IJPSR (2016), Vol. 7, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 October, 2015; received in revised form, 14 January, 2016; accepted, 18 March, 2016; published 01 April, 2016

FORMULATION, OPTIMIZATION & EVALUATION OF SOLID DISPERSION BASED GASTRORETENTIVE FLOATING TABLETS OF CEFPODOXIME PROXETIL

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Key words:

Gastroretentive drug delivery system, floating system, solid dispersion, PEG, HPMC, Cepodoxime proxetil

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ABSTRACT: The objective of present study was to preclude of poor dissolution of relatively water insoluble and poorly permeable drug by formulating gastroretentive floating tablet using solid dispersion (SD) of the drug. It aimed to increase the drug solubility and gastric retention of the drug for better absorption profile. Cefpodoxime proxetil is an orally absorbed third generation cephalosporin antibiotic. The oral bioavailability and biological half life is 50% and 2.09 to 2.84 hrs respectively. Two grades of Polyethylene glycol (PEG); PEG 4000 and PEG 6000 in combination were used for the formulation of solid dispersion. Formulation batch SD8 was found to be optimized according to the face centred cube design (FCCD). Solubility and the drug release from batch SD8 was maximum in 0.1N HCL, 18.93mg/ml and 94.66% respectively as compared to physical mixtures (PM) and pure drug. The physical mixture having same carrier ratio (PEG 4000+PEG 6000) that is PM8 has solubility and drug release 13.93mg/ml and 76.34% respectively. The study showed that solubility and drug release has linear relationship with PEG concentration. The optimized batch of the SD was further used for the formulation of the gastroretentive floating tablets by using HPMC K15 M as the hydrophilic polymer and sodium bicarbonate as gas generating agent. The gastroretentive floating tablets was formulated by direct compression method and tested for various physicochemical parameters for tablets like tablet weight variation, thickness, hardness, friability, content uniformity, *in vitro* buoyancy studies, swelling index and *in vitro* drug release.

INTRODUCTION: Cefpodoxime Proxetil (CP) is chemically (6R, 7R)-7-[(2Z)-2-(2-amino-1, 3-thizol-4-yl)-2-(methoxyimino acetamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. CP is wide spectrum, rapidly hydrolysed, orally active third generation semisynthetic antibiotic of class cephalosporin, active against *Enterobacteriaceae*, *Hemophilus* species, *Moraxella* species including lactamase producers, many gram-positive and gram-negative bacteria by inhibition of cell wall synthesis.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(4).1734-39

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (4).1734-39

Many organisms which are resistant to penicillins and cephalosporins may be susceptible to cefpodoxime due to production of beta-lactamase by them. CP is widely used for respiratory tract infections, effective against tonsillitis, pharyngotonsillitis, acute bronchitis, urinary tract infection. CP (pKa 3.2), exists predominantly in ionic form at intestinal pH and with poor permeability and practically insoluble in water. The aqueous solubility of the drug is 400µg/ml (BCS Class IV drugs).

Solid dispersions are the best way to improve the solubility and dissolution rate of the drug. It is stable and well absorbed within pH range 1-4, above 4 it undergoes hydrolysis to form active cefpodoxime but its active form not absorbed from gastrointestinal tract. So bioavailability of CP may be increased by reducing its hydrolysis. The half-

life of CP (2-3 hr) suggests that it is rationale drug for sustained drug delivery.

Chiou and Reigelman defined solid dispersion as "a dispersion involving the formation of eutectic mixture of drugs with water soluble carriers by melting of their physical mixtures". In this method one or more active ingredients dispersed in an inert matrix at solid stage to alter their physical properties and to enhance the release of drugs from ointment, suppository bases, to improve solubility, stability, to increase dissolution rate and sustained release of drug [1]. To prolong the gastric residence time from solid dispersions of CP floating tablets formulated by direct compression method. Floating drug delivery system (FDDS) remain buoyant in the stomach without affecting gastric emptying rate for a prolonged time because this system have a bulk density less than gastric fluids [2]. After release of drug, the rest of the system is emptied from the stomach this result in an increased gastric retention time (GRT).

