Int. J. Pharm. Investigation, 2020;10(3):368-373 Original Article

Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation

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ABSTRACT

Background: Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class. Cefpodoxime proxetil has a short elimination half-life and also possesses high solubility, chemical, enzymatic stability and absorption profiles in acidic pH which makes Cefpodoxime proxetil suitable candidate for formulating it as a gastroretentive dosage form for improved bioavailability. **Methods:** The formulation of floating tablets of Cefpodoxime proxetil was prepared by the direct compression technique using Pomegranate peel powder as release retarded material. The floating tablets of Cefpodoxime proxetil are prepared by applying design of experiment in that 3^2 Factorial Design was selected. *In vivo* gastro-retention of the optimized floating formulation was determined by X-ray imaging studies on healthy rabbits. **Results:** The F3 Formulation containing Pomegranate peel powder peel powder of 50mg and sodium bicarbonate 100 mg has shown sustained release for 24 hr. The Floating lag time of all the prepared batches was found to be from 49±0.5 to 57±0.5 in sec. The minimum lag time was 49 sec. The *in vitro* release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero-order kinetics with anomalous transport mechanism. *In vivo* Gastroretention of the optimized formulation F3 determined by X-ray imaging studies on healthy rabbits shows retention of the tablet in stomach for sufficient period of time. **Conclusion:** The prepared gastro retentive floating tablet formulation using Pomegranate peel powder as rate control polymer shows better-floating properties and effective gastro retention when Pomegranate peel powder and drug is used in the ration of 1:2.5. Hence CFP floating tablet formulation can be a suitable alternative to immediate release CFP tablets to increase gastricresidence time and thereby improving its bioavailability.

Key words: Floating Tablets, Cefpodoxime Proxetil, Pomegranate Peel Powder, Gastroretentive Drug Delivery, Natural Polymer, Bio-availability.

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DOI: 10.5330/ijpi.2020.3.65

INTRODUCTION

The administration of active moiety through oral route among other types of drug delivery systems is the most chosen way for achieving systemic effects owing to its comfortable management, good patient compliance and cheap method. Persistent release dosage form releases the active moiety at a slow rate through the oral route. It is exceedingly alluring to create supported medication conveyance frameworks, which discharges the medication at a modified rate to accomplish ideal dynamic particle fixations at the site of activity. These frameworks have weaknesses like non-appropriateness for the active moiety having site-explicit ingestion in the upper part of the GIT, precipitation of active moiety, debasement of the active moiety in the distal part of GIT. This has resulted in the development of gastric retention delivery systems which overpowers the drawbacks connected with continued-release formulations.[1]

A bubbly floating gastro-retentive dosage form is developed for CFP and assessed in rodents. The outcomes showed a potential for development of gastro retentive dosage using Eudragit S100 polymer.[2] It has also been demonstrated successfully the release of the drug CFP from mucoadhesive gastro retentive tablets using Sodium Alginate and Chitosan in a controlled manner.[3]

Literature also confirms the advantages, restrictions, showcased dosage form and patents of floating and non-floating gastro-retentive drug delivery system.[4-6]

The formulator's has highlighted the benefits of gastro-retentive drug delivery system including the organic and formulation factors influencing gastric maintenance and ways to deal with configuration of single-unit and multiple unit floating systems.[7]

CFP is an orally administered extended-spectrum; semi-synthetic antibiotic of the cephalosporin class has a short elimination half-life. It has high solubility, chemical and enzymatic stability. It is absorbed well in acidic pH which makes it suitable candidate for formulating in a gastro retentive dosage form for improving bioavailability. PMG peel powder is used as a polymer in formulations as support release material. It contains Phenolic composites like punicalagins, gallic acid, catechin, epigallocatechin gallate, quercetin, rutin, anthocyanidin's and different flavonoids and acts as a neutral polymer.[8]

MATERIALS

CFP was received as a gift sample from Lupin Pharma Ltd., Aurangabad. Pomegranate peel powder was purchased from Heilen Biopharm. Hydroxy propyl methyl cellulose K4M, Acacia, Sodium bicarbonate,

Polyvinyl Pyrrolidone, Lactose and magnesium stearate is purchased from local market.

METHODS

Preformulation studies

Preformulation studies involve investigation of the physical and chemical properties of a pure drug and with or without excipients. It is the first step in the rational development of dosage forms.

