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Evaluation of Prepared Sustained Release Floating Tablet of Cefpodoxime Proxetil

Krishna Murari[1], Amresh Gupta[2], Ajay Kumar Dubey[3], Umesh Kumar Mishra[4] and Arpita Singh[5]
[1, 2 & 4]Goel Institute of Pharmacy & Sciences, Lucknow, U.P.
[3]B.S.A. College of Engineering and Technology, Mathura, U.P.

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***Corresponding Author Email:** kishankushwaha2010@gmail.com

Abstract

Cefpodoxime proxetil (CP) is an orally active broad spectrum, third generation cephalosporin ester prodrug. It has been widely used in the treatment of mild to moderate respiratory tract infections; pharyngitis and tonsillitis. In spite of its favorable clinical response, Cefpodoxime proxetil is a prodrug with poor bioavailability because of its metabolism to Cefpodoxime acid in the luminal contents and intestinal epithelial cells. However, the high solubility, chemical and enzymatic stability, and absorption profile of CP in acidic pH values (of stomach) and time dependent killing of bacteria's, points to the potential of a sustained release gastro retentive dosage form in altering the absorption profile of Cefpodoxime proxetil and to maximize the duration of exposure to the bacteria's. Thus the objective of the present study was development and optimization of sustained release gastro retentive drug delivery system (bi-layered floating tablet) for Cefpodoxime proxetil. HPMC is a semi-synthetic polymer selected for the study because it is nontoxic, nonirritant stable in wide pH range and freely available. The solubility and solution stability studies of Cefpodoxime proxetil were conducted in different dissolution media. The drug excipients compatibility studies were carried out by FT-IR analysis. Bi-layered floating tablets were prepared by direct compression method. The tablets were subjected to physicochemical, buoyancy, swelling index and in-vitro release studies. Other excipients like sodium bicarbonate and citric acid were added in floating layer to achieve desired buoyancy. Microcrystalline cellulose and lactose were added in the release layer to achieve a sustained release product with drug release profile as uniform as possible. 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 two-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.

Keywords
Cefpodoxime proxetil, prodrug, polymer, analysis.

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1. INTRODUCTION

The administration of drugs to the *gastrointestinal tract* (GIT) normally involves an immediate release formulation, typically a tablet or a capsule. Although such formulations are still preferred for their relative simplicity and low cost, formulations that address specific issues in oral drug delivery require more sophisticated attributes. *Extended release dosage forms* are now used in a number of products.

Advantages of Extended Release Formulation:

The advantages of a sustained release formulation over a conventional dosage forms are as follows [3]**:**

1. Improved patient convenience and compliance
2. Reduction in drug blood level fluctuation
3. Increased safety margin of highly potent drug
4. Maximum utilization of drug
5. Reduction in overall health care cost

Disadvantages of Extended Release Formulation (3):

1. Decreased systemic availability due to incomplete release
2. Poor in vitro – in vivo correlation
3. Possibility of dose dumping
4. Retrieval of drug is difficult in case of toxicity
5. High cost of formulation

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. For example:

1. Drugs that have absorption window in upper gastrointestinal tract **(4)**
2. Drugs that are unstable in lower GIT, either due to pH variation or enzymes present in intestinal lumen
3. Drugs that have poor solubility at higher pH e.g. Ofloxacin **(5-6)** and Tetracycline
4. Drugs having adverse activity in colon
5. Drugs given for local action in gastric region

Types of Gastro retentive Drug Delivery Systems:

- Gastro retentive drug delivery systems can be classified as follows **(10)**:
- High-density systems
- Floating systems
- Hydrodynamically Balanced Systems (HBS)
- Gas-generating systems
- Raft-forming systems
- Low-density systems
- Expandable systems
- Superporous hydrogels
- Mucoadhesive or bioadhesive systems
- Magnetic systems

1.2. Factors affecting the Gastric Residence Time (GRT)

Factor affecting the gastric residence time are as follows **(1, 9)**:

• **Density–**GRT is a function of dosage form buoyancy that is dependent on the density.

• **Size–**dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a lesser diameter.

• **Shape of dosage form–**tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5-kilo pounds per square inch (KSI) are reported to have better GRT ≈ 90% to 100% retention at 24 hours compared with other shapes.

• **Single or multiple unit formulation –** multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

• **Fed or unfed state –** under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the Stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

• **Nature of meal –** feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

• **Caloric content –** GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

• **Frequency of feed –** the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

• **Gender –** mean ambulatory GRT in males (3.4±0.6hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).

• **Age –** elderly people, especially those over 70, have a significantly longer GRT.

• **Posture –** GRT can vary between supine and upright ambulatory states of the patient.

•**Concomitant drug administration–** anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

• **Biological factors –** diabetes and Crohn's disease etc.

2. MATERIALS AND METHODS:
DEVELOPMENT OF FORMULATION

Table: 1 List of excipients used in the formulation

S.NO	EXCIPIENTS	FUNCTIONAL CATEGORY
1	Hydroxy Propyl Methyl Cellulose (Methocel K100M)	Matrix Former
2	Sodium bicarbonate and Citric acid mixture	Gas former
3	Cefpodoxime proxetil	Active ingredient
4	Hydroxy Propyl Methyl Cellulose (Methocel K15M)	Release Retarding and matrix former Polymer
5	Microcrystalline Cellulose (Avicel PH-101)	Diluent (Insoluble)
6	Lactose (anhydrous)	Diluent (Soluble)
7	Magnesium stearate	Lubricant
8	Talc	Lubricant and Glidant

- For the formulation of Bi-layered floating extended release matrix tablet of Cefpodoxime proxetil, HPMC K15M was used as a matrix former. HPMC K15M formulations are relatively insensitive to changes in stirring speed of dissolution test, compaction pressure, or storage under accelerated stress conditions. However, HPMC K15M alone may not sustain drug release satisfactorily and it is difficult to achieve the tablet with desired pharmaco technical properties (compressibility, flow and mechanical strength) requiring the addition of fillers and release modifiers.
- Lactose and microcrystalline cellulose were used as diluents to improve tableting characteristics (like compressibility, flow and mechanical strength) as well as to modify the drug release. The inclusion of diluents affects the dissolution performance of a matrix by "dilution effect" on the polymer.

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.

Preparation of the Bi-layered floating tablet

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

1. *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).
2. *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.

Note- Moisture contents of dried powder was controlled and maintained between 1-2 %. (if it was not within the limit then the powder was further reprocessed.)

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/cm^2) and coded as F15(H1), F15(H2), F15(H3), F16(H1), F16(H2) andF16(H3).

3 EVALUATION

A) PHYSICAL CHARACTERISTICS

1) Weight variation

The test ensures that all the tablets in each batch are of same potency, within reasonable limits. Each tablet in the batch should be uniform in weight and weight variation if any, should be generally within ± 10% for tablets weighing 130 mg or less, ± 7.5% for

tablets weighing more than 130 mg and up to 324 mg and ± 5% for tablets weighing 325 mg or more.

According to the official test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation.

