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Formulation and *in-vitro* evaluation gastroretentive drug delivery system of Cefixime for prolong release

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ABSTRACT

In present research work to develop cefixime gastroretentive tablets for prolong release and increased gastric retention time. Cefixime is third generation cephalosporin antibiotic. Cefixime is slowly and incompletely absorbed from the GIT, which resulting into the poor bioavailability 40-50 %. Cefixime gastroretentive tablets were prepared by direct compression method. The powder blend was subjected for pre-compressional parameters. The prepared tablets are evaluated to post-compressional parameters. 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. The values of post-compressional parameters evaluated were within acceptable limits. The results of buoyancy and lag time study, the values of in-vitro buoyancy time ranges from 32 to 654 min where as floating lag time ranges from 2.36 to 57 min. The formulation GRT-5 shows the lag time 2.36 min and buoyancy time 654 min. These results revealed that as the concentration of sodium bicarbonate increases there is increase in total buoyancy time and decrease in lag time. The citric acid level in the formulations greatly influenced the drug release. The release of cefixime from all the formulations in the range of 33.53 - 58.15 % at the end of 6 hrs and 58.41 - 95.34 % at the end of 12 hrs. The formulation, GRT-5 shows 58.15 % drug release in 6 hrs and 95.34 % drug release at the end of 12 hrs. 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. Form this study, it is concluded that, the formulation retained for longer periods of time in the stomach and provides prolong release of the drug. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability.

Key wards: Cefixime, HPMC K4M, floating tablets, prolong release, bioavailability.

INTRODUCTION

Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time. Dosage form with prolonged gastric residence time or gastro-retentive dosage form (GRDF) provides an important option [1]. Under certain circumstances

prolonging the gastro-retentive 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. Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, which of short gastric residence time and unpredictable gastric emptying rate [2]. Depending on the mechanism of buoyancy, two distinctly different methods viz., effervescent and non effervescent systems have been used in the development of floating drug delivery systems (FDDS) [3].

Effervescent drug delivery systems utilize matrices prepared with swellable polymers such as methocel [4] or polysaccharides and effervescent components are like sodium bicarbonate and citric acid. 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 gastroretentive 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 [5-7].

Cefixime gastroretentive tablets were prepared by using different concentrations of hydroxy propyl methyl cellulose (HPMC K4M), carbopol, sodium carboxy methyl cellulose (NaCMC), sodium bicarbonate and citric acid. 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 % [8-9] 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 [10-12]. Hence, we are planning to develop cefixime gastroretentive tablets (GRT) for prolong release and increased gastric retention time. The cefixime gastroretentive tablets were prepared by direct compression method using different concentrations of hydrophilic polymers. The compositions of gastroretentive tablets are given in **[Table 1].**

MATERIALS AND METHODS

Cefixime drug is procured as a gift sample from Karnataka antibiotics, Bangalore, India. HPMC K4M was procured as gift sample from AstraZeneca Pharma India Ltd, Bangalore. Carbopol 934, magnesium stearate and citric acid are purchased from Hi media laboratories Pvt. Ltd,

Mumbai. India, Sodium bicarbonate, sodium CMC, lactose, and talc were purchased from SD. Fine Chemicals, Mumbai. All other materials used were of pharmaceutical grade.

Preparation of cefixime gastroretentive tablets: Gastroretentive tablets were prepared by mixing the drug cefixime 200 mg with the gas generating component, citric acid as acid source and other ingredients 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 [13].

Evaluation of cefixime gastroretentive tablets:

The powder blend was subjected for pre-compressional parameters. The prepared gastroretentive 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 [14-16] 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 [11] 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 100 ml 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^o 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).

Swelling index [16]: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation GRT-1, GRT-2 GRT-3, GRT-4, GRT-5 and GRT-6 was studied. One tablet from each formulation was kept in a Petridish containing 0.1N HCL. At the end of 1 hrs, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 hrs, weights of the tablet were noted, and the process was continued till the end of 12 hrs. % weight gain by the tablet was calculated by formula;

S.I = {(Mt-Mo) / Mo} X 100,

Where, S.I = swelling index, Mt = weight of tablet at time 't' and Mo = weight of tablet at time t = 0.

