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Formulation and in vitro evaluation of gastric oral floating tablets of cefixime for controlled release

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ABSTRACT

Cefixime is third generation cephalosporin antibiotic. Cefixime is slowly and incompletely absorbed from the GIT, which resulting into the poor bioavailability 40-50 %. So, in order to improve the therapeutic effect of the drug by increasing its bioavailability. In present research work to develop cefixime gastric oral floating tablets for controlled release and increased gastric retention time. The cefixime floating tablets were prepared by direct compression method. The powder blend was subjected for pre-compressional parameters. The prepared tablets were subjected to post-compressional analysis for the parameters such as hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. Drug compatibility with excipients was checked by DSC and FTIR studies. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. In all the formulations, hardness test indicated good mechanical strength, friability is less than 1%, and weight variation of tablets was within acceptable limits. The results of *in vitro* buoyancy time and lag time study revealed that as the concentration of sodium bicarbonate increases there is increase in total buoyancy time and decrease in lag time. In all the formulations buoyancy time ranges from 40-690 min and lag time ranges from 60-8 min. The formulation F2 shows the lag time of 8 min. and buoyancy time 600 min. The release of cefixime from all the formulations ranges from 54.52-79.09 % at the end of 12 hrs. The results were revealed that as the concentration of sodium bicarbonate increases from 30-60 mg per tablet, there is increase in the drug release and floating time has been increased. DSC and FT-IR studies revealed that, there was no incompatibility of the drug with the excipients used. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. From this study, it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence, may improve the therapeutic effect of the drug by increasing the bioavailability.

Keywords: Cefixime, gastric oral floating, hydroxyl propyl methyl cellulose, hydroxy ethyl cellulose.

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INTRODUCTION

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size. The present invention relates to a pharmaceutical composition in the form of tablets is designed to deliver effectively a drug to a patient over a specific period of time (temporal control) and from particular portion of the patients GI tract (spatial control) [1]. A controlled drug delivery system is usually designed to deliver the drug in order to maintain blood levels above its minimum effective concentration and below its maximum safe concentration. The gastric oral floating tablets results in release of the drug in to the more absorptive regions of the GIT, is in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drug so that it is about the same as or less than the retention time of the tablets at the site of absorption. Thus the system is not transported past the "absorption window" prior to releasing the entire drug, and the maximum bioavailability is attained [2-4]. For designing of gastric oral floating tablets different excipients were used are a gas generating agent (sodium bicarbonate), swelling agent (cross linked CMC), viscolyzing agent (xanthan gum, Guar gum) and a gel forming polymer (sodium alginate). Further, the pharmaceutical composition also contains an additional hydrophilic polymer (HPMC K4M, and HEC) were used.

In present research work Cefixime is used, it is third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. Cefixime with p^{Ka} value of 2.5 a weak acid which will remain unionized at acidic pH thus increases absorption in the stomach region. It is primarily absorbed from the stomach and upper part of intestine. In view of this absorption characteristic, the hypothesis of current investigation is that if the gastric residence time of Cefixime containing formulation is prolonged and allowed to float in the stomach for a long period, the oral bioavailability might be increased. Cefixime is a not soluble in water after its oral administration; it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability around 40-50 % [5-6] So, in order to improve the therapeutic effect of the drug by increasing its bioavailability, safe and effective levels are maintained for a long period time [2, 8-10]. Hence, we are planning to develop cefixime gastric oral floating tablets for controlled release and increased gastric retention time. The cefixime floating tablets were prepared by direct compression method using different concentrations of hydrophilic polymers. The compositions of floating tablets are given in **[Table 1].**

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Table 1: Composition of cefixime floating tablets.

Ingredients	F1	F2	F3	F4	F5	F6
Cefixime	200	200	200	200	200	200
Sodium bicarbonate	30	40	50	60	70	60
Cross linked PVP	10	10	15	20	20	20
Xanthan gum	10	10	5	10	10	10
Gaur Gum	10	10	15	20	20	20
Sodium Alginate	10	10	15	20	10	10
HPMC K4M	30	40	50	60	60	70
HEC	40	40	60	60	50	60
NaCMC	10	20	30	-	-	-
MCC	-	-	-	20	20	20
Lactose	120	80	30	10	10	-
Citric acid	00	10	10	10	10	10
Mannitol	20	20	10	10	10	10
Magnesium stearate	10	10	10	10	10	10
Total	500	500	500	500	500	500

MATERIALS AND METHODS

Cefixime drug is procured as a gift sample from Karnataka antibiotics, Bangalore, India. HPMC K4M purchased from Ozone international, Mumbai. Carbopol 934, xanthan gum (XG), hydroxyl ethyl cellulose (HEC), Guar gum, magnesium stearate and citric acid are purchased from Hi media laboratories Pvt. Ltd, Mumbai. India, Cross-linked polyvinyl pyrrolidone (PVP) from signet Chemical Corporation, worli, Mumbai. Sodium bicarbonate, sodium alginate, lactose, mannitol and talc were purchased from S.D. Fine Chemicals. Mumbai. All other materials used were of pharmaceutical grade.