Pre-compression parameters of powder blends

Micromeritic properties of pre-compressed powder of CFP Floating tablets were analyzed by measuring the bulk density, tapped density, Carr's index, Hausner's ratio and Angle of repose.[9]

Angle of repose

The angle of repose is the maximum angle between the surface heap of granules and flat planes. A fixed measure of the mix was precisely taken and deliberately poured through the channel whose tip was made sure about at a stature of 2.5 cm over the graph paper which is put on an even surface. The mix was poured until the summit of the cone-shaped heap just contacts the tip of the channel. The angle of repose is determined by the following formula.

$\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, r = radius of the pile, h = height of the pile.

Bulk density

Bulk density is characterized as the proportion mass of an untapped blend partitioned by the mass volume. Evident bulk thickness (BD) was calculated by emptying the mix into a graduated chamber. The mass volume (V) and the heaviness of the powder (M) were resolved. The bulk density was calculated using the formula.

$BD = M/V$

Tapped density

The tapped thickness accomplished after precisely tapping a graduated measuring cylinder containing the powder test by raising the chamber or vessel and permitting it to drop, under its mass. The measuring cylinder containing a known mass of mix was tapped for a fixed time around 100 tapping. The minimum volume (V_t) involved in the cylinder and the weight (M) of the mix were estimated. The tapped density (TD) was calculated using the formula,

$TD=M/ (V_t)$.

Compressibility index

The compressibility index is an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials. The correlation between compressibility index and powder flow properties is given in the formula,

CI (%) = Tapped density (TD) – Bulk density (BD) / Tapped density (TD) × 100.

Hausner's ratio

It is an indirect index of ease of powder flow and is measured by the ratio of the tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density.

Drug-excipients compatibility studies

The spectral analysis of pure drug and a physical blend of drug and diverse excipients that are utilized for the preparation of tablets were studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks utilizing a Shimadzu Corporation (Kyoto, Japan). KBr disks were prepared by blending sample with potassium bromide. The resultant disk was mounted in a reasonable holder in the IR spectrophotometer and the range was recorded from 4000 cm^{-1} to 500 cm^{-1}.

Formulation of CFP floating tablets

CFP has good stability, solubility in acidic pH. Tablets were prepared by the direct compression method using PMG peel powder as retardant material.

Dose calculation

Since 125 mg of CFP is equivalent to 100 mg of cefpodoxime.

(Not less than 690 micrograms and not more than 804 micrograms of cefpodoxime per mg).

Preparation of tablets

The floating tablets of CFP are prepared by applying design of experiment in that 3^2 Factorial Design was selected and accordingly batches were prepared. The different variables and their levels are given in Table 1. The actual quantities of the ingredients in factorial batches are shown in Table 2. All additives and the drug except sodium bicarbonate and magnesium

Table 1: Factorial design batches with different variables and their levels.

Formulation codes	Variable level code	
	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

X1- Amount of PMG peel powder (-1=50, 1=70, +1=100)
X2- Amount of sodium bicarbonate (-1=25, 1=50, +1=100)

Table 2: Formulation of CFP floating tablets.

Ingredients	Formulation codes								
(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
CFP	125	125	125	125	125	125	125	125	125
PMG Peel powder	50	50	50	75	75	75	100	100	100
Sodium bicarbonate	25	50	100	25	50	100	25	50	100
PVP K30	10	10	10	10	10	10	10	10	10
Lactose	59	54	49	39	34	29	19	14	09
Magnesium stearate	06	06	06	06	06	06	06	06	06
Total	275	275	275	275	275	275	275	275	275

stearate were sifted through sieve no. 30. These ingredients are blended in a polybag. Finally sodium bicarbonate sifted through sieve no. 60 and Magnesium stearate sifted through sieve no. 40 was added to the blend. The above blend was compressed on Karnavati mini tab eight-station compression machine using a round-shaped 8.5 mm punch.[10]

Evaluation of CFP Floating Tablets

The prepared Floating tablets are evaluated for various parameters like weight variation, thickness, hardness, friability, drug content, content uniformity and *in vitro* dissolution studies.[11]

Tablet thickness

The thickness in millimeters (mm) was estimated independently for 20 pre-gauged tablets by utilizing Vernier Calipers. The normal thickness and standard deviation are reported.

