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Gastro Retentive Drug Delivery System for Cefpodoxime Proxetil - Development and Optimization

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ABSTRACT

Therapy with oral medications posses a significant transit vagary .Here the drug Cefpodoxime Proxetil Chemically acidic nature, which shows more absorption in the stomach as per literature review show minimum absorption from the stomach since gastric emptying place a predominant role in the per oral medications, here the candidate shows maximum instability due to free soluble nature in aqueous environment with its high acidity moreover the stomach and solubilised drug impacts severe acidity to the mucous membrane of stomach which leads to ultimate perforation and calls for concomitant H_2 antagonist and other antacids by thinking at most need of the drugs here the author formulated bilayered tablets to stay in the stomach for longer period by reducing gastric irritation and stability of drug at different P^H were studied and invitro dissolution model also performed by this work the candidate not affected by gastric emptying and acidic P^H by formulating the drug with polymer as above set formulation. Fore there more the formulated bilayer tablet dosage forms and powder mixer prior to compression was subjected for Preformulation and instrumentation studies it reveals that the Cefpodoxime Proxetil bilayer tablet dosage forms it most suitable for human administration for various disease.

Keywords: Buoyancy, Bilayer tablets, Cefpodoxime Proxetil

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INTRODUCTION

Extended release (ER) dosage forms have been extensively used to improve therapy of many important medications. However, this simple pharmaceutical approach of extended release could not be beneficial for oral (i.e. most preferable route) delivery of certain drugs[1], for example: Drugs that have absorption window in upper gastrointestinal tract e.g. cyclosporine, Metformine hydrochloride, Ciprofloxacin etc. Drugs that are unstable in lower GIT, either due to pH variation or enzymes present in intestinal lumen [2]. e.g. *Cefpodoxime proxetil*, Cefuroxime Axetil, Doxyfluridine, Digoxin and Cyclosporine. Drugs that have poor solubility at higher pH e.g. Ofloxacin[3] and Tetracycline [4]Drugs having adverse activity in colon [5] e.g. Antibiotics like Amoxicillin, *Cefpodoxime proxetil*, Cefuroxime Axetil, Clindamycine, Azithromycine, Ciprofloxacin etc. Drugs given for local action in gastric region [6] e.g. Amoxicillin, Clarithromycine, Cimetidine, Ranitidine etc. Thus, the optimal site of absorption and the mechanism of a drug's action often suggest that something other than *immediate* or *extended release formulations* is required to develop the best possible product [2].Enhancing the gastric residence time (GRT) of this type of drugs may significantly improve the net extent of its absorption [7-8].Thus, incorporation of the drug in a controlled release gastro retentive dosage forms (CR-GRDF) can yield significant therapeutic advantages.

MATERIALS AND METHODS

Materials

Cefpodoxime Proxetil as a gift sample by orchid pharma, Chennai, Hydroxy propyl Methyl Cellose (Methocel 100M),(Methocel K15M) purchased from Himedia LaboratoriesPvt Ltd,Mumbai,Sodium bicarbonate,Lactose (anhydrous),Magnesium stearate and Talc were purchased from Finar chemicals Limited , Ahmedabad and citric acid mixture purchased from Rankem limited ,New Delhi. Other reagents used are analytical grade.

Preformulation Studies

Organoleptic Evaluation

It is white to light brownish white powder, having faint odor and has bitter taste.

Infrared spectrum

FT-IR spectrum of Cefpodoxime proxetil (Fig 1).The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method (Schimadzu IR – Prestige-21 and observed for the charecterstic peaks of drug.FT- IR spectrum of drug shows major peaks at 3317.67, 2985.91, 1763.46, 1681.98, 1377.22, and 1053.17(cm -1) which corresponds to the –NH2, S-CH2, -C=O (lactam), -C=N-, -C-N- (aromatic primary amine) and C-Ostretching groups respectively, present in the Cefpodoxime proxetil molecule.(Fig 1).

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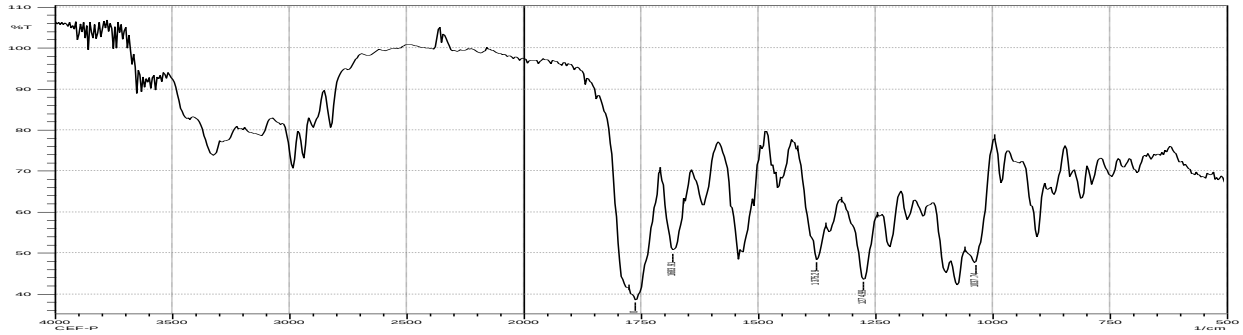
Fig. 1: FT-IR Spectrum of Cefpodoxime Proxetil with major peaks



Analysis of drug

Scanning of Cefpodoxime proxetil was performed in to acid buffer pH 1.2, glycine buffer pH 3.0 and Phosphate buffer pH 6.8. The charecterstics peak, λmax was found to be at 257.8 nm, 259.2 nm and 232.0 nm respectively.(Fig 2,3,4) (Table 1).Calibration curve of Cefpodoxime proxetil was plotted in acid buffer (pH 1.2) (Fig5) (Table 2), Glycine buffer (pH 3.0) (Fig 6) (Table 3) and phosphate buffer (pH 6.8) (Fig 7) (Table 4). The critical values for regression co-efficient (P) in each plot was less 0.001 (i.e., $P < 0.001$). That indicates that there was high correlation between concentrations (0-25 mcg/ml) of drug with absorbances.