MATERIALS AND METHODS:

Materials:

Cepodoxime proxetil drug was procured as gift sample from Nector Life sciences Ltd. Derabassi (Punjab), HPMC K15 M was procured from M/S Leo Chem Pvt. Ltd., Mumbai. Poly vinyl pyrrolidone (PVP), Poly ethylene glycol (PEG), Sodium bicarbonate and other ingredients of analytical grade were purchased from HiMedia Laboratories Pvt. Ltd., Mumbai.

Methods:

Experimental Design: The statistical strategy for detailed experiment planned in such a way that the required information is obtained as efficiently and precisely as possible. The commonly employed designs for response surface methodology, screening and factor- influencing studies in pharmaceutical product development are: Factorial designs (FD), Fractional factorial designs (FFD), Box-Burman designs, Central Composite Designs(CCD), etc. [3] These are most commonly employed for nonlinear responses requiring second order models. CCD is also known as Box- Wilson design. The 'composite design' contains embedded(2k) FD or (2k-r) FFD, augmented with a group of star points (2R) and a central point [4, 5]. A face centred cube design(FCCD) result when both factorial and star points in a CCD possess same positive and negative distance from centre.

Experimental design for formulations of solid dispersion:

Two independent variables, the amount of PEG 6000(X^1) and PEG 4000(X^2) were studied at 3 levels each and the central point (0, 0) was studied at quintuplicate. All other formulation and processing variables were kept invariant throughout the study.

TABLE 1: FACTORS COMBINATIONS AS PER THE CHOSEN EXPERIMENTAL DESIGN

Formulation Code	Coded Factor Levels	
	X_1	X_2
SD1	-1	-1
SD2	+1	-1
SD3	-1	+1
SD4	+1	+1
SD5	-1	0
SD6	+1	0
SD7	0	-1
SD8	0	+1
SD9	0	0
SD10	0	0
SD11	0	0
SD12	0	0
SD13	0	0

TABLE 2: THE AMOUNT OF FACTOR X_1 SELECTED FOR OPTIMIZATION IN DIFFERENT LEVELS

Coded Level	-1	0	+1
X_1: PEG 6000(mg)	1000	2000	3000

TABLE 3: THE AMOUNT OF FACTOR X_2 SELECTED FOR OPTOMIZATION IN DIFFERENT LEVELS

Coded Level	-1	0	+1
X_2: PEG 4000(mg)	1000	2000	3000

Preparation of Cefpodoxime proxetil –PEG Physical mixture:

Physical mixture of CP with the combination of PEG 4000 and PEG 6000 in different ratios obtained from design expert were prepared by weighing accurate quantity of drug and carrier in pestle and mortar. These were mixed thoroughly for 5 min and sieved through a 0.25 mm sieve (#60) and stored in a desiccators for 24 hrs and used for further studies.

Preparation of Cefpodoxime proxetil - PEG solid dispersions:

The solid dispersions of CP and PEG (carrier) in different drug-to-carrier ratios were prepared by solvent evaporation method. 500 mg of drug was dissolved in 20 ml of methanol in a beaker; carrier was added and mixed to dissolve at 40^0 C on a heating mantle to get clear solution. Solvent was allowed to evaporate at room temperature until constant weight obtained for about 48 hrs. Prepared SD were crushed, pulverized and sifted through mesh no. 60 and stored in desiccators [6].

Characterization of solid dispersions:

Determination of drug content:

The percent drug content of each SD was determined as, powder equivalent to 10mg CP was dissolved in a minimum amount of methanol and the volume was made up to 100 ml using 0.1N HCL. The solution then filtered through Whattman filter paper, required dilution being made and the assay of drug content was done by using UV double beam spectrometer at 263 nm.

***In-vitro* dissolution studies:**

In-vitro dissolution studies of SD were carried out in USP type 2 dissolution apparatus with three replicates, the rotation speed of paddle was 75 rpm using 900ml of 0.1 N HCL as dissolution medium and the temperature maintained at 37 ± 0.5^0C, 5 ml of sample was withdrawn at 5 min interval upto 1 hr, filtered the sample using 0.45 mm Whatman filter paper, and replaced with an equal volume of fresh medium to maintain constant volume. The samples were analysed by using UV/Visible spectrophotometer at 263nm [7].