Tablet hardness

Tablet hardness was estimated utilizing Monsanto hardness tester. The average crushing strength of the 10 tablets with known weight and thickness of each was reported.

Friability test

Ten tablets were precisely gauged and set in the friability test mechanical assembly (Roche Friabilator), pivoted at 25 rpm for 4 min. The tablets were removed dedusted and weighed. The friability was determined as the weight reduction it should be below 1%. The formula for estimation of friability is give below.

% Friability = (W1 – W2) /W1 × 100

Where, W1 = initial weight of the tablets, W2 = final weight of the tablets

Weight Variation Test

To consider weight variation individual weights (WI) and average weight (WA) of 20 tablets from every preparation were noted down utilizing an electronic balance. The percentage weight variation was calculated using the formula below.

% Weight variation = $(W_A – W_I) / W_A \times 100$

Drug content

Twenty tablets were gauged and taken into a mortar and squashed into a fine powder. A precisely gauged bit of the powder comparable to 100 mg of CFP was moved to a 100 ml volumetric flask containing methanol. It was shaken by mechanical methods for 1hr. At that point, it was separated through the Whatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 0.1N HCl and absorbance was measured against blank at 264 nm using UV-Spectrophotometer (Shimadzu, Japan). The drug content of the floating tablets meets the requirements if the tablet amount lies within the range of 90% to 110%.

Buoyancy / Buoyant test

The tablet is introduced into a 100 ml beaker consisting of 0.1N HCl solution and the period between the introduction of the tablet in the solution and emergence of the tablet onto the surface of the solution is counted and it is called as floating lag time. The total period by which the dosage form remains Floating is also estimated and is called as Total floating time.

In vitro dissolution studies

The tablet was placed in a dissolution test apparatus USP II (Electro lab TDT), containing 900 ml of 0.1N HCl and rotated at a speed of 50 rpm. 5 ml of aliquots were withdrawn for every 1 hr. up to 12 hr and replenished with 5 ml of fresh dissolution medium. Each sample was analyzed at 264 nm using a double beam UV spectrophotometer against blank solution.

In vivo Gastroretention study

Evaluation of gastric retention of CFP sintered floating tablet was performed on the rabbit by the use of radio-opaque marker barium sulfate. X-Ray imaging studies are the non-invasive method which provides identification or monitoring of total GI residence time without affecting normal gastrointestinal motility. Healthy rabbits weighing 2 to 3 kg were fasted overnight and on the next day, optimized tablet formulation F3 containing barium sulfate in place of CFP was administered to rabbits through plastic tubing followed by flushing of 25–30 ml of water. During the entire study, the rabbits had free access to water only. At different time intervals of 0, 1, 2, 4, 6 and 8 hr, rabbit G.I.T. was X-Ray photographed in the supine position and observed for the nature and position of the CFP floating tablet.[12]

Accelerated stability studies

Optimized formulation F3 was subjected to stability studies at 40°C ± 2°C/75% ± 5% RH and 25°C ± 2°C/75% ± 5% RH and analyzed for its physical characteristics, drug content and dissolution.

RESULTS

Preformulation studies

Drug-excipients compatibility study by FTIR

CFP compatibility with excipients was studied by FTIR and is shown in Figure 1. From the IR spectra the peaks representing the pure drug were similar in all the graphs suggesting that there is no interaction and the pure drug is unaltered when mixed with PMG peel powder. The

