tester. Friability of tablets was determined by using Friability test apparatus. The drug content in each formulation was determined by taking 20 tablets from each batch were weighed and powdered. The powder equivalent to 10 mg was taken and dissolved in 10 ml of 0.1 N HCL. This stock solution was shaken for 20 min. on a sonicator. This resulting solution is further diluted with 0.1 N HCL to achieve concentration up to 10 µg /ml and the absorbance measured at the 257 nm. [25-27]

***In -vitro* buoyancy study**

The in-vitro buoyancy study was characterized by floating lag time and total floating time. The test was performed using a USP type II paddle apparatus (Electrolab) using 900 ml of 0.1 N HCL at paddle rotation of 50 rpm at 37 ± 0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and total floating time respectively.

Swelling characteristics (water uptake study)

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of 0.1 N HCL at 37 ± 0.5 °C. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) show relationship between swelling index and time.[28-30]

$$WU\ \% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

***In- vitro* drug release study**

The release rate of cephalexin floating tablets were determined by using Dissolution testing apparatus USP type II (Paddle type)(Electro lab). The dissolution testing was performed using 900 ml of 0.1N HCL at 37 ± 0.5°C temperature and speed 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution testing apparatus hourly for 12 hours and the samples were replaced with fresh dissolution medium.[31,32] The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCL. Absorbance of these solutions was measured at 257 nm wavelength using JASCO UV530 spectrophotometer. Analysis of data was done by using 'PCP Disso V-3' software, India.

Infrared spectra analysis

Infrared spectrum of Cephalexin was determined on Fourier Transform Infrared Spectrophotometer (FTIR-4100s) using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.

Scanning electron microscopy

The SEM images of the tablet has been used to examine surface topography, texture and morphology of fractured surface. SEM analysis was conducted using JOEL JSM-T330A scanning microscope for optimized formulation.

***In-vivo* Study**

Gamma scintigraphy study of batch CET6

In gamma scintigraphy the gamma rays emitted by radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract. The preparation of cephalexin radiolabelled floating tablet with Technetium-99m (99mTcO4) as a radioisotopes and various excipients such as hydrophilic polymer HPMC K100M and sodium bicarbonate, citric acid as gas forming agent. The in-vivo floating ability was studied by gamma scintigraphy in 2 healthy males with ranging ages (25-58 years), weight (60-79 kg) and height (163-183 cm) were selected. The study was conducted under medical supervision in the Spect Lab nuclear medicine services, Pune. [33-36]

Stability study of batch CET6: The batch CET6 was selected as an optimum batch for the stability study was carried out at accelerated conditions of 40 °C / 75 % RH for period of three month. Dissolution study was conducted after three month and dissolution profile was analyzed and find out cumulative drug release. [37]

RESULTS AND DISCUSSION

Characterization of Cephalexin

The sample of cephalexin was off white or almost, white, crystalline powder, odour characteristic. The reported melting point values for cephalexin are in the range of 326.8°C. The observed melting point ranged between 321 – 324 °C. The absorption maximum of the standard solution was scanned between 200-400 nm regions on JASCO UV 530 spectrophotometer. The absorption maximum was found to be 257 nm.

Infrared absorption spectrum of Cephalexin: IR spectrum shows all prominent peaks of Cephalexin. The major IR peaks observed in Cephalexin were 3335.12 (3300-3500) (N-H), 1686.44 (1680 - 1760 (C=O), 3054.69 (3300 - 2500 (O-H), 2525.12 (2590 – 2550 (S-H), 1196.61 1220 -1020 (C-N) and 1282.43(1000 –1300) (C-O) (Figure 1.).