2) Hardness test

Tablets require a certain amount of strength, or resistance to friability, to withstand the mechanical shocks of handling in manufacture, packaging, and shipping. The strength of the tablet was determined by Monsanto hardness tester. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. The force of fracture was recorded, and the zero force reading was deduced from it.

3) Friability

Friability test was performed to assess the effect of friction and shock which may often cause tablets to chip, cap or break. It generally reflects poor cohesion of tablet ingredients. Weighed tablets sample was placed in the chamber and the friabilator was operated for 100 revolutions and the tablets were weighed again. Compressed tablets should not lose more than 1% of their weight.

4) Tablet thickness

Variation in the tablet thickness may cause problems in counting and packaging in addition to weight variation beyond the permissible limits. Tablet thickness should be controlled within a ± 5% of a standard value. Tablet thickness was measured by Vernier caliper.

B) Drug content

3 tablets were powdered in a mortar and powder equivalent to 200 mg of Cefpodoxime proxetil was taken in a 100 ml volumetric flask. The powder was dissolved in a minimum volume of methanol and then volume was further adjusted with Acid buffer pH 1.2. The solution was filtered through Whatmann filter paper (No.1). Then the solution was further diluted as per requirement and analyzed spectrophotometrically.

C) Floating lag time, Total time of floating and Dimensional stability

The floating lag time and total time of floating was determined in the USP dissolution Apparatus II in an acid environment (pH 1.2). Volume of the medium was 900 ml and the temperature was maintained at 37 ± 0.5 0C. 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)**.

D) Swelling Behaviors 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;

Swelling Index (SI) = {(Mt-Mo)/Mo} x 100

Where,

S.I = Swelling Index

Mt= weight of tablet at time t

Mo= weight of tablet at time t=0

E) *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.

DRUG RELEASE KINETICS

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where ft. is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of generic equation that translates the dissolution curve, function of some parameters related with the pharmaceutical dosage forms. Drug dissolved from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models,

Weibull models. These models are used to characterize drug dissolution/release profiles.

(i) Zero Order Kinetics

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate).

The following equation is used to express the model:

$Q_t = Q_o + K_o t$

Where

Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K_o is the zero order release constant

For practical purposes the equation is rearranged:

Percent drug released = Kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(ii) First Order Kinetics

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish.

The following equation is used to express the model:

$\log Q_t = \log Q_o + Kt/2.303$

Where

Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K is the first order release constant

For practical purposes the equation is rearranged:

log % of drug unreleased = Kt/2.303

This model is applicable to dosage forms such as those containing water-soluble drugs in porous matrices.

(iii) Higuchi Model

Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent.

The following equation is used to express the model:

$Q_t = K_h t^{1/2}$

Where Q_t is the amount of drug dissolved in time t

K_h is the first order release constant

For practical purposes the equation is rearranged:

Percent drug released = $Kt^{1/2}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

(iv) Peppas-Korsmeyer Model

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved

The following equation is used to express the model

$Q_t/Q_\infty = Kt^n$

Where

Q_t is the amount of drug dissolved in time t

Q_∞ is the amount of drug dissolved in infinite time

n is the release exponent indicative of drug release mechanism

K is the kinetic constant

For practical purposes the equation is rearranged

Log percent drug released = log k +n log t

Peppas used n value in order to characterize different release mechanism concluding for values of n = 0.5 for Fickian diffusion and values of n, between 0.5 to 1.0 for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and higher values of n, n=1 or n>1 for case-ii transport (corresponds to erosion and relaxation of swollen polymer layer).

DRUG-EXCIPIENTS COMPATIBILITY STUDIES BY FT-IR ANALYSIS

The IR absorption spectra of the pure drug, drug with individual excipients, mixture of drug with all excipients, and formulation number F14 were taken in the range of 4000-400 cm-1 using KBr disc method (Schimadzu IR – Prestige-21) and observed for characteristic peaks of drug.

