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FORMULATION AND EVALUATION OF GAS POWERED SYSTEMS OF CEFIXIME TABLETS FOR CONTROLLED RELEASE

RAGHAVENDRA RAO N. G[1*], PENTEWAR RAM[1], S. S. BUSSETTI[2]

1. Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga – 585 102. Karnataka, India.
2. Department of Pharmaceutics, HKE's College of Pharmacy, Gulbarga – 585 103. Karnataka, India

.***Corresponding author*** ngraghu@rediffmail.com and ngraghavendra@gmail.com

ABSTRACT

The present invention relates to a pharmaceutical composition providing a combination of spatial and temporal control in the form of tablets for effective therapeutic results. Cefixime is third generation cephalosporin antibiotic. Cefixime is slowly and incompletely absorbed from the GIT, and poor bioavailability 40 - 50%. The gas powered tablets of Cefixime were prepared by direct compression method to increase the gastric retention time using different concentrations of hydrophilic polymers. 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, diameter, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. Drug compatibility with excipients was checked by DSC and FTIR studies. In all the formulations, hardness test indicated good mechanical strength, friability is less than 1%, indicated that tablets had a good mechanical resistance. The results were revealed that as concentration of sodium bicarbonate increases from 50 - 80 mg/tab there is decrease in drug release but lag time decreases as increase in concentration of sodium bicarbonate and duration of floating has been increased with increase in concentration of sodium bicarbonate. 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 (spatial control) and provides controlled release of the drug. Hence, improve the therapeutic effect of the drug by increasing its bioavailability.

KEYWORDS

Cefixime, hydro dynamically balanced systems, hydroxyl propyl methyl cellulose, controlled gas powered system, hydroxy ethyl cellulose,

INTRODUCTION

The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper part of the small intestine until all the drug is completely released in the upper part of gastrointestinal tract can be accomplished by gas powered systems for controlled release over a period of time. 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).

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. Controlled Gas Powered System

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(CGPS) of the present invention is retained for longer periods of time in the stomach (spatial control) than previously known hydrophilic matrix tablets, floating capsules and bioadhesive tablets when these systems are administered with food. Thus, the longer period of gastric retention as compared to other oral controlled drug delivery systems can be attributed to the use of the CGPS as here in described. The CGPS 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[1-3]. For designing of CGPS different excipients were used are a gas generating agent (sodium bicarbonate), swelling agent (cross linked CMC), viscolyzing agent (xanthan gum) and a gel forming polymer (sodium alginate). Further, the pharmaceutical composition also contains an additional hydrophilic water soluble polymer (HPMC K4M, and carbopol) such a combination is referred to here in at times as CGPS. The swelling agent used along with superdisintegrants which usually function to promote disintegration of tablet by absorbing large amounts of water and there by swelling. This expansion, as well as hydrostatic pressure, causes the tablet to burst. In a tablet which also contains a gas generating component, the generated gas is entrapped and the superdisintegrant acts as swelling agent who swells to, preferably, at least twice its original volume. Thus, the composition of gas generating component, the swelling agent which is actually a superdisintegrant, and the viscolyzing agent permit the CGPS to act as a controlled drug delivery system. Additionally, with the passage of time, the gel forming polymer produces a cross-linked three-dimensional molecular network resulting in a hydro dynamically balanced system that is retained in the stomach and releases the drug over a sustained period of time.

In present research work Cefixime is used as a model drug. Cefixime 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 %[4-6]. 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. It gives constant blood levels of active ingredient as compared to uncontrolled fluctuations observed when multiple dosage of quick releasing conventional dosage forms are administered to a patient. It not only reduces the frequency of dosing but may reduce the severity and frequency of side effects[1,7-9]. Hence, we are planning to develop cefixime gas powered tablets for controlled release and increased gastric retention time. The cefixime gas powered tablets were prepared by direct compression method using

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different concentrations of hydrophilic polymers. The compositions of which are given in **[Table 1].**

