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RESEARCH ARTICLE

Formulation and Evaluation of Gas Powered Systems of Cefepime Tablets for Controlled Release

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ABSTRACT

The present work is aimed to formulate Cefepime floating tablets using different hydrophilic and hydrophobic polymers like hydroxypropylmethylcellulose (HPMC), Ethyl cellulose, Xanthum gum, guar gum, and gas generating agent Sodium bicarbonate. The develop gastroretentive dosage form that could retain the agent, namely, Cefepime in the stomach for longer periods of time delivering the drug to the site of action, that is, stomach. HPMC is used as a swelling agent, Guar gum and Xanthum gum are used as binding agent. Ethyl cellulose is used as matrix form agent. PVP is used as a suspending agent. Sodium bicarbonate is used as a gas forming agent. MCC is used as a disintergrant and diluent. Magnesium stearate is used as a lubricant. The prepared Cefepime tablets will be evaluated for drug content, entrapment efficiency, post-compression studies, *in vitro* buoyancy studies, swelling index studies, *in vitro* dissolution studies, release kinetics, and stability studies. All these parameters were found to be within the pharmacopoeial limits. Formulation F5 was selected for drug release and stability study on the basis of appropriate results of post-compression study. *In vitro* dissolution study was carried out and showed controlled release pattern.

Keywords: Cefepime, Controlled release, Floating drug delivery, Gas powered systems

INTRODUCTION

Cefepime is a broad-spectrum, semi synthetic, and third-generation cephalosporin. It possess a broad spectrum of activity, excellent therapeutic action against susceptible Gram-positive and Gram-negative bacteria.[1] It exhibits potent antimicrobial activity, excellent efficacy, convenient dosing, and favorable tolerability compared with other antimicrobial agents.[2] It belongs to BCS Class IV with low solubility and low permeability characteristics. Cefepime is available in only two dosage forms: Capsules and suspension forms. Its show crystalline nature, with compressibility problem and thus, not formulated easily in tablet dosage form.[3] Various approaches have been proposed to control the residence of drug delivery systems in the upper part of the gastrointestinal tract such as mucoadhesive systems, swelling/expanding systems, high density systems, magnetic systems, and floating systems.[4] Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[5] The controlled gastric retention of solid dosage forms may be achieved

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by mucoadhesion,[6] floatation,[7] sedimentation,[8] expansion,[9] modified shape system,[10] and simultaneous administration of pharmacological agents.[11] Gastroretentive floating drug delivery system has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and inter subject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and increased patient compliance, reduced Cmax and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high Cmax.[12,13] In the present study, a floating drug delivery system was designed and developed. The buoyancy principle providing floating dosage forms with prolonged gastric residence time seems to offer a greater safety of use compared to the other approaches. The tablets were prepared with effervescent component (sodium bicarbonate) using hydroxypropylmethylcellulose (HPMC) as a binder. The prepared Cefepime tablets evaluated for drug content, entrapment efficiency, post-compression studies, *In vitro* buoyancy studies, swelling index studies, *in vitro* dissolution studies, release kinetics, and stability studies.

MATERIALS AND METHODS

Cefepime was supplied as a gift from M/s Hetero Drugs Ltd., Hyderabad, India. HPMC, Xanthum Gum, Guar Gum, PVP, Ethyl Cellulose, Sodium Bicarbonate, Micro Crystalline Cellulose, and Magnesium Stearate were used of pharmaceutical grades. All other chemicals were used of analytical grade.

Preparation of calibration curve of cefepime

100 mg of Cefepime was accurately weighted into 100 mL volumetric flask, dissolved in 0.1 N HCL and volume was made up with 0.1N HCL. Pipette 1 mL of this solution into another 10 mL volumetric flask and the volume was made with 0.1N HCl and marked as Stock. From this Cefepime standard stock solution (1000 µg/mL), 1 mL solution was diluted to 10 mL using 0.1N HCl solution to get concentrations of 100 µg/mL. from this solution, aliquots of, 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1.0 mL, 1.2 mL, and 1.4 mL from standard drug solution were diluted to 10 mL with 0.1 M. The absorbance of these solutions was measured at 286 nm 0.1N HCL as a blank.

Formulation of cefepime floating tablets

All the formulations were prepared by direct compression method using different polymers Table 1.

1. Cefepime and all other ingredients were individually passed through sieve ≠ 60
2. All the ingredients were mixed thoroughly by triturating up to 15 min
3. The powder mixture was lubricated with Magnesium stearate
4. The tablets were prepared by using direct compression method according to the formulation table.