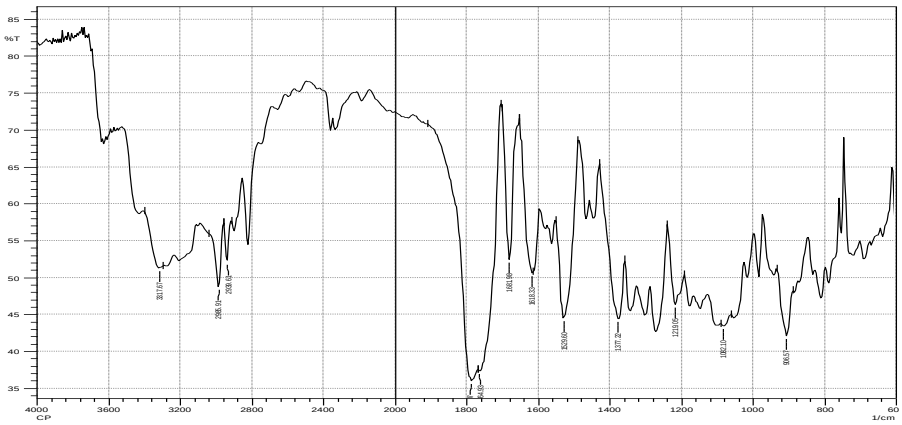

Fig. 1 (i): IR Spectrum of Cefpodoxime proxetil

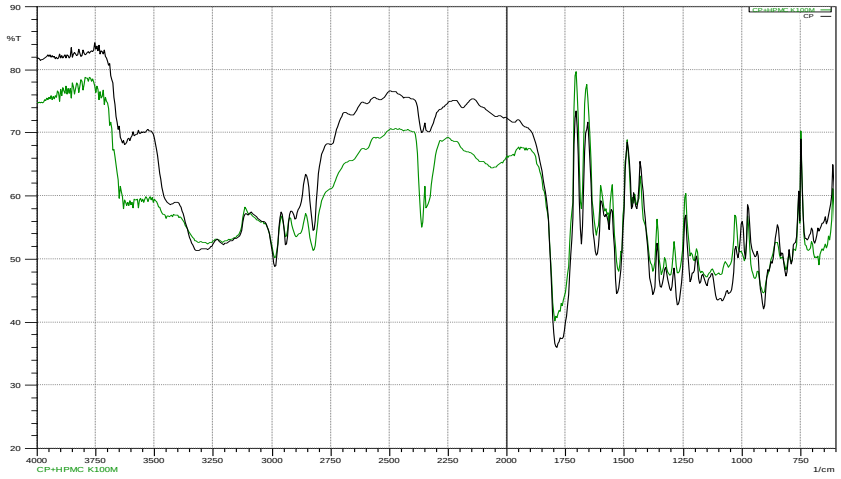

Fig. 2(ii): IR Spectrum of Cefpodoxime proxetil with HPMC K15M

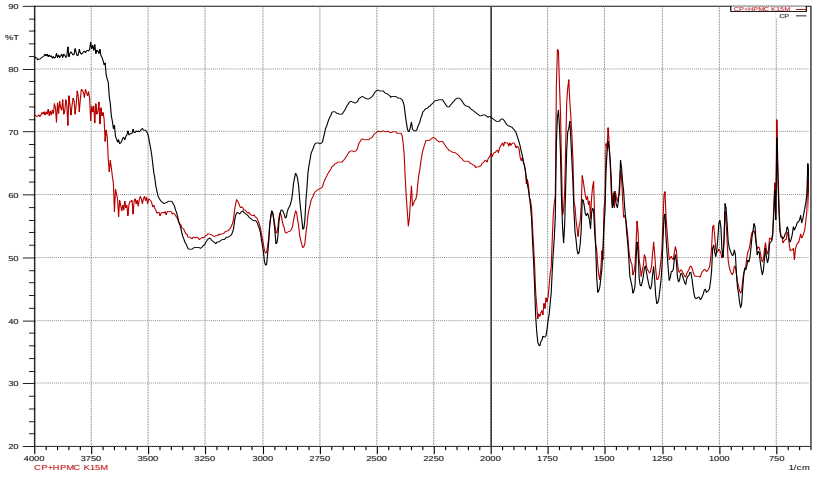

Fig. 3(iii): IR Spectrum of Cefpodoxime proxetil with microcrystalline cellulose

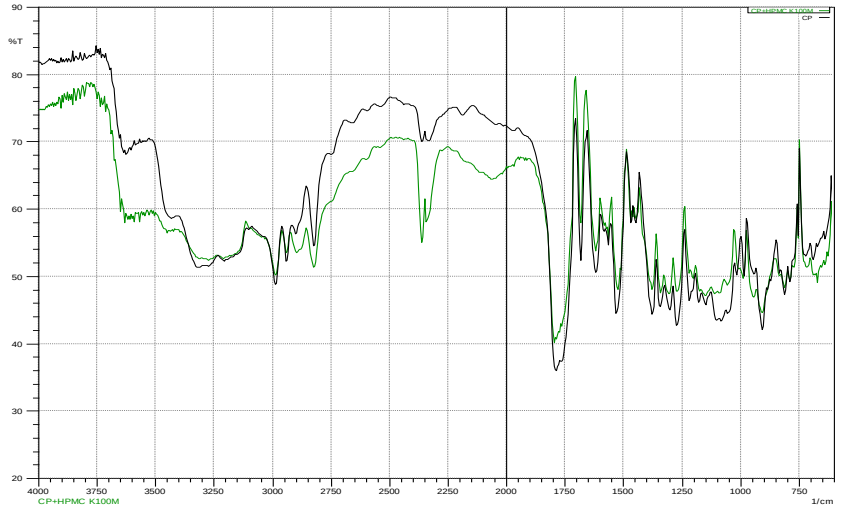

Fig. 4(iv): IR Spectrum of Cefpodoxime proxetil with citric acid

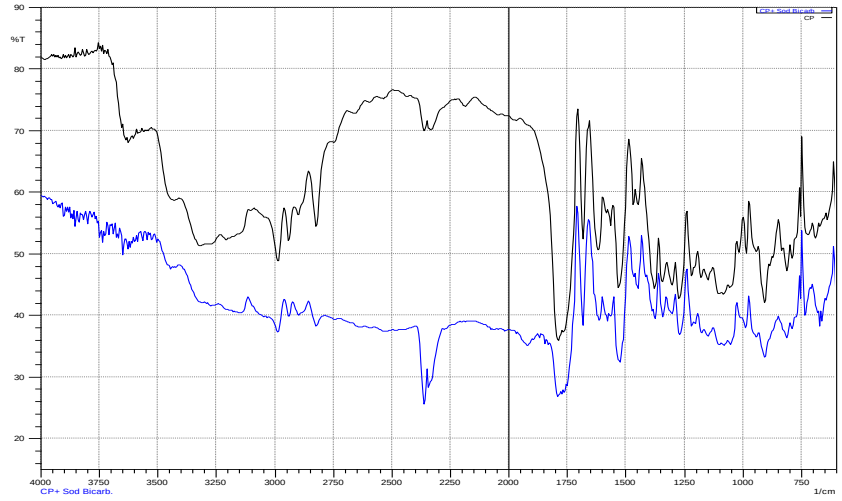

Fig. 5(v): IR Spectrum of Cefpodoxime proxetil with sodium bicarbonate

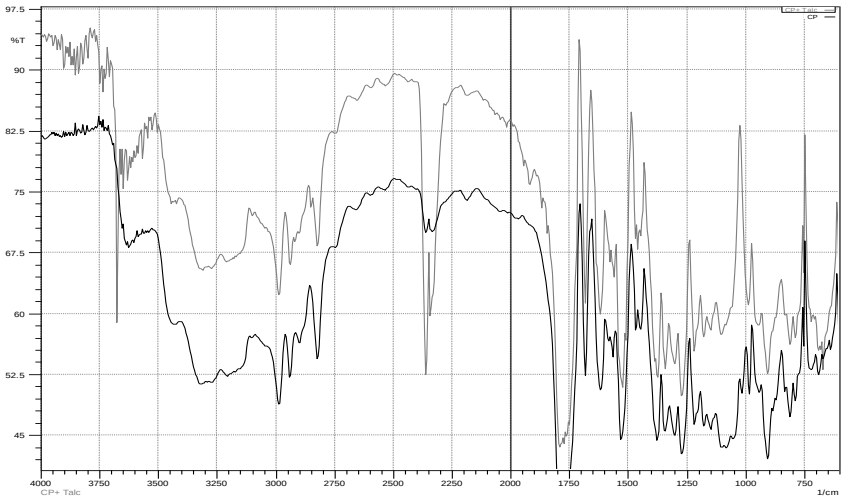

Fig. 6(vi): IR Spectrum of Cefpodoxime proxetil with talc

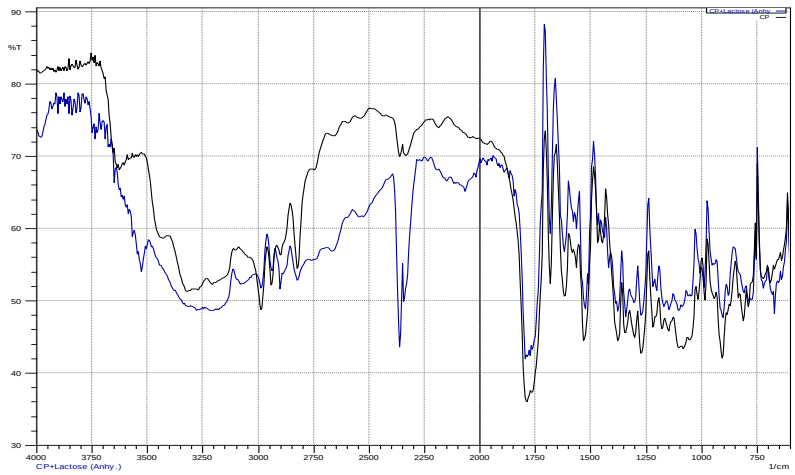

Fig. 7(vii): IR Spectrum of Cefpodoxime proxetil with lactose (anhydrous)