Fig. 2: UV spectrum of Cefpodoxime Proxetil in Acid buffer pH 1.2

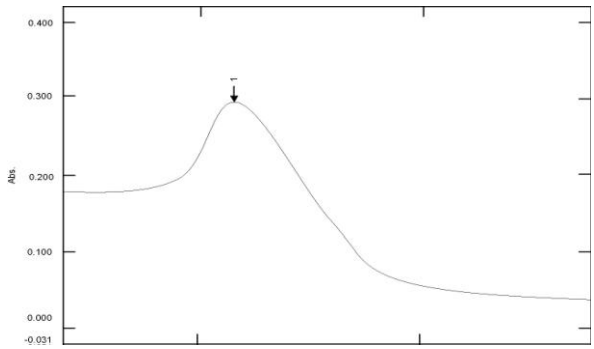


Fig. 3: UV spectrum of Cefpodoxime Proxetil in Acid buffer pH 3.0

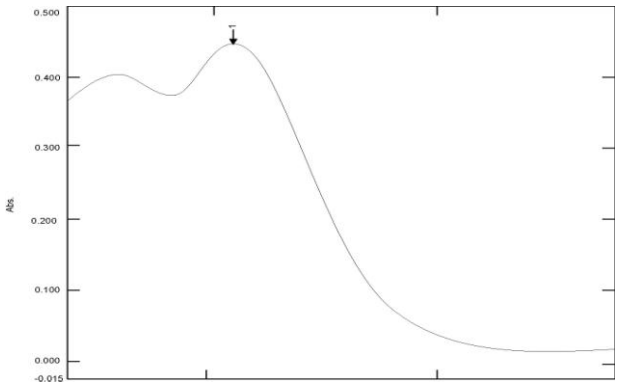


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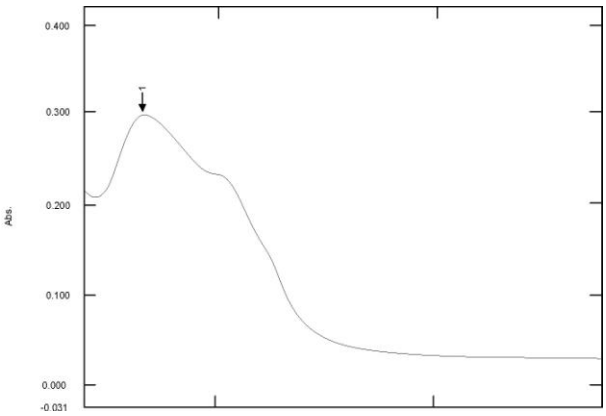
Fig. 4: UV spectrum of Cefpodoxime Proxetil in Phosphate buffer pH 6.8

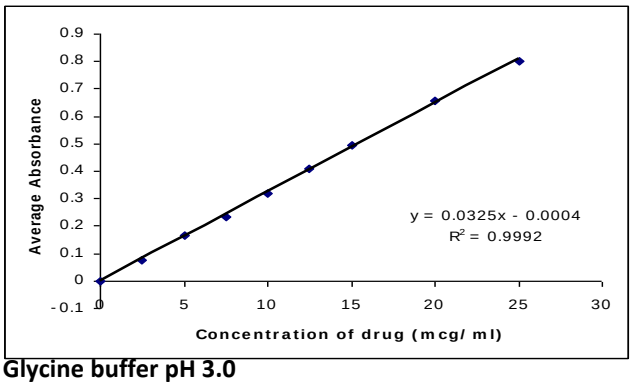


Standard Plot of Drug in Acid buffer pH 1.2

Conc. of stock solution = 250 mcg/ml Drug = Cefpodoxime proxetil

Max. wave-length (λmax) = 257.8 nm Solvent = Acid buffer pH 1.2

Fig 5: Average absorbance of Drug at different concentration in Acid buffer pH 1.2

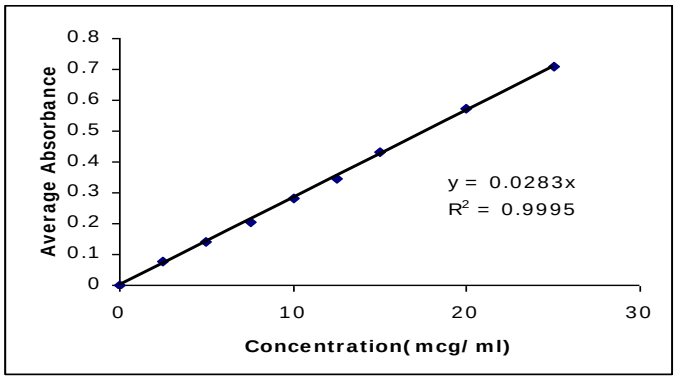


Standard Plot of Drug in Glycine buffer pH 3.0

Conc. of stock solution = 250 mcg/ml Drug = Cefpodoxime proxetil

Max. wave-length (λmax) = 259.2 nm Solvent = Glycine buffer pH 3.0

Fig 6: Average absorbance of Drug at different concentration in Glycine buffer pH 3.0



