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Original Research Paper

PREPARATION AND IN VITRO CHARACTERIZATION OF NON EFFERVESCENT FLOATING DELIVERY SYSTEM OF CEFPODOXIME PROXETIL

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ABSTRACT

The purpose of this study was to evaluate the potential for floating drug delivery system (FDDS) of cefpodoxime proxetil chosen as model drug with an aim to prolong the gastric resident time of floating dosage form as well as increase total floating time. Direct compression method was used for preparation of floating tablets. The prepare formulation were evaluated for various parameters like hardness, thickness, average weight, floating lag time, total floating time, drug content, % cumulative drug release. In preliminary batches 3 polymers were used in combinations, from the obtained evaluation data of preliminary batches polymers (Plasdone S 630 & WSR 303) were selected for further factorial design batches, from the evaluation parameter data, tablets of all batches complied with the mass variation requirement of Indian Pharmacopoeia