Pre-compression studies

Bulk density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution,

Table 1: Composition of different formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Cefepime	75	75	75	75	75	75
HPMC	105	122.5	140	--	--	--
Xanthum gum	--	--		105	--	--
Guar gum	--	--		--	105	--
Ethyl cellulose	--	--		--	--	105
PVP	17.5	17.5	17.5	17.5	17.5	17.5
Sodium bicarbonate	52.5	52.5	52.5	52.5	52.5	52.5
MCC	96.5	79	61.5	96.5	96.5	96.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5
Total weight	350 mg	350 mg	350 mg	350 mg	350 mg	350 mg

shape, and cohesiveness of particles. Accurately weighed quantity of powder as carefully poured into graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in g/mL and is given by the formula:

Bulk density=M/Vo

Where, M = mass of the powder, Vo = bulk volume of the powder.

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation:

Angle of repose Ø = tan-1(h/r)

Where, h=height of the pile, r = radius of the pile

Tapped density

10 g of powder was introduced into a clean, dry 100 mL measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in g/mL and is given by:

Tapped density=M/Vt

Where, M = mass of the powder, Vt = final tapping volume of the powder.

Compressibility index (Carr's index)

Compressibility index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is Simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by Equation:

$$Compressibility\ index(\%) = \left[\frac{TD - BD}{TD}\right] \times 100$$

Hausner's ratio

Hausner's ratio is used to predict the flow ability of the powders. This method is similar to compressibility index. Hausner's ratio can be represented by Equation:

$$Hausner\ sratio = \frac{Tapped\ density}{Bulk\ density}$$

Evaluation of prepared formulation

Weight variation

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

PD = [(Wavg–Winitial)/(Wavg)] × 100

Where, PD = Percentage deviation, Wavg = Average weight of tablet, Winitial = Individual weight of tablet.

Thickness

The thickness and diameter of tablets was determined using Vernier Caliper. Twenty tablets from each batch were used and average values were calculated.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm^2. For each formulation, the hardness of six tablets was determined and average value was calculated.

Drug content

Tablets were crushed and the powder equivalent to 100 mg of drug were accurately weighed and transferred to 50 mL volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then,

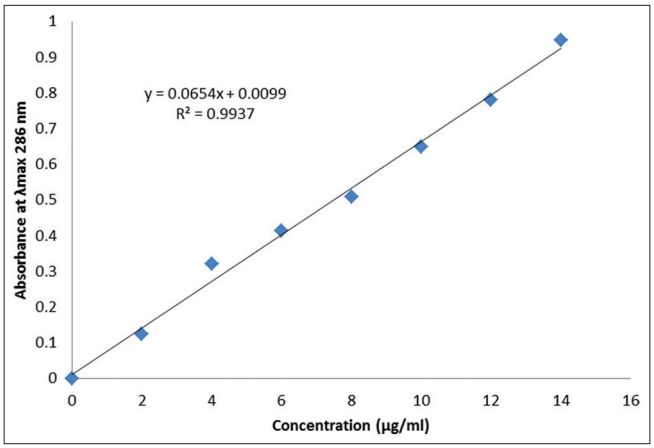

Figure 1: Standard calibration curve of cefepime in 0.1N HCL

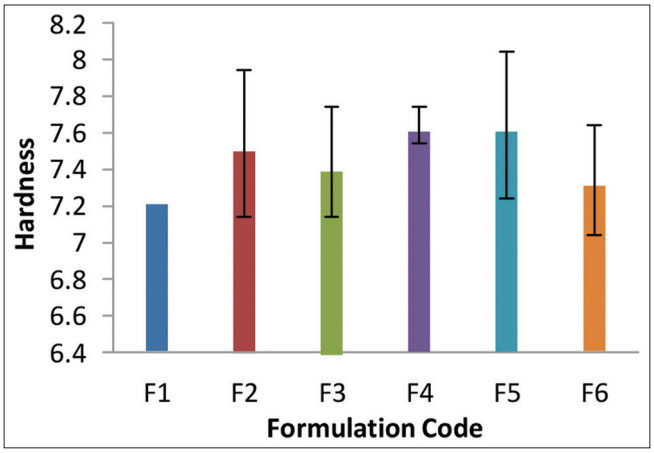

Figure 2: Hardness studies of cefepime floating tablets formulations

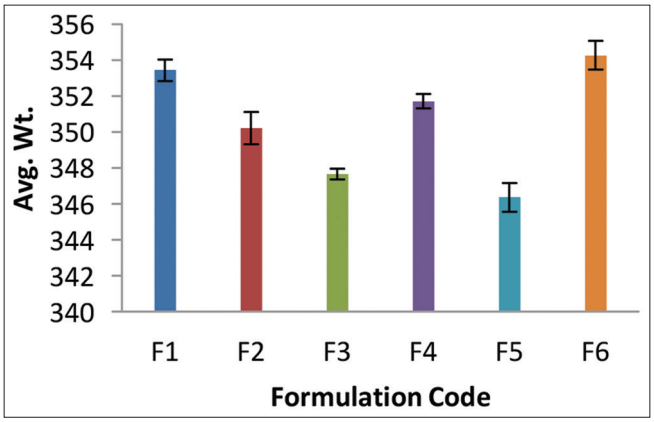

Figure 3: Average weight of cefepime floating tablets formulations

the volume of flask was made up to the mark with same solvent. From this solution, 1 mL of the sample was pipetted out and transferred to 10 mL volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6 mL, 0.8 mL and 1 mL samples were withdrawn and volume was made up to 10 mL to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically at 286 nm.