In-vitro dissolution study [16-17] was carried out in the USP dissolution test apparatus (Electrolab TDT – 08 L Dissolution testers USP) type 2 (paddle). The drug release study was carried out in 0.1 N HCl for 12 hrs in 900 ml of dissolution media, temperature maintained at 37 ± 0.5^{o}C and agitated at 100 rpm. Periodically 5 ml samples were withdrawn and filtered through Whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Cefixime was measured spectrophotometrically at 288 nm.

Floating or Buoyancy Test [18]: The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT).The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37 ± 0.5^{o}C and agitated at 50 rpm in 900ml of simulated gastric fluid at 0.1N HCl. The time of duration of floatation was observed visually.

Characterization of cefixime gastroretentive tablets:

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

DSC Studies: 5 mg of pure drug cefixime and cefixime gastroretentive 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^{o}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 [18-19].

Stability study: The fabricated gastroretentive tablets formulations were subjected for stability study [20]. 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 of prepared gastroretentive tablets evaluated were within prescribed limits and indicated good free flowing property. The results of pre-compression parameters were given in **Table 2.**

In all the formulations, the weight variation of gastroretentive tablets was ranges between 497 to 504 mg. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit. 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 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 of quality control tests reveal that all the gastroretentive tablets are meeting the official pharmacopoeia requirements **(Table 3).**

Table 01: Composition of cefixime gastroretentive tablets.

FC	Cefixime	HPMC K4M	NaHCO3	Carbopol	citric acid	Lactose	Sod CMC	Talc	Mag Stea	Total tablet weight (mg)
GRT1	200	250	-	-	-	110	20	10	10	600
GRT2	200	250	40	-	20	50	20	10	10	600
GRT3	200	200	50	30	20	60	20	10	10	600
GRT4	200	200	60	30	20	50	20	10	10	600
GRT5	200	200	60	30	30	40	20	10	10	600
GRT6	200	200	50	30	20	60	20	10	10	600

FC – Formulation code, Magnesium Stearate - Mag Stae, Sodium Bicarbonate - NaHCO3,

Table 02: Pre-compressional parameters for cefixime gastroretentive tablets

FC	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
GRT1	0.750 ± 0.04	0.865 ± 0.02	13.29 ± 0.04	1.15 ± 0.04	29.05 ± 0.14
GRT2	0.624 ± 0.02	0.786 ± 0.03	20.60 ± 0.03	1.25 ± 0.02	29.24 ± 0.13
GRT3	0.636 ± 0.03	0.769 ± 0.02	17.29 ± 0.02	1.20 ± 0.04	26.84 ± 0.14
GRT4	0.646 ± 0.05	0.876 ± 0.05	26.25 ± 0.06	1.35 ± 0.06	28.24 ± 0.16
GRT5	0.634 ± 0.03	0.824 ± 0.05	23.05 ± 0.07	1.29 ± 0.06	28.36 ± 0.16
GRT6	0.664 ± 0.05	0.745 ± 0.03	10.87 ± 0.03	1.12 ± 0.08	27.22 ± 0.14

**The values represent mean ±S.D; n=3, FC = Formulation Code.*

Table 03: Post-compressional parameters for cefixime gastroretentive tablets

FC	Thickness	Hardness	Friability	Average	Drug Content	Swelling
GRT1	4.06 ± 0.04	6.0 ± 0.02	0.28	548	97.46	47.35
GRT2	4.14 ± 0.08	7.0 ± 0.04	0.36	551	98.42	58.00
GRT3	4.12± 0.06	7.5 ± 0.06	0.48	553	98.24	40.00
GRT4	4.08± 0.02	7.2 ± 0.02	0.56	548	99.58	72.60
GRT5	3.96 ± 0.04	7.3 ± 0.04	0.34	547	99.84	72.60
GRT6	4.16 ± 0.06	7.0 ± 0.04	0.64	552	97.56	58.00

**The values represent mean ±S.D; n=3. FC = Formulation Code.*

Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the gastroretentive tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled readily and axially during *in-vitro* buoyancy studies. The pH of the stomach is

elevated under fed condition (~3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; more over citric acid has an stabilizing effect on cefixime formulation. The effect of three different grades of methocel in the tablet with varying proportion of citric acid and sodium bicarbonate was studied on the release characteristics.