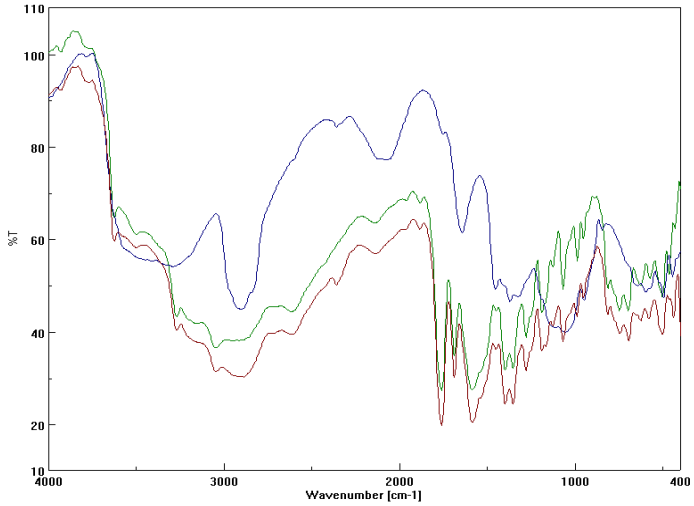

Fig. 1: Overlain FTIR spectral analysis of Cephalexin(green), HPMC K100M (blue), physical mixture(brown)

Infrared absorption spectrum of HPMC K 100: The spectrum shows all prominent peaks of HPMC K100M. The major IR peaks observed in HPMC K100M were 2922.59 (2850 – 3000) (C-H), 3420.14 (3300 – 3500) (N-H), 1058.73 (1000 – 1300) (C-O) cm-1

Infrared absorption spectrum of Physical mixture: The IR spectra of physical mixture of polymers (HPMC K100M) and cephalexin was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug as well as polymer. The major IR peaks observed in matrices were 2884.02 (2850 – 3000) (C-H), 1757.8 (1680 – 1760) (C=O), 1594.84 (1550 – 1650) (N-H), 1353.78 (1350 – 1550) (N=O), 1070.3 (1000 – 1300) (C-O). Hence it can be concluded that there were no any significant changes and behavior in the physical mixture of cephalexin and polymer (HPMC K100M)

Differential Scanning Calorimetry: DSC thermogram of Cephalexin show endothermic peak at 327.5 ºC. Where as HPMC K100M show melting endodermic peak at 34.40 ºC. Physical mixtures show endothermic and exothermic peak at 105 ºC and 190 ºC respectively. While optimized batch also show the endothermic peak at 70.7 ºC and 180.2 ºC (Figure 2).

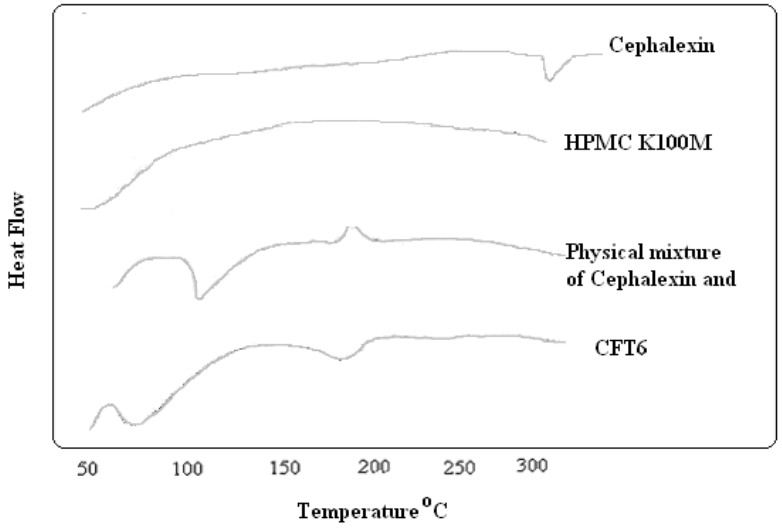

Fig 2: DSC thermogram of HPMC K100M; Cephalexin; Physical mixture; CFT6 Optimized formulation

A 3^2 factorial design was constructed to study the effect of the amount of citric acid (X1) and HPMC K100M (X2) on the drug release from floating cephalexin tablet respectively. The dependent variables chosen were times required for 50% drug release ($t_{50\%}$), percentage drug release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) shown in **(Table no.2).**

Table 2: Formulation and dissolution characteristics of batches in 3^2 factorial designs

