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Formulation and Evaluation of Gastroretentive Floating Tablets of Cefexime using HPMC and Carbopol

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Abstract

An appropriately designed controlled release drug delivery system can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. The low bioavailability and short biological half life Cefexime following oral administration favors development of a gastro retentive formulation. Cefixime is an orally active third generation semisynthetic cephalosporin type of beta lactam antibiotic. Hence, the aim of present work was to develop a Floating tablets of to prolong gastric residence time and to increase drug absorption and hence bioavailability. 4 formulations (F1 to F4) floating tablets of Cefexime were prepared by direct compression method using cefixime with polymers like HPMC K4M and carbopol in variable concentrations. The buoyancy lag time and the total floating time was studied for all the formulations. From the preformulation studies for drug excipients compatibility it was observed that there was no compatibility problem with the excipients used in study. The drug release from the formulations follows fickian diffusion. All the formulations possessed good floating properties with total floating time between 8 – 12 hrs. Thus from the studies it can be concluded that the prepared Tablets exhibited satisfactory physicochemical characteristics and all the prepared batches showed good in vitro buoyancy. Formulations showed better control of drug release and the drug release was similar to that of marketed product.

Keywords: Cefexime, floating, HPMC K4M, carbopol

Contents

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1. Introduction

Oral ingestion is the predominant and most preferable route for drug delivery of drugs for systemic effect. Controlled drug delivery systems have been developed to overcome the problems of fluctuating drug levels associated with conventional dosage forms. Time controlled oral drug delivery systems offer several advantages over immediate release dosage forms, including the minimization of fluctuations in drug concentrations in the

plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency, leading to improved patient compliance [1]. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Drugs that are slowly absorbed from G.I.T can be given as slow release gastric retention system to improve the absorption and bioavailability. To design such a system many factors are to be considered. Recently several approaches have been developed to increase gastric residence time of drug formulation [2-4].

An appropriately designed controlled release drug delivery system can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. Cefixime trihydrate is a 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 [5].

Cefixime trihydrate having pKa value of 2.5 is 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. The low bioavailability and short biological half life of Cefexime favor development of a gastro retentive formulation.The objective of present work was to develop a floating tablets of Cefexime to prolong gastric residence time and to increase drug absorption and hence bioavailability and to evaluate the prepared tablets for physicochemical properties, buoyancy lag time, total floating time and *invitro* drug release.

2. Materials and Methods

Materials:
HPMC, carbopol, sodium bicarbonate, methyl cellulose, citric acid, lactose, magnesium stearate and talc was purchased from the provider. All ingredient used were of analytical grade.

Formulation of floating tablets of Cefexime
The Cefexime floating tablets were prepared by blending the drug (Cefexime), polymers (HPMCK4M) and carbopol in different proportions respectively. To this sodium bicarbonate, lactose, citric acid was added to mortar and pestle according to their geometric dilution and finally makes up the total weight (515mg) of tablet using micro crystalline cellulose. The powder was passed through sieve no.60. The obtained samples were collected and re triturated. To this required amount of talc is added and compressed finally. In the present work, 4 formulations (F1 to F4) floating tablets were prepared using variable concentrations of HPMC K15M and carbopol.

Table 1. Development of formulation containing varying proportions of polymers

Formulation	Drug (mg)	HPMC (mg)	Carbopol (mg)	Sodium bicarbonate (mg)	Methyl cellulose (mg)	Citric acid (mg)	Lactose (mg)	Magnesium stearate (mg)	Talc (mg)
F1	200	100	25	50	75	25	25	5	10
F2	200	75	50	50	75	25	25	5	10
F3	200	50	75	50	75	25	25	5	10
F4	200	25	100	50	75	25	25	5	10

Evaluation of tablets [6, 7]
Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

Determination of drug content
Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in a suitable solvent and make up the final volume with the suitable buffer solution. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer, using buffer solution as a blank.

***In-vitro* dissolution study**
Invitro release studies were carried out by using United States Pharmacopoeia (USP) 23 Dissolution Testing Apparatus II (Paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH 1.2) at 37±0.5oC. 50 rpm was maintained, 5 ml of sample was withdrawn at predetermined time intervals for 24 hours and the same volume of the fresh medium was replaced. The absorbance of the withdrawn sample was measured

spectrophotometrically at a wavelength of about 294 nm and cumulative percentage drug release was calculated using an equation obtained from a standard curve [8].

Determination of floating parameter [9]

a) *Invitro* buoyancy test: The *invitro* buoyancy was determined by observing floating lag time, as per the method described by Rosa. 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 considered as the floating lag time.

b) Swelling study: For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again upto 8 hours. The percentage weight gain by the tablet was calculated

c) Floating lag time and floating time: *In vitro* buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration in which the tablet remains floating was determined as floating time.