Fig 1: Photograph showing floating ability of cefixime floating tablets

Table 4: Floating ability of cefixime gastroretentive tablets

Formulation code	Floating lag time (min)	Floating duration(min)
GRT1	55min 30 sec	38
GRT2	60 min 50 sec	180
GRT3	20 min 48 sec	460
GRT4	03 min 53 sec	558
GRT5	02 min 36 sec	654
GRT6	19 min 47 sec	367

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

FC	% drug release after 6 hrs	% drug release after 12hrs
GRT1	33.53 ± 1.60	58.41 ± 0.23
GRT2	37.19 ± 0.24	63.12 ± 0.74
GRT3	42.96 ± 0.74	68.63 ± 0.66
GRT4	50.03 ± 1.02	74.65 ± 0.42
GRT5	58.15 ± 0.86	95.34 ± 0.76
GRT6	52.65 ± 1.12	83.56 ± 0.78

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

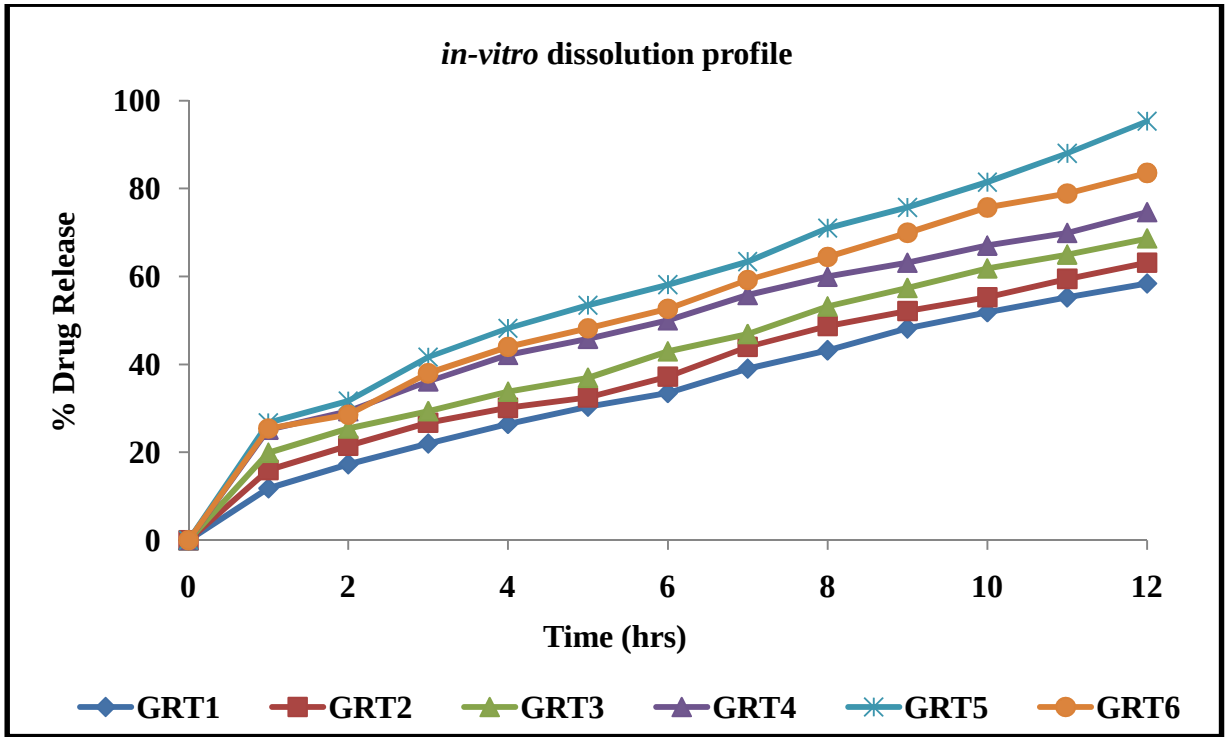

Fig 2: Comparative drug release profile of formulations GRT1 to GRT6.

