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Research Article

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

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Abstract

With the use of several hydrophilic and hydrophobic polymers such HPMC, Ethyl cellulose, Xanthum gum, and guar gum as well as the gas-producing substance Sodium bicarbonate, the current work aims to create Cefepime floating tablets. The creation of a gastro-retentive dosage form allowed scientists to deliver the medication to the stomach, the site of action for Cefepime, for extended periods of time. Guar gum and Xanthum gum are utilized as binding agents, and HPMC is employed as a swelling agent. The substance utilized to create the matrix is ethyl cellulose. As a suspending agent, PVP is employed. A gas-forming agent is sodium bicarbonate. MCC is employed as a diluent and a disintegrant. A lubricant called magnesium stearate is employed. Drug content, entrapment effectiveness, post compression tests, in-vitro buoyancy studies, swelling index studies, in-vitro dissolving studies, release kinetics, and stability studies will all be assessed for the manufactured Cefepime tablets. The pharmacopoeial limits were determined to apply to each of these parameters. On the basis of relevant findings from the post compression investigation, Formulation F5 was chosen for the drug release and stability study. A regulated release pattern was revealed by an in vitro dissolution investigation.

Keywords: Gas Powered Systems, Cefepime, Controlled release, Floating drug delivery.

INTRODUCTION

Cefepime is a third-generation, broad-spectrum cephalosporin that is semi-synthetic. With regard to susceptible Gram-positive and Gram-negative bacteria, it has a wide range of activity and effective therapeutic action[1]. When compared to other antimicrobial medicines, it demonstrates strong antibacterial activity, great efficacy, convenient dosing, and favourable tolerability[2]. Low solubility and low permeability qualities place it in BCS Class IV. There are only two dosing forms of cefepime: capsules and suspensions. Its crystalline structure and difficulty in compressing make it difficult to produce in tablet dosage form[3]. Many methods, including mucoadhesive systems, swelling/expanding systems, high density systems, magnetic systems, and floating systems, have been suggested to manage the residence of drug delivery systems in the upper gastrointestinal tract[4]. Drugs' stomach residence times can be greatly extended by gastroretentive systems since they can stay in the gastric region for several hours. For medications that are less soluble in a high pH environment, prolonged stomach retention increases bioavailability, lowers drug waste, and enhances solubility. It can be used to administer medications locally to the stomach and nearby small intestines. Gastro retention aids in improving patient access to novel medications with novel therapeutic prospects and significant advantages[5]. Mucoadhesion[6], Floatation[7], Sedimentation[8], Expansion[9], Modified shape system[10], and Simultaneous delivery of pharmacological agents[11] are some methods for achieving regulated gastric retention of solid dosage forms. The gastroretentive floating drug delivery system (GRFDDS) floats in the stomach for a long time without slowing down the gastric emptying rate because its bulk density is lower than that of gastric fluids. The medicine is released from the body slowly and at the desired rate while the system is floating on the gastric contents. Floating drug delivery systems have a number of benefits, including reduced intra- and inter-subject variability in plasma drug levels, effectiveness for drugs with narrow absorption windows, reduced dosing and improved patient compliance, decreased Cmax and prolonged drug levels above the minimum effective concentration, and enhanced safety profile for medications with side effects linked to high Cmax[12, 13]. A floating drug delivery device was created and developed for the current study. In comparison to previous methods, the buoyancy principle that produces floating dose forms with extended gastric residence time appears to provide a higher level of user safety. The tablets were created utilising hydroxypropylmethylcellulose (HPMC) as a binder and an effervescent component (sodium bicarbonate). Drug content, entrapment effectiveness, post compression investigations, in-vitro buoyancy studies, swelling index research, in-vitro dissolving studies, release kinetics, and stability tests were all performed on the manufactured Cefepime tablets.