Table .1
Composition of cefixime gas powered tablets

Composition (mg/tab)	F1	F2	F3	F4	F5	F6
Cefixime	200	200	200	200	200	200
$NaHCO_3$	50	60	70	80	80	70
Cross Na CMC	20	20	20	20	10	20
Xanthan gum	30	20	20	30	20	20
Sodium alginate	10	10	10	10	10	10
HPMC K4M	30	40	40	50	60	60
carbopol	10	20	30	20	20	20
MCC	30	30	30	30	20	30
Lactose	100	70	60	40	50	40
Citric Acid	--	10	10	10	20	10

****** All the tablet formulations contain 10 mg of magnesium stearate, talc.
* The weight of all the tablet is 500 mg.

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), magnesium stearate and citric acid are purchased from Hi media laboratories Pvt. Ltd, Mumbai. India, Cross-linked sodium carboxy methylcellulose (NaCMC) 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.

1. Preparation of cefixime gas powered tablets

According to present invention, the pharmaceutical composition is 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].

2. Evaluation of cefixime gas powered tablets

The powder blend was subjected for pre-compressional parameters. The prepared tablets were evaluated for post-compressional parameters as

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weight variation, hardness, friability, thickness, diameter, 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 [10,11] 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[12] 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 [11,12] 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 volume being 900 ml. The temperature was maintained at 37°± 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.

3. Characterization of cefixime tablets

FTIR Studies

IR spectra for pure drug, F2 tablets were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies

5 mg of Cefixime and F2 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 release and release rate kinetics of the dosage form[13-16], the data obtained were fitted into First order, Higuchi matrix,

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Peppas and Based on the r-value, the best-fit model was selected.

Stability study

The fabricated gas powered tablet formulations were subjected for stability study. The stability study was carried out according to ICH guidelines at 40°C and relative humidity at 75 % for three weeks. For stability study[17], 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 gas powered tablets

Formulation codes	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (I_C)	Hausner ratio (H_R)	Angle of repose (θ)
F1	0.3253 ± 0.07	0.3945 ± 0.03	17.45 ± 0.11	1.21 ± 0.03	24.85 ± 0.13
F2	0.3164 ± 0.06	0.4114 ± 0.08	19.18 ± 0.11	1.23 ± 0.07	23.05 ± 0.10
F3	0.3325 ± 0.05	0.3799 ± 0.05	16.71 ± 0.11	1.20 ± 0.05	26.98 ± 0.15
F4	0.3694 ± 0.04	0.4454 ± 0.07	17.06 ± 0.11	1.20 ± 0.06	24.36 ± 0.12
F5	0.3655 ± 0.05	0.3965 ± 0.12	20 ± 0.09	1.22 ± 0.07	27.67 ± 0.13
F6	0.3325 ± 0.05	0.3789 ± 0.12	21.06 ± 0.11	1.21 ± 0.03	24.20 ± 0.12

All above reading are average ± SD, n=3

In all the formulations, the weight variation of tablets was ranges between 495-505. 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 6.5 to 7.5kg/cm^2 and 0.65 to 0.80 respectively. Friability is less than 1%, indicated that tablets had a good mechanical resistance. Thickness of the tablets was ranges from 3.90 to 4.20 mm. 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 101.12% to 102.81% which is within acceptable limits. The swelling index of the tablets was in the range 78.42-110.40 %. The results were shown in **Table 3.**

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Table .3
Post-compressional parameters of cefixime gas powered tablets

FC	Avg. wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm2)	Friability (%)	Drug content (%)	Swelling index
F1	505	4.15 ± 0.04	12.10 ± 0.05	6.5 ± 0.05	0.78 ± 0.04	99.38 ± 0.21	78.42 ± 0.45
F2	495	4.10 ± 0.02	12.05 ± 0.02	7.0 ± 0.04	0.70 ± 0.039	101.58 ± 0.20	110.40 ± 0.92
F3	503	4.20 ± 0.06	12.06 ± 0.02	6.5 ± 0.04	0.65 ± 0.08	96.38 ± 0.12	98.20 ± 0.63
F4	505	4.20 ± 0.02	12.10 ± 0.05	6.00 ± 0.04	0.75 ± 0.045	104.48 ± 0.20	108.20 ± 0.45
F5	498	3.90 ± 0.03	12.05 ± 0.07	7.00 ± 0.04	0.80 ± 0.06	98.68 ± 0.20	96.40 ± 0.23
F6	502	4.00 ± 0.05	12.15 ± 0.04	7.5 ± 0.04	0.76 ± 0.06	99.63 ± 0.12	102.10 ± 0.25