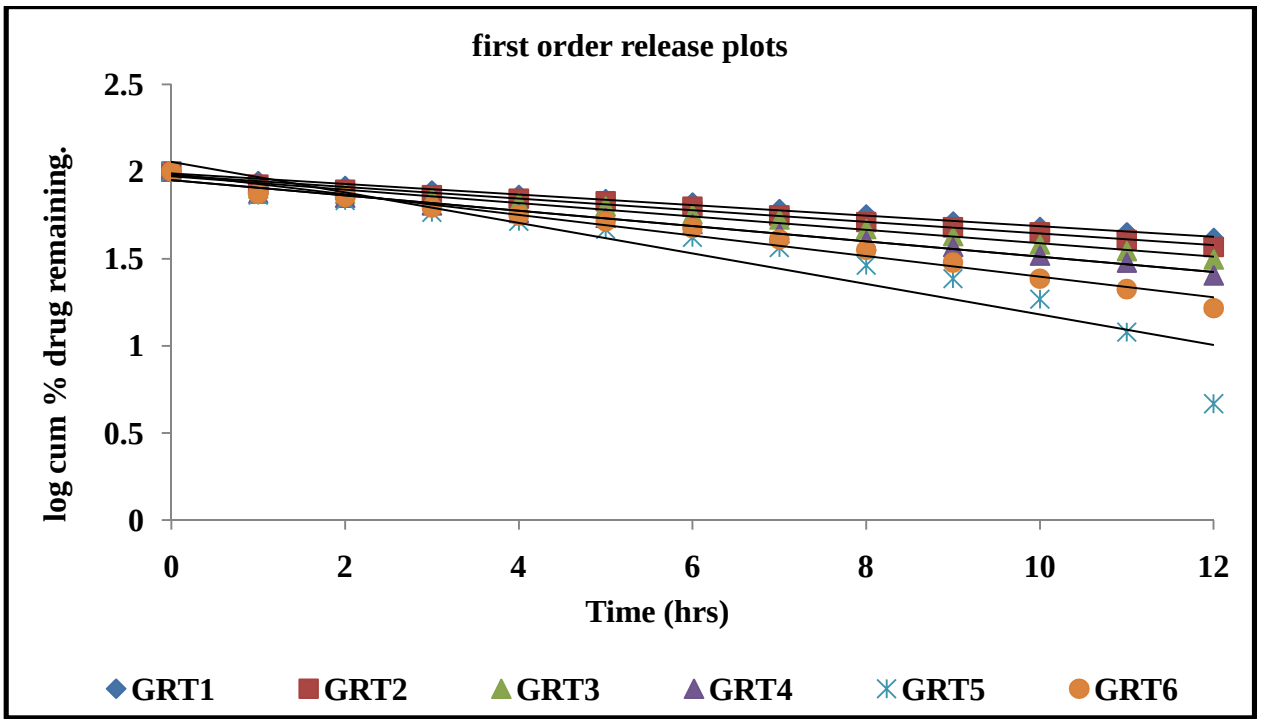

Fig 3 First order release plots of cefixime gastroretentive tablet formulations GRT1 to GRT6