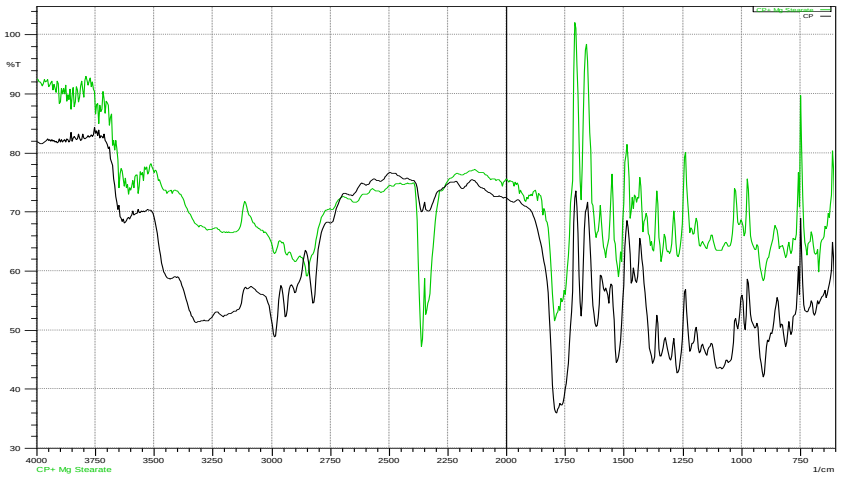

Fig. 8(viii): IR Spectrum of Cefpodoxime proxetil with magnesium stearate

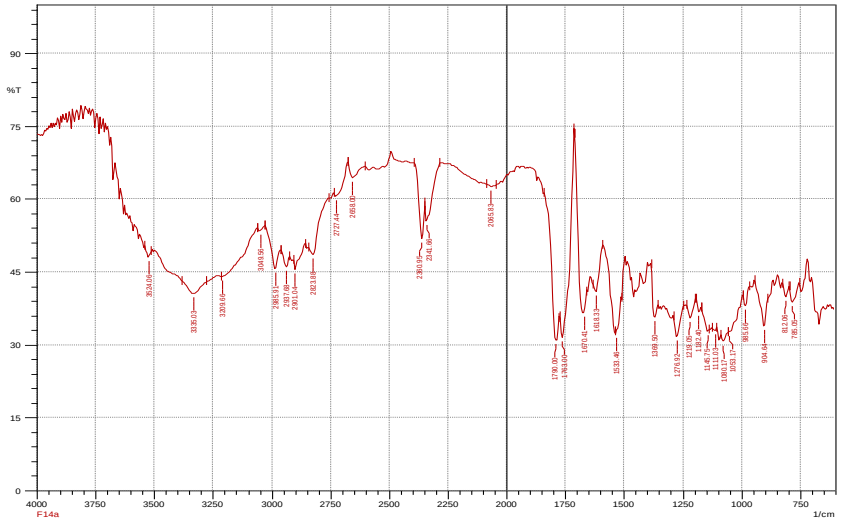

Fig. 9 (ix): IR Spectrum of formulation F14

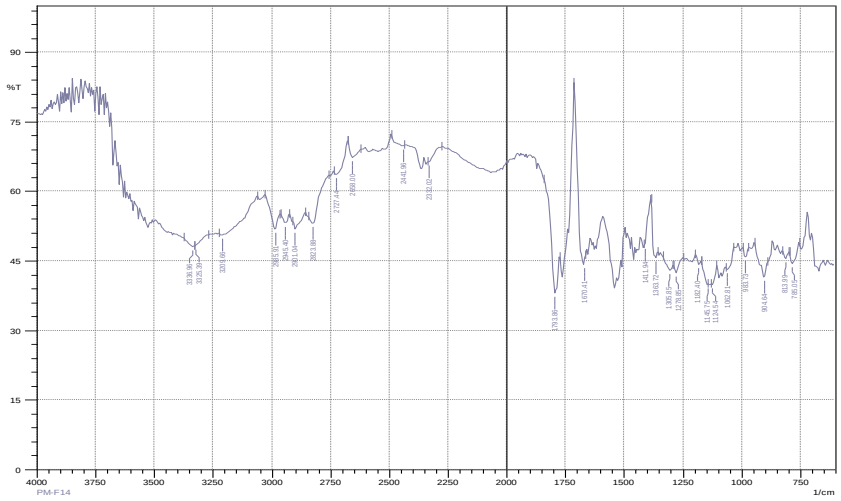

Fig. 10(x): IR Spectrum of physical mixture with composition similar to F14

This technique is used to determine any chemical interactions between drug and excipients. The Fourier transformed infrared (FTIR) spectra of drug, drug with individual excipients, formulation (F14)

and physical mixture with composition similar to formulation (F14) were obtained using FTIR Spectrophotometer (IR Prestige 21, SHIMADZU). Spectra's were shown in **Fig (i)- (x)** and results were tabulated below –

Table 2: wavelengths of different functional groups present in Cefpodoxime proxetil.

S.N.	Composition	Peak for NH_2 group of CP (cm^{-1})	Peak for S-CH_2 group CP (cm^{-1})	Peak for C=O (lactam) group of CP (cm^{-1})	Peak for C-O stretching group of CP (cm^{-1})
1	Cefpodoxime proxetil (CP)	3317.67	2984.93	1762.45	1053.17
2	CP + HPMC K100M	3315.67	2985.91	1763.42	1050.14
3	CP + HPMC K15M	3317.64	2985.93	1763.42	1053.13
4	CP + MCC	3314.62	2985.91	1765.45	1053.17
5	CP + citric acid	3317.67	2985.83	1763.45	1051.17
6	CP + sodium bicarbonate	3317.67	2985.62	1763.43	1053.17
7	CP + talc	3316.67	2985.91	1763.45	1052.28
8	CP + lactose (anhydrous)	3317.67	2985.91	1763.45	1053.16
9	CP + magnessium stearate	3317.65	2985.62	1763.45	1049.37
10	F14	3317.67	2986.73	1760.35	1053.17
11	Physical mixture with composition similar to F14	3317.62	2985.91	1763.45	1053.17

After observing the spectra and above data, it could be concluded that the peak of NH_2 group, S-CH_2 group, C=O (lactam) and C-O stretching functional group was intact in the drug with individual excipients, formulation and immediate physical mixture with composition similar to the F14. As there was no shifting, deleting and broadening of the peak observed in the spectrum, it can be concluded that no chemical interactions had been occurred.

A) PHYSICAL CHARACTERISTICS AND

B) DRUG CONTENT

Various physical characteristics and drug content of the prepared trial batches were determined as the procedure given in the chapter 6 and the results obtained are tabulated bellow.