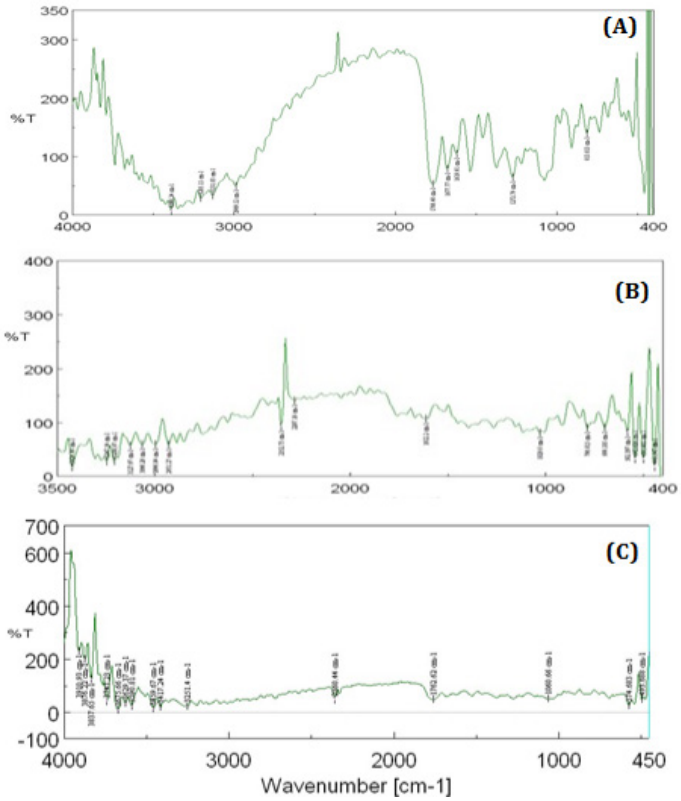

Figure 1: FTIR spectra of (a) CFP (b) PMG peel powder and (c) physical mixture of CFP and PMG peel powder.

characteristic peaks observed is 3396 and 3240, 1633, 1259, 3166, 1648, 1743 cm^{-1}.

Evaluation of flow properties

It was found that the drug and the other powder blends possess the required flow characteristics for direct compression as the values of batches of F1 to F9 are within acceptable limits possessing good flow properties. The Angle of repose was found be between 23.65±0.43 and 28.44±0.39. Hausner's ratio was between 1.06±0.31 and 1.1±0.39. Carr's index range was 5.71±0.39 to 10±0.39, Bulk density was found to be 0.37±0.42 to 0.40±0.4 and Tapped density was between 0.40±0.39 and 0.44±0.39.

Evaluation of CFP Floating tablets

Prepared Floating tablets were evaluated for hardness, thickness, weight variation, friability and drug content. The hardness of CFP Floating tablets was found to be in the range of 4.3 – 4.5 kg/cm^2. The thickness of the tablets was found to be in the range of 4.10 – 4.40 mm. In the weight variation test, the pharmacopeia limit for the % deviation for the tablets of 130 mg to 324 mg (USP) is ± 7.5%. The average % deviation of all the tablet formulations was found to be within the limits. The percentage friability of all the formulations was below 1% indicating that the friability was within the prescribed limits. The drug content values varied between 95.63 – 99.53%. Thus all the parameters of the Floating tablets were within compendia standards.[13]

Buoyancy test

From the results obtained it is evident that sodium bicarbonate has a significant effect on lag time. Total Floating time was increased and floating lag time decreased with an increase in sodium bicarbonate concentrations. The Floating lag time (sec) for batches F1 to F9 was found to be from 49±0.5 sec to 57±0.5. The minimum lag time was found to be 49 Sec.[14]

In vitro drug dissolution test

From the results given in Table 3, the *in-vitro* drug dissolution of the formulations F1 to F9 is subjected to dissolution studies for further optimization. Formulation F3 containing PMG peel powder of 50mg and sodium bicarbonate 100 mg has shown sustained release for 24 hr. CFP dissolution in 0.1 N HCl exhibited that, as the concentration of $NaHCO_3$ increases the effervescence or liberation of CO_2 increases thereby reduces the Floating lag time and increases Floating buoyancy due to increased porosity by the gas-forming agent. Dissolution profiles of all the batches in which the F3 batch shows exceptional drug release.

In vivo Gastro-retention study

In vivo buoyancy of the optimized formulation F3 was determined by X-ray imaging studies on healthy rabbits. The animal dose was calculated using dose translation based on body Surface Area. Figure 2 X-ray photographs of rabbit showing location of the floating tablet before and after administration.[15]

Drug release kinetic-model dependent method

The release data was analyzed by fitting the drug release profiles of all the formulations into zero, first, Higuchi and Korsmeyer-Peppas model.[16]

