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RESEARCH ARTICLE

Development of Non-Effervescent Low Density Floating Tablets of Cefpodoxime Proxetil

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ABSTRACT

The aim of the work is to modify the solubility and bioavailability of cefpodoxime proxetil, by employing noneffervescent floating drug delivery (tablet dosage forms). Non-effervescent systems are a type of floating drug delivery systems that have been used to boost the gastric residence and the floatation time in the gastro intestinal tract. The study included formulation of floating tablets using polymers like gum damar and HPMC K15M as matrix forming agents. Accurel® MP 1000 was used as floating agent. The tablets were prepared by direct compression technique. DSC studies conformed that there was no incompatibility between the polymer and the drug. Tablet preformulation parameters were within the Pharmacopoeial limit. Tablet showed zero lag time, continuance of buoyancy for >12 h. The tablet showed good *in vitro* release. Drug release was through swelling and abided by the gellation mechanism. *In vivo* X-ray studies depicted that tablets continued to float in the GIT for 12 h. Accelerated stability showed that, tablets were stable for over 6 month. Thus the prepared non-effervescent floating tablet of cefpodoxime proxetil can be used for the treatment of hypertension for more than 12 h with single dose administration.

KEYWORDS

Cefpodoxime Proxetil, Accurel® MP 1000, Gum Dammar, HPMC K15M, Non-Effervescent

INTRODUCTION

Oral sustained release dosage forms deliver the drug for longer period and help in producing the therapeutic effect for 24 h for those drugs which are having low plasma halflife.[1] Drugs that have narrow absorption window in the gastro intestinal tract (GIT) will have poor absorption.[2,3] For these drugs, gastroretentive drug delivery systems (GRDDSs) have been developed. Oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. Gastroretentive dosage systems (GRDDSs) help in maintenance of constant therapeutic levels for prolonged periods, increases therapeutic efficacy and thereby reduce the total dose of administration. Floating drug delivery system (FDDS) has less density (<1.004 g/cm^3) than gastric fluid, so they remain buoyant in gastric fluid and show sustained drug release.[4] It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro re-tentive properties would enable an

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extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for these drugs.[5] The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.[6] These efforts resulted in gastroretentive (GR) dosage forms that were designed in large part based on the following approaches[7]: (a) low density form of the dosage forms that causes buoyancy above gastric fluid[3]; (b) high density dosage forms that is retained in the bottom of the stomach; (c) bioadhesion to stomach mucosa[8]; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients[9]; (e) expansion by swelling or unfolding to a large size which limits emptying of the dosage forms through the pyloric sphincter. Sustained or controlled-release drug delivery systems can provide several advantages over conventional dosage forms including reduced frequency of administration, the strength of the required dose, and the number and/or severity of side effects, whilst increasing the drug effectiveness, improving patient compliance and providing a constant, prolonged, and uniform therapeutic effect.[10] Among the many approaches widely used for designing oral controlled release dosage forms, hydrophilic matrix tablets offer precise modulation of drug release as a result of hydration of the constituent polymer(s), flexibility to obtain desired drug release profiles, cost effectiveness and broad Food and Drug Administration (FDA) acceptability.[11] Cefpodoxime proxetil is a third generation cephalosporin prodrug, having a white to light brownish white powder, odourless, slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in acetonitrile and in methyl alcohol which is administered orally. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%.[12]

Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil. The half-life of cefpodoxime proxetil is 2.2 hours. Cefpodoxime proxetil is a β lactum antibiotic. Its action is by binding to specific penicillin binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta - lactamase enzymes.[12]

MATERIALS AND METHOD

Materials

Cefpodoxime proxetil was provided as a gift sample from Cadila Pharma, Ahmedabad, India. Accurel® MP1000 was received as a gift sample from Membrana GmbH, Germany. Gum damar was obtained from Innovative Marketing Services, Mumbai, India. Methocel K15 (HPMC K15M) was purchased from E Merck (India) Ltd, Mumbai. Lactose and magnesium stearate were purchased from SD Fine Chem. Ltd. Mumbai, India. All other ingredients used were of analytical grade.

Preparation of Floating Matrix Tablets

Floating matrix tablets were prepared by direct compression method. All the ingredients were blended together to get homogenous mixture. Accurel® MP1000 as low density polypropylene foam powder, gum damar as release retardant, HPMC K15M as swellable polymer, lactose as diluent and magnesium stearate as lubricant were used. Powder mass was compressed into tablets using a 10 station rotary tablet punching press with 12 mm punch and die set. Each tablet contained 50 mg of cefpodoxime proxetil. Composition of each tablet is given in Table 1.