MATERIALS AND METHODS

Cefepime was a gift from Hyderabad, India's M/s Hetero Drugs Ltd. Pharmaceutical-grade ingredients included HPMC, Xanthum Gum, Guar Gum, PVP, Ethyl Cellulose, Sodium Bicarbonate, Micro Crystalline Cellulose, and Magnesium

Stearate. Analytical-grade compounds were employed for all other substances.

Preparation of calibration curve of Cefepime

Cefepime was carefully weighed out at 100 mg and added to a 100 ml volumetric flask along with 0.1N HCL to dissolve it. Pipette 1 ml of this solution, which was produced with 0.1 N HCl and labelled "Stock," into a separate 10 ml volumetric flask. To get concentrations of 100 µg/ml, 1 ml of the cefepime standard stock solution (1000µg/ml) was diluted to 10 ml using 0.1N HCl 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 the reference drug solution were added to this solution and diluted to a final volume of 10 ml with 0.1M. At 286 nm, 0.1N HCL was used as a blank to determine the absorbance of these solutions.

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.

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	350mg	350mg	350mg	350mg	350mg	350mg

Pre compression studies

Bulk density

It is the proportion of powder mass to bulk volume. The particle size distribution, shape, and cohesiveness all affect the bulk density. Initial bulk volume was calculated using an accurately weighed quantity of powder that was carefully poured into a graduated measuring cylinder through a big funnel. The following formula determines it in gm/ml:

Bulk density=M/Vo

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

Angle of repose (θ)

It is described as the greatest angle that can be formed between the powder pile's surface and the horizontal. It was done with a fixed funnel. A graph paper was laid on a level horizontal surface to which a funnel was fixed with the tip at a specific height, h. The conical pile's peak was carefully poured through a funnel until it touched the funnel's tip. The following equation was then used to compute the angle of repose:

Angle of repose Ø = tan-1(h/r)

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

Tapped density

A 100 ml measuring cylinder was filled with 10 g of dry, clean powder. Following that, the cylinder was struck 100 times from a fixed height, and the tapped volume was recorded. It is provided by: and is represented in gm/ml.

Tapped density=M/Vt

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

Compressibility index (Carr's index)

An essential factor in determining the powder's flow behaviour is the compressibility index. It is inextricably linked to cohesion, particle size, and relative flow property rate. The method is easy, quick, and well-liked for forecasting flow properties. Equation can be used to represent Carr's index.

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

Hausner's ratio

The Hausner's ratio is used to forecast the powders' ability to flow. Comparable to compressibility index is this approach. Equation can be used to represent Hausner's ratio.

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Evaluation of Prepared Formulation

Weight variation

Twenty randomly chosen pills were weighed in a single pan balance both individually and collectively. The standard deviation was computed after noting the average weight. If no more than two tablets deviate by more than the permitted percentage and no two tablets differ by more than twice the permitted percentage, the tablets pass the test.

PD = [(Wavg – Winitial) / (Wavg)] x 100

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

Thickness

Vernier Calliper was used to measure the tablets' diameter and thickness. Average values were computed using 20 pills from each batch.

Hardness

The hardness of the tablet was assessed using the Monsanto hardness tester. The tablet was held in place by the moving jaw and fixed jaw. The load was steadily increased until the tablet shattered when the scale was set to zero. The amount of force there provides a measurement of the tablet's hardness. The unit of measurement is kg/cm2. Six pills from each recipe were tested for hardness, and an average value was computed.

Drug content

The tablets were broken apart, and the powder containing 100 mg of the medication was precisely weighed and added to a 50 ml volumetric flask. This flask was filled with just enough distilled water to completely dissolve the pills. The flask's volume was then adjusted using the same solvent. 1 ml of the sample was pipetted from this solution into a 10 ml volumetric flask. With distilled water, the volume in the second flask was brought up to the required level. To keep the concentration within the beer's range, 0.6, 0.8, and 1 millilitre samples were taken from this and the volume was increased to 10 millilitres. The UV spectrophotometric estimate for this final diluted solution was 286 nm.

