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Formulation, characterization and *in-vitro* evaluation of Cefixime floating matrix tablets

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ABSTRACT

The present study was aimed to develop and evaluate the floating matrix tablets of Cefixime. The bioavailability of Cefixime is around 40-50 %. The gas powered tablets of Cefixime were prepared by direct compression method. Drug compatibility with excipients was checked by FTIR studies and these results were revealed that, no interaction between drug with the excipients used. The results of In-vitro buoyancy time and lag time study revealed that as the concentration of sodium bicarbonate increases, there is an increase in total buoyancy time and decrease in lag time. The formulation F8 shows the lag time of <1 min and buoyancy time 720 min. The release of Cefixime from all the formulations was in the range of 23.35±18- 89.00±99 % at the end of 16 hrs 75.95±13% and at the end of 24 hrs 89.28±43. From this study, it can be concluded that, the formulation retained for longer periods of time in the stomach.

Keywords: Cefixime, Lactose, HPMC, Carbopol 974P, Eudragit RS, Sodium bicarbonate

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INTRODUCTION

Oral drug delivery is the most broadly utilized routes of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered more natural, simple, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process [1]. Conventional oral controlled dosage forms undergo from mainly two adversities [2]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). One of the most feasible approaches for achieving an extended and predictable drug delivery profile in the gastrointestinal tract is to control the gastric residence time (GRT) using *gastro retentive dosage forms (GRDF)* that offer a novel and improved option for drug therapy [3]. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase the solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having a site-specific absorption restriction [4].A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts [5].These include: Floating Drug Delivery Systems(FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. Bio-adhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can hold to the epithelial surface in the stomach [6].Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are Effervescent System and Non-Effervescent System. Effervescent systems include the use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. Citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float in the gastric fluid. An alternative is the incorporation of a matrix containing portion of liquid, which produce gas that evaporates at body temperature [7]. Noneffervescent Systems, after swallowing, swells unrestrained via inhibition of gastric fluid to an extent that it

prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [8]. Carbopols or carbomers (hydrophilic polymer) compress very well and have strong binding characteristics which make them ideal for direct compression process. They show compatibility with various active ingredients and other excipients [9]. Carbopol974P and Carbapol934 are oral pharmaceutical grades of carbomers. Their hydrophilic nature and highly cross linked structure make them suitable candidates for CR formulations [10]. The most interesting acrylic polymers are high permeable Eudragit® RL and low permeable Eudragit® RS, both of which are neutral copolymers of poly (ethylacrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride, and are insoluble in water and digestive juices; but they swell and are permeable, which means that drugs embedded in their matrices can be released by diffusion[11].Therefore, the permeability of drug through Eudragit RS and/or RL is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. The proportion of functional quaternary ammonium groups in Eudragit RL and Eudragit RS is 10 and 5%, respectively. Eudragit RL PO and RS PO are fine, white powders with a slight amine like odor. They are characteristically the same polymers as Eudragit RS and RL.

The aim of this work was to prepare floating matrix tablets containing Cefixime as a model drug, Eudragit RS, carbopol974P and HPMC are polymer matrix to retard drug release. Another objective of this work was characterization and in- vitro drug release studies.

MATERIALS AND METHODS

Materials

Cefixime gift sample from Bioplus, Bangalore. Carbopol, Eudragit from Otto chemicals, Mumbai, India. All other reagents used were of analytical grade.

Methods

Table 1: composition of Cefixime floating matrix tablets

Composition (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8
Cefixime	200	200	200	200	200	200	200	200
Lactose	90	40	90	40	90	40	140	40
Hpmc	100	150	-	20	-	50	50	50
Carbopol	-	-	100	130	-	-	-	-
Eudragit	-	-	-	-	100	100	-	
Sodium bicarbonate	80	80	80	80	80	80	80	80
Citric acid	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5

Formulation of floating tablets of Cefixime by direct compression method

Floating tablets of Cefixime were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. HPMC, Carbopol, and Eudragit were used as rate controlling polymers. The concentrations of the above ingredients were optimized on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers and other excipients, except talc and Magnesiumsterate, in ascending order of their weight. The powder mix was blended for 20 minutes to have uniform distribution of drugs in the formulation. Then, Magnesium stearate was added and mixed for not more than 1 minute (to ensure good lubrication.) About 500 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 12mm flat- surface punches. The hardness of the tablets was adjusted at 4-5 kg/cm^2 using a Pfizer hardness tester.