Evaluation of Floating Matrix Tablet

Thickness

Thickness and diameter of the tablets were determined by using micrometer screw gauge. The average of five tablets from each

Table 1: Formulation chart showing composition of each cefpodoxime Proxetil floating matrix tablet

Ingredients (mg)	FT-1	FT-2	FT-3	FT-4	FT-5	FT-6	FT-7	FT-8	FT-9
Cefpodoxime Proxetil	50	50	50	50	50	50	50	50	50
Accurel® MP1000	140	140	140	140	140	140	140	140	140
Gum damar	40	50	60	40	50	60	40	50	60
HPMC K15M	30	40	50	40	50	30	50	30	40
Lactose	87	67	47	77	57	67	67	77	67
Magnesium stearate	3	3	3	3	3	3	3	3	3

formulation was taken. It is expressed in millimeter.[13]

Friability

Ten tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 mins. The tablets were taken out, dedusted, and reweighed.[13]

The percentage friability of the tablets was calculated using the equation:

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F is friability in percentage, W is the initial weight of tablet and W_t is the final weight of tablets after revolutions. Compressed tablets with a loss of less than 1 % are generally considered acceptable.

Density Measurement

The densities (ρ) of the formulations were calculated by following equation:

$$\rho = W/V$$

Where 'W' is the weight of dried hydrogel and 'V' is its volume. The volume of the hydrogel was determined by the solvent displacement method using hexane as the displacement fluid. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it.[14]

Hardness

The hardness of core tablets was measured using Erweka hardness tester. A total of five tablets from each formulation were taken for the study and the average of the three is reported. It is expressed in kg.[13]

Weight Variation Test

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. For the tablets of average weight 350 mg, the % deviation allowed is ± 5 %.[13]

$$\% \, Deviation = \frac{Avg.\ weight\ of\ tablets - Individual\ tablet\ weight}{Avg.\ weight\ of\ tablets} \times 100$$

Drug Content

Formulation equivalent to 50 mg of cefpodoxime Proxetil was taken and transferred to 100 ml volumetric flask, dissolved and diluted with pH 1.2 HCl buffer. The absorbance of the resulting solution was measured at the λ_{max} of 264 nm using a UV spectrophotometer after filtration through whatmann filter paper. The drug content was calculated using the following equation:

% Drug content = conc. (µg/ml) × Dilution factor × 100/ 50

Floating Lag Time and Duration of Buoyancy

Floating lag time is the time taken by the tablet to emerge onto the surface of the dissolution medium after adding to simulated gastric fluid without pepsin (500 ml of pH 1.2 HCl buffer). The time taken by the tablet to raise to the surface of the dissolution media and time taken for it to sink was noted, the difference of which gives the duration of buoyancy.[15]

Swelling Studies

Each tablet was weighed initially and then placed in 900 ml pH 1.2 HCl buffer in a basket at 37 ± 0.5 °C. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed.[16] Swelling characteristics of the tablets were expressed in terms of % water uptake (WU).

$$\% \text{ Swelling} = \frac{Wt - Wi}{Wi}$$

Where 'Wt' is weight of the swollen tablet at time 't' and 'Wi' is initial weight of the tablet.

In Vitro Release Studies

In vitro drug release of cefpodoxime Proxetil from the formulations were evaluated in triplicate at 37±0.5 °C using a USP XXIV dissolution testing apparatus type 2 (paddle method) at a rotation speed of 75 rpm in 900 ml of pH 1.2 HCl buffer for 12 h. At regular time intervals, 5 ml of the dissolution medium were withdrawn, replaced with an equivalent volume of fresh dissolution fluid and analyzed for the drug content using a UV-Vis spectrophotometer at 264 nm.[17]

In Vivo Studies

In vivo studies were carried out to monitor the gastric retention property of formulations. Barium sulfate loaded formulations were used as X- ray markers. The study was conducted after obtaining approval from the Institutional animal ethics committee of JSS College of Pharmacy, Mysore. Albino rabbits (2.6 kg) were used in the study. Before the test the rabbits were fasted overnight with and the formulations were administered orally to the rabbits with water. X- ray pictures were taken at different time intervals after the administration of the formulations.[18]

Stability Study

To determine the stability study the floating tablets of cefpodoxime proxetil were packed in glass bottle and stored at 40±2°C and 75%±5% RH for a period of six months as per the ICH guidelines. The tablets were withdrawn after a period of 0, 30 and 180 days and evaluated for hardness, friability, content uniformity, *in vitro* floating behavior and dissolution study.[19] The differences in parameters from floating tablets were evaluated using unpaired *t*-test. In *t*-test, a probability value of $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Gastroretentive tablets of cefpodoxime proxetil were developed to increase the gastric retention time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 12 h. The floating tablets were made using gel-forming polymers, gum dammar and HPMC K15M. The combination of low density polypropylene foam powder (Accurel® MP1000) and controlled-release system found, to be beneficial in improving the buoyancy and drug release characteristics.