Friability

Twenty pill samples were precisely weighed and put into the Roche Friabilator. Loose dust was removed from the tablets after the allotted time (4 minutes at 25 rpm). Tablets were finally weighed. The weight reduction demonstrates the tablets' resistance to this kind of wear. Next, the% friability was determined using:

$$\% \text{ Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

In-vitro buoyancy studies

The total floating time and floating lag time were used to calculate the in-vitro buoyancy. 0.1N HCl was added to a 100ml beaker that contained the pills. The total floating time (TFT) is the amount of time the tablet spends floating continuously on the dissolution medium. The floating lag time (FLT) is the amount of time needed for the tablet to rise to the surface and float.

Swelling index studies

A dose unit's swelling behaviour was evaluated by examining its weight increase. By inserting the tablets in the basket of the dissolving device with 0.1N HCl at 370.5°C as the dissolution media, the swelling index of the tablets was calculated. Each dissolution basket containing a tablet was removed at 1, 4, and 6 hours to be blotted with tissue paper to remove excess water before being weighed on an analytical balance (Schimdzu, AXE 120). For each time point, the experiment was carried out in triplicate.

In vitro drug release studies

The jar was filled with 900ml of 0.1 HCl, and the USP apparatus II (Paddle Method) was put together. The medium was given time to reach equilibrium at 37± 0.5 °C. After inserting the tablet and covering the vessel, the equipment was run at 50 revolutions per minute for 10 hours. Five millilitres of the fluid were removed, filtered, and then five millilitres of fresh buffer were added at predetermined intervals. The samples were appropriately diluted using the dissolving fluid, and Cefepime at 286 nm was determined spectrophotometrically (Systronics, India).

RESULTS AND DISCUSSION

Calibration curve of Cefepime

Since the linearity was noted in the concentration range of 2 to 14µ g/ml, the Bear- Lambert's law is followed.

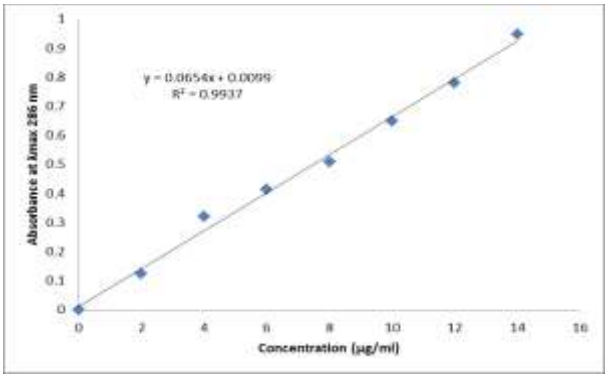

Figure 1: Standard calibration curve of Cefepimein 0.1N HCL

Pre compression studies

Precompression studies of powdered blend were performed on parameters like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose as shown in the table below. 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 0.445g/cm3, tapped density 0.872, 0.879, 0.483, 0.525, 0.505 and 0.502 g/cm3, 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.

Table 2: Precompression Studies

Formulation code	Bulk density(gm/mL)	Tapped density(gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose ($^{\theta}$)
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

Organoleptic and hardness

The organoleptic qualities of the prepared tablets were assessed. The pills are white and have a circular shape. Each tablet had a refined appearance. A Monsonto hardness tester was used to gauge the tablets' hardness. All of the formulations were found to have hardness between 7.2 and 7.6 kg/cm2. It shows that the mechanical strength of each pill is sufficient.