Table 3: Physical parameters of Bi-layered floating tablets

Trial no.	Average weight (mg)*	Hardness of tablet (Kg/cm^2)	Friability (%)	Thickness (mm)	Percent drug content
F1	507.6	4.63 ± 0.15	0.48	4.0	99.03 ± 2.350
F2	538.9	3.53 ± 0.06	0.35	4.0	98.92 ± 2.161
F3	550.8	3.83 ± 0.15	0.33	4.0	98.15 ± 0.615
F4	560.2	4.33 ± 0.15	0.28	4.0	100.72 ± 2.161
F5	570.0	3.93 ± 0.12	0.29	4.1	100.00 ±3.076
F6	582.0	3.83 ± 0.15	0.31	4.1	99.18 ± 4.003
F7	573.3	3.83 ± 0.21	0.25	4.1	99.85 ± 2.153
F8	550.1	4.17 ± 0.29	0.22	4.1	98.77 ± 3.743
F9	537.2	4.43 ± 0.12	0.19	4.0	99.23 ± 1 .538
F10	529.8	3.80 ± 0.20	0.22	4.0	97.85 ± 1.230
F11	510.0	3.53 ± 0.06	0.17	4.0	97.69 ± 0.307
F12	478.7	3.77 ± 0.25	0.19	4.0	100.26 ± 2.350
F13	520.3	4.23 ± 0.25	0.22	4.0	99.38 ± 4.646
F14	537.9	3.70 ± 0.17	0.23	4.1	100.46 ± 3.384
F15	549.9	4.20 ± 0.26	0.21	4.1	98.46 ± 1.230
F16	557.4	3.53 ± 0.06	0.31	4.1	99.79 ± 3.097

***All values are expressed as Mean ± S.D, n=3**

C) Floating lag time, Total time of floating and Dimensional stability-

Table4: Floating lag time and Total floating time for trial batches of floating layers

Floating layer	Floating lag time (sec.)	Total floating time (Hrs)
FL1	100.3 ± 13.1	> 12
FL2	49.5 ± 6.3	> 12
FL3	45.2 ± 5.0	> 12
FL4	60.6 ± 4.5	10.3 ± 2.1
FL5	28.4 ± 4.7	8.3 ± 1.2
FL6	23.2 ± 3.6	6.5 ± 1.0
FL7	36.7 ± 3.4	Layer starts dispersing in 8 hours
FL8	15.0 ± 2.8	Layer starts dispersing in 4 hours

***All values are expressed as Mean ± S.D, n=3**

Table 5: Floating lag time and Total floating time for trial batches of bi-layered floating tablets.

Trial	Floating lag time (sec.)	Total floating time (Hrs)
F1	121.0 ± 15.3	> 12
F2	109.4 ± 13.5	> 12
F3	98.5 ± 8.4	> 12
F4	87.6 ± 7.2	> 12
F5	83.5 ± 7.9	> 12
F6	62.6 ± 6.2	> 12
F7	68.4 ± 5.8	> 12
F8	92.2 ± 8.2	> 12
F9	96.2 ± 9.0	> 12
F10	103.7 ± 9.2	> 12
F11	110.3 ± 9.8	> 12
F12	78.0 ± 8.2	> 24
F13	97.6 ± 8.5	> 12
F14	109.2 ± 9.5	> 12
F15	115.4 ± 12.3	> 12
F16	131.1 ± 15.5	> 12

***All values are expressed as Mean ± S.D, n=3**

First, the floating layer was prepared and evaluated on the basis of floating behavior studies, such as floating lag time and total time of floating. It contained the effervescent mixture and K-grade HPMC to retain the carbon-dioxide produced from the effervescent mixture by the reaction of sodium bicarbonate with citric acid in presence of the dissolution medium. Because the gas generated is trapped in and protected by the gel formed by the hydration of HPMC, the expansion of the floating section keeps the whole tablet buoyant on the surface of the medium. In the formulation of floating layer, HPMC K100 M and HPMC K15 M were tried to obtain a stickier gel to prevent the rapture of air bubble. Floating layer prepared with HPMC K15 M has short floating lag time, but after some time floating layer starts dispersing. This may be because of shorter polymeric chains of HPMC K15 M hydrates more rapidly and after complete hydration, the polymeric chains become completely relaxed and can no longer maintain the integrity of the floating layer. On the other hand, HPMC K100 M produces more stable and persistent buoyant layer which has desired floating lag time and total time of floating. In an attempt to shorten the floating lag time by increasing the concentration of effervescent mixture, it was observed that tablets were dispersed; on the other hand, lower concentrations caused this duration to prolong. The best proportion for floating was found to be 160 mg for HPMC K100M, 20 mg for sodium bicarbonate, and 20 mg for citric acid (FL2). After the determination of this arrangement of effervescent powders, some formulations were prepared with floating layer (FL2) to determine the proportion of floating layer needed to achieve the desired floating lag time and total time of floating.

After the determination of proportion of floating layer, formulations given in the table were prepared to determine polymers composition needed to provide delivery of active material near the target profile from the release layer that contained active material.

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/cm^2) and coded as F15(H1), F15(H2), F15(H3), F16(H1), F16(H2) andF16(H3). Prepared tablets were evaluated for floating lag time and total time of floating according to the procedure given in chapter number 6. Results obtained were as follows.

Table 6: Effect of Hardness on the buoyancy of bi-layered floating tablets

Trial	Hardness of tablets (kg/cm^2)	Buoyancy of BFT	
		Floating lag time (sec.)	Total time of floating (Hours)
F15 (H1)	4.20 ± 0.26	115.4 ± 12.3	> 12
F15 (H2)	5.33 ± 0.22	635.8 ± 15.8	> 12
F15 (H3)	6.53± 0.24	NF	NF
F16 (H1)	3.53 ± 0.06	131.1 ± 15.5	>12
F16 (H2)	5.23 ±0.26	725.3 ± 17.5	>12
F16 (H3)	6.43 ±0.30	NF	NF

Results in table shows that, Tablets of hardness 4 kg/cm^2 and 5 kg/cm^2 of different batches{F15(H1), F15(H2), F16(H1) and F16(H2)} take 115-131 sec. and 635-725 sec. respectively to come up to the surface in 0.1 N HCl (pH 1.2) at 37 °C ± 0.5°C. The tablets of these hardness's remain buoyant greater than 12 hrs without disintegration. Tablets of hardness ≈ 6.5 kg/cm^2 did not float till the end of test period. In fact, buoyancy of the tablet is governed by both the swelling of the outer surface of the tablet when it comes in contact with the dissolution medium, and the presence of internal voids in the dry center of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density less than one which helps to remain buoyant on the gastric fluid. Compression of these tablets to high degree hardness may result in reduction of the porosity of the tablets and moreover, the compressed hydrocolloid particles on the surface of the tablets fail to hydrate rapidly when tablet comes in contact with the dissolution medium and as a result of this, capability of the tablet to float is significantly reduced. Results obtained are in support to the reported study **(24)**.