Batch code	Coded values		$t_{50\%}$ (min)	% release at 6hr (Q_6)	% release at 12hr (Q_{12})
	X1	X2			
CET1	-1	-1	234.8	61.9	87.87
CET2	-1	0	383.9	48.4	71.74
CET3	-1	+1	454.3	41.01	72.28
CET4	0	-1	40.2	78.7	94.59
CET5	0	0	254.1	57.2	73.92
CET6	0	+1	442.3	43.5	73.24
CET7	+1	-1	61.0	78.1	99.46
CET8	+1	0	232.6	62.2	88.89
CET9	+1	+1	296.5	55.1	79.14

Translation of Coded Values to Actual Values

Coded values	Actual values	
	X_1	X_2
-1	20	125
0	25	150
+1	30	175

*Where X1 - Amount of citric acid, X2 - Amount of HPMC K100 M., $t_{50\%}$ - time required for 50% of drug release, Q_{12} - percentage drug release at 12hours, Q6 - percentage drug release at 6 hours.

A statistical model incorporating interactive and polynomial term was used to evaluate the responses.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2$$

Where, Y is dependent variable, b0 is the arithmetic mean response of the 9 runs, and b_i (b_1, b_2 , b_{12} , b_{11} and b_{22} is the estimated coefficient for the factor X_1). The main effect (X1 and X2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X_1X_2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity. The $t_{50\%}$, Q_{12} and Q6, for 9 batches (CET1-CET9) showed a wide variation (i.e. 40.2 - 454.3 min, 71.74 - 99.46, 41.0 – 78.7 min respectively). The responses of formulation prepared by 3^2 factorial designs are indicated in Table no.2. The data clearly indicate that the $t_{50\%}$, Q_{12} and Q_6 were strongly dependent on the selected independent variables. The fitted equation relating the response $t_{50\%}$, Q_{12} and Q_6 to the transformed factors are, $t_{50\%}$ = 266.63 - $80.4833X_1$+$142.85X_2$, (R2 = 0.9133) Q12 = 82.34 + $5.9262X_1$ - $9.5363X_2$ (R2 = 0.8472) and Q6 = 58.45 + 7.3500X1 – 13.1833X2 (R2 = 0.9337).