Physico-chemical Characterization of Floating Tablets

The experimental results of the tablet evaluation parameters are summarized in Table 2. The thickness all tablets was found to be in the range of 2.85 to 2.97 mm. Sufficient strength of all tablets was also evident since the friability was less than 1%, indicating compliance with the requirements of Indian pharmacopeia. Density of all formulations below 1 gm/cm^3 indicating the density of formulations lower than gastric fluid. Hardness of tablets were found to be between 5.1 to 6.7 Kg indicated good strength. The average weight of the prepared tablets were in the range of from 345 to 352 mg. Tablets of all batches complied with the mass variation requirement of Indian Pharmacopoeia and no batch varied more than 5% of the average weight indicating consistency in the preparation

Table 2: Physico-chemical characterization of floating tablets of cefpodoxime proxetil

Form^{n} code	Thickness (mm)	Friability (%)	Density (g/cm^3)	Hardness (Kg)	Weight variation (mg)*	Drug content (%)	Duration of buoyancy (h)
FT-1	2.85±0.06	0.55±0.03	0.88±0.02	5.2±0.24	346±0.3	97.21±0.62	>12
FT-2	2.97±0.08	0.40±0.06	0.89±0.03	5.5±0.34	352±0.4	95.95±0.72	>12
FT-3	2.89±0.05	0.46±0.05	0.91±0.04	6.1±0.52	348±0.2	98.46±0.88	>12
FT-4	2.90±0.07	0.61±0.04	0.88±0.03	5.8±0.20	346±0.3	102.39±0.69	>12
FT-5	2.92±0.08	0.39±0.07	0.90±0.02	5.1±0.33	349±0.2	100.65±0.77	>12
FT-6	2.94±0.09	0.53±0.04	0.89±0.03	5.8±0.36	351±0.3	98.20±0.73	>12
FT-7	2.85±0.07	0.54±0.05	0.93±0.02	5.9±0.30	352±0.5	96.47±0.79	>12
FT-8	2.86±0.05	0.56±0.07	0.91±0.03	6.7±0.52	347±0.4	98.34±0.62	>12
FT-9	2.87±0.07	0.51±0.02	0.94±0.02	5.9±0.27	345±0.3	96.53±0.68	>12

of the tablet with minimal batch to batch variation. The drug content analysis showed that there was proper distribution of the drug in the floating matrix tablets and well within the range of 96.47 -102.39 % of the total amount of the drug added in floating matrix tablets and therefore comply with the pharmacopoeial limits.

Floating Lag Time and Duration of Buoyancy

All the formulations showed good *in vitro* buoyancy with no floating lag time (Zero) because of low density polypropylene foam powder. The tablets remained buoyant for more than 12 h achieving the gastric retention properties.

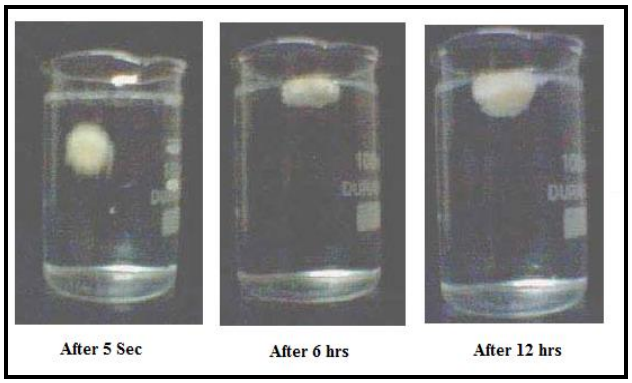

Figure 1. Photographs of *in vitro* floating behavior and dimensional changes of matrix tablet formulation

The results obtained are shown in Table 2 and photographs taken at different time intervals were shown in Figure 1.

Differential Scanning Calorimetry

DSC studies were carried out for cefpodoxime proxetil and formulation FT-7 and the thermograms obtained are presented in Figure 2. Thermogram of pure drug shows a sharp endothermic peak at 158.2^{o}C, which corresponds to its melting point. Matrix tablet formulation FT-7 also showed endothermic peak at 158.9^{o}C, which corresponds to the melting point of the drug. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients.