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

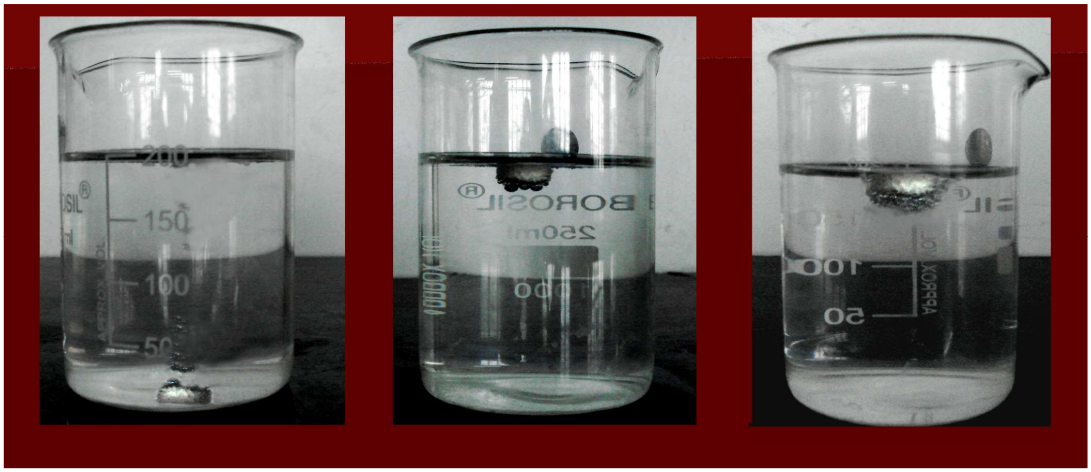

Fig .1
Photograph showing Floating time Gas powered tablets.

The results of *in vitro* buoyancy time and lag time study (**Fig 1)** 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 120 - 720 min and lag time ranges from 12- 3 min. The formulation F2 shows the lag time of 4min and buoyancy time 670 min. Sodium bicarbonate induced CO_2 generation in the presence of dissolution medium (pH1.2 hydrochloric acid buffer). The gas generated is trapped and

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protected within the gel formed by hydration of polymer, thus decreasing the density of tablet. As the density of tablet falls below 1 the tablet becomes buoyant [18]. The results were shown in **Table 4**.

Table .4

Floating ability of cefixime gas powered tablets.

FC	Floating Lag time (min)	Floating duration (min)	Integrity
F1	12	120	Broken
F2	4	>670	Intact
F3	3	>720	Intact
F4	5	>720	Intact
F5	3	>720	Intact
F6	3	>720	Intact

F=Formulation code

The release of cefixime from all the formulations **(Fig 2)** was in the range of 46.74-68.18 % at the end of 6 hrs and 81.85-97.35 % 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 60 -80 mg per tablet, there is decrease in the drug release but 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 F2 containing 60 mg of sodium bicarbonate, HPMC K4M 40 mg and carbopol 20 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 gas powered tablets.

Formulation code	% drug release after 6 hrs	% drug release after 12hrs
F1	46.74 ± 1.43	81.85 ± 0.98
F2	68.18 ± 1.34	97.35 ± 1.09
F3	61.34 ± 4.90	93.51 ± 1.31
F4	58.51 ± 1.14	91.69 ± 0.57
F5	53.89 ± 4.87	89.99 ± 0.90
F6	57.55 ± 2.16	90.76 ± 1.20