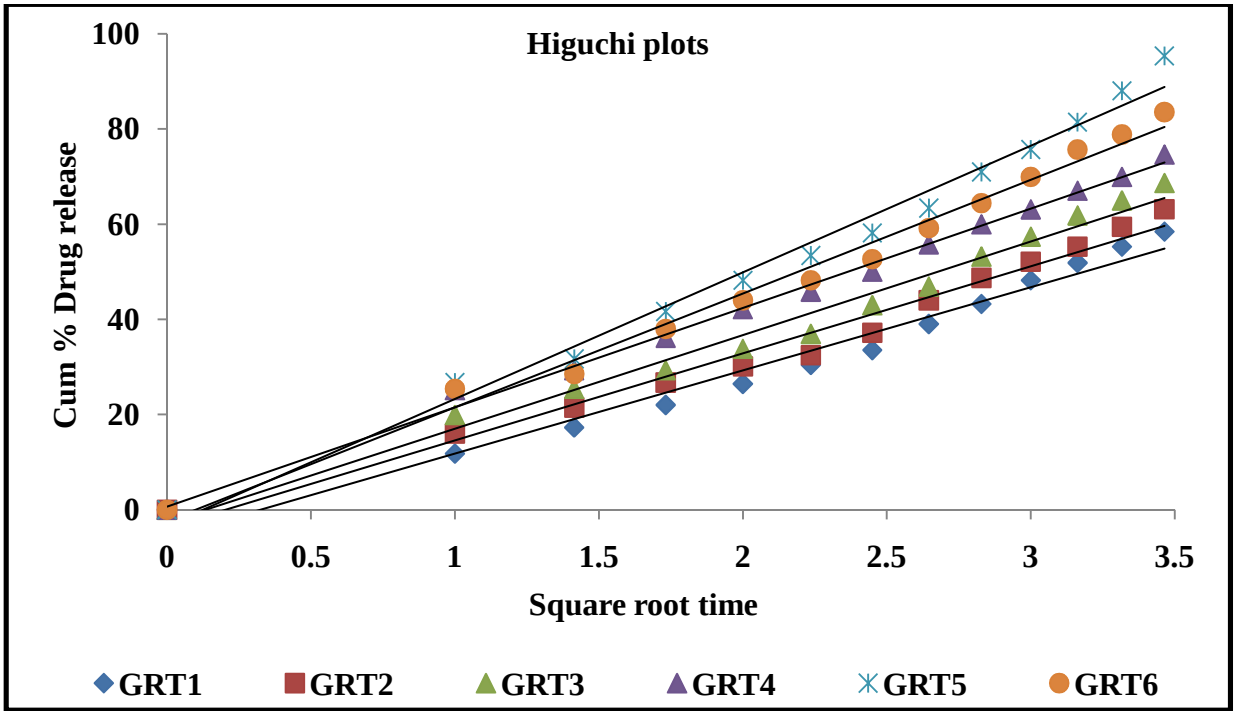

Fig 4: Higuchi diffusion plots of cefixime gastroretentive tablet formulations GRT1 to GRT6

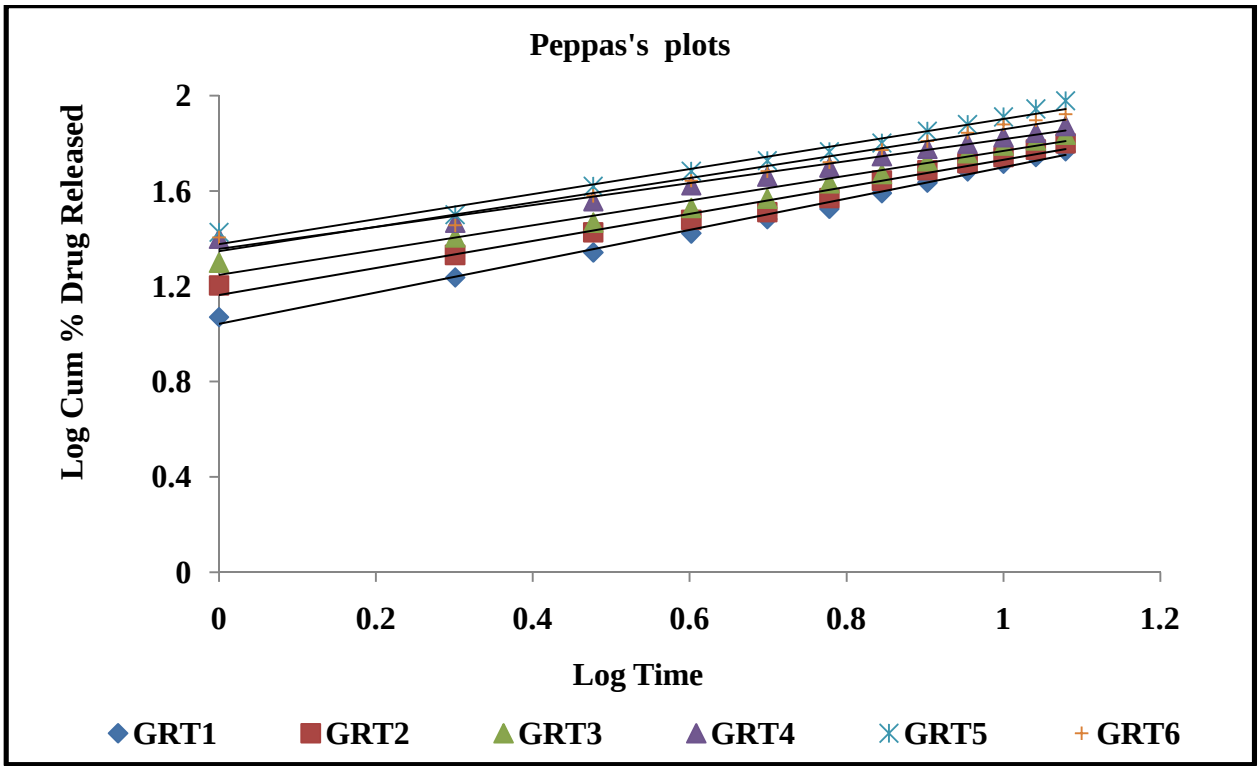

Fig 5: Peppas log-log plots of cefixime gastroretentive tablet formulations GRT1 to GRT6