Preparation of cefixime floating tablets

Floating tablets were prepared by mixing the drug Cefixime 200 mg with the gas generating component, the swelling agent, the gas entrapping viscolyzing agent and the optionally included gel forming polymer, citric acid as acid source and lactose by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2min.The lubricated blend was compressed into tablets using 12 mm flat-face round tooling on CLIT Pilot Press rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4.0 mm tablet thickness [7-9].

Evaluation of cefixime floating tablets

The powder blend was subjected for pre-compressional parameters. The prepared tablets were evaluated for post-compressional parameters as weight variation, hardness, friability, thickness, drug content, lag time subsequently buoyancy time, *in-vitro* dissolution

studies, and stability studies. For weight variation ten tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation. Pfizer [10-12] hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. The thickness and diameter of 4 tablets (3 tablets from each batch) were recorded during the process of compression using vernier calipers (Mitotoyo; Japan). The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Two tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula.

$$F = (1- W_0 / W) \times 100$$

Where,
W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

For the drug content [9] uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 100 mg of cefixime was dissolved in 100ml methanol and liquid was filtered using Whatman filter paper and diluted up to 50µg/ml. The cefixime content was determined by measuring the absorbance at 288 nm (using UV-VIS spectrophotometer, Shimadzu 1700) after appropriate dilution with methanol. The mean percent drug content was calculated as an average of three determinations. The buoyancy test of tablet was studied by placing then in 200 ml beaker containing 0.1 N HCL, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCL, maintained at 37 ± 0.5^0 C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation. The measurements were carried out for each series of tablets (N=3).

In-vitro dissolution study [12, 13] was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution testers USP) type 2 (paddle). The dissolution medium was phosphate buffer pH 1.2 for 12 hrs. The temperature was maintained at $37^0 \pm 0.5^0$C. The rotation speed was 100 rpm. Five ml of aliquots were withdrawn at predetermined time. The medium was replenished 5 ml of fresh buffer each time sample was analyzed by using UV spectrophotometry at 288 nm.

Characterization of cefixime tablets

FTIR Studies: IR spectra for drug, tablets were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

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DSC Studies: 5 mg of pure Cefixime and cefixime floating tablets were sealed in perforated aluminium pans for DSC scanning using an automatic thermal analyzer system (Mettler Toledo, USA). Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10^0 C/min from 50-300^{0}C.

Kinetic study: To analyze the mechanism of drug release form the tablets the in vitro dissolution data were fitted to zero order (K=kt), korsmeyer and peppas model ($F=kt^n$), higuchi ($F=k\sqrt{t}$) release models. Where F is the fraction of drug release, k is the release constant and t is time [14-17].

Stability study: The fabricated floating tablets formulations were subjected for stability study[18]. The stability study was carried out according to ICH guidelines at 40^0 C and relative humidity at 75 % for three weeks. For stability study, the tablets were sealed in aluminum packing coated inside with polyethylene. These sample containers were placed in desiccators maintained at 75% RH. The product was evaluated for *In-vitro* drug release and drug content. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions.

RESULT AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. The results of pre-compression parameters were given in **Table 2.**

Table 2: Pre-compressional parameters of cefixime floating tablets.

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (I_C)	Hausner ratio (H_R)	Angle of repose (θ)
F1	0.3333 ± 0.05	0.4166 ± 0.03	20 ± 0.10	1.25 ± 0.02	24.20 ± 0.12
F2	0.3061 ± 0.04	0.3658 ± 0.05	16.32 ± 0.11	1.19 ± 0.04	26.76 ± 0.14
F3	0.3191 ± 0.06	0.3750 ± 0.02	14.89 ± 0.03	1.17 ± 0.06	21.36 ± 0.18
F4	0.3488 ± 0.02	0.4166 ± 0.04	16.27 ± 0.06	1.19 ± 0.03	27.67 ± 0.13
F5	0.3140 ± 0.03	0.4058 ± 0.05	16.23 ± 0.10	1.20 ± 0.05	22.70 ± 0.12
F6	0.3221 ± 0.04	0.3658 ± 0.05	16.30 ± 0.11	1.18 ± 0.04	26.56 ± 0.10

All above reading are average ± SD, n=3

In all the formulations, the weight variation of tablets was ranges between 497 to 504 mg. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit [8]. Hardness test indicated good mechanical strength, the hardness and percentage friability of the tablets of all the batches remained in the range of 7.0 to 9.0 kg/cm^2 and 0.64 to

0.95% respectively. Friability is less than 1%, indicated that tablets had a good mechanical resistance. Thickness of the tablets was ranges from 3.98 to 4.18mm. The evaluation parameters were within acceptable range for all the formulations. The results of weight variation, hardness, thickness, friability and were shown in **Table 3.** The drug content of the tablets was ranges from 99.60% to 106.91% which is within acceptable limits. The swelling index of the tablets was in the range 38.18 to 82.4 %. The results are given in **Table 3.**

Table 3: Post-compressional parameters of cefixime floating tablets.