Standard Plot of Drug in Phosphate buffer pH 6.8

Conc. of stock solution = 250 mcg/ml Drug = Cefpodoxime proxetil

Max. wave-length (λmax) = 232.0 nm Solvent = Phosphate buffer pH 6.8

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Fig 7: Average absorbance of Drug at different concentration in Phosphate buffer pH 6.8

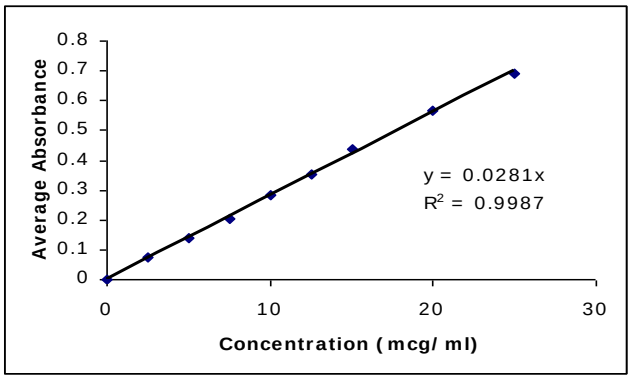

Table 1: Summary of the UV Scanning of Cefpodoxime proxetil in different Buffers

Sl. No.	Amount of Cefpodoxime proxetil (mg)	Solvent used to dissolve drug	Solvent used to make up volume	Final volume (ml)	Concentration of stock solution (mcg/ml)	Concentration of scanning solution (mcg/ml)	Scanning range (nm)	Characteristic peak, λ_{max} (nm)
1	25	15 % Methanol	Acid Buffer, pH 1.2	100	250	10	220 to 340	257.8
2	25		Glycine buffer, pH 3.0		250	15		259.2
3	25		Phosphate Buffer, pH 6.8		250	10		232.0

Solubility Studies of Cefpodoxime Proxetil In Different Buffers

Solubility study was done by 'Shake Flask Method' as given in USP. The solubility of Cefpodoxime proxetil was studied in buffers of different pH range (pH 1.2, pH 3, and pH 6.8) at 37oC ± 0.5. The solubility of Cefpodoxime proxetil was determined by adding excess but measured amount of drug in 100 ml volumetric flask with different buffers (acid buffer pH 1.2, glycine buffer pH 3.0 and phosphate buffer pH 6.8) and kept under agitated conditions at 37 °C ± 0.5 °C in water bath shaker for 2 hrs. The dispersions were filtered through Whatmann filter paper (No.1) and analyzed for the quantity of drug dissolved by taking the absorbances at 257.8, 259.2 and 232.0 nm against respective blank. Amount dissolved was determined from their respective standard plot. Cefpodoxime proxetil exhibited a strong pH dependent solubility phenomenon in various buffers. A very high solubility of Cefpodoxime proxetil was observed in acidic pH values (10.47 mg/ml at pH 1.2), while the solubility dropped rapidly as the pH increased (0.45 mg/ml at pH 6.8) (Table 5) (Fig 8).

Fig 8: Solubility of Cefpodoxime proxetil observed at different pH

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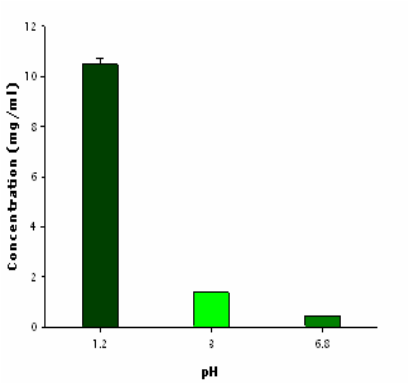

Stability of cefpodoxime proxetil in different buffers

The solution stability of the drug was assessed in buffers of pH values 1.2, 3.0 and 6.8 for 24 hour at 37±0.5 °C as they present the local environment of the stomach, duodenum and ileum respectively. 40 mg of drug was dissolved in 100 ml of buffers of pH 1.2, 3.0 and 6.8. Then, these solutions were kept at 37 ± 0.5°C in hot air oven. Samples were taken at different time intervals and absorbance's were taken. The percent of drug remained in the solution was then calculated. After observing the IR spectra and above data, it could be concluded that the peak of NH2 group, S-CH_2 group, C=O (lactam) and C-O stretching functional group was intact in the drug with individual excipients, formulation F14 and immediate physical mixture with composition similar to the F14. As there was no shifting, deleting and broadening of the peak observed in the IR spectrum, it can be concluded that no chemical interactions had been occurred. (Fig 9, 10, 11)