3. Results and Discussion

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. In the present study 4 formulations (F1 to F4) floating tablets of Cefexime were prepared by direct compression method using cefixime with polymers like HPMC K4M and carbopol in variable concentrations. The prepared Cefexime floating tablets were subjected to various evaluation studies done like weight uniformity test, hardness, thickness, friability, content uniformity, *in vitro* buoyancy study, swelling index disintegration studies, *in vitro* dissolution studies.

Weight Variation, Thickness, Hardness and Friability

The results showed that weight variation, thickness were lying within limits. There is a slight variation in hardness of tablets. As the proportion of polymers increases the hardness of the tablets was found to increase in case of HPMC. The friability loss was found to be within the limits in all the friability tablet was found to mechanically strong.

Table 2. Thickness, Hardness and Friability of different formulation

Formula	Weight variations	Thickness	Hardness	Friability
F1	0.238	0.38±0.031	5.5	0.2
F2	0.246	0.40±0.011	6.0	0.4
F3	0.235	0.41±0.007	4.0	0.7
F4	0.245	0.43±0.007	3.5	0.6

Drug content

Drug content of all the formulations are within the acceptable range which shows the proper mixing of the drug with excipients as shown in table 3.

Table 3. Drug content of different formulation

Formulation code	% Drug Content
F1	95
F2	94
F3	92
F4	91

In-vitro drug release

In-vitro drug release study for all the formulations was conducted and represented in fig 1. Formulations showed sustained release. Formulations with polymers showed high less which retards the drug release to a greater extent. Thus the HPMC Decreasing and Carbopol 940 Increasing concentration provide the optimum drug release.

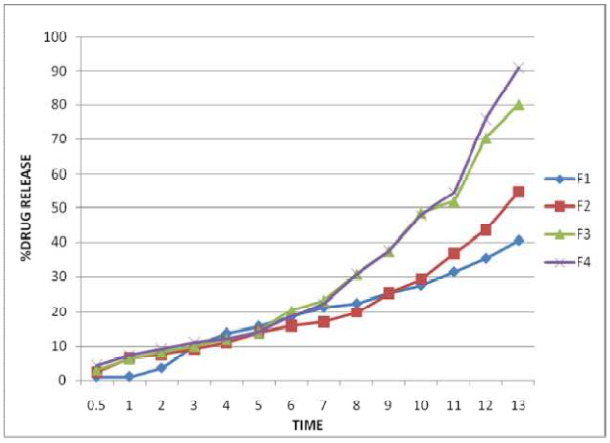

Figure 1. In-Vitro % Drug Release Profiles for All the Prepared Formulations

Buoyancy and total Flotation test

From the results, it was observed that as the buoyancy lag time and the total floating time was studied for all the formulations. F1, F2, F3 and F4 total floating time were found to be 12, 10, 5.5 and 7 hrs respectively as shown in table 4. F1 showed optimum buoyancy lag time. for all the F1 and F2 formulations showed more total floating time when compared to F3 and F4 due to the presence of hydrophobic polymer which decreased the solubility. Thus with an increase in the concentration of the hydrophilic polymer total floating time was found to be decreased due to increase in the solubility. All formulations possessed good floating properties with total floating time between 8-12 hrs.

Table 4. Buoyancy and total Flotation test

Formulation code	Buoyancy lag time (min)	Total floatation time (hrs)
F1	2.5 min	12
F2	2.0 min	10
F3	4.0 min	5.5
F4	4.5 min	7

Before **After 60 min**

Figure 2. In vitro buoyancy study of cefexime floating tablets

Swelling thickness

The extent of swelling was found out by measuring the thickness of the tablet before and after one hour stay of the tablet in pH 6.8 buffer at 37 ± 0.5^{0}C. FormulationF1 and F2 tablets were found to swell more and formulationF3 and F4 tablets were swelling to lesser extent.

4. Conclusion

Thus from the studies it can be concluded that the prepared Tablets exhibited satisfactory physicochemical characteristics and all the prepared batches showed good in vitro buoyancy. Formulations showed better control of drug release and the drug release was similar to that of marketed product. It was concluded that the formulation of sustained release tablet of cefixime containing a combination of both polymers were taken as ideal or optimized formulation for 13 hours release as it fulfils all the requirement of Floating Drug Delivery System of sustained release dosage form. Further work is required to stabilize the product; in-vivo studies estimate the amount of drug present in the various organs with disposition kinetics and establish appropriate dosage regimen to gauge the significant changes in the metabolism of the drug before further studies.

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