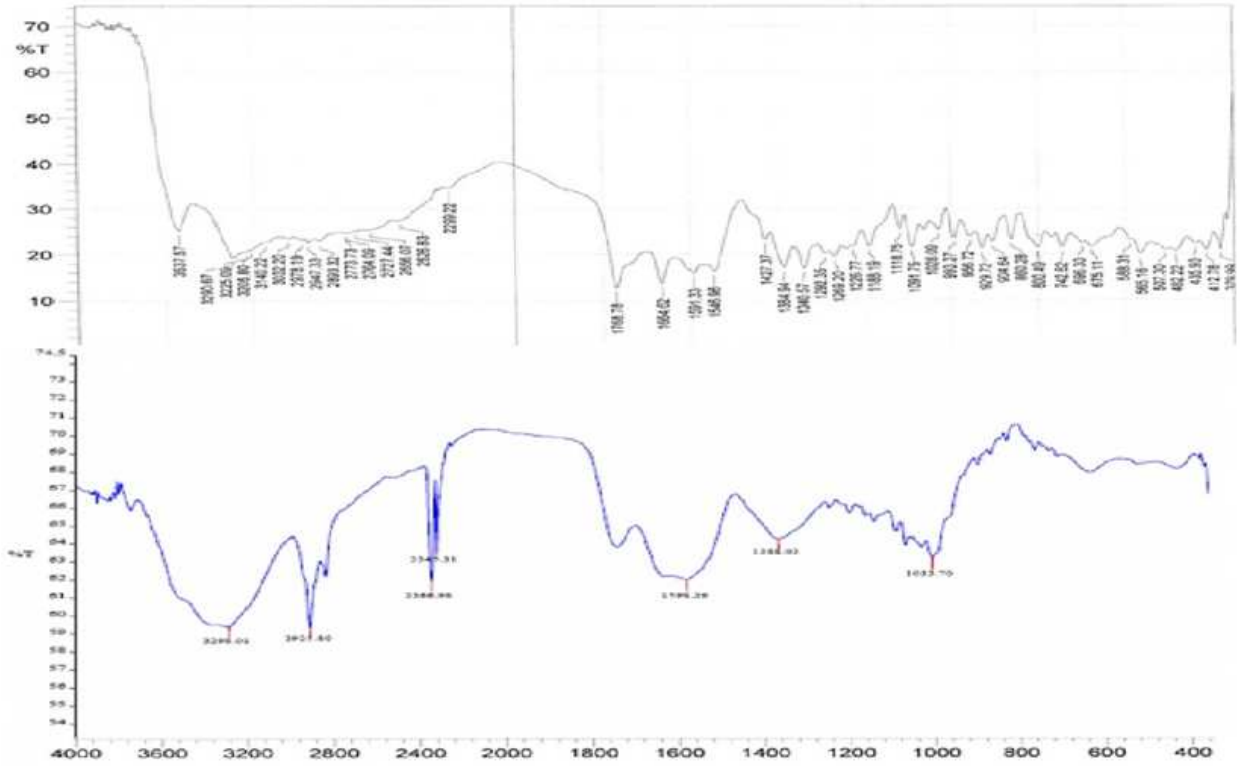

Fig 6: IR spectra of pure drug Cefixime [A], IR spectra of formulation GRT5 [B].

Table 6: Curve fitting analysis for different cefixime gastroretentive tablet formulations

FC	Zero order (R)	First order (R)	Higuchi's (R)	Korsemeyer Model	
				(R)	(n)
GRT1	0.9835	0.9945	0.9729	0.9935	0.66
GRT2	0.9687	0.9890	0.9798	0.9812	0.57
GRT3	0.9606	0.9867	0.9829	0.9723	0.52
GRT4	0.9265	0.9864	0.9957	0.9834	0.46
GRT5	0.9585	0.9793	0.9860	0.9801	0.51
GRT6	0.9529	0.8807	0.9892	0.9757	0.52

FC = Formulation code

Table 7: Cefixime released from formulation (GRT5).