Fig. 9: IR Spectrum of Cefpodoxime proxetil with magnesium stearate

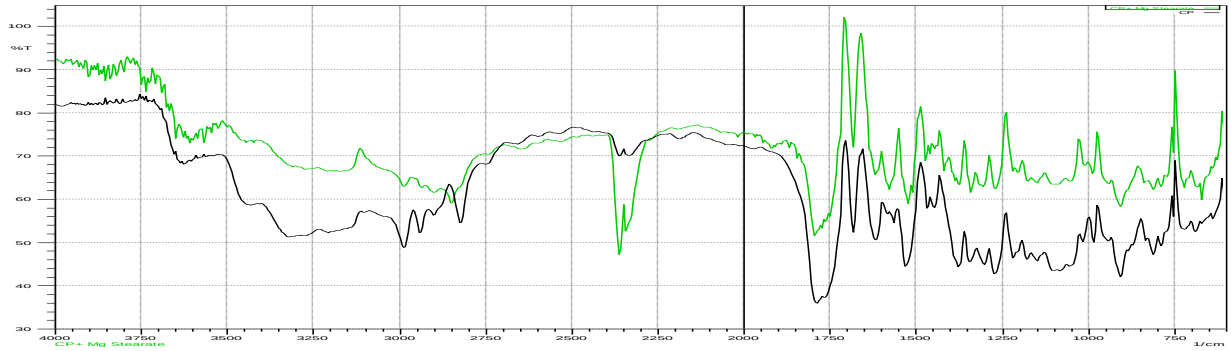

Fig. 10: IR Spectrum of formulation F14

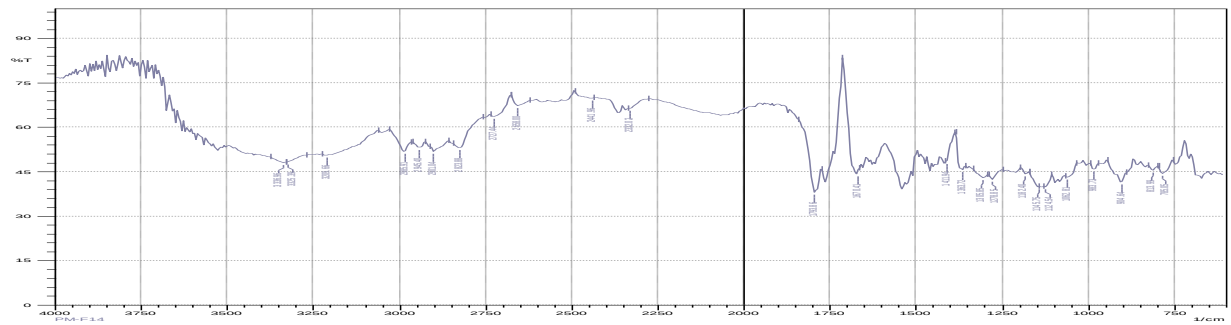

Fig. 11 : IR Spectrum of physical mixture with composition similar to F14

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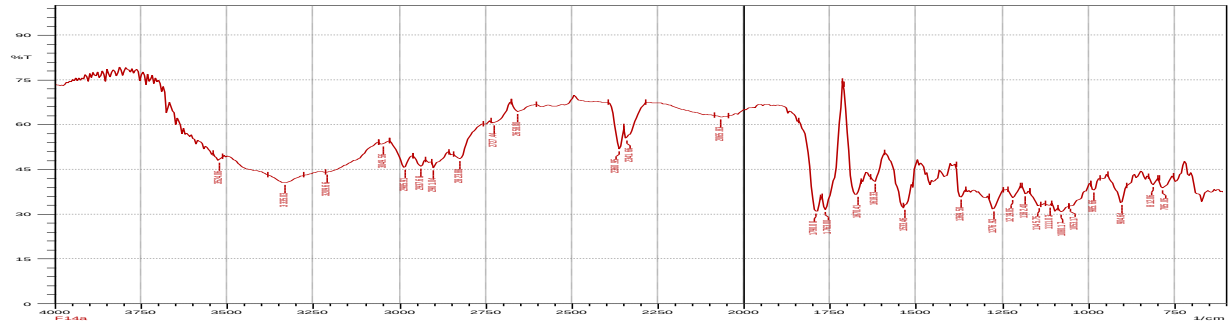


Preparation of Bi-Layered Floating Tablet

Preparation of floating layer

Accurately weighed quantity of HPMC K100M or HPMC K15M, Sodium bicarbonate and Citric acid (and if any other excipients like Talc and Magnesium stearate) were taken in a Motor, mixed well and sifted through 40-mesh screen and then this powder mixture was subjected to compression.[17](Table 7)

Preparation of the Bi-layered floating tablet

The preparation of the Bi-layer tablet had two steps.

Preparation of powder mixture for floating layer and release layer

Accurately weighed quantity of HPMC K100M, Sodium bicarbonate and Citric acid (and if any other excipients like Talc and Magnesium stearate) were taken in a Motor, mixed well and sifted through 40-mesh screen (powder mixture optimized for floating layer) and then accurately weighed quantity of Cefpodoxime proxetil, HPMC K15M, Microcrystalline cellulose and Lactose (Anhydrous) (and if any other excipients like Talc and Magnesium stearate) were taken in a Motor, mixed well and sifted through 40-mesh screen (powder mixture for release layer) (Table 8).