FC	Average wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Swelling index
F1	498	4.15 ± 0.04	7.50± 0.02	0.64±0.085	102.08 ± 0.13	38.18±0.23
F2	500	3.98 ± 0.02	8.4± 0.04	0.78±0.041	99.63 ± 0.12	52.72±0.14
F3	497	4.05 ± 0.07	9.0± 0.06	0.77±0.039	104.71 ± 0.22	68.2±0.80
F4	502	4.18 ± 0.02	8.0± 0.05	0.95±0.075	106.91 ± 0.15	74.5±0.16
F5	504	4.10 ± 0.03	8.5± 0.02	0.76 ± 0.040	101.30 ± 0.10	76.5±0.14
F6	502	4.16 ± 0.04	7.0± 0.03	0.68±0.080	99.60 ± 0.18	82.4±0.10

All above reading are average ± SD, n=3, FC= Formulation code

The results of *in-vitro* buoyancy time and lag time study revealed that as the concentration of sodium bicarbonate increases there is increase in total buoyancy time and decrease in lag time as shown in (**Fig 1).** In all the formulations buoyancy time ranges from 40-690 min and lag time ranges from 60-8 min. The formulation F2 shows the lag time of 8 min. and buoyancy time 600 min. The results were shown in **Table 4**.

Table 4: Floating ability of cefixime floating tablets.

FC	Floating Lag time (min)	Floating duration (min)	Integrity
F1	45	40	Broken
F2	60	60	Broken
F3	20	480	Intact
F4	8	600	Intact
F5	16	630	Intact
F6	14	690	Intact

FC=Formulation code, n=3

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The release of cefixime from all the formulations **(Fig 2)** was in the range of 33.16 -45.93 % at the end of 6 hrs and 54.52-79.09 % at the end of 12 hrs. The results are given in **Table 5**. The results were revealed that as the concentration of sodium bicarbonate increases from 30-60 mg per tablet, there is increase in the drug release and floating time has been increased. The formulation containing large concentration of high viscosity polymers induced formation of strong viscous gel layer that leads to decreased water diffusion into the tablet matrix which results in decrease drug release. The formulation F4containing 60 mg of sodium bicarbonate, HPMC K4M 60 mg and HEC 60 mg showed the maximum drug release when compare to other formulations containing increased concentrations of high viscous polymers.

Table 5: *In- vitro* release study of cefixime floating tablets.

Formulation code	% drug release after 6 hrs	% drug release after 12hrs
F1	35.51 ± 1.60	60.87 ± 0.23
F2	33.16 ± 0.91	54.52 ± 0.69
F3	40.24 ± 1.64	69.89 ± 0.47
F4	45.93 ± 2.02	79.09 ± 1.02
F5	38.24 ± 1.64	64.52 ± 0.43
F6	39.20 ± 1.64	62.40 ± 0.32

All values are expressed as mean ± SD, n=3

Table 6: Curve fitting analysis for different formulations

Formulations	Zero order (R)	First order (R)	Higuchi's (R)	Peppa's	
				R	N
F1	0.9746	0.9807	0.9709	0.9863	0.60
F2	0.9396	0.9734	0.9871	0.9788	0.60
F3	0.9816	0.9800	0.9598	0.9571	0.61
F4	0.9741	0.975	0.9766	0.973	0.58
F5	0.9935	0.8984	0.9935	0.9842	0.58
F6	0.9829	0.9214	0.9829	0.9861	0.50

The kinetic study **(Fig 3-5)** results suggest that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism the *in vitro* release data were also subjected to Higuchi's diffusion equation the r-values **(Table 6)** of all the formulations were 0.9709 to 0.9871. It suggests that the drug released by diffusion mechanism. The formulations are also treated to Peppa's plots by taking log percent drug release versus log time. The plots are found to be fairly linear and the regression values (n value) of all formulations ranges **(Table 6)** from lowest 0.58 to highest 0.61 which in the range of $0.45 < n < 0.89$. This suggests that the drug was released by Non-Fickian control (Anomalous diffusion) with swelling.