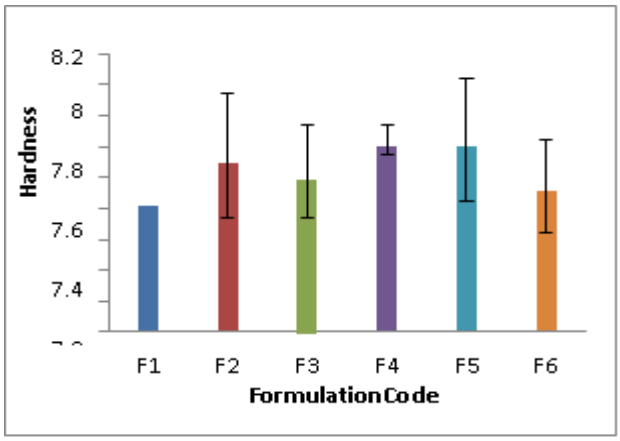

Figure 2: Hardness studies of Cefepime floating tablets formulations

Weight variation

For the weight variation test, 20 pills of each formulation were chosen. For weight-reduction tablets containing 130-324 mg, the acceptable percentage deviation was 7.5. The weight variation test was passed by all of the pills, and it was within the I.P. limit. The Roche Friabilitor performed the friability test. A maximum weight decrease of 1% is recommended. The friability test was successful for every tablet.

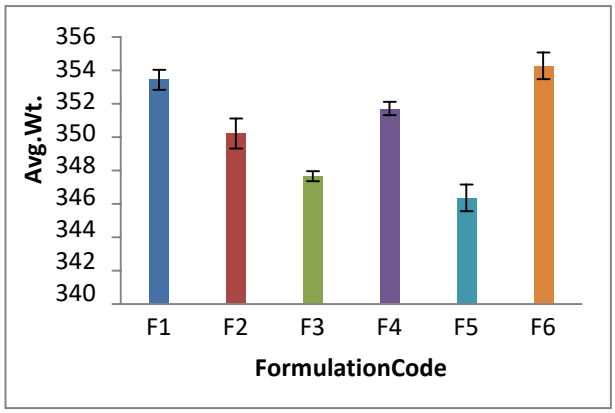

Figure 3: Average weight of Cefepime floating tablets formulations

Tablets formulations total floating time and *in-vitro* buoyancy studies

The tablets from each formulation (F1 to F6) were measured for in-vitro buoyancy (Figure). Where, with the formulations F1 and F6, respectively, the largest and lowest floating lag times (FLT) were recorded. The overall floating duration recorded for all formulations was >10 hours, and as the concentration of the natural polymers increases, so does the floating lag time.

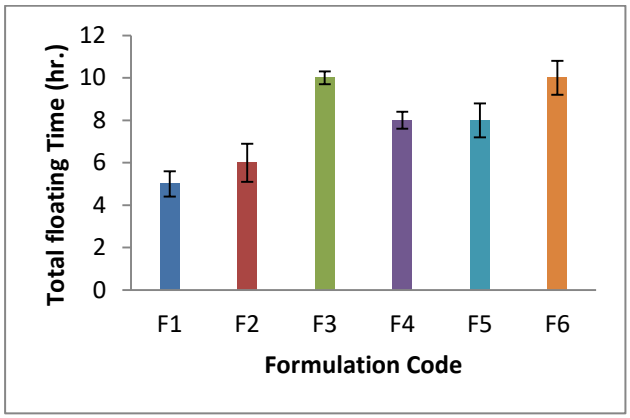

Figure 4: Total floating time studies of Cefepime floating tablets formulations

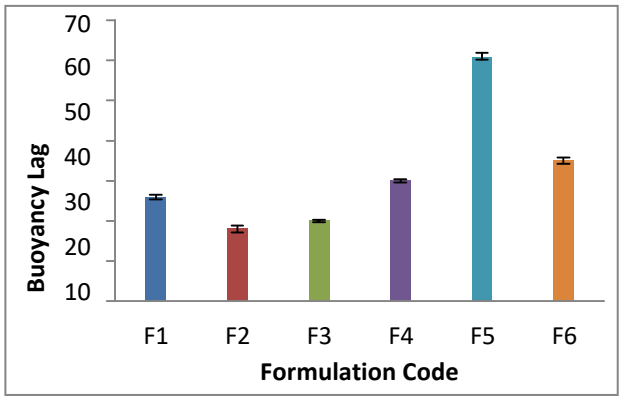

Figure 5: buoyancy lag time (min.) studies of Cefepime floating tablets formulations