Compression

At the beginning, powder mixture optimized for floating layer (FL2) was placed in dye cavity (diameter 12 mm) of single-punch machine and preparatory pressing was done. Thereafter, a powder mixture for release was added and subjected to final compression. In order to study the effect of hardness on the buoyancy and *in-vitro* drug release tablets having the composition similar to the batches F15 and F16 were punched at different compression pressure (4, 5, and 6 kg/cm2) and coded as F15(H1), F15(H2), F15(H3), F16(H1), F16(H2) andF16(H3).(Table 6)

Evaluation of Bi-Layered Floating Tablets [17]

Thickness

The tablet thickness is influenced by the amount of filled material in the die cavity, die diameter and the compression force applied. The factors that affecting the thickness are

true density, bulk density, particle size, size distribution of particles. Vernier calipers is used for the measurement of thickness of single tablet at a time.

Hardness

The hardness of the tablet can be determined as the compression force required to break the tablet. When the force is applied diametrically the hardness can be influenced by three variables like bond strength, internal strain, brittleness. Hardness is used for the measurement of hardness of single tablet at a time.

Friability

Friability of a tablet means resistible to shock, abrasion encountered during the process, packing, transport. Factors affecting friability are moisture content, poor conditioned concave punches. Take 10 tablets and weigh accurately, keep the friabilator on and rotate up to 4 min 25rpm. After 4 minutes remove the tablets and weigh the friability from initial weight to final weight. The acceptable friability value is 0.5 to 1%.

In vitro buoyancy studies

In vitro buoyancy studies were performed for all ten formulations as per the method described by rosetal. The randomly selected tablets from each formulation were kept in a 100 ml beaker contain simulated gastric fluid, ph 1.2 as per USP. The time taken for the tablet to rise to surface and float was taken as floating lag time t. The duration of time the dosage form constantly remained on surface of medium was determined as total floating time.

Swelling behavior of bi-layered floating tablets

The extent of swelling was measured in terms of percent weight gain by the tablet. Three tablets from each formulation were kept in Petri dishes containing pH 1.2 acid buffer. At the end of one hr tablets were withdrawn, surface patted with tissue paper, and weighed. At the end of second hr the process was repeated and weights of tablets were noted. Then for every 2 hr. weights of tablets were noted, and the process was continued till the end of 12 hrs [25].

Percent weight gain by tablet was calculated by using the following formula;

$$\text{Swelling Index (SI)} = \{(Mt-Mo)/Mo\} \times 100$$

Where,

S.I = Swelling Index
Mt= weight of tablet at time t
Mo= weight of tablet at time t=0

Drug content estimation

Drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was determined and added in100ml of o.1N HCL

followed by stirring for 30 mins. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 315nm using 0.1 N Hcl as blank.

RESULT AND DISCUSSION

Physical characteristic and drug content

Physical characteristic of Average weight (mg), Hardness of tablet (Kg/cm^2),Friability (%),Thickness(mm), Percent drug in formulation are determined for the above procedure.(Table 9)

Floating lag time, total time of floating and dimensional stability studies

The floating lag time and total time of floating was determined in the USP dissolution Apparatus II (Paddle Type) in an acid environment (pH 1.2). Volume of the medium was 900 ml and the temperature was maintained at 37 ± 0.5 ^{0}C. The rotation speed was 100 rpm. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium is taken as floating lag time and the Total time of floating and Dimensional stability was observed visually [5]. (Table 10)

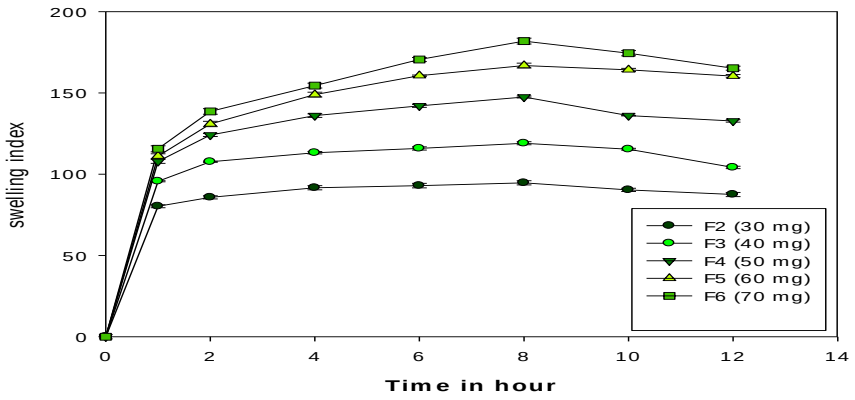
Effect of Hardness on the buoyancy of bi-layered floating tablets (BFT):

In order to study the effect of hardness on the buoyancy tablets having the composition similar to the batches F15 and F16 were punched at different compression pressure (4, 5, and 6 kg/cm2). Prepared tablets were evaluated for floating lag time and total time of floating. (Table 11).

Effect of HPMC K15M on the swelling index

The result suggests that swelling index increased with increase in HPMC K15M concentration in the formulations (F2, F3, F4, F5 and F6). The continuous increase in swelling may be attributed to the high viscosity of HPMC K15M, which retain water and form a thick swollen mass and minimizes the erosion of the polymers. (Table 12) (Fig 12)

Fig. 12: Swelling behaviors of formulations containing different concentration of HPMC K15M



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Effect of MCC on the swelling index

Data obtained from the swelling index of formulations containing increasing amount of MCC (F11, F10, F9, F8, F4 and F7) shows that as we increase the amount of MCC per tablet initial swelling increases but rapidly decreases in the later phase of the study. This could be explained on the basis that MCC is very porous [50] and weakly swellable polymer due to this property initial swelling was more but decrease of swelling index in the later phase of study may be attributed to the high insolubility of MCC in water. Due to this MCC does not form gel layer around the matrix and when MCC is used in higher proportion gel layer formed due to HPMC K15M was unable to retain the MCC in the gel layer and hence hasten the erosion of matrix. (Table 13) (Fig 13)