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

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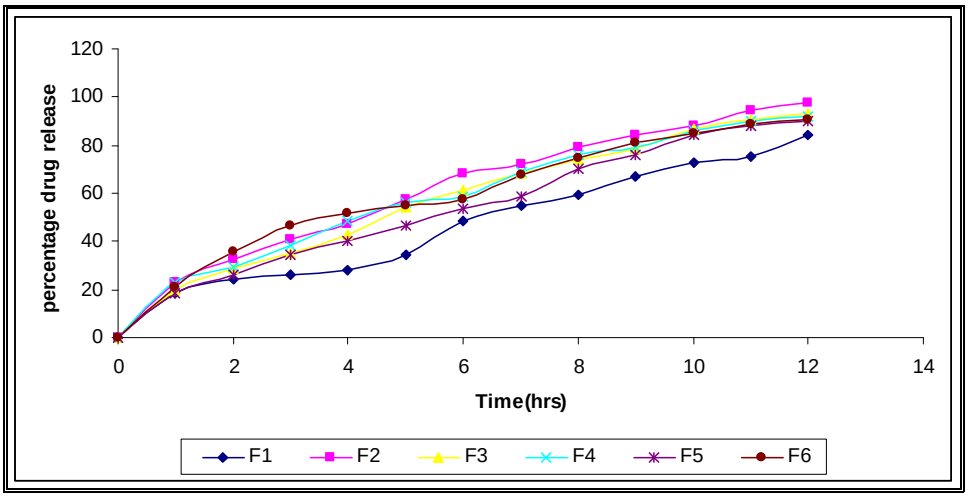

Fig .2

Comparative drug release profile of formulations F1 to F6.

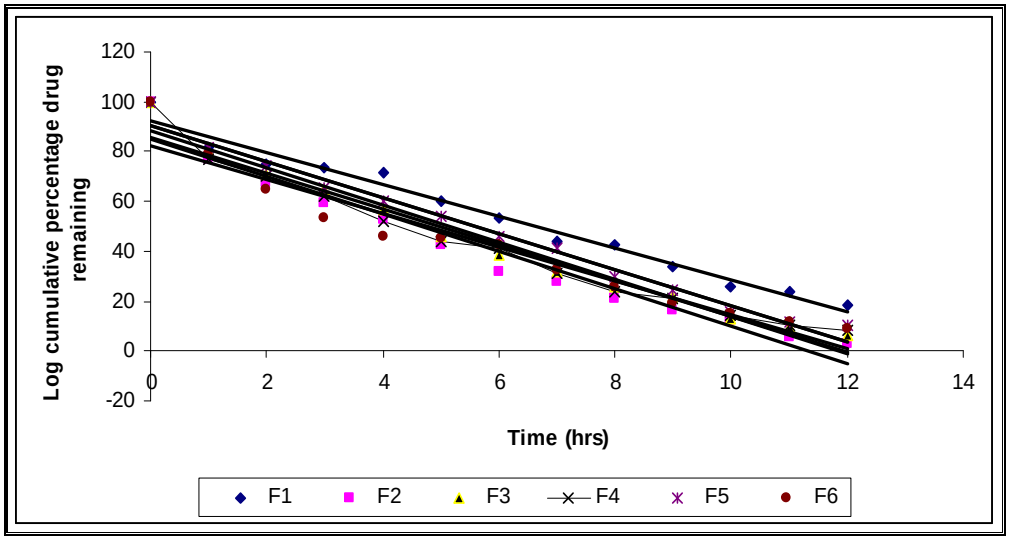

Fig. 3

Comparative First-order drug release profile of formulations F1 to F6.

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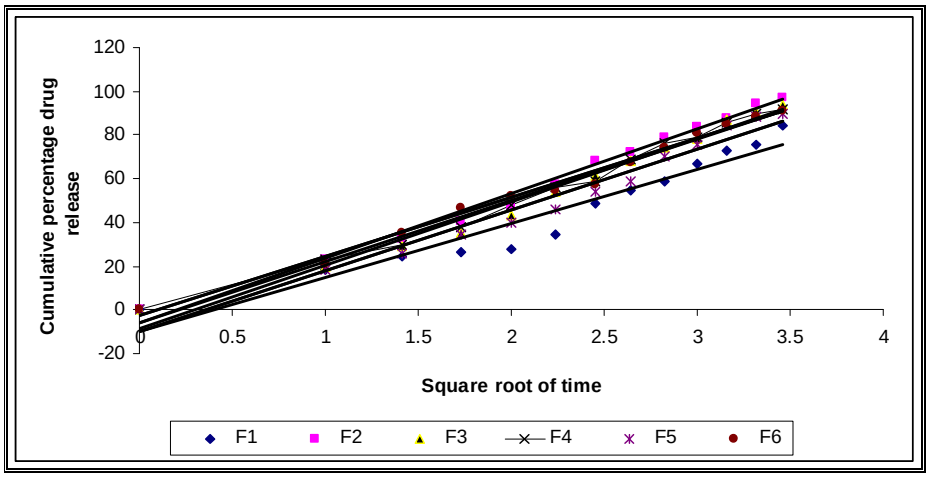