Time (hrs)	% Cumulative Drug Release		
	Initial	25 ^{0}C/60 % RH	40 ^{0}C/75 % RH
	(0 Months)	(3 Months)	
1	26.72	26.45	26.19
2	31.69	31.43	31.17
3	41.65	41.38	41.12
4	48.19	47.93	47.67
5	53.43	53.17	52.91
6	58.15	57.89	57.62
7	63.39	63.12	62.86
8	70.98	70.72	70.46
9	75.70	75.44	75.17
10	81.46	81.20	80.94
11	88.01	87.75	87.48
12	95.34	95.08	95.08

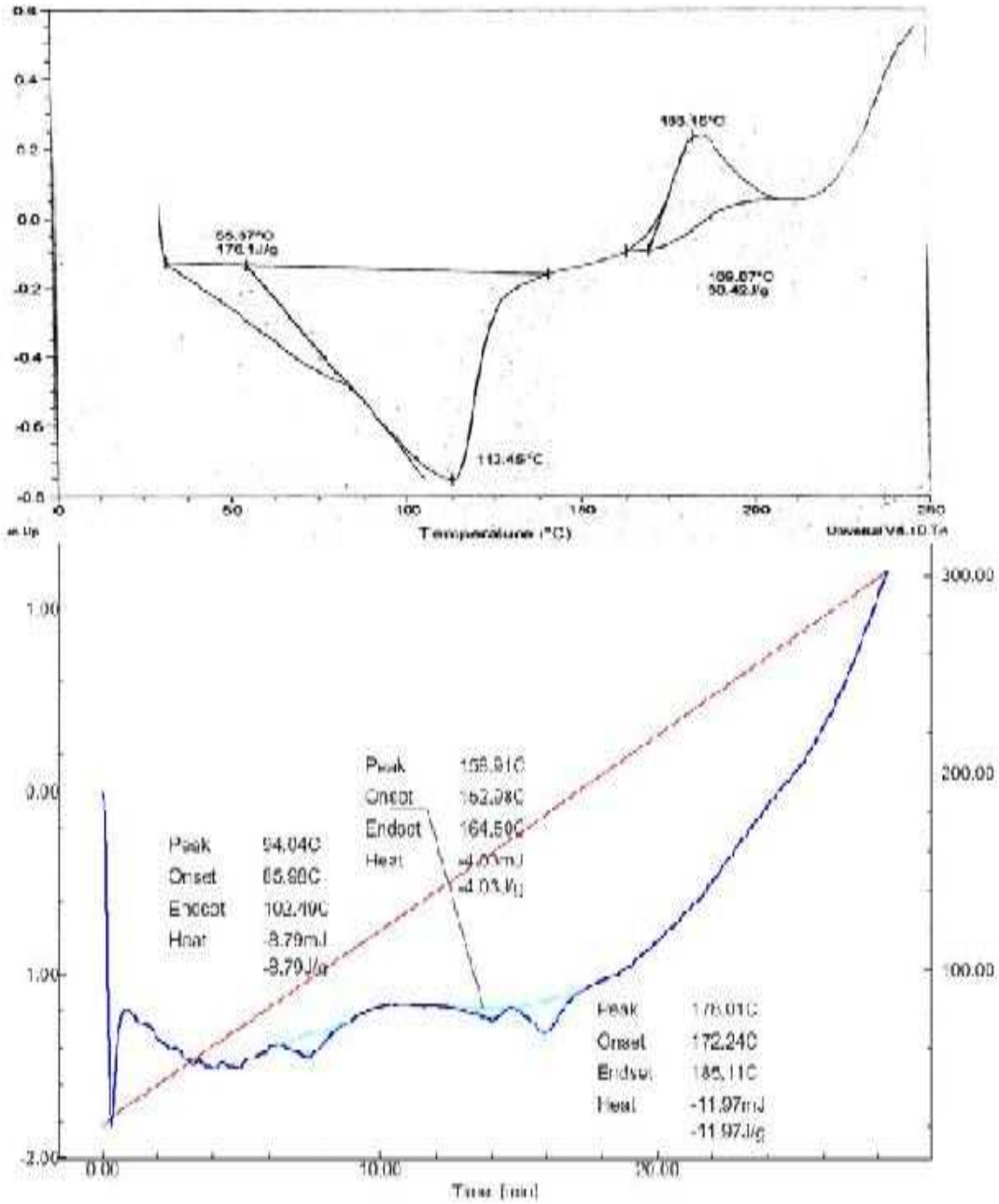

Fig 7: Differential scanning colorimetric study of pure drug cefixime [A], DSC study of formulation GRT5