D) Swelling Behaviors of Bi-Layered Floating Tablets

Table7: Average swelling index for trial F2, F3, F4, F5 and F6

Time (Hrs)	Average swelling index ± S.D				
	F2	F3	F4	F5	F6
0	0.00 ± 0.00	0.00 ± 0.00	0.0 ± 0.00	0.00 ±0.00	0.00 ± 0.00
1	80.26 ± 0.92	95.63 ± 0.32	107.9 ± 1.20	111.09 ± 1.44	115.61 ± 1.87
2	85.74 ± 0.96	107.62 ± 0.33	124.1 ± 0.92	130.88 ± 1.67	138.60 ± 1.73
4	91.66 ± 1.30	113.20 ± 0.70	136.0 ± 1.09	148.93 ± 1.48	154.46 ± 1.48
6	92.96 ± 1.41	115.85 ± 1.00	142.0 ± 0.91	160.59 ± 0.42	170.55 ± 1.26
8	94.66 ± 1.28	119.02 ± 0.92	147.5 ± 0.58	166.84 ± 1.50	181.88 ± 1.81
10	90.33 ± 1.00	115.36 ± 0.56	136.0 ± 0.16	164.19 ± 0.94	174.44 ± 1.58
12	87.49 ± 1.29	104.14 ± 0.75	132.7 ± 0.72	160.31 ± 0.97	165.18 ± 1.23

***All values are expressed as Mean ± S.D, n=3**

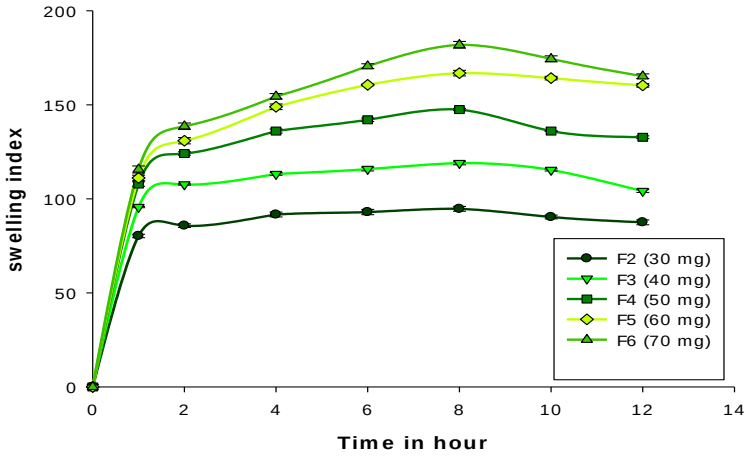

Fig. 11: Average swelling index for trial F2, F3, F4, F5 and F6

Table 8: Average swelling index for trial F7, F4, F8, F9, F10 and F11

Time	Average swelling index ± S.D					
(Hrs)	F7	F4	F8	F9	F10	F11
0	0.00 ± 0.00	0.0 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	116.50 ± 1.76	107.9 ± 1.20	98.07 ± 1.36	73.55 ± 0.87	67.31 ± 1.98	52.94 ± 1.54
2	140.34 ± 1.36	124.1 ± 0.92	117.52 ± 0.79	96.21 ± 1.03	87.01 ± 1.20	76.46 ± 1.55
4	152.62 ± 1.10	136.0 ± 1.09	132.19 ± 2.86	121.82 ± 1.32	107.34 ± 1.97	98.55 ± 1.66
6	161.23 ± 1.29	142.0 ± 0.91	136.29 ± 1.08	127.58 ± 1.38	119.53 ± 2.60	107.31 ± 0.80
8	167.20 ± 1.85	147.5 ± 0.58	139.20 ± 1.03	130.51 ± 0.90	127.44 ± 1.22	113.26 ± 1.62
10	149.48 ± 1.00	136.0 ± 0.16	142.83 ± 1.05	133.74 ± 0.96	130.90 ± 0.74	115.58 ± 1.21
12	136.93 ± 2.79	132.7 ± 0.72	130.39 ± 0.90	128.98 ± 1.23	125.56 ± 1.28	111.84 ± 1.10

***All values are expressed as Mean ± S.D, n=3**

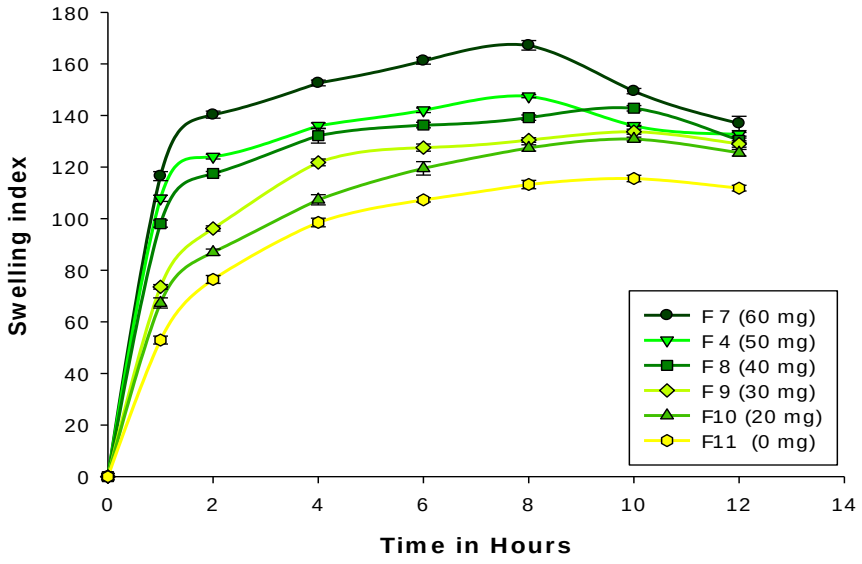

Fig. 12: Average swelling index for trial F7, F4, F8, F9, F10 and F11

Table 9: Average swelling index for trial F12, F13, F10, F14, F15 and F16

Time (Hrs)	Average swelling index ± S.D					
	F12	F13	F10	F14	F15	F16
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	59.50 ± 1.14	62.48 ± 1.57	67.31 ± 1.98	72.31 ± 1.84	76.33 ± 1.66	84.78 ± 1.18
2	94.52 ± 1.86	98.40 ± 0.83	87.01 ± 1.20	104.64 ± 0.94	108.65 ± 1.07	119.58 ± 1.25
4	112.63 ± 0.96	116.78 ± 1.13	107.34 ± 1.97	120.95 ± 1.29	122.91 ± 0.67	128.90 ± 0.82
6	129.88 ± 2.39	126.37 ± 1.82	119.53 ± 2.60	127.39 ± 1.29	129.72 ± 1.48	132.58 ± 1.02
8	134.60 ± 1.01	130.69 ± 0.95	127.44 ± 1.22	132.56 ± 1.70	135.54 ± 2.04	115.47 ± 1.45
10	141.07 ± 1.61	132.95 ± 0.94	130.90 ± 0.74	122.77 ± 1.02	120.56 ± 1.98	111.41 ± 1.98
12	135.96 ± 0.90	128.02 ± 0.98	125.56 ± 1.28	117.36 ± 1.19	105.56 ± 1.55	101.23 ± 2.36