FT-IR studies, Cefixime exhibited characteristic **(Fig 6)** NH_2 absorption peak at 3290 cm^{-1} which is a normal range of absorption of primary amines. The NH of the amide group has shown absorption range at 30 to 25cm^{-1} and corresponding the C-H of the aromatic as well as

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aliphatic functionalities are observed at 3140, 3032, 2978 and 2947 cm^{-1}. The C=O absorption peak of the carboxylic acid have given rise to a overlapping absorption of two carboxylic acids functional groups. C=O of the amide both cyclic imides and amide are seen at 1664 cm^{-1}. These observations are in concurrence with the structure of the drug molecule.. In this experiment of F4 along with drug and polymer hydroxy ethyl cellulose (HEC) is taken for the studies. In this case **(Fig.7)**also expected broad humps are observed at 3398, 1700 cm^{-1} corresponding to the NH_2, NH, OH functionalities and COOH, CO functional groups present in the drug suggesting that, this formulation is not a reaction product but it is a mixture of the drug and the polymer.

Table 7:*In- vitro* release and drug content data of stability study of formulation F4

Time (hrs.)	Cum. % Drug released ± SD.		Drug content	
	1st Day	21st Day	1st Day	21st Day
01	19.92	18.12	101.10	100.60
02	25.54	20.84	99.10	104.23
03	31.63	39.80	102.5	102.70
04	37.03	40.89	99.70	99.10
05	41.98	41.87	102.20	102.35
06	45.93	44.78	101.10	99.40
07	52.01	50.98	100.60	99.30
08	57.57	54.57	97.92	99.70
09	64.94	60	99.70	102.22
10	69.66	64.30	105.03	99.10
11	73.54	72.14	104.23	100.60
12	79.09	76.10	106.91	105.03

In the DSC study of pure Cefixime shows that the drug started melting at 55.37^{0}C and ends at 112.45^{0}C **(Fig.8).** The CGPS tablet formulation prepared with Cefixime, HPMC, HEC, sodium alginate were subjected for DSC studies, wherein formulation product F4 (**Fig.9**) started melting at 85^{0}C and completed at 164^{0}C. This wide range of melting process suggests that formulation F4 is a product of physical mixture of all the constituents mentioned herein, if it is a reaction product which might have formed during the formulation, it has given rise to short range of melting process with 2 to 3^{0}C, which has not happened in this case, it confirms the drug used in the formulation is in the free state rather than in the chemically reacted form. Drug is freely available to the system whenever administered.

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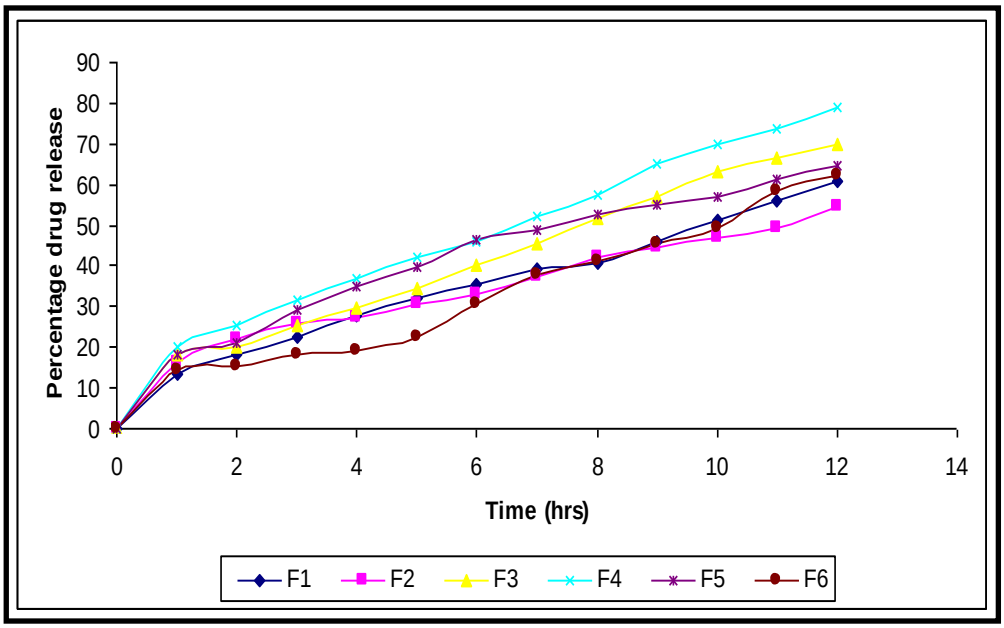
Fig 1: Photograph showing Floating ability of cefixime floating tablets.

Fig 2: Comparative drug release profile of formulations F1 to F6.