Fig .4

Comparative study of Higuchi plots of formulations F1 to F6.

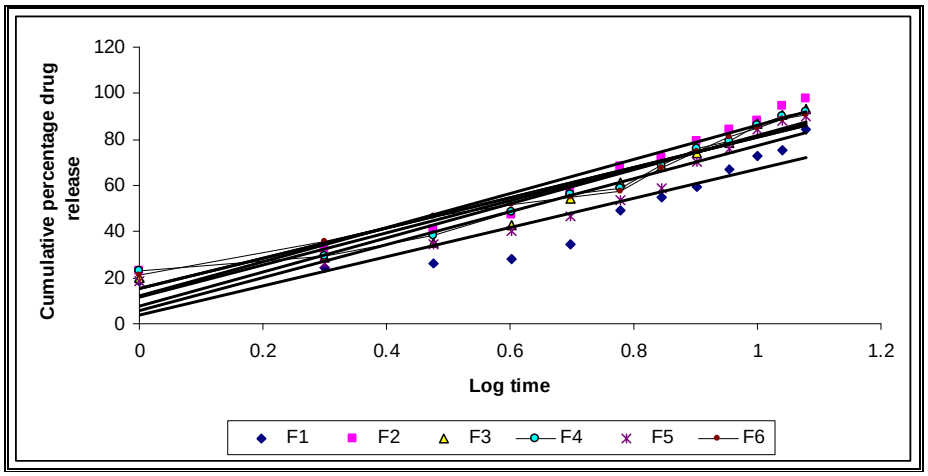

Fig .5

Comparative study of Peppa's plots of formulations F1 to F6

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 0.9443 to 0.9899. 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 0.5508 to highest 0.6614 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.

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Table .6
Curve fitting analysis for different formulations

Formulations	Zero order (R)	First order (R)	Higuchi's (R)	Peppa's	
				R	N
F1	0.9785	0.9751	0.9443	0.9355	0.64
F2	0.9579	0.917	0.989	0.9937	0.60
F3	0.9711	0.9562	0.9806	0.91	0.66
F4	0.9586	0.9723	0.9872	0.9882	0.59
F5	0.9833	0.9475	0.966	0.988	0.66
F6	0.9397	0.9724	0.9909	0.982	0.56

All values are expressed as mean ± SD, n=3, F= Formulation codes.