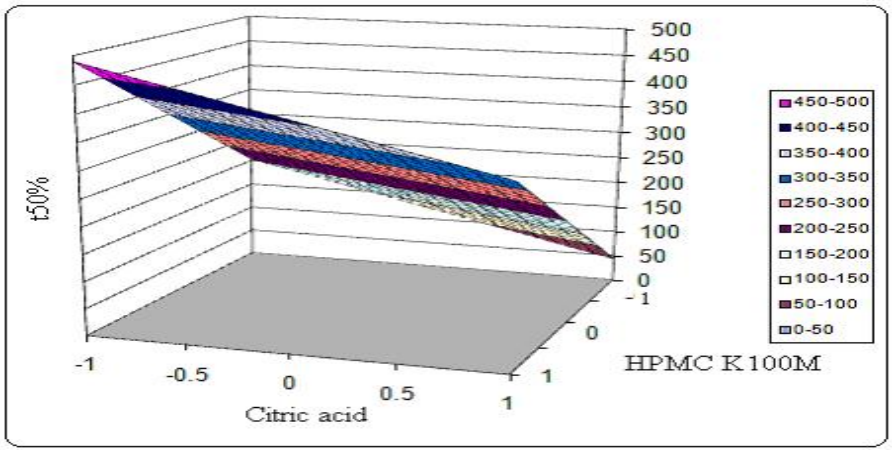

Fig. 3: Response surface plot for $t_{50\%}$

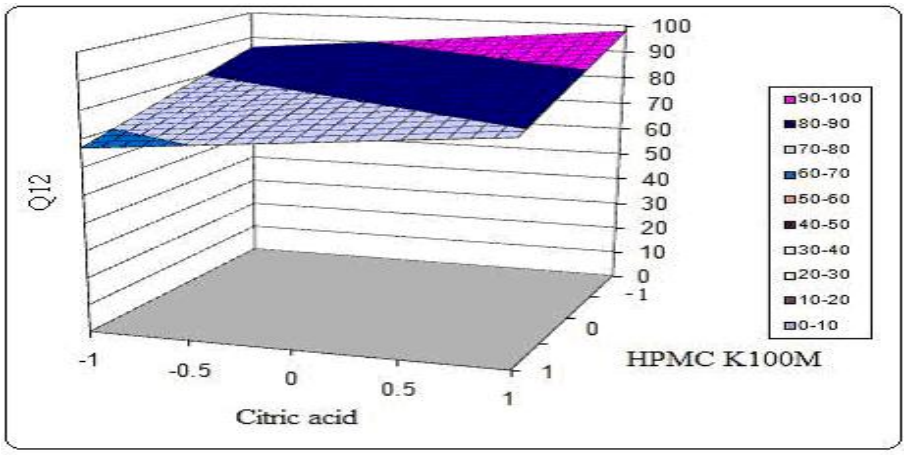

Fig. 4: Response surface plot for Q_{12}

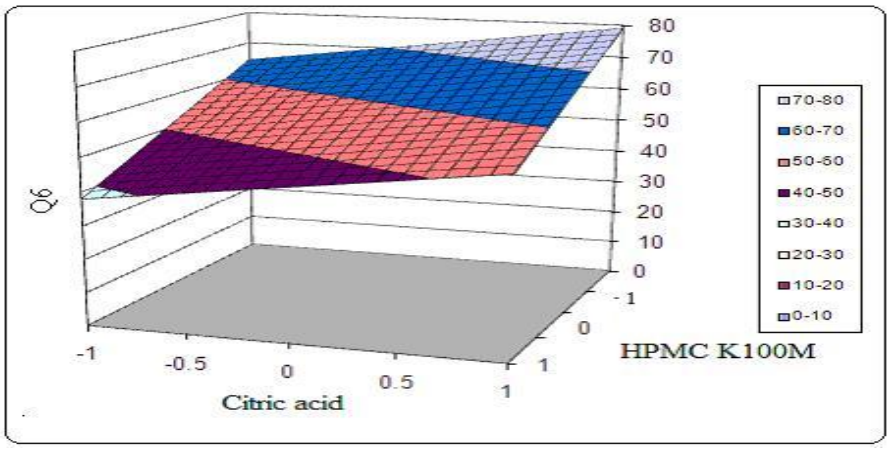

Fig. 5: Response surface plot for Q_6

The values of the correlation coefficient indicate a good fit. (Figures 3, 4, 5) shows the plot of the amount of citric acid (X1) and amount of HPMC K100M (X2) versus t50%, Q12 and Q6 respectively. The data demonstrate that both X1 and X2 affect the drug release (t50%, Q12 and Q6). It was concluded that the low level of X1 (amount of citric acid) and the higher level of X2 (amount of HPMC K100M) favor the preparation of floating sustained release cephalexin tablets. The high value of X1X2 coefficient also suggests that the interaction between X1 and X2 has a significant effect on t50%. An increase in the concentration of citric acid (X1) and amount of HPMC K100M (X2), decrease rate of release of cephalexin floating tablet respectively. All the tablets of factorial design batches showed good in vitro buoyancy, having floating lag time between 40 - 60 sec and remaining buoyant for 12 hours. The bulk density of granules was found to be between 0.3061 ± 0.04 to 0.3658 ± 0.07 g/cm^3. This indicates good packing capacity of granules. Carr's index was found to be between 14.89 ± 0.03 to 20 ± 0.10 showing good flow characteristics. Hausner's ratio low range was indicates good flowability. The angle of repose of all the formulations within the range of 16.09 ± 0.08 to 21.96 ± 0.12 i.e. granules were of good flow properties.

All the formulations from batch CET1 to CET9 were evaluated with Thickness and diameter of tablets, measured by vernier caliper. Thickness and diameter was in range of 4.85 ± 0.04 to 5.30 ± 0.05. The hardness of tablet was in range of 13 ± 0.23 to 13 ± 0.40 measured by Monsanto hardness tester. The friability was in range of 0.0010 ± 0.02 to 0.0027 ± 0.01. The values of average weight are within limit. Drug content was in range of 99.63 ± 0.12 to 115.73 ± 0.13 indicating good content uniformity in the prepared formulation results shown in (Table No. 3).