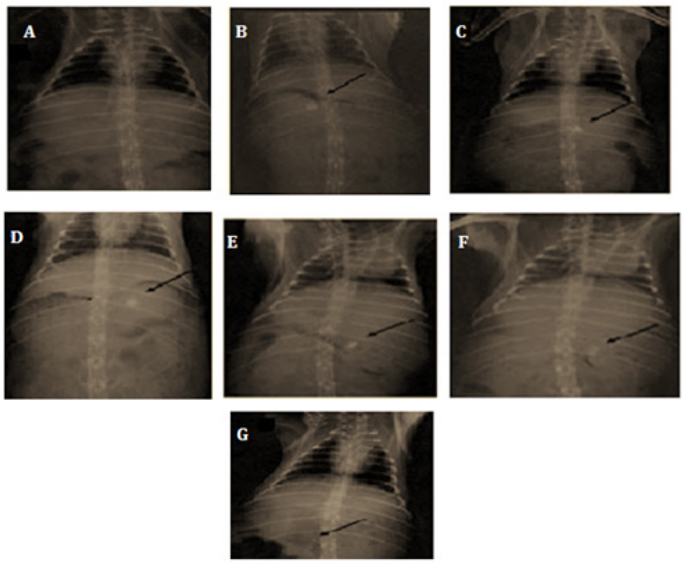

Figure 2: X-ray photographs of GIT of rabbit showing location of the floating tablet at Different time intervals after administration.
X-ray photographs of rabbit showing location of floating tablets at different time period. A) Before administration of floating tablet. B) Immediately after administration. C) After 1 hr D) After 2 hr E) After 4 hr F) After 6 hr and G) After 8 hr post administration.

Table 3: The *in-vitro* drug release profile for batches F1 to F9.

Time (Hr)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	13.55±0.32	17.24±0.34	18.36±0.32	09.11±0.23	09.55±0.52	12.21±0.65	9.16±0.32	10.32±0.22	20.13±0.53
2	19.33±0.12	23.76±0.42	25.73±0.14	14.41±0.36	12.36±0.65	18.88±0.55	14.45±0.55	15.36±0.12	30.12±0.63
4	23.96±0.63	28.43±0.63	38.63±0.36	20.83±0.35	22.42±0.55	23.44±0.33	18.10±0.54	20.66±0.35	36.88±0.42
6	33.78±0.32	35.33±0.35	49.75±0.52	34.85±0.42	34.08±0.44	37.20±0.36	29.22±0.52	28.66±0.22	47.42±0.36
8	41.55±0.12	45.11±0.31	56.22±0.33	40.26±0.12	38.33±0.45	43.60±0.53	36.22±0.15	29.47±0.47	56.44±0.15
10	57.56±0.32	53.41±0.45	67.43±0.46	49.23±0.63	45.55±0.35	60.33±0.43	45.65±0.15	36.88±0.54	61.44±0.25
12	69.45±0.65	69.21±0.12	78.24±0.11	57.11±0.52	56.33±0.63	69.55±0.26	55.88±0.22	47.33±0.59	74.22±0.55
16	76.66±0.32	75.80±0.25	89.63±0.21	65.64±0.56	70.15±0.32	78.35±0.24	62.66±0.36	58.95±0.56	77.65±0.61
20	84.45±0.25	88.71±0.32	93.82±0.69	76.33±0.64	85.63±0.11	83.66±0.15	70.55±0.44	64.32±0.58	79.55±0.43
24	88.61±0.14	92.45±0.14	98.67±0.44	88.65±0.45	92.66±0.65	94.76±0.59	76.58±0.45	79.55±0.41	83.45±0.25

Table 4: Evaluation of F3 formulation after 3 month stability study.

Parameters	Initial readings	After 3 month stability study	
		40°C ± 2°C/ 75% ± 5% RH	25°C ± 2°C/ 75% ± 5% RH
Floating lag time	49±0.4 sec.	52 sec.	48 sec.
Total Floating time	24 hr	24 hr	24 hr
Hardness	4.4±0.54 kg/cm^2	4.6 kg/cm^2	4.4 kg/cm^2
Drug content	98.12±0.53 %	98.01 %	99.01 %
Percent drug release in 12 hr	98.62±0.44 %	95.61 %	97.45 %
Thickness	4.1±0.32 mm	4.1 mm	4.1 mm
Friability	0.42±0.59 %	0.56 %	0.43 %
Weight of tablet	248±0.54 mg	248.2 mg	249.5 mg
Swelling index	99.41±1.4 %	98.23 %	97.19 %