TABLE 1: *IN VITRO* DISSOLUTION PROFILE OF FORMULATIONS

Time (min)	Formulation code								
	Pure drug	SD2	PM2	SD4	PM4	SD6	PM6	SD8	PM8
5	5.586	9.310	7.448	9.931	7.448	11.793	8.690	13.655	6.828
10	10.552	21.103	14.276	16.759	17.379	19.862	15.517	26.690	16.759
15	13.034	37.862	21.103	37.241	25.448	38.483	24.207	36.000	21.724
20	17.379	46.552	34.138	45.931	36.621	49.034	36.621	44.690	40.345
25	20.483	57.103	42.828	55.241	44.690	55.241	40.345	60.828	49.034
30	23.586	67.034	55.862	69.517	60.207	75.724	60.207	75.103	55.241
35	28.552	72.000	61.448	76.345	65.172	78.828	65.172	78.207	61.448
40	31.635	78.828	65.793	79.448	68.276	80.069	70.759	83.172	68.276
45	35.379	83.172	73.241	83.172	71.379	82.554	73.862	87.517	71.379
50	37.862	88.759	75.103	86.276	76.345	86.276	74.103	89.379	73.868
55	39.724	89.379	76.966	88.759	76.966	90.621	77.580	91.241	75.103
60	42.209	91.241	79.448	92.483	78.828	92.483	78.207	94.660	76.345

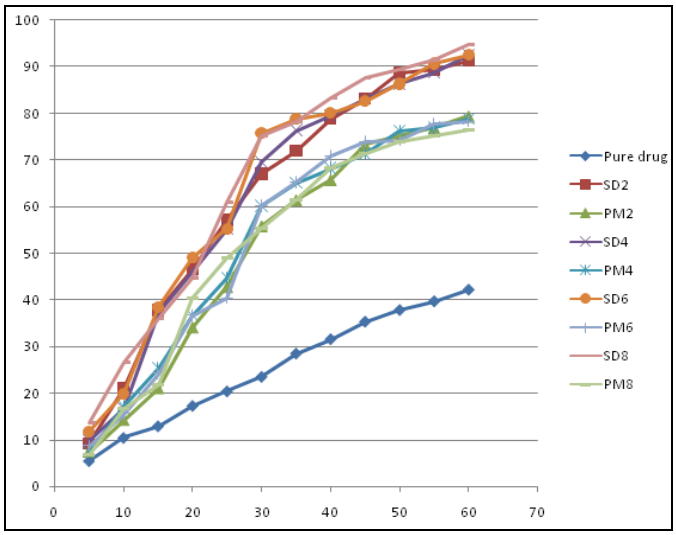


FIG.1: DISSOLUTION CURVE OF PURE DRUG AND ITS SOLID DISPERSION (SD) AND PHYSICAL MIXTURE (PM) OF FORMULATION BATCHES

The dissolution curves CP, PM and SD are shown in above figures, proves that the solid dispersion technique has improved the dissolution rate of CP to a greater extent.

Preparation of Floating Tablets with and without Solid Dispersion:

Optimized batch of solid dispersion was further used for the formulation of floating tablets. HPMC K15M a water soluble polymer was selected as a hydrophilic matrix. The solid dispersion and all other ingredients were individually passed through sieve # 60 and mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. Sodium bicarbonate used as a gas generating agent to decrease the floating lag time and HPMC

K 15M used to retard release rate to obtain prolonged release of the drug up to 8 hrs. The tablets prepared by using direct compression method.

TABLE 2: COMPOSITION OF DRUG AND POLYMER USED IN PREPARATION OF FLOATING TABLETS

Ingredients	Weight (mg/ tablet)
CP/Solid dispersion (powder eq.to 100mg of pure drug)	100
HPMC-K-15M	50
Sodium bicarbonate	45
Magnesium stearate	2.5
Talc	2.5
Microcrystalline cellulose	150
Total	300

Evaluation of Gastroretentive Floating Tablets

Weight variation:

Average weight of twenty randomly selected tablets from each batch was calculated. Then individual weight of each tablet was determined and compared with average weight. The mean ± standard deviation values of weight variation were calculated [8].