CHARACTERIZATION

Fourier Transform Infra-Red spectroscopy analysis

IR spectral analysis of pure drug and polymers was carried out and observation was made whether changes in the chemical constitution of drug after combining it with the polymers occurred. The samples were crushed with kbr to get pellets by applying pressure of 600 Kg/cm^2 and scanned in (Shimadzu, 8400 Series, Tokyo, Japan) from 400 to 4000 cm^{-1} at a resolution of 4 cm^{-1} **.**

Thickness
The thickness of the tablets was determined using Verniercalipers. Five tablets from each batch were used.

Weight variation
Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit.

Content Uniformity Test
For determination of drug content three tablets from each formulation were weighed individually, crushed and a quantity of powder equivalent to 100mg weighed and is dissolved in 100ml of water to give a solution of 1mg/ml. 1.0 ml of this solution was further diluted up to 10.0 ml with distilled water to give a solution of concentrations 100ug/ml. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 235 nm against the blank.

Hardness
The hardness of ten tablets was found using a Pfizer Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Friability
The friability of the tablets was determined using Roche friabilator (Remi Electronics, Mumbai, India). It is expressed in percentage.10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

$$\%\ of\ \ Friability\ = \frac{Initial\ Weight\ -\ Final\ Weight\ \ x100}{Initial\ Weight}$$

In-vitro Dissolution studies
The in-vitro release of Cefixime from formulating tablets was carried out for 24 hours in 0.1N Hcl. The studies were performed in USP dissolution apparatus II (Electro lab, Mumbai, India) at 37 ± 0.5° C and 50 rpm speed. Samples were taken at 2, 4, 8, 16, 20 & 24hours and diluted to suitable concentration and analyzed for Cefixime content at 235 nm by using UV–visible spectrophotometer.

Swelling Index:
This was measured in terms of percentage (%) weight gain by the tablet. First prepare the 0.1NHcl take for each formulation separate Petri-dish and pour the buffer into the Petri-dish, insert the tablet in according the sequence and measure the % gain of the tablet with the interval.

RESULTS AND DISCUSSION

Hardness, Diameter, Thickness, Friability, Swelling index results was shown in Table: 2

Table 2: Evaluation parameters of the Cefixime Matrix Tablet

Batch code	Average weight mg	Thinkness mm	Diameter mm	Hardness Kg/cm	Friability %	Drug content %	Swelling index %
F1	503.55	4.13	12.16	7	0.51	97.15	92.05
F2	505.33	4.15	12.1	7.1	0.55	96.12	94.06
F3	507.51	4.1	12.13	6.8	0.47	95.21	94.22
F4	506.43	4.19	12.11	7.3	0.45	97.03	97.87
F5	501.37	4.12	12.05	6.9	0.6	96.36	95.55
F6	502.21	4.11	12.12	6.9	0.47	95.01	92.05
F7	501.05	4.14	12.1	7.5	0.62	97.36	93.45
F8	498.83	4.2	12.14	7.4	0.65	96.25	98.25

Figure:1(a) Before swelling index of F8

Figure:1(b) After swelling index of F8

In Vitro Buoyancy Studies

In-vitro buoyancy studies were carried out for all formulations. Based on the In-vitro buoyancy study results F8 formulation was optimized. The Results were shown in Table 3.

Table 3: Floating properties of formulations F-1 to F-8

S.No	Formulation Code	Lag Time (min)	Floating Time (hr)	Swelling index %
1	F-1	<1	>10	92.05
2	F-2	<1	>11	94.06
3	F-3	<1	>11	94.22
4	F-4	<1	>12	97.87
5	F-5	<1	>11	95.55
6	F-6	<1	>10	92.05
7	F-7	<1	>10	93.45
8	F-8	<1	>12	98.25

Figure:2 Floating ability of Cefixime floating matrix tablet

Table 4: Percentage Cumulative drug release of formulations F-1 to F-8

Time(hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	0	0	0	0	0	0	0	0
2	40.25	55.23	42.89	37.52	39.05	23.56	35.06	23.25
4	55.27	60.25	48.32	46.49	50.99	35.96	40.25	33.62
8	66.25	65.54	55.65	52.49	55.14	50.25	42.65	52.25
16	75.28	85.62	67.89	64.82	67.47	65.23	55.98	75.95
20	80.25	83.85	85.32	74.56	78.33	72.35	58.61	86.28
24	82.25	87.32	87.41	89.96	85.06	80.45	81.12	89.35

In-Vitro Drug Release

The in-vitro release of Cefixime from formulating tablets was carried out for 24 hours in 0.1N Hcl. The studies were performed in USP dissolution apparatus II (Electro lab, Mumbai, India) at 37 ± 0.5° C and 50 rpm speed. Results were shown in Table 4.