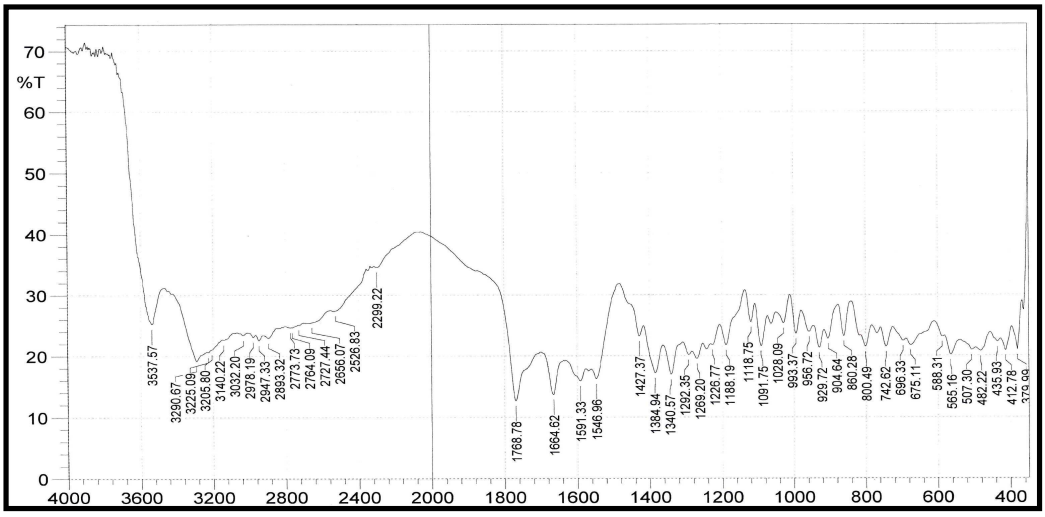

Fig .6
IR spectra of pure drug Cefixime Trihydrate

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. The formulation **(Fig 7)** is carried out HPMC and the drug as given rise to absorption peaks at 3298 cm^{-1} as a broad hump

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corresponding to NH, NH_2, and OH functionalities present sin the drug as well as polymer HPMC. Similarly broad peaks are observed at 1700, 1710 and 1600 cm^{-1} corresponding to the C=O of the drug and polymer molecules. Cefixime and formulation reveled that there is no appreciable changes in the position of absorption band. This reveled that there was no chemical interaction between drug and the polymer.