Table 3: Tablet properties of Cephalexin floating tablets

Batch code	Average wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
CET1	878.65	4.85 ± 0.04	13.11 ± 0.05	13 ± 0.32	0.0027 ± 0.01	102.08 ± 0.13
CET2	906.00	4.88 ± 0.02	13.07 ± 0.02	13 ± 0.40	0.0019 ± 0.06	99.63 ± 0.12
CET3	932.25	5.05 ± 0.07	13.06 ± 0.04	13 ± 0.23	0.0019 ± 0.04	104.71 ± 0.22
CET4	887.50	4.78 ± 0.02	13.07 ± 0.07	13 ± 0.40	0.0024 ± 0.02	106.91 ± 0.15
CET5	914.10	4.90 ± 0.04	13.06 ± 0.02	13 ± 0.27	0.0021 ± 0.07	107.47 ± 0.10
CET6	939.65	5.07 ± 0.02	13.05 ± 0.09	13 ± 0.35	0.0010 ± 0.02	108.44 ± 0.12
CET7	882.40	4.85 ± 0.07	13.10 ± 0.03	13 ± 0.28	0.0018 ± 0.05	103.36 ± 0.14
CET8	917.65	4.98 ± 0.04	13.07 ± 0.05	13 ± 0.39	0.0015 ± 0.08	115.73 ± 0.13
CET9	942.15	5.30 ± 0.05	13.01 ± 0.07	13 ± 0.25	0.0014 ± 0.06	106.28 ± 0.10

*All reading are average ± (SD)

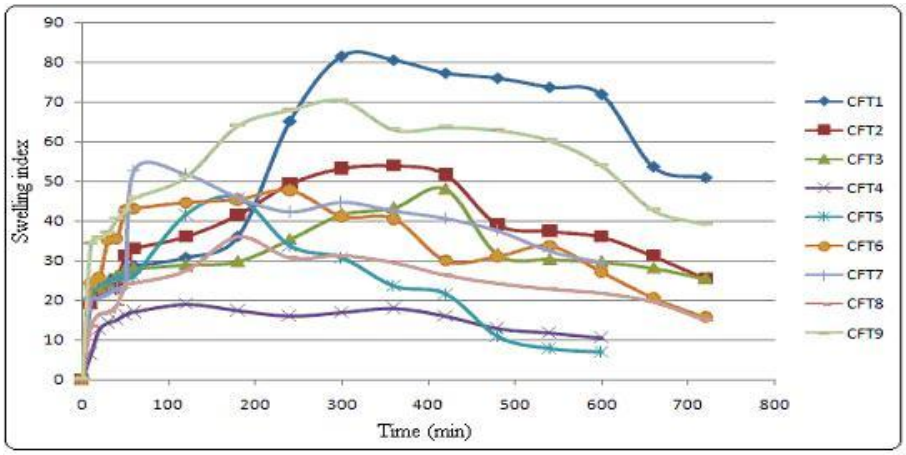

Fig. 6: Relationship between swelling index and time

In Vitro Buoyancy Studies conducted, the gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. In Vitro Buoyancy Studies Floating lag time was in range of 40sec to 60sec.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and HPMC K100M concentration and as HPMC K100M concentration increase, swelling index was increased shown in (Figure 6).

From the dissolution study of batch CET1 to CET9, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrs. The percentage drug release from batch CET1 to CET9 vary from 72.28 to 99.461 %. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release (CET3). Dissolution profiles for all batches were shown in (Figure 7).