***All values are expressed as Mean ± S.D, n=3**

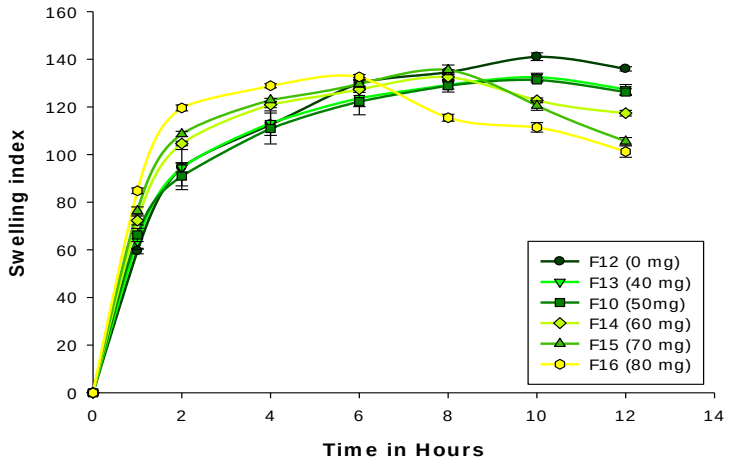

Fig. 14: Average swelling index for trial F12, F13, F10, F14, F15 and F16

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.

Effect of MCC on the swelling index

Data obtained from the swelling index of formulations containing increasing amount of MCC (F7, F4, F8, F9, F10 and F11) 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 swell able 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.

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 hour's 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)**.

4.REFERENCES

1. Garg, S., Sharma, S., 2003. Gastroretentive drug delivery systems. Drug Deliv. Oral. 24,160-166.

2. Friend, D.R., 2007. Targeted GI Delivery. In: Touitou, E., Barry, B.W. (Eds.), Enhancement in Drug Delivery, CRC Press, New York, pp. 69-71.
3. Hui, H.W., Robinson, J.R., 1990. Design and fabrication of oral controlled release drug delivery systems. In: J.R., Lee, V.H.L. (Eds.), Controlled Drug Delivery Fundamentals and Applications, 2nd ed. Marcel Dekker, New York, pp 374-422.
4. Streubel, A., Siepmann, J., Bodmeier, R., 2006. Drug delivery to the upper small intestine window using gastro retentive technologies. Current Opini. Pharmacol. 6, 501-508.
5. Chavanpatil, M., Jain, P., Chaudhari, S., Shear, R., Vavia P.R., 2005. Development of sustained release gastro retentive drug delivery system for ofloxacin: In vitro and in vivo evaluation. Int. J. Pharm. 304, 178-184.
6. Chavanpatil, M., Jain, P., Chaudhari, S., Shear, R., Vavia P.R., 2006. Novel sustained release, swell able and bio adhesive gastro retentive drug delivery system for Ofloxacin. Int. J. Pharm. 316, 86-92.
7. Hoffmana, A., Stepensky, D., Lavy, E., Eyal, S., Klausner, E., Friedman, M., 2004. Pharmacokinetic and pharmacodynamics aspects of gastro retentive dosage forms. Int. J. Pharm. 277, 141-153.
8. Singh, B.N., Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Controlled Release 63, 235-259.
9. Rubinstein, A., 2007. Gastrointestinal Anatomy, Physiology and Permeation Pathways. In: Touitou, E., Barry, B.W. (Eds.), Enhancement in Drug Delivery, CRC Press, New York, pp. 4-28.
10. Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F., 2006. Gastro retentive dosage forms: Overview and special case of Helicobacter pylori. J. Controlled Release. 111, 1-18.
11. Arora, S., Ali, J., Ahuja, A., Khar, R.K., Baboota, S., 2005. Floating drug delivery systems: A review. AAPS Pharm. Sci.Technol. 6, Article 47.
12. Shell, J.W., Louie-Helm, J., Markey, M., 2003. Extending the duration of drug release within the stomach during the fed mod. US Patent 6,635,280.
13. Kakumanua, V.K., Arora, V., Bansal, A.K., 2006. Investigation of factors responsible for low oral bioavailability of cefpodoxime proxetil. Int. J. Pharm. 317, 155-160.
14. Crauste-Manciet, S., Decroix, M., Farinotti, R., Chaumeil, J.C., 1997. Cefpodoxime-proxetil hydrolysis and food effects in the intestinal lumen before absorption: in vitro comparison of rabbit and human material. Int. J. Pharm. 157, 153-161.
15. Kakumanua, V.K., Arora, V., Bansal, A.K., 2006. Investigation on physicochemical and biological differences of cefpodoxime proxetil enantiomers. Eur. J. Pharm. Sci. 64, 255-259.
16. Rahman, Z., Ali, M., Khar, R.K., 2006. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm. 56, 49–57.
17. Srivastava, A.K., Wadhwa, S., Ridhurkar, D., Mishra, B., 2005. Oral sustained delivery of atenolol from floating matrix tablets: formulation and in vitro evaluation. Drug Dev. Ind. Pharm. 31, 367-374.
18. Varshosaz, J., Tavakoli, N., Roozbahani, F., 2006. Formulation and in vitro characterization of ciprofloxacin floating and bioadhesive extended-release tablets. Drug Deliv. 13, 277-285.
19. Narendra, C., Srinath, M.S., Babu, G., 2006. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS Pharm. Sci. Technol. 7 Article 34.
20. Dave, B.S., Amin, A.F., Patel, M.M., 2004. gastro retentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. AAPS Pharm. Sci. Technol. 5, Article 34.
21. Sungthongjeen, S., Sriamornsak, P., Puttipipatkhachorn, S., 2007. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur. J. Pharm. Sci.
22. Choi, B.Y., Park, H.J., Hwang, S.J., Park, J.B., 2002. Preparation of alginate beads for floating drug delivery system: effects of CO2 gas-forming agents. Int. J. Pharm. 239, 81-91.
23. Xiaoqiang, X., Minjie, S., Feng, Z., Yiqiao, H., 2006. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. Int. J. Pharm. 310, 139-145.
24. Singh, S., Singh, J., Muthu, M.S., Balasubramaniam, J., Mishra, B., 2007. Gastro retentive drug delivery system of metoclopramide hydrochloride: formulation and in vitro evaluation. Current Drug Deliv. 4, 269-275.
25. Jaimini, M., Rana, A.C., Tanwar, Y.S., 2007. Formulation and evaluation of famotidine floating tablets. Current Drug Deliv. 4, 51-55.
26. Gel, I.K., Bodmeier, R., 1999. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm. 187, 175-184.
27. Streubel, A., Siepmann, J., Bodmeier, R., 2003. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci. 18, 37-45.
28. Ichikawa, M., Watanabe, S., Miyake, Y., 1991. A new multiple unit oral floating dosage system. I: Preparation and in vitro evaluation of floating and sustained-release kinetics. J Pharm Sci. 80, 1062-1066.
29. Yang, L., Esharghi, J., Fassihi, R., 1999. A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers: in vitro evaluation. J Controlled Release. 57, 215-222.
30. Zdemir, N.O., Ordu, S., Ozkan, Y., 2000. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluations of bilayer tablet formulations. Drug Dev. Ind. Pharm. 26, 857-866.
31. Penners, G., Lustig, K., Jorg, P.V.G., 1997. Expandable pharmaceutical forms. US patent 5 651 985.