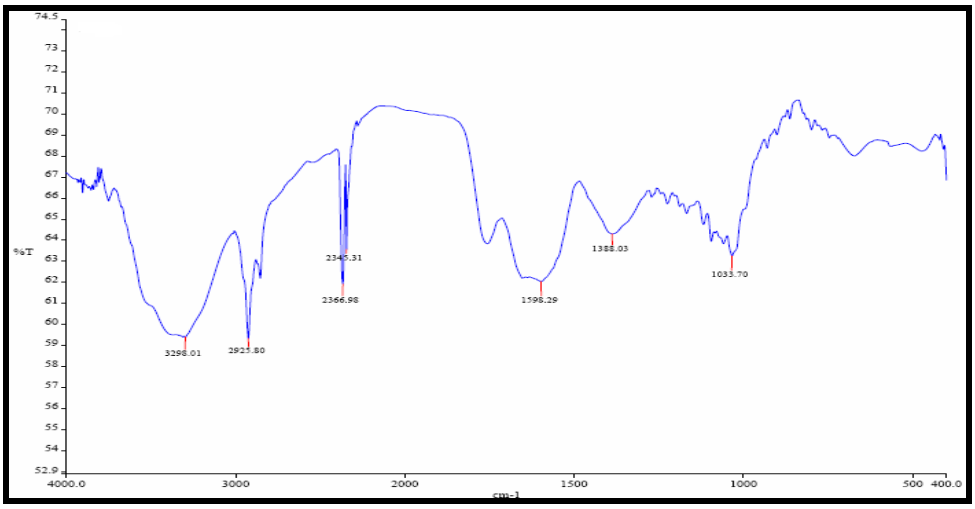

Fig .7

IR spectra of formulation F 2

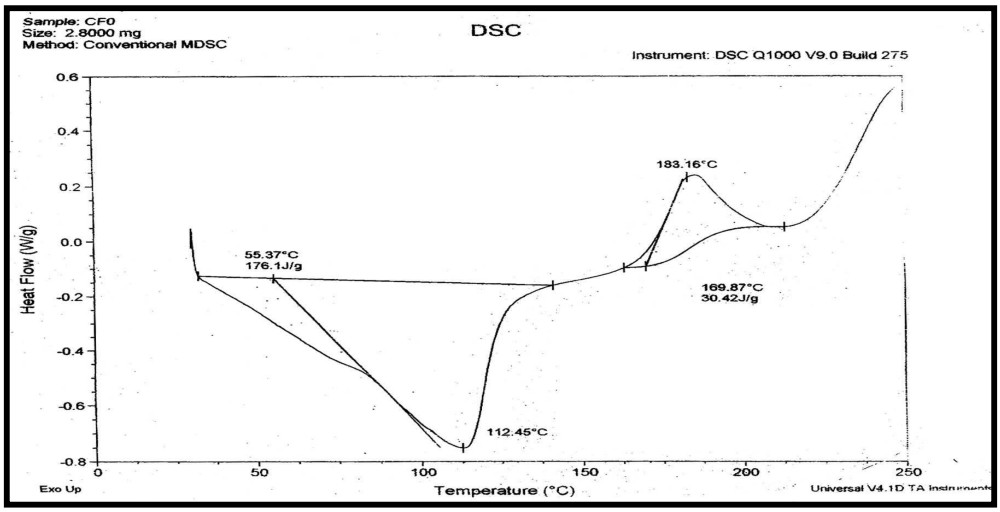

Fig .8

Differential scanning colorimetric study of pure drug cefixime

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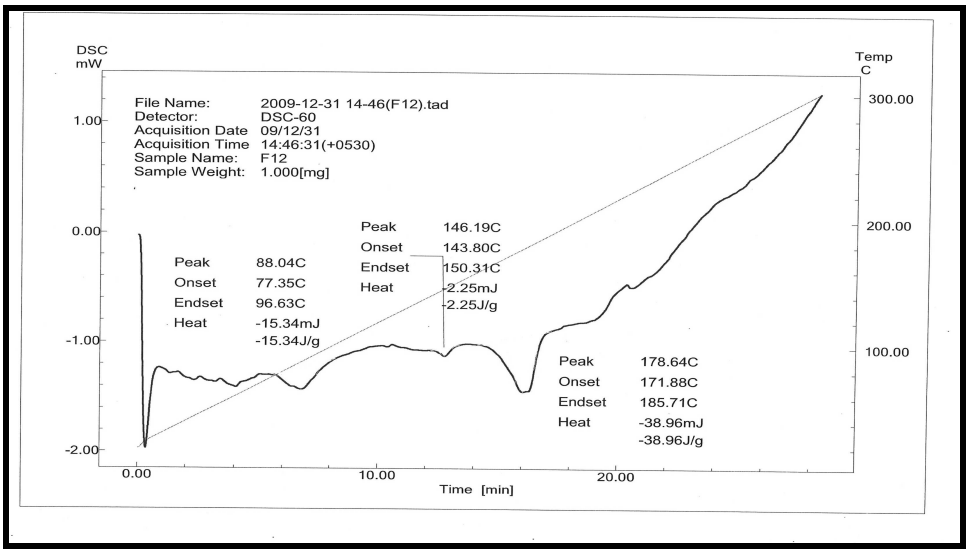

Fig .9

Differential scanning colorimetric study of F2

Thermograms of pure drug Cefixime and the formulation F2 revealed that the pure drug **(Fig 8)** has a sharp endotherm at 112^0 C. However the drug and its formulation showed characteristic changes in the appearance of the thermogram. The formulation F2 prepared with Cefixime, HPMC, carbopol, sodium alginate were subjected for DSC studies, wherein formulation F2 **(Fig 9)** started melting at 77^0C and completed at 150^0C. This wide range of melting process suggests that formulation F2 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 3^0C, 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 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 7].** In the present invention, it has found that a xanthan gum helps in maintaining tablet integrity.

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Table .7
In-vitro release and drug content data of stability study of formulation F2

Time (hrs.)	Cum. % Drug released ± SD.		Drug content	
	1st Day	21st Day	1st Day	21st Day
01	22.84	20.84	101.10	100.60
02	32.60	39.80	99.10	97.92
03	40.89	41.87	102.5	96.70
04	47.39	45.78	99.70	99.10
05	57.46	54.32	102.20	99.35
06	68.18	66.28	101.10	98.40
07	72.21	71.21	100.60	99.30
08	79.11	78.46	97.92	97.22
09	83.99	86.87	99.70	97.22
10	87.93	88.87	99.10	99.10
11	94.26	92.48	99.35	96.70
12	97.35	96.78	101.10	99.10

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, controlled gas powered system tablets retained for longer periods of time in the stomach which may leads to improve the therapeutic effect of the drug by increasing its bioavailability.

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