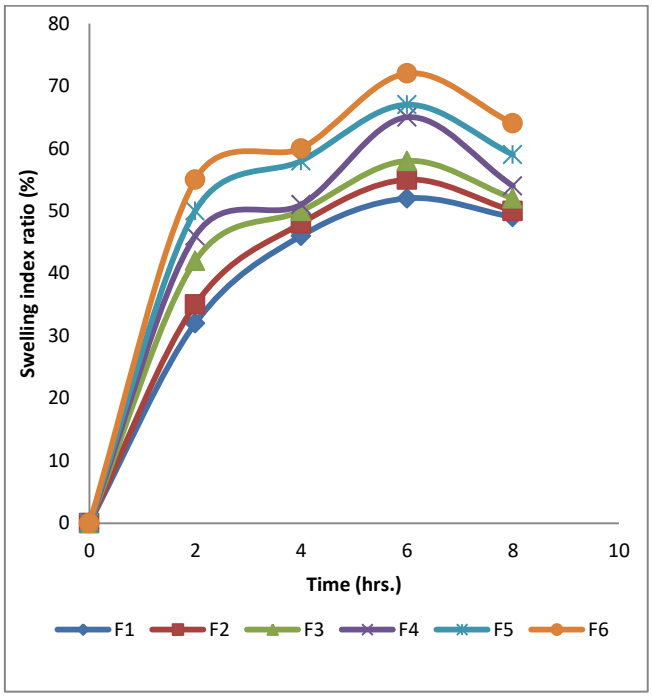

Figure6: Swelling index ratio (%) studies of floating tablets formulations

At Intial **At 10Sec** **At 10hrs**

Figure7: Photographic representation of swelling index ratio(%)studies

In-vitro drug release studies

For the chosen research formulations, in-vitro drug release investigations were carried out. As illustrated in figure 8, the drug release for F5 was determined to be at its maximum with 97.4% in 10 hours.

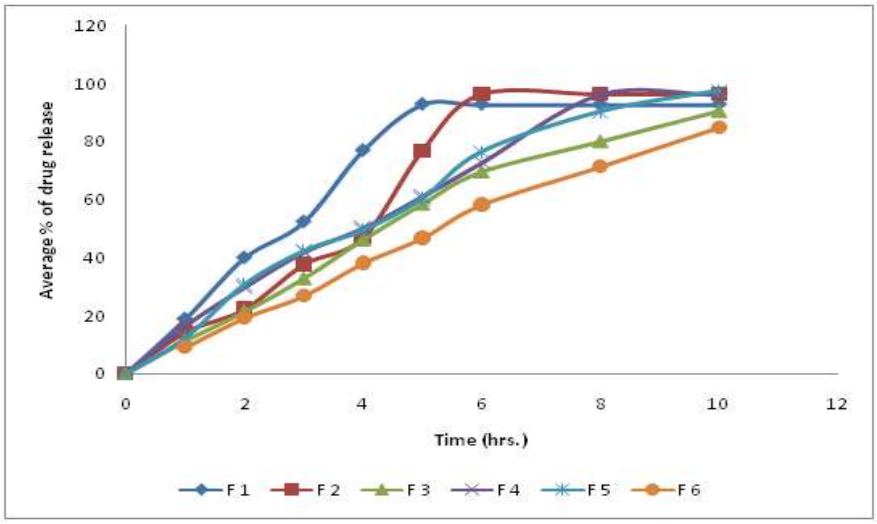

Figure 8: % of Drug release studies of floating tablets formulations

CONCLUSION

Cefepime is an antibacterial substance. This study prepares and assesses a series of gastroretentive Cefepime tablet formulations using various excipients for controlled release. The current study's findings amply demonstrate that the Cefepime floating tablet was a stable dosage form with promising possibilities for the Cefepime gastroretentive system as a substitute for the traditional dosage form for controlled release. Formulation demonstrated good release results. To evaluate the effectiveness of the gastroretentive Cefepime floating formulation, additional clinical investigations are required.

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