The results of *in-vitro* buoyancy time and lag time study, the values of *in-vitro* buoyancy time ranges from 48 to 678 min where as floating lag time ranges from 2.5 to 60 min. Formulations prepared with effervescent have shown good floating lag time and good floating characters, whereas the formulations prepared with carbopol have longer floating lag times. Carbopol slowly swells and attains the density < 1 for floating. Increased floating time was observed with formulations containing carbopol. The presence of effervescent reduced floating lag time, which may be because of entrapment of gas in the tablets. The formulation GRT-5 shows the lag time 2.5 min and buoyancy time 678 min. The results are shown in **Table 4**. 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).** It is evident from the *in-vitro* dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to of excess carbon dioxide,

disturbing the monolithic tablet. The citric acid level in the formulations greatly influenced the drug release.

The dissolution profiles of the formulations from GRT1 to GRT6 are represented graphically in **Fig 2** and the results are shown in **Table 5.** The release of cefixime from all the formulations in the range of 33.53 - 58.15 % at the end of 6 hrs and 58.41 - 95.34 % 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. 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 GRT-5 containing 50 mg of sodium bicarbonate, HPMC K4M 250 mg and Carbopol 20 mg showed the maximum drug release when compare to other formulations containing increased concentrations of high viscous polymers. A retarded drug release is seen in formulation GRT-5 and containing effervescent and carbopol because of the reduced surface area of contact and retardation of hydration. The preliminary studies revealed the HPMC K4M matrix could not sustained the drug release for a period of 12 hrs, and this may due the fact that HPMC upon contact with water forms a hydrogel layer which acts as a gel boundary for the delivery system, but it failed to retard the release of drug through the matrix because of the high solubility of drug in the stomach pH. The incorporation of Carbopol 934 not only retarded the release but also sustain the release for a period for 12 hrs.

The data obtained from *in-vitro* dissolution studies were fitted in different models viz. zero order, first order and Korsemeyer's equation represented graphically in **Fig 3-5** and the results are shown in **Table 6.** Kinetics drug release result reveals that all formulations follow first-order kinetics as correlation coefficient (r^2) values are higher than that of zero-order release kinetics. To ascertain, the drug release mechanism the *in-vitro* release data were also subjected to Higuchi's diffusion equation the r-values of all the formulations were 0.9729 to 0.9957 It suggests that the drug released by diffusion mechanism. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsemeyer's equation [21-22]. Regression analysis was performed and regression values 'R' were 0.9757 to 0.9935 for different formulations. Slope values were in the range of 0.46 to 0.66. Slope values ($0.45<n<1.0$) suggest that the release of cefixime from gastroretentive tablets followed non-Fickian and first order 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 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 GRT5 along with drug and polymer hydroxy ethyl cellulose (HEC) is taken for the studies. In this case 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.

In the DSC study of pure cefixime shows that the drug started melting at 55.37^0C and ends at 112.45^0C**.** The CGPS tablet formulation prepared with Cefixime, HPMC, HEC, sodium alginate were subjected for DSC studies, wherein formulation product GRT5 started melting at 85^oC and completed at 164^oC **(Fig 8)**. This wide range of melting process suggests that formulation GRT5

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^{o}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.

The stability study conducted as per the ICH guidelines for 3 months and the formulation GRT5 was found to be stable. No appreciable change in drug content and *in-vitro* release study was observed even after the evaluation for 3 months. Results were showed in **[Table 6].**

CONCLUSION

Effervescent is essential for the formulations to have well floating property and Carbopol retards the drug release in the floating formulations. The drug release from the tablets was sufficiently controlled and non- Fickian transport of the drug from tablets was confirmed. The formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence it may be increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

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