Thickness:

Thickness of three randomly selected tablets from each formulation was examined by using Vernier calliper and the mean ± standard deviation values were calculated [9].

Hardness:

Hardness of tablets was measured by using Pfizer type tester. Three tablets were taken from each formulation and average reading was noted [10].

Friability:

Ten pre-weighed tablets were placed in Roche friabilator and operated for 4 min at 25 rpm. After that the tablets were dedusted and reweighed. The percentage friability of tablets was measured as per the following formula [9].

$$\text{Percentage friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity:

In-vitro buoyancy studies:

In-vitro buoyancy was determined by floating lag time by placing tablets were in a 100 ml beaker containing 0.1N HCL. The time required for the tablet to rise and float to the surface -on the surface of the medium was determined as the "total floating time". The mean ± standard deviation values of buoyancy were calculated. [12]

Swelling Characteristics:

HPMC is a hydrophilic polymer which swells on contact with water. The thickness of swollen layer formed around the matrix core. The swelling index was calculated with respect to time. As time increase, the swelling index was increased.

In vitro dissolution study:

In vitro dissolution test was performed on USP type 2 test apparatus. The drug release study was carried out in 900 ml of 0.1 N HCL dissolution media, maintained at 37±5ºC and agitated at 50 rpm for 12 hrs. 5ml of sample were withdrawn periodically and filtered through whatman filter paper and the samples were replaced by equivalent volume of dissolution media. The absorbance of Cefpodoxime proxetil was measured at 263 nm by using UV/Visible spectrophotometrically [13].

TABLE 3: EVALUATION PARAMETERS OF TABLETS

Parameters	OPT-B	CP
Hardness(kg/cm^2)	7.8	7.1
Friability (%)	0.56	0.43
Thickness(mm)	4.21	4.32
Wt. Variation(gm)	293.65	291.30
Drug content (%)	95.78	95

TABLE 4: *IN VITRO* BUOYANCY STUDIES

Floating lag time (min.)	Total floating time(hr.)
6.5	9
5.9	8

TABLE 5: PERCENT SWELLING INDEX OF FLOATING TABLETS

Time (hrs.)	% Swelling index OPT-B	% Swelling index CP
1	29.00	27.01
2	41.66	38.33
3	59.00	57.66
4	66.33	64.12
5	67.66	65.33
6	74.33	72.66

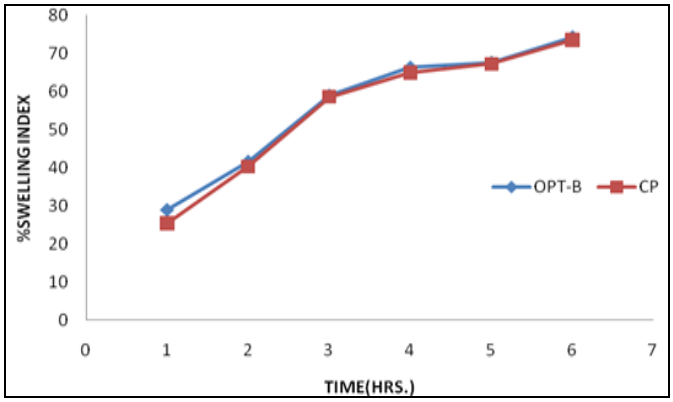


FIG.2: PERCENT SWELLING INDEX OF FLOATING TABLETS

TABLE 6: CUMULATIVE PERCENT DRUG RELEASED (%CDR) FROM FLOATING TABLETS WITH SD (OPT-B) AND WITHOUT SD

Time (min)	OPT-B	CP
60	19.21	12.31
120	26.90	12.31
180	34.13	29.69
240	41.58	34.64
300	49.03	42.06
360	54.62	4.67
420	63.93	55.99
480	75.10	69.98
540	88.13	80.10
600	96.82	87.13