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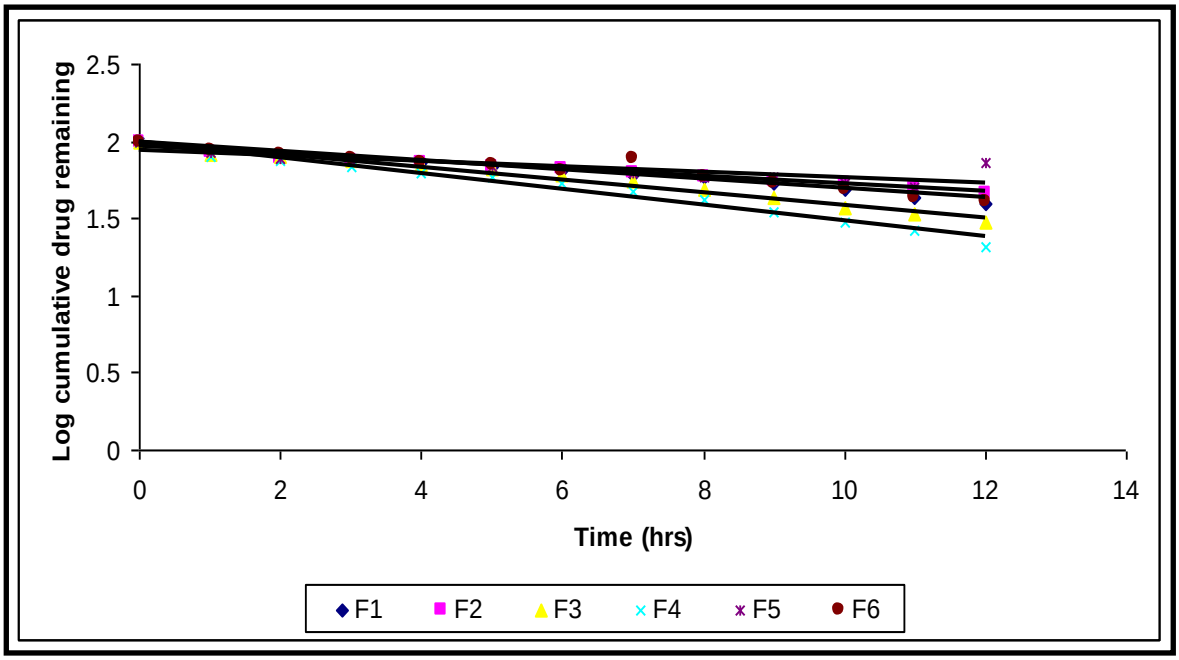
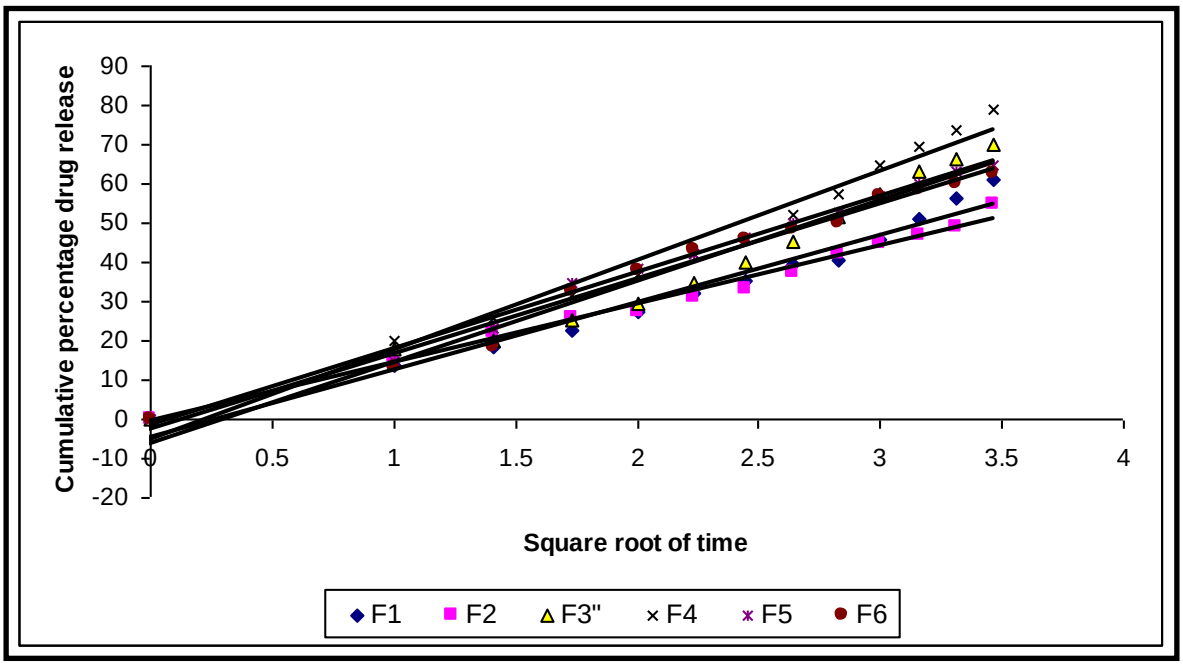


Fig 3: Comparative First-order plots of formulations F1 to F6.