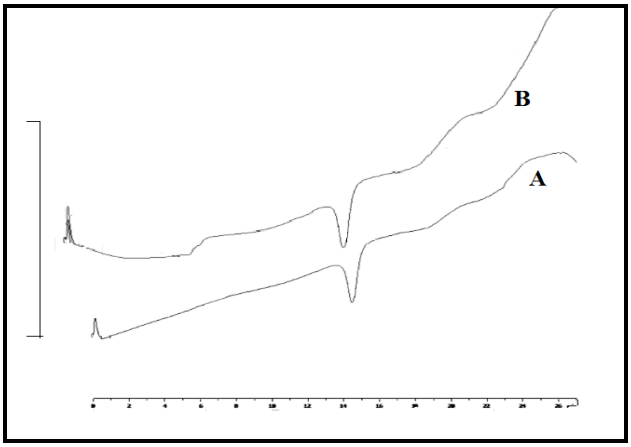

Figure 2: DSC thermograms: (A) pure cefpodoxime proxetil API; (B) Formulation FT-7

From the thermograms it was evident that melting point of cefpodoxime proxetil was not changed when it was formulated as a floating matrix tablets.

Swelling Studies

The swelling behavior indicates the rate at which tablets absorb the water from dissolution media and swells. Swelling of matrix tablets increases with respect to time because weight gain by tablets was increased proportionally with rate of hydration up to 6 h and matrix appeared swollen almost from the beginning. Later on swelling was decreased due to dissolution of outermost gelled layer of tablets. The complete swelling was achieved by the end of 7 h. The percent swelling of the all formulations studied in pH 1.2 HCl buffer and results were graphically represented in Figure 2. The swelling was directly proportional to amount of HPMC K15M and inversely related to amount of gum damar. Diffusion of drug significantly depends on the water content of the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system.

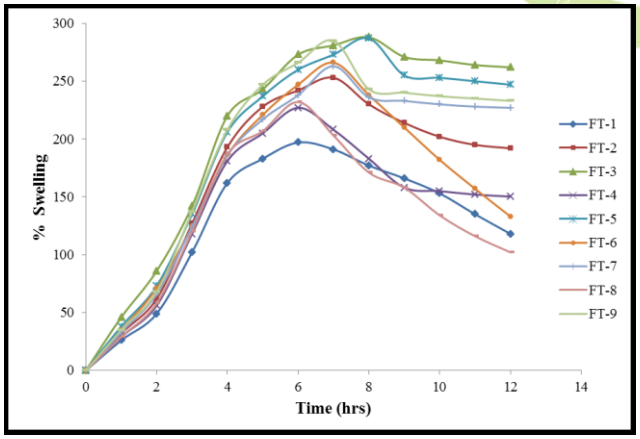

Figure 3: Percent swelling profile of different cefpodoxime proxetil floating matrix tablet formulations in pH 1.2 HCl buffer

Formulation FT-1 has showed lowest percentage of swelling because of highest amount of gum damar and lowest amount of HPMC K15M, whereas swelling was increased for formulation FT-5 due to highest concentration of HPMC K15M. Drug release was directly proportional to the percentage of swelling[16].

***In vitro* Drug Release Studies from Floating Matrix Tablets**

The release of the drug was found to be dependent on the amount of gum damar and HPMC K15M. Drug release was found to be inversely related to the amount of release retardant (gum damar) and directly proportional to amount of swellable polymer (HPMC K15M). The *in vitro* cefpodoxime proxetil release data from the floating matrix tablets is depicted in Figure 4. Data obtained showed that with increase in concentration of HPMC K15M and decrease in amount of gum damar prolongs the release of the drug. Complete drug release was observed upto 12 h for formulation FT-7 due to the optimized concentration of gum damar and HPMC K15M (1:0.5), whereas the formulations FT-1, FT-2, FT-4, FT-6, FT-8 and FT-9 showed complete release in 10 h because the amount of gum damar was high and low amount of HPMC K15M. At the end of 12 h 69.9 to 99.6 % drug release was observed for the formulations FT-3, FT-5 and FT-9. This was due to further increase in amount of HPMC K15M.

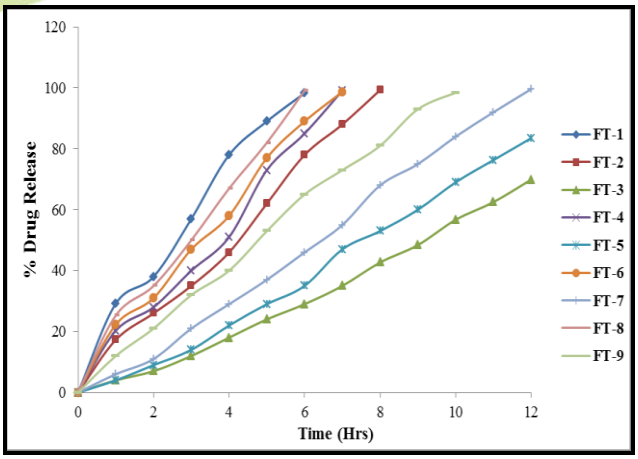

Figure 4: *In vitro* drug release profile of cefpodoxime proxetil from floating matrix tablet formulations

By maintaining HPMC K15M concentration constant, increase in amount of gum damar the

drug release was decreased. Drug release was directly proportional to percentage of swelling. By comparing all formulations FT-7 taken as an optimized formulation which shows 99.6 % drug release at the end of 12 h.