Friability

Twenty tablets samples were weighed accurately and placed in friabilator (Roche Friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by:

% Friability = (Loss in weight/Initial weight) × 100

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time (FLT) and total floating time (TFT). The tablets were placed in a 100 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as FLT and the duration of the time the tablet constantly floats on the dissolution medium was noted as the, respectively, TFT.

Swelling index studies

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37 ± 0.5°C. After 1, 4, and 6 h, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water, and weighed on the analytical balance (Schimdzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated using the following formula [Figures 6 and 7].

In vitro drug release studies

900 mL of 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 ± 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 10 h at 50 rpm. At definite time intervals, 5 mL

of the fluid was withdrawn; filtered and again 5 mL of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically (Systronics, India) for Cefepime at 286 nm.

RESULTS AND DISCUSSION

Calibration curve of cefepime

The linearity was observed in the concentration range of 2–14 µg/mL and thus it follows the Bear-Lambert's law [Figure 1].

Pre-compression studies

Pre-compression studies of powdered blend were performed on parameters such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose as shown in the table. Angle of repose was found to be 26.62, 27.46, 28.32, 28.06, 27.58, and 28.44. Bulk density was found to be 0.721, 0.710, 0.415, 0.454, 0.458, and 0.445 g/cm^3, tapped density 0.872, 0.879, 0.483, 0.525, 0.505 and 0.502 g/cm^3, Hausner's ratio 1.206, 1.251, 1.178, 1.155,1.119, and 1.123, Carrs index 17.126, 19.714, 15.113, 15.602, 12.234, and 12.585 were found for F1, F2, F3,F4, F5, and F6 formulation, respectively, and reported in Table 2.

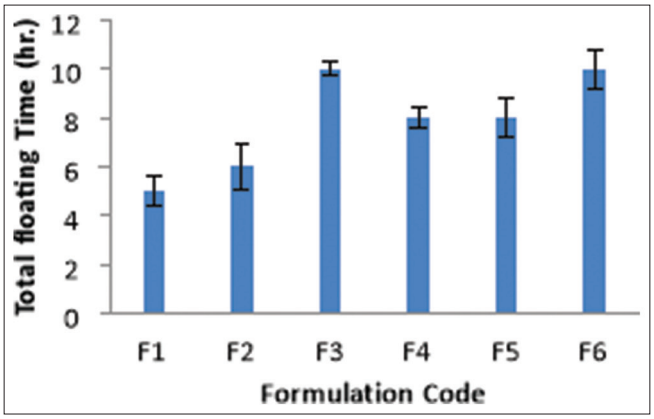

Figure 4: Total floating time studies of cefepime floating tablets formulations

Organoleptic and hardness

The formulated tablets were evaluated for their organoleptic characters. The tablets are round in shape and white in color. All the tablets showed elegance in appearance. The hardness of the tablets was measured by Monsonto hardness tester. The hardness of all the formulations was found to be in the range of 7.2–7.6 kg/cm^2 [Figure 2]. It indicates all the tablets have adequate mechanical strength.

Weight variation

Twenty tablets of each formulation were selected for weight variation test. The accepted percentage deviation was ± 7.5 for 130–324 mg weight tablets [Figure 3]. It was within the I.P. limit and all the tablets passed the weight variation test. Friability test was carried out by Roche friabilitor. The maximum weight loss should be not more than 1%. All the tablets passed the friability test.

TFT and *in vitro* buoyancy studies

In vitro buoyancy of the tablets from each formulation (F1 to F6) was evaluated [Figures 4 and 5]. Where, the highest and lowest FLT was observed with the formulation F1 and F6, respectively. The concentration of the natural polymers increases the FLT also increases and TFT observed for all the formulations was >10 h.