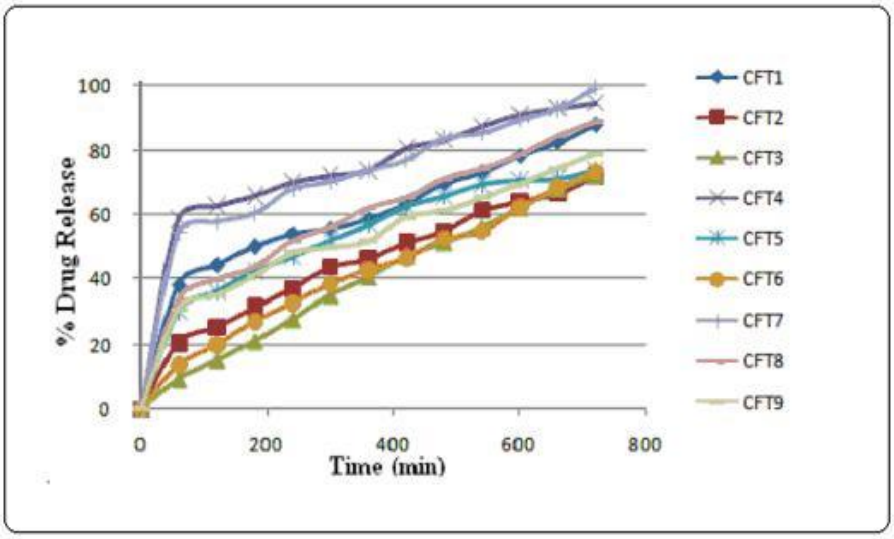

Fig. 7: Results of % drug release Vs time

Table No. 4. Release kinetics for Korsmeyer- Peppas Mode

Formulations	n	k	r	Best fit model
CET1	0.3318	9.0500	0.9401	Matrix
CET2	0.5274	2.2115	0.9926	Matrix
CET3	0.8511	0.2737	0.9973	Peppas
CET4	0.2067	23.307	0.9587	Peppas
CET5	0.3874	5.8499	0.9926	Peppas
CET6	0.6752	0.8175	0.9975	Peppas
CET7	0.2511	17.808	0.9630	Peppas
CET8	0.4053	5.8056	0.9856	Matrix
CET9	0.3885	5.7085	0.9835	Matrix

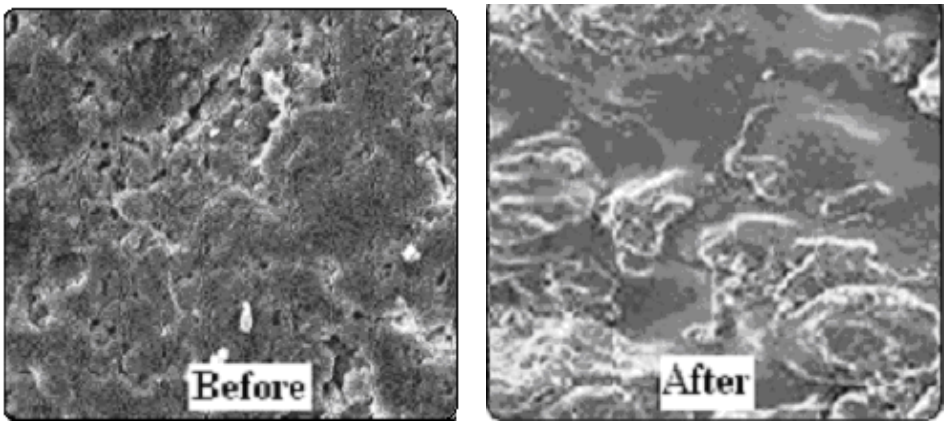

Fig. 8: Scanning electron microscopy images of tablet surfaces before and after Dissolution Original magnification X 1,000