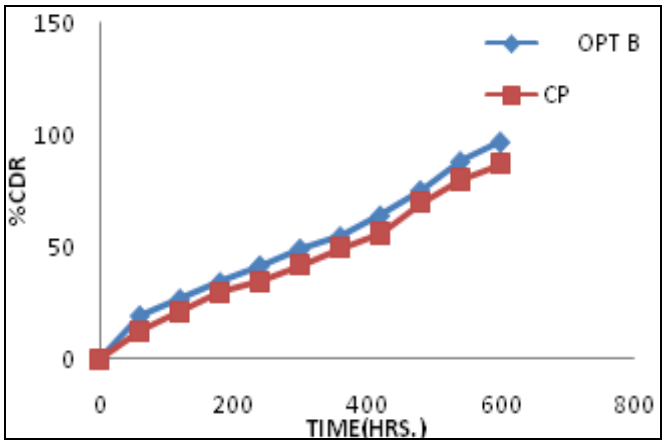
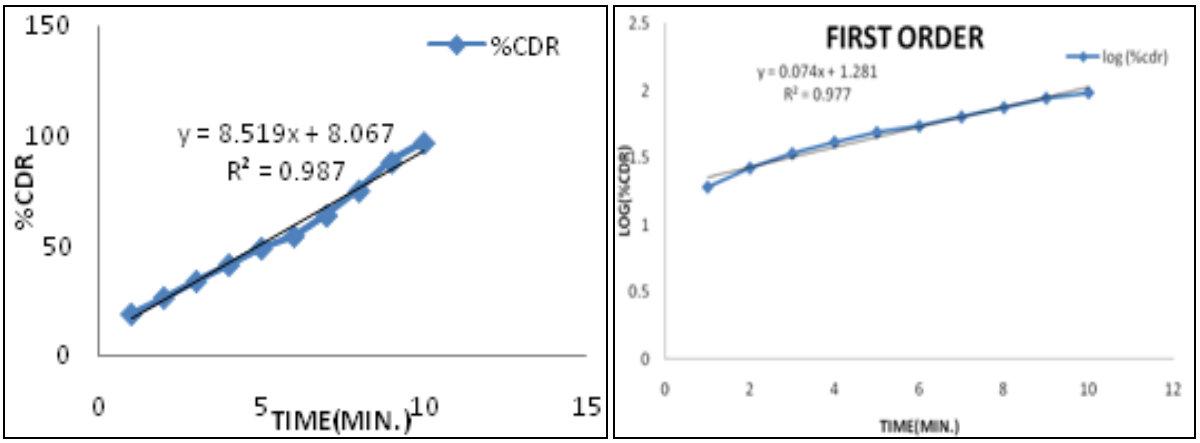


FIG.3: GRAPHICAL REPRESENTATION OF PERCENT CUMULATIVE DRUG RELEASE FROM TABLETS WITH SD AND WITHOUT SD



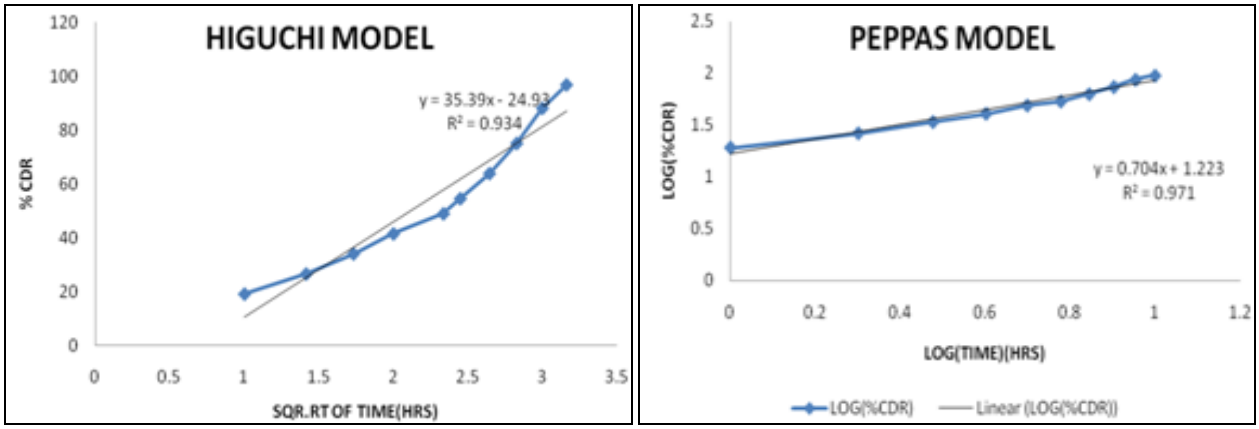


FIG.4: GRAPHICAL REPRESENTATION OF IN-VITRO RELEASE DATA OF OPTIMIZED FORMULATIONS CODE OPT-B: ZERO ORDER, FIRST ORDER KINETICS, HIGUCHI MODEL AND KORSMEYER PEPPAS MODEL