32. Talwar, N., Sen, H., Staniforth, J.N., 2001. Orally administered controlled drug delivery system providing temporal and spatial control. US patent 6 261601.
33. Baumgartner, S., Kristel, J., Vreer, F., Vodopivec, P., Zorko, B., 2000. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 195, 125-135.
34. Nur, A.O., Zhang, J.S., 2000. Captopril floating and/or bio adhesive tablets: design and release kinetics. Drug Dev Ind. Pharm. 26, 965-969.
35. Franz, M.R., Oth, M.P., 1993. Sustained release, bilayer buoyant dosage form. US patent 5 232 704.
36. Wu, W., Zhou, Q., Zhang, H.B., Ma, G.D., Fu, C.D., 1997. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao. 32, 786-790.
37. Wong, P.S.L., Dong, L.C., Edgren, D.E., Theeuwes, F., 2000. Prolonged release active agent dosage form adapted for gastric retention. US patent 6 120803.
38. Stoeckel, K., Hofheinz, W., Laneury, J.P., Duchene, P., Shedlofsky, S., Blouin, R.A., 1998. Stability of cephalosporin prodrug esters in human intestinal juice: implications for oral bioavailability. Antimicrob. Agents Chemother. 42, 2602-2606.
39. Crauste-Manciet, S., Huneau, J.F., Decroix, M.O., Tom, D., Farinotti, R., Chaumeil, J.C., 1997. Cefpodoxime proxetil esterase activity in rabbit small intestine: a role in the partial cefpodoxime absorption. Int. J. Pharm. 149, 241-249.
40. Saathoff, N., Lode, H., Neider, K., Depperman, K.M., Borner, K., Koeppe, P., 1992. Pharmacokinetics of cefpodoxime proxetil and interactions with an antacid and an H2 receptor antagonist. Antimicrob. Agents Chemother. 36, 796-800.
41. Crauste-Manciet, S., Brossard, D., Decroix, M.O., Farinotti, R., Chaumeil, J.C., 1998. Cefpodoxime-proxetil protection from intestinal lumen hydrolysis by oil-in-water submicron emulsions. Int. J. Pharm. 165, 97-106.
42. Nicolaos, G., Crauste-Manciet, S., Farinotti, R., Brossard, D., 2003. Improvement of cefpodoxime proxetil oral absorption in rats by an oil-in-water submicron emulsion. Int. J. Pharm. 263, 165-171.
43. Merchant, H.A., Shoaib, H.M., Tazeen, J., Yousuf, R.I., 2006. Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxypropyl methylcellulose: A technical note. AAPS Pharm. Sci. Technol. 7, Article 78.
44. Tripathi, K.D., 2004. Essentials of Medical Pharmacology, 5th ed. Jaypee Brotheres Medical Publishers (P) Ltd. New Delhi, pp. 662-665.
45. Mandell, G.L., Petri, W.A., 1996. Antimicrobial agents: Penicillins, Cephalosporins, and other beta lactam antibiotics. In: Gilman, A.G., Ruddon, R.W., Molinoff, P.B., Limbrid, L.E., Hardman, J.G., The Pharmacological Basis of Therapeutics, 9th ed. McGraw Hill, London, pp. 1095.
46. Sweetman, S.(Ed.), 2007. Martindale: The Complete Drug Reference, 35th ed. Pharmaceutical press, (electronic version). From: http://www.medicinescomplete.com/mc/martindale
47. USP XXIX, From: http://www.pharmacopeia.cn
48. Bethesda, M.D., 2007. AHFS Drug Information, American Society of Health Systems Pharmacists (electronic version). From: http://www.medicinescomplete.com/mc/ahfs
49. Row, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients, 4th ed. American Pharmaceutical Association and Pharmaceutical Press, Washington, DC, pp. 237-241, 260-265.
50. Tiwari, S.B., Rajabi-Siahboomi, A.R., 2008. Extended-Release oral drug delivery Technologies: Monolithic Matrix Systems. In: Jain, K.K. (Ed.), Methods in Molecular Biology, Vol. 437: Drug Delivery Systems, Human Press, Totowa, NJ, pp 217-243.
51. Kaur, P., Dhiman, S., Arora, S., 2013. Floating Bilayer Tablet Technology: A Review, Int. J. Pharm Sciences Review and Research. 19(1): 112-122.
52. Dubey J, Verma N, Floating drug delivery system: A review, Indian Journal of Pharmaceutical Science and Research, 2013; 2893-2899.
53. Parsekar, S.D., Prabhu, S., Shetty, A., Azharuddin, M. and Shabaraya, A.R., 2014. A Brief Review on Floating Bilayer Tablet as a Convenient Gastro retentive Drug Delivery System International Journal of Pharmaceuticle and Chemicle Sciences. 3(2): 420-430.
54. Amritha V., Kaur S., Pandey K., 2014. Formulation and in vitro evaluation of floating tablets of hydroxypropylmethylcellulose K4M and carbopol using Metronidazole as model drug, International Journal of Pharmaceutical Science and Research. 2244-2249.
55. Keshari A., Tripathi D., Srivastava A., Vishwas R., 2015. Formulation and evaluation of effervecent floating tablets of antidiabetic drug. Journal of Drug Delivery and Therapeutics. 5(6):43-55.
56. Pant S., Badola A., Kothiyal P., 2016. A review on gastro retentive drug delivery system, Indian Journal of Pharmaceutical Science and Research. 4(2) :1-10.
57. Gurjar G., Bhowmick M., Rathi V., Rathi J., 2017. Design and evaluation of extended release cefuroxime axetil floating tablets with improved GI absorption. Journal of Drug Delivery and Therapeutics. 7(1):49-59.
58. Sahoo C., Rao S., Sudhakar M., 2017. Formulation and evaluation of controlled porosity osmotic pump tablets for zidovudine and lamivudine combination using fructose as osmogene. Journal of Drug Delivery and Therapeutics. 7(4):41-50.
59. Momin S., Khan S., Ghadage D., Yadav A., Wagh A., 2017. Formulation and evaluation of bilayer tablets of propranolol hydrochloride. Journal of Drug Delivery and Therapeutics. 7(2):50-57.
60. Yerikala R., Pudi V., Saravana Kumar K., Vadhi Reddy S., 2017. Formulation and evaluation of floating drug delivery of cefotaxime using raft forming approach. Journal of Drug Delivery and Therapeutics. 7(4):110-119.

61. Sharma A., Sharma P., Darwhekar G., 2017. Formulation and evaluation of bilayer tablet of metronidazole and dicyclomine hydrochloride for treatment of irritable bowel disease. Journal of Drug Delivery and Therapeutics. 7(7):56-58.

62. Soni A., Ghulaxe C., Upadhyay S., Pillai S., 2018. Development and *in vitro* evaluation of an oral floating tablet of Metronidazole. Journal of Drug Delivery & Therapeutics. 8(2):83-86.