Effect of Anhydrous Lactose on the swelling index

Results obtained from the formulations F12, F13, F10, F14, F15 and F16 shows that as we increase the concentration of anhydrous lactose initially swelling index was increased but swelling index in the later hours decrease. Initial rapid swelling could be explained on the basis that lactose dissolves rapidly from the matrix tablet in to the medium and it creates porosity in the matrix, this results in more rapid hydration of the HPMC K15M. decrease of swelling index in the later hours could be explained on the basis that, as the outer layer of matrix become fully hydrated polymeric chains becomes completely relaxed and can no longer maintain the integrity of gel layer leading to the erosion of the surface[51].(Table 14) (Fig 14)

Fig 13: Swelling behaviors of formulations containing different concentration of Microcrystalline cellulose

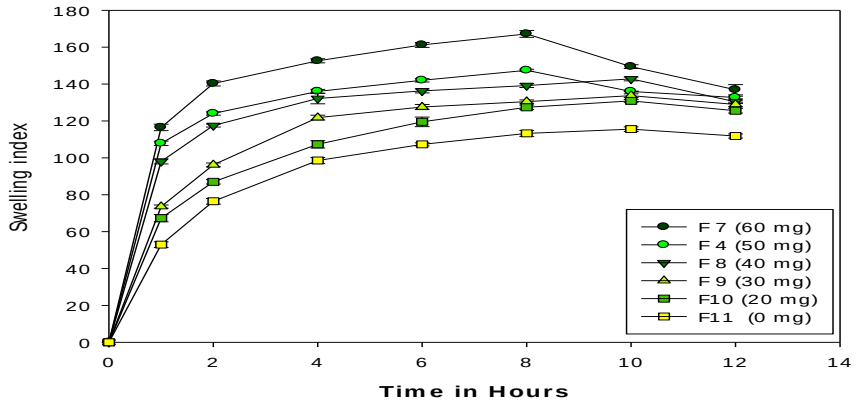
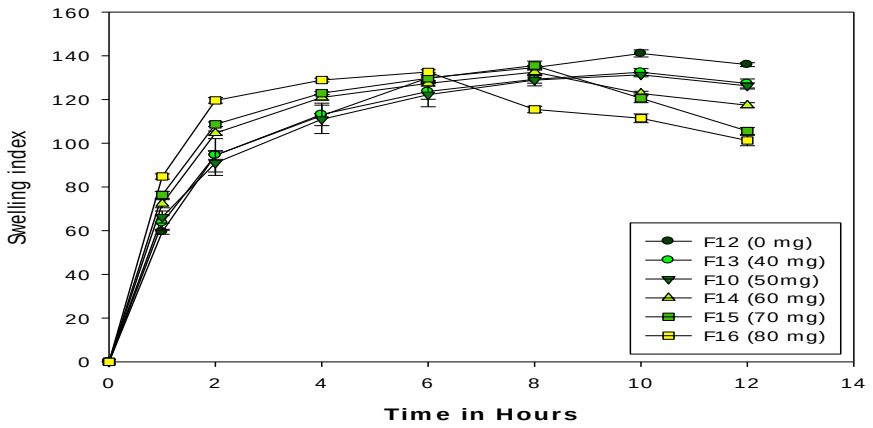


Fig 14: Swelling behaviors of formulations containing different concentration of Lactose (Anhydrous)



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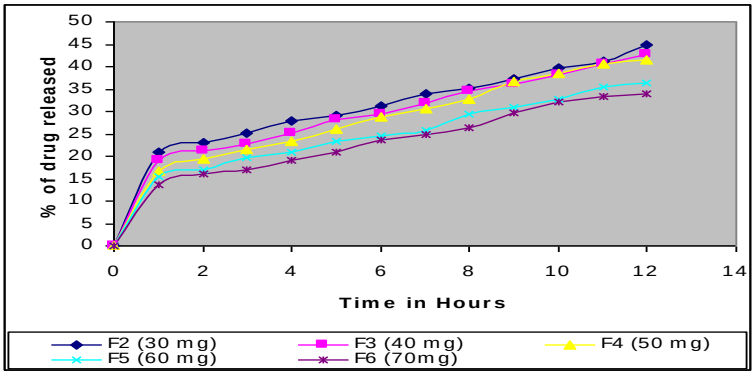
***In-Vitro* dissolution Studies**

The *in-vitro* dissolution study was carried out using USP Type-I dissolution apparatus. The study was carried out in 900 ml of 0.1N HCl buffer (pH 1.2) for 12 hours. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37 ± 0.5°C. The pre-weighed tablet was then introduced into the dissolution jar and the basket was rotated at 100 rpm. At different time intervals, 5ml sample was withdrawn and analyzed spectrophotometrically at 258 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

Effect of HPMC K15M on in-vitro release of Cefpodoxime proxetil and integrity of formulations

Effect of different concentration of HPMC K15M on *in-vitro* release of Cefpodoxime proxetil was studied. Initially a trial batch (F1) without HPMC K 15M was prepared but this trial batch could not retain its physical integrity. After that HPMC K 15M was tried in concentration of 30 mg per tablet (F2). The formulation provided higher burst drug release. Therefore, amount of HPMC K15M was increased to 40, 50, 60 and 70 mg per tablet (F3, F4, F5, and F6). From the in-vitro dissolution studies it was observed that initial burst release of drug and also the release of drug in the later hours was decreased significantly (t calculated is greater than critical value of $t_{0.05}$) as the concentration of HPMC K15M was increased. It can be explained on the basis that high HPMC K15M content results in greater amount of gel formation. This gel increases the diffusion path length of the drug and its viscous nature also effects diffusion coefficient of drug. It results decrease in initial burst release of drug and release of drug in the later phase.(Table 15) (Fig 15)

Fig 15 Effect of HPMC K15M concentration on *in-vitro* release of Cefpodoxime proxetil.