TABLE 7: VALUE OF R^2 OBTAINED FROM DIFFERENT KINETIC MODELS

Formulation Code	R^2			
	Zero Order	First Order	Higuchi Model	Korsmeyer Peppas Model
OPT-B	0.987	0.977	0.934	0.971

From the results of data fitting to various models, it was found that the optimized batch OPT-B showed zero order kinetics of drug release, i.e. mechanism followed for the drug release from the cefpodoxime proxetil floating tablets was Non- fickian diffusion as value of n is 0.74.

REFERENCES:

1. Sharma D, Soni M, Kumar S, Gupta GD: Solubility enhancement – eminent role in poorly soluble drugs. Research Journal Pharm and Tech, 2009; 2: 220-224.
2. Nayak AK, Maji R and Das B: Gastroretentive drug delivery systems- A review. Asian Journal of Pharmaceutical and Clinical Research. 2010; 3(3): 2-10.
3. Singh B, Kumar R, Ahuja N: Optimizing drug delivery systems using systemic design of experiments Part I: Fundamental Aspects. Critical Reviews in Therapeutics Drug Carrier Systems. 2004; 22:27-105.
4. Kamalakkannan V, Kannan C, Jaganathan K, Kumaran Arul KSG and Sambath Kumar R: Gastro retentive drug delivery system for Cefpodoxime proxetil development and optimization. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013; 4(2): 1150- 1167.
5. Swidan SA, Ghonaim HM, Ghorab MM and Samy AM: Design, formulation and evaluation of Piroxicam capsules prepared by solid dispersion technique. British Journal of Pharmaceutical Research, 2013; 3(1): 108-134.
6. Jahan T, Khan MSR, Moniruzzaman M: Enhancement of dissolution profile for oral delivery of Fexofenadine Hydrochloride by solid dispersion (solvent evaporation) technique. American Journal of Scientific and Industrial Research, 2011; 2: 112-115.
7. Tiwari G, Tiwari R: Development and optimization of multi-unit solid dispersion systems of poorly water soluble drug. Research Journal of Pharmacy and Technology, 2008; 1:444-449.
8. Menon A, Ritschel WA, Sakar A: Development and evaluation of monolithic floating dosage form for furosemide. Journal of Pharmacy Research, 1994; 83: 239-45.
9. Karkhile VG, Karmarkar RR, Sontakke M A, Badgujar S D, Nemade LS: Formulation and evaluation of floating tablets of furosemide. International Journal of Pharma Research and Development, 2010; 1(2): 1-9.
10. Vidyadhara S, Babu JR, Sasidhar RLC: Formulation and evaluation of glimepiride solid dispersions and their tablet formulations for enhanced bioavailability. Pharmanest – An International Journal of Advances in Pharmaceutical Sciences, 2011; 2:15-20.
11. Dave BS, Amin AF, and Patel MM: Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and *in vitro* evaluation. American Association of Pharmaceutical Scientists, 2004; 5(2): Article 34.
12. Castellanos MRJ, Zia H, and Rhodes CT: Design and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. International Journal of Pharmaceutics, 1994; 105: 65-70.
13. Sharma N, Jain N, Sudhakar CK and Jain S: Formulation and evaluation of gastroretentive floating tablets containing Cefpodoxime proxetil solid dispersions. International Journal of Current Pharmaceutical, 2012; 4(4): 82-87.

How to cite this article:
Saini N, Kumar R, Yadav M and Saroha K: Formulation, Optimization & Evaluation of Solid Dispersion Based Gastroretentive Floating Tablets of Cefpodoxime Proxetil. Int J Pharm Sci Res 2016; 7(4): 1734-39.doi: 10.13040/IJPSR.0975-8232.7(4).1734-39.