Regression coefficient (R^2) was calculated for all the formulations. It was found that the passage of the drug through the matrix is dependent on the square root of time. When the release profile was plotted versus square root of time a linear relationship was observed with the regression coefficient close to one. Batches show 'n' higher than 0.5 and lower than 1, which concludes that the formulation exhibit anomalous transport mechanism.[17] To analyze the release of a CFP release mechanism, *in vitro* drug release data was fitted in various release equation and kinetic models (Zero order, First order, Higuchi and Korsmeyer-Peppas) for all formulated batches. For matrix treatment, the R^2 value for F3, F4 and F5 shows close to one which exhibit matrix release kinetics. Whereas, F2 exhibit Korsmeyer-Peppas kinetics of drug release.[18]

Accelerated stability studies

Optimized formulation F3 was analyzed for its physical characteristics, drug content and dissolution. The results are summarized in Table 4.

DISCUSSION

The CFP Floating tablets were prepared successfully using PMG peel powder as a sustained release polymer and sodium bicarbonate as a gas generating agent. Lesser Floating lag time and prolong Floating duration could be achieved by varying amounts of gas generating agent i.e. sodium bicarbonate. PMG peel powder and sodium bicarbonate can be used for the formulating Gastro retentive Floating tablets. Drug-excipients compatibility study conducted by FTIR spectrometry shows no change in drug content due presence of other excipients. From the IR spectra the peaks representing the pure drug were similar in all the graphs suggesting that there is no interaction and the pure drug is unaltered when mixed with PMG peel powder. The characteristic peaks observed is N-H stretching at 3396 and 3240 cm^{-1} which represents primary amine. N-H bending 1633 cm^{-1} is for aromatic primary amine. C-N bond is at 1259 cm^{-1}, 3166 cm^{-1} is for aromatic C-H stretch, C=N bond is at 1648 cm^{-1}, C=O is at 1743 cm^{-1} for Lactam.

The fabricated tablets show acceptable hardness, Floating lag time and Floating duration. The *in-vitro* drug release profile of all the batches shows an efficient drug release profile. The concentration of polymer affects the drug release rate and mechanism of release. The swelling capacity study of all batches exhibited significant water uptake leading to significant gastric retention. The factorial design selected for preparation of CFP tablets was significant and the results confirmed that concentration of PMG peel powder and sodium carbonate plays a major role in floating of tablets and drug dissolution. Based on 3^2 full factorial design study F3 batch fits in the Higuchi model and it follows anomalous transport release mechanism. The optimized formulation contains 12% of PMG peel powder and 22% of sodium bicarbonate. Which gives the best dissolution of 98.67±0.44 % in 24 hr in 0.1N HCl. Optimized batch was further subjected to stability studies for one month and all quality parameters evaluated and batch shows the stability. Based on the results it can be concluded that optimized tablets were stable during accelerated stability studies, with an insignificant change in the Floating lag time, Floating time, drug content and *in vitro* drug release characteristics. It is evident from the X-ray photographs of rabbit that the floating tablets are retained in the stomach for more than 8 hr which is sufficient for the dosage form to release the drug in the abdominal cavity. The stability study of F3 tablet formulation does not reveled any significant changes in the physical characteristics, such as Total Floating time, Floating lag time, drug content, friability, dissolution and swelling index, hence the prepared CFP floating tablets were stable in accelerated and long term stability study.

CONCLUSION

The prepared gastro-retentive floating tablet formulation using PMG peel powder as rate control polymer shows better-floating properties and effective gastro-retention when PMG peel powder and drug is used in the ration of 1:2.5. PMG peel powder and sodium carbonate plays a major role in floating of tablets and drug dissolution. Based on 3^2 full factorial design study F3 batch fits in the Higuchi model and it follows anomalous transport release mechanism. Hence CFP floating tablet formulation can be a suitable alternative to immediate release CFP tablets to increase gastric residence time and thereby improving its bioavailability.

ACKNOWLEDGEMENT

I am very grateful to my Colleagues namely Dr. Furquan Khan and Dr. Shahed Baig for providing me huge support while doing my research work and literature survey to facilitate the preparation of this research paper.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CFP: Cefpodoxime Proxetil; **PMG:** Pomegranate; **GR:** Gastroretentive.

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Article History: Submission Date : 26-03-2020; Revised Date : 11-06-2020; Acceptance Date : 10-09-2020.
Cite this article: Hasan M. Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation. Int. J. Pharm. Investigation, 2020;10(3):368-73.