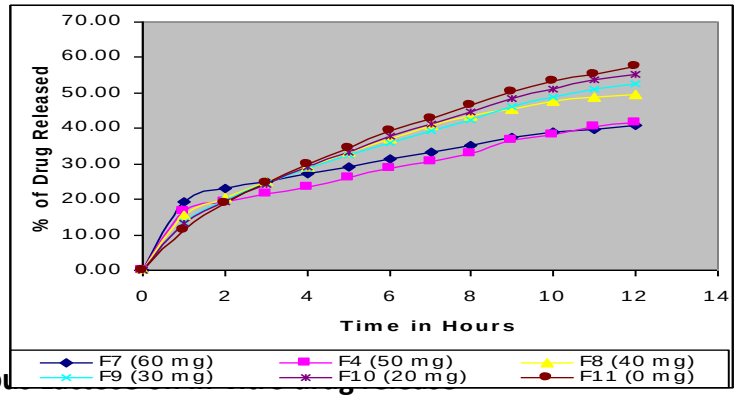


Effect of Microcrystalline cellulose on in-vitro release of Cefpodoxime proxetil

In order to achieve hydrophilic matrices with enhanced pharmaco technical properties (improved compressibility, flow and mechanical strength) and to modify drug release directly compressible polymer MCC was added in different proportions to trial number F7, F4, F8, F9, F10 and F11. From the dissolution profile it was clear that as the concentration of MCC was decreased initial burst release was decreased but drug release in the later was increased. This could be explained on the basis of very porous structure and weakly swellable behavior of MCC. Due to the higher porosity MCC absorbs water more rapidly before the formation of gel layer of HPMC this cause's initial burst release but, after

the gel layer was formed insoluble MCC remain within the gel structure and slows down the hydration of HPMC. This result in decrease release rate in the later hours. (Table 16) (Fig 16)

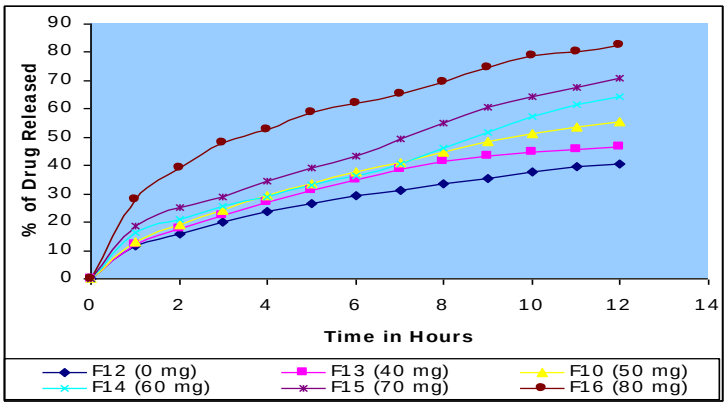
Fig 16 Effect of microcrystalline cellulose concentration on *in-vitro* release of Cefpodoxime proxetil



Effect of Anhydrou

In order to increase the release profile of the formulations especially in the later phase, concentration of anhydrous lactose was increased. As the concentration of anhydrous lactose increases from 0 – 80 mg per tablet (F12, F13, F10, F14, F15 and F16), initial burst release as well as drug release in the later hours have been increased. This could be explained on the basis that anhydrous lactose dissolves rapidly from the tablet matrix in to the medium and it creates porosity in the tablet matrix, which result in increase in drug release from the tablet matrix. (Table 17) (Fig17)

Fig 17- **Effect of lactose (unhydrous) concentration on in-vitro release of cefpodoxime proxetil**

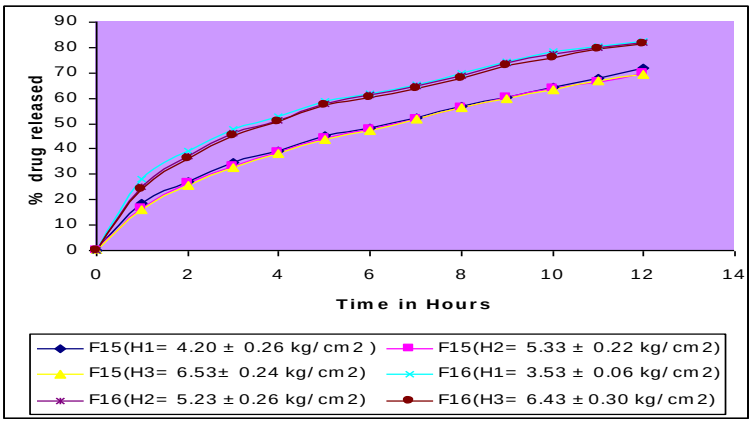


Effect of hardness on the *in-vitro* release of Cefpodoxime proxetil from bi-layered floating tablets