Table 2: Pre-compression studies

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose (⁰)
F1	0.721	0.872	17.126	1.206	26.62
F2	0.710	0.879	19.714	1.251	27.46
F3	0.415	0.483	15.113	1.178	28.32
F4	0.454	0.525	15.602	1.155	28.06
F5	0.458	0.505	12.234	1.119	27.58
F6	0.445	0.502	12.585	1.123	28.44

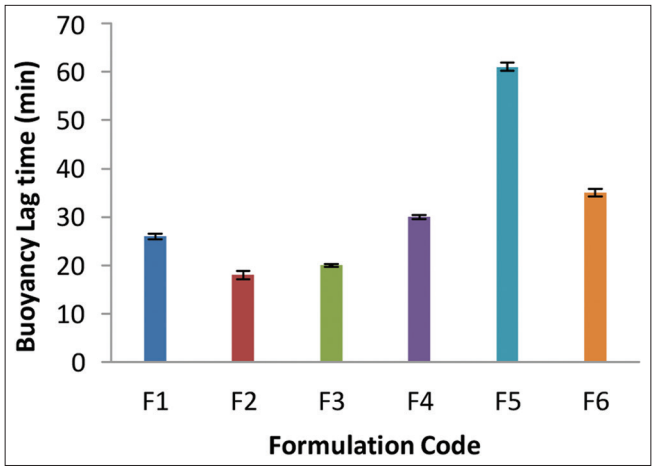

Figure 5: Buoyancy lag time (min.) studies of cefepime floating tablets formulations

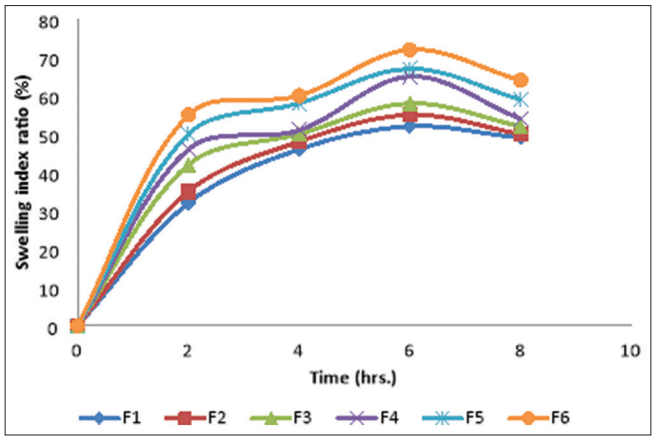

Figure 6: Swelling index ratio (%) studies of floating tablets formulations

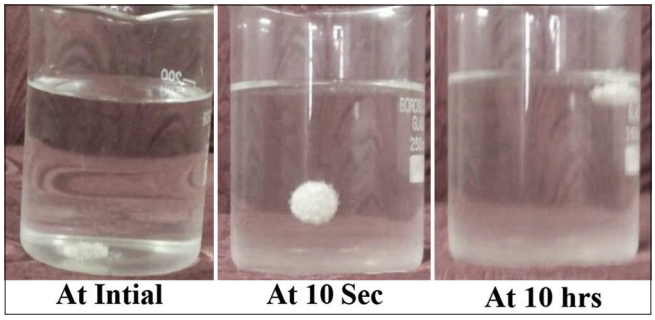

Figure 7: Photographic representation of swelling index ratio (%) studies

In vitro drug release studies

In vitro drug release studies were done for the selected study formulations. The drug release was found to show maximum drug release in case of F5 with 97.4% in 10 h as shown in Figure 8.

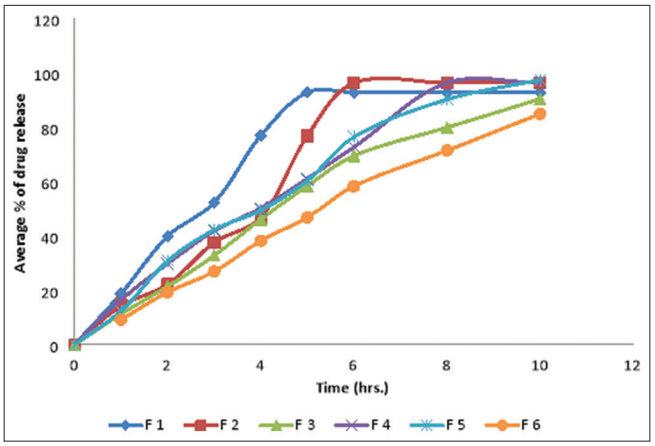

Figure 8: % of Drug release studies of floating tablets formulations

CONCLUSION

The Cefepime is antimicrobial agent. In this study, the gastroretentive Cefepime tablet formulation with different excipients for controlled release is successively prepared and evaluated. Formulation showed good release results thus, results of the present study clearly indicate, Cefepime floating tablet was a stable dosage form and a promising potential of the Cefepime gastroretentive system as an alternative to the conventional dosage form for controlled release. However, further clinical studies are needed to assess the utility of gastroretentive Cefepime floating formulation.

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