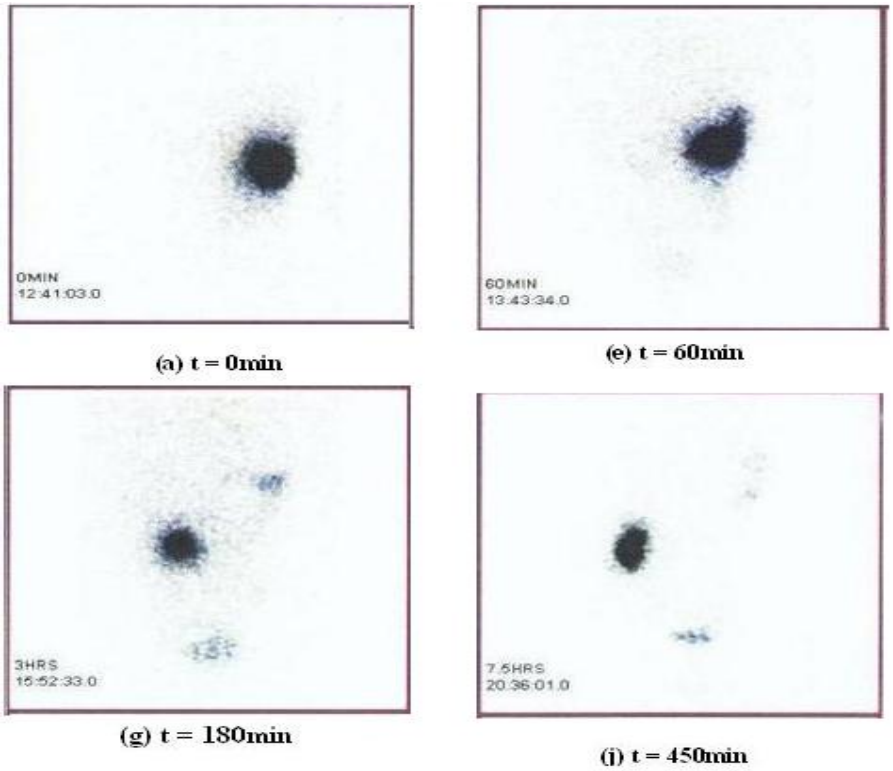

Fig. 9: Gamma scintigraphy images showing the movement of Cephalexin floating tablets (CET6) for volunteer at selected time point when the tablets were administered with 200ml water (g) t = 360min, (j) t = 450min

Table 5: Cumulative % drug release for stability study of batch CFT6

Time (min)	Cumulative % Drug Release (Initial)	Cumulative % Drug Release (After storage at 40°C after 3 month)
0	0.00	0.00
60	13.65	13.60
120	19.90	18.86
180	27.23	27.02
240	32.75	31.56
300	38.41	37.88
360	42.89	42.09
420	46.47	46.23
480	52.43	52.25
540	54.62	54.56
600	62.24	62.07
660	68.37	68.21
720	73.24	73.15

All these formulations presented a dissolution behavior controlled by anomalous transport mechanism, when treated with kinetic equations and cephalexin release from hydrophilic binder matrices followed Fickian diffusion shown in Table No. 4. The SEM images of the tablet showed a network in the swollen polymer through, which the drug diffused to the surrounding medium and intact surface without any perforations, channels, or troughs shown in (Figure 8.) .

In vivo study (Gamma scintigraphy study) Gastro retention studies of the formulation CET6 was carried out in two healthy human volunteer. When tested for 7 hrs, the gamma scintigraphy outputs have shown that the tablets maintained matrix integrity, indicating no effect of gastric conditions on the gelling properties of tablets. The gamma scintigraphy outputs of one human volunteer was shown in (figure 9).

Stability study of batch CET6 was conducted and it will indicate that no any change in physical appearance in the dosage form of batch CET6 over a period of three months in accelerated conditions (40°C/75 % RH). The results of stability study after three months, cumulative % drug release of batch CET6 shows 73.15 % in 3 months given in (Table no. 5)

CONCLUSION

A systemically study using a 3^2 full factorial design revealed that the amount of citric acid (X_1) and amount of hydroxypropylmethylcellulose (HPMC K100M) (X_2) had a significantly effect on t_{50}%, Q_{12} and Q_6. The formulation CET6 was selected as an optimized formulation because it gave the best results in terms of the required in vitro buoyancy study, good matrix integrity and drug release in sustained release manner. In dissolution study of all formulation, it was observed that by increasing concentration of polymer, release rate of drug was retarded. All the formulations were presented a dissolution behavior controlled by anomalous transport mechanism, It also followed best-fit model for all batches were the peppas and matrix kinetic model. Thus, it was concluded that the drug was released from matrix by diffusion mechanism.

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