In vivo Studies

The gastric retention property of the floating matrix tablet formulation FT-7 was examined in rabbit. Barium sulphate was used as a radio opaque marker. After the formulation (without drug) was administered to a fasted rabbits, X-ray pictures were taken at different time intervals are represented in Figure 5. The X- ray image of rabbit taken with empty stomach prior to administration floating matrix tablet formulation (Figure 5 A). X- ray image taken at 2^{nd} and 8^{th} h (Figure 5 B and C) have shown the presence of tablet in the stomach region, which indicates its retention in the stomach. X- ray image at 12th h (Figure 5 D) indicates tablet is disintegrated but still remains in the stomach. This experiment clearly shows that floating matrix tablets could prolong the gastric retention time to more than 12 h.

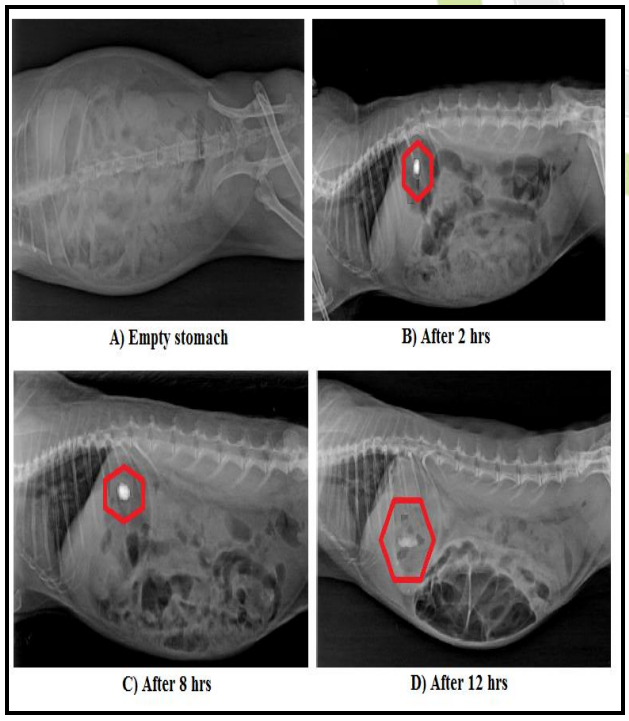

Figure 5: X-ray images showing gastric retention of floating matrix tablet formulation FT-7 in a rabbit model at different time intervals

Stability Study

The prepared floating tablets were subjected to stability study. The tablets were stored at 40°C/75% RH in closed high glass bottles for a period of 6 months. The results do not show any significant change ($p > 0.05$) in physical appearance, hardness, friability, content uniformity, buoyancy and dissolution behaviour of floating tablets in comparison with initial values. Thus, it was found that the floating tablets of cefpodoxime proxetil tablets were stable under these storage conditions.

CONCLUSION

Floating cefpodoxime proxetil matrix tablets formulated employing polypropylene foam powder (Accurel® MP1000) as low density polymer to achieve immediate gastric floating, gum dammar and HPMC K15M polymers for sustained drug delivery by direct compression technique. Characterization and evaluation of the prepared tablets were carried out. The following conclusions were drawn from the results obtained. The evaluation parameters of tablets were found be within pharmacopoeial limits. Density of tablets were found be less than that of gastric fluid (< 1.004 g/cm^3) which indicates that the tablet floats in gastric fluid. The tablets floated immediately with floating lag time zero and remained buoyant for more than 12 h. From the DSC curves, it was observed that characteristic peaks appeared with minor differences for both the drug and formulation. Hence, it was confirmed that no chemical interaction has taken place between the drug and the polymers used. Based on the *in vitro* evaluation data formulation FT-7 was considered as optimized formulation which controlled the drug release up to 12 h. The *in-vivo* study confirmed that floating matrix tablets could prolong the gastric retention time to more than 12 h. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance of tablets. This study demonstrated that the floating matrix tablets based on low density polypropylene foam powder may be used as a gastric floating drug delivery system.

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