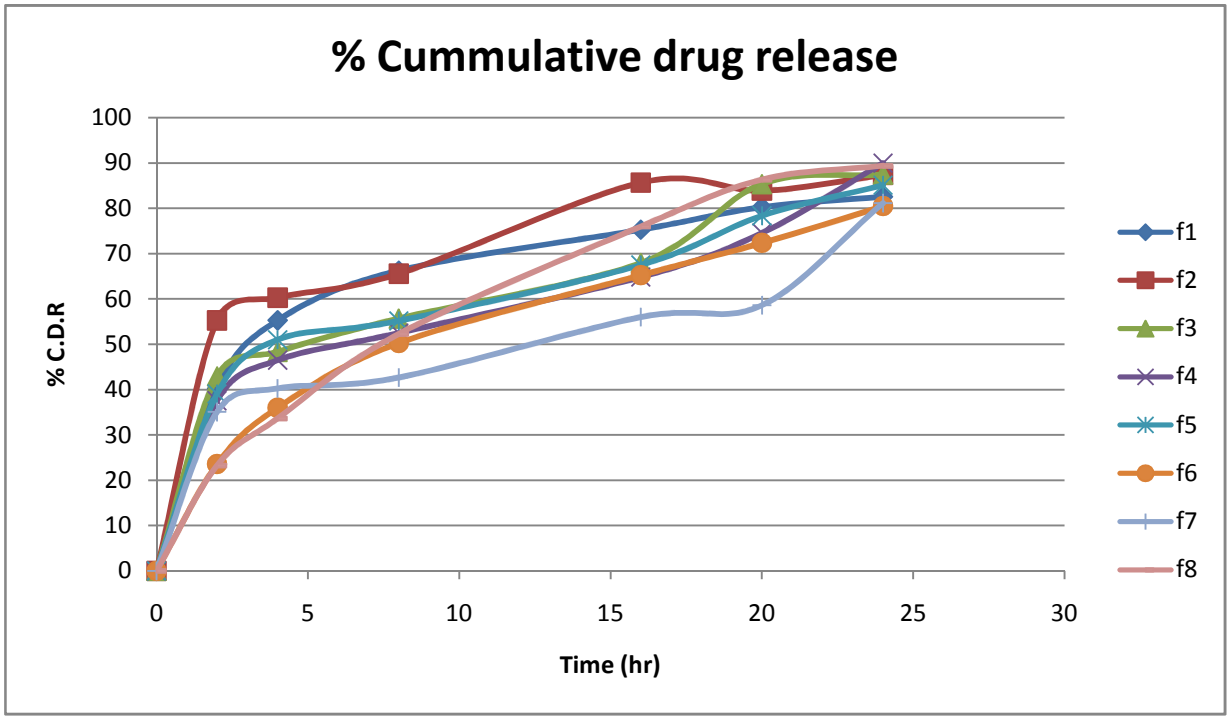

FIGURE:3 Percentage Cumulative drug release graphs of formulations F-1 to F-8

In-vitro dissolution studies of all the formulations are shown. Three different polymers and their combination were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulations contain equal amount of gas generating agent (Sodium Bicarbonate) and Citric Acid. Drug release from **F-8** is high due to high permeability. Although combination of significantly release the drug as compared with other formulations. As expected drug release depends upon viscosity grade and concentration of polymer used. Tablet containing Lactose, Carbopol, HPMC, Eudragit etc. (F8) showed better drug release up to 24hours. As Carbopol has a greater tendency to water, it can sustained the drug for 24 hours.

CONCLUSION

From the results of In-vitro drug release studies using USP dissolution apparatus, it concludes that F8 had better-sustained release than the other formulation (F1, F2, F3, F4, F5, F6, & F7). Formulation F-8 was found to be optimum because it had shown most consistent (89.35±0.20%) up to 24 hrs with floating lag time of <1 min and good swelling index (98.25±0.8%) up to 24 hrs.

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