Figure 19 shows the release profile of Cefpodoxime proxetil from floating tablets of formulation F15 and F16 of different hardness. Statistical analysis revealed no significant difference in the release rate constants ($p < 0.05$). A difference in tablet hardness reflects differences in tablet density and porosity, which were supposed to result in different release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet and formation of the gel barrier. Therefore, such an effect is expected to be prominent during the initial phase of the dissolution curve. However, results showed

that tablet hardness had no (or little) effect on the release profile; this can be attributed to the fact that once a sufficient tablet hardness suitable for processing is achieved, tablet hardness would have little further effect on drug release profile because porosity of hydrated matrix is independent of initial porosity (51).These dissolution profiles were analyzed statistically by ANOVA. From the ANOVA test it was found that there was no significant difference among the batches prepared at different compression pressure because F calculated is less than the critical value of F at 5% level of significance. (Table 18) (Fig 18)

Fig 18: Effect of hardness on the *in-vitro* release of Cefpodoxime proxetil from bi-layered floating tablets



Various Drug Release Kinetic Models to Describe the Release Kinetics of Drug from Bi-Layered Floating Tablets

The best fit was obtained in case of the Peppas drug release kinetic model with the highest determination coefficients (r^2) than the other drug release kinetic models. Peppas model is a simple, semiepirical model, relating exponentially the drug release to the elapsed time. This model is used to analyze the release of drug from pharmaceutical polymeric dosage forms, when the release mechanism is well known or when more than one type of release phenomenon can be involved. In case of formulations F14 and F15 the value of n was between 0.5 to 1 indicating contributions of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-fickian, anomalous or first order release)[51]. (Table 19) (Fig19)

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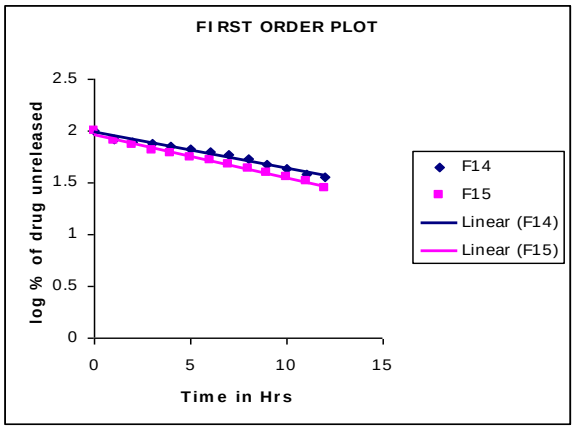
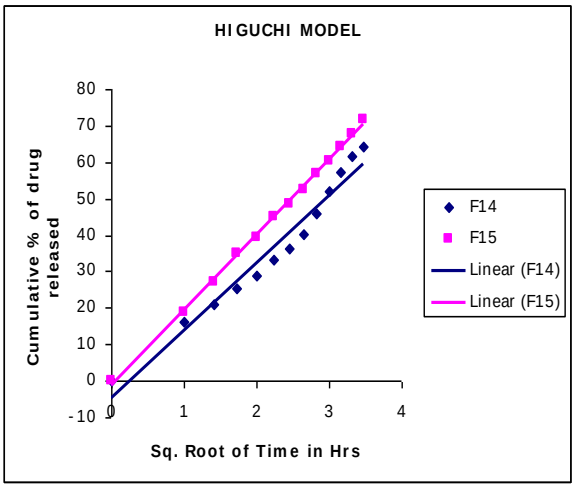
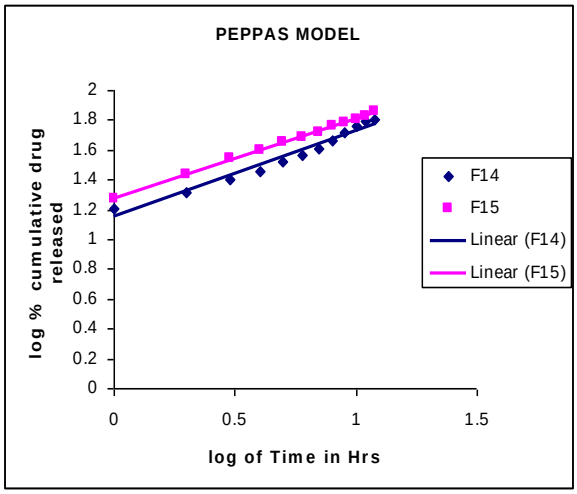
Fig 19 Various Drug Release Kinetic Models To Describe The Release Kinetics Of Drug From Bi-Layered Floating Tablets







SUMMARY AND CONCLUSION

Solubility and solution stability studies of Cefpodoxime proxetil in buffers of different pH showed that solubility and solution stability of Cefpodoxime proxetil is highly dependent on the pH of the buffers. A very high solubility and solution stability was observed in the acidic pH values. Sustained release bi-layered floating tablets of Cefpodoxime proxetil were prepared by direct compression method. All the formulated tablets met the pharmacopoeial standard of uniformity of weight, percentage friability, thickness and drug content. The results concluded that stable and persistent buoyancy was achieved by trapping the gas by the hydration of high viscosity grade HPMC K100M. This study showed that there is a potential for this novel intragastric, floating Bi-layer tablet to remain in the stomach for a longer time. Moreover, the two distinct layers allow separate regulation of the floating ability and drug release kinetics.

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