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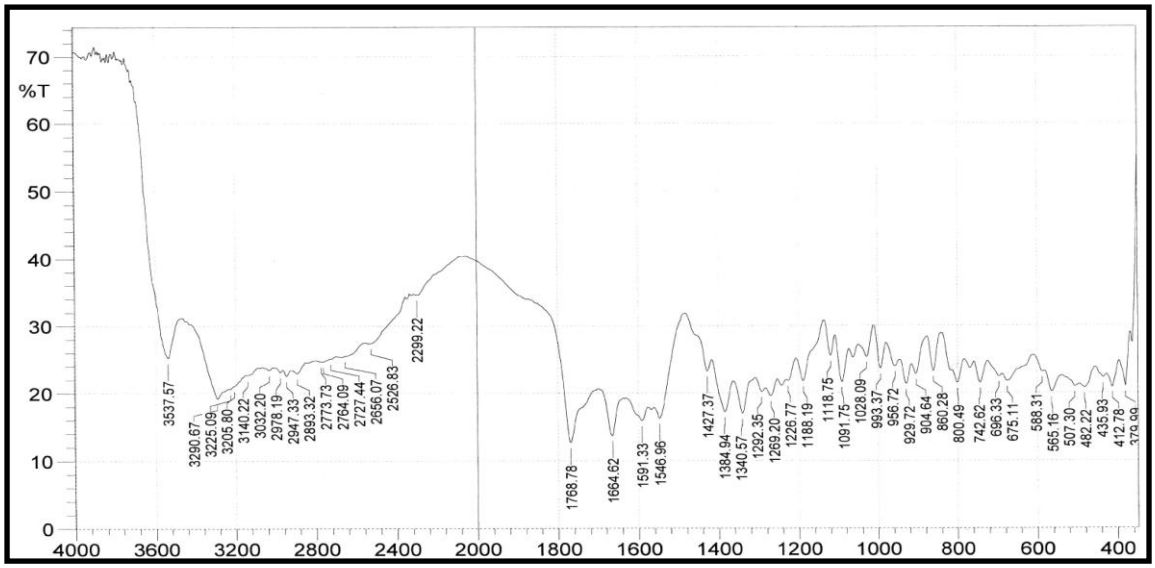

Fig 4: Comparative study of Higuchi plots of formulations F1 to F6.

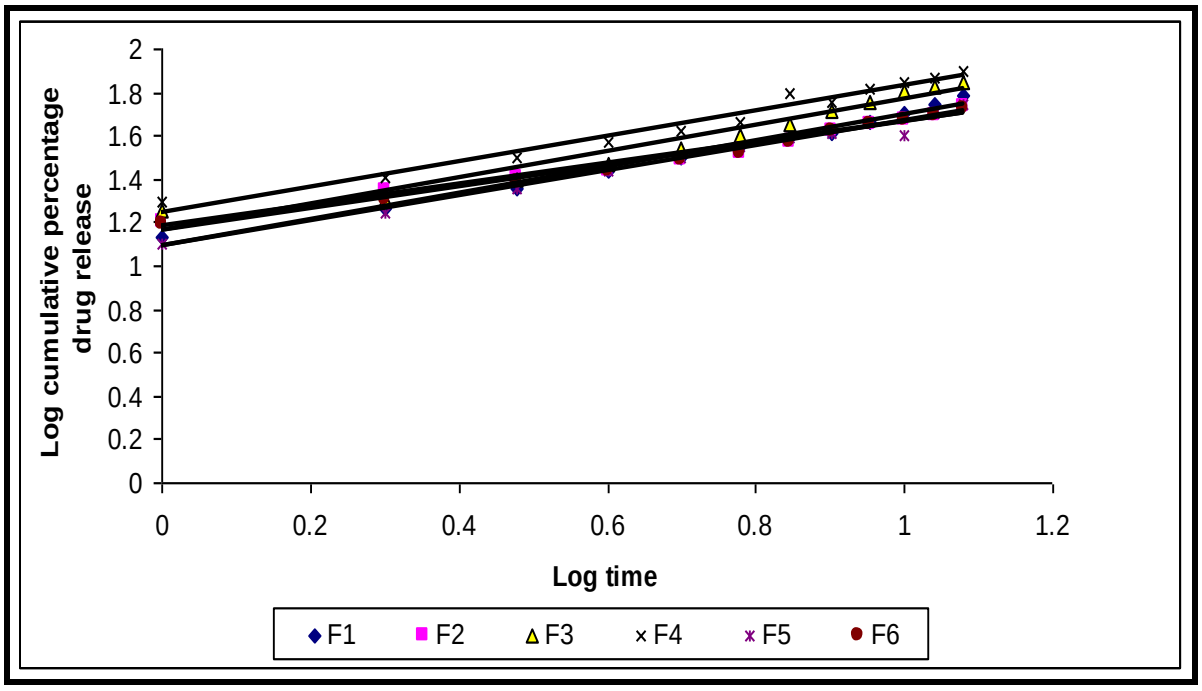

Fig 5: Comparative study of Peppa's plots of formulations F1 to F6

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Fig 6: IR spectra of pure drug Cefixime Trihydrate

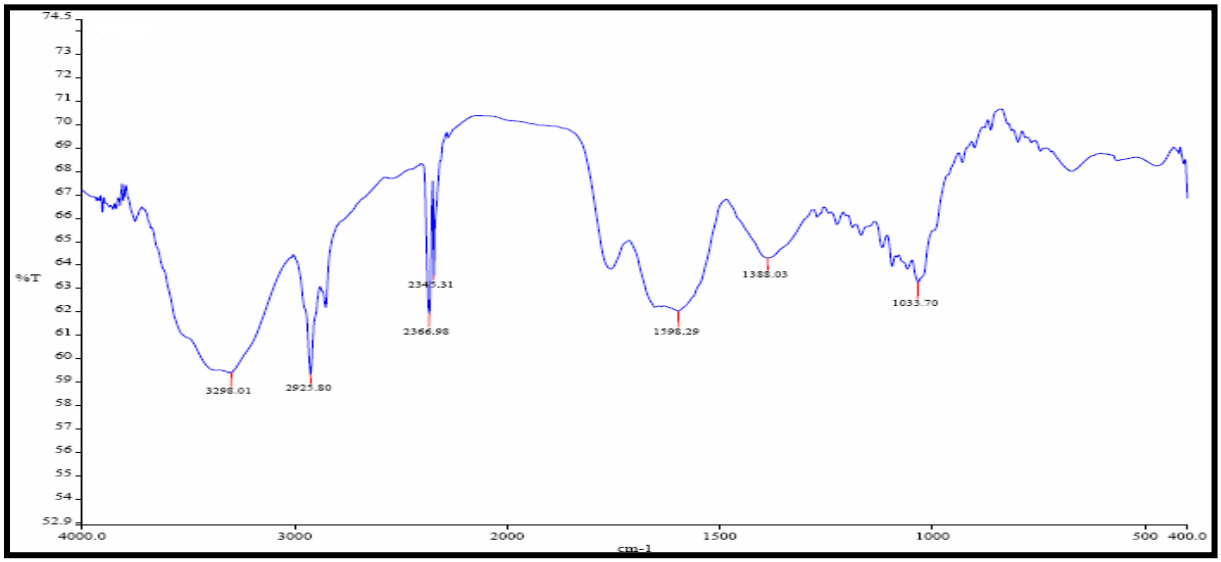

Fig 7: IR spectra of formulation F4.

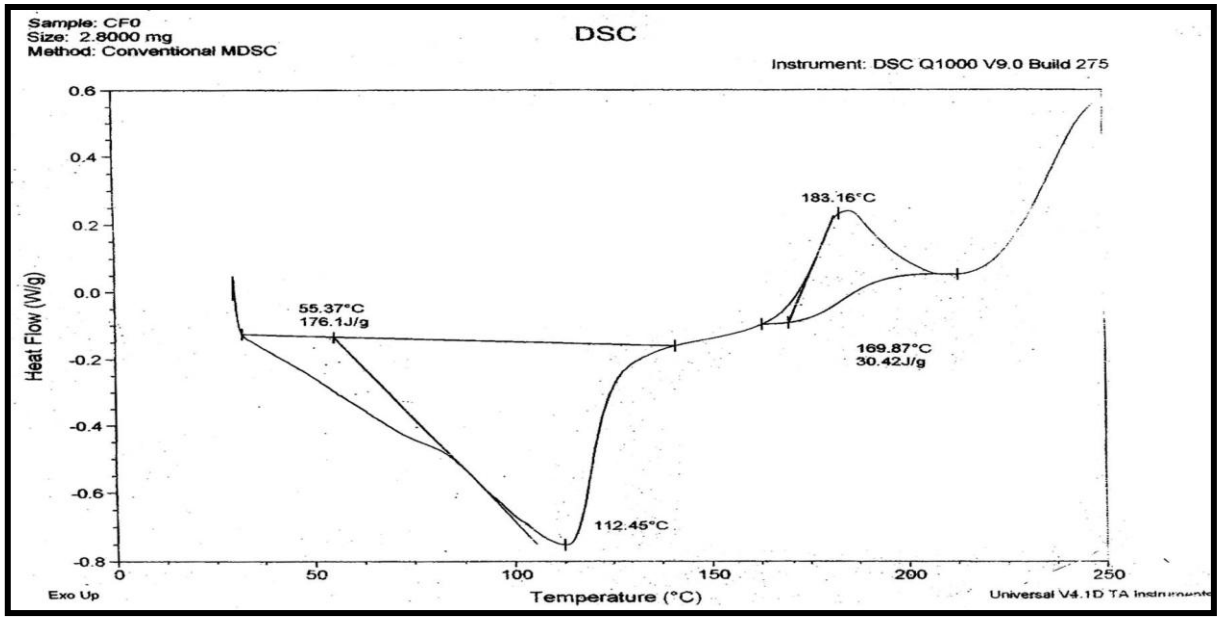

Fig 8: Differential scanning colorimetric study of pure drug cefixime.

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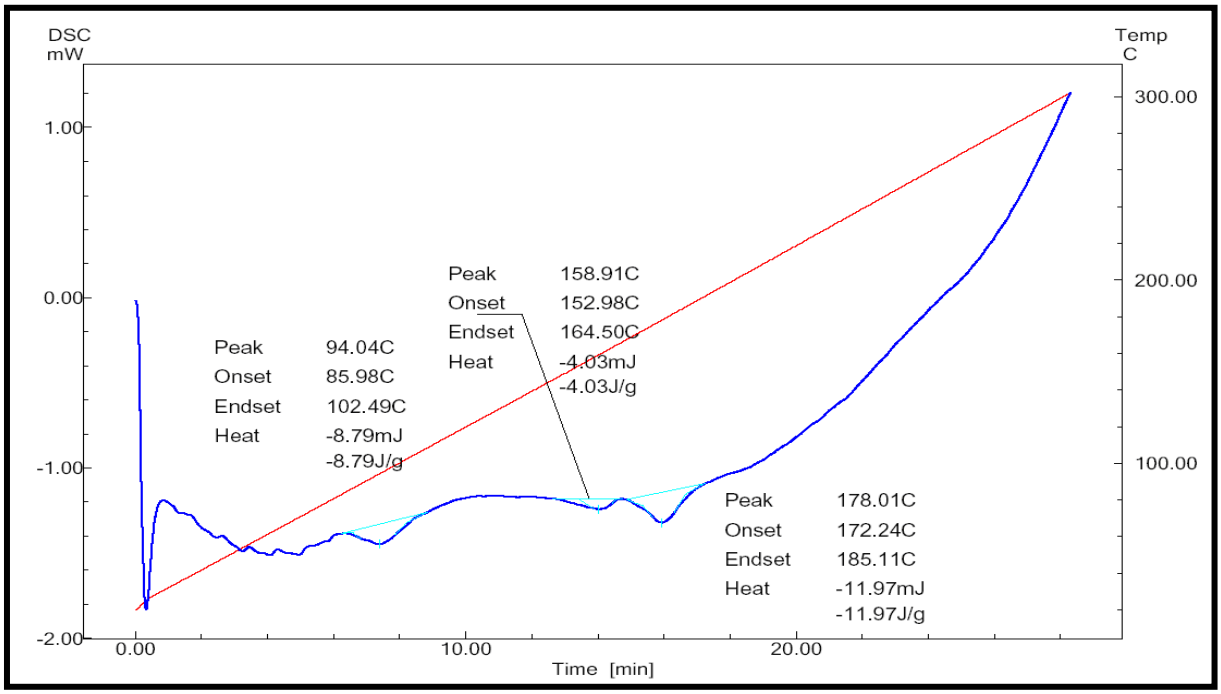

Fig. 9: Differential scanning colorimetric study of F4.

The stability study conducted as per the ICH guidelines for twenty one days and the formulations were found to be stable. No appreciable change in drug content and *in vitro* release study was observed even after the evaluation for 21 days. Results were showed in **[Table 6].** In the present invention, it has found that a xanthan gum helps in maintaining tablet integrity.

CONCLUSION

From this study, it can be concluded that, the formulation retained for longer periods of time in the stomach (spatial control) and provides controlled release of the drug. Hence, CGPS tablets retained for longer periods of time in the stomach may leads to improve the therapeutic effect of the drug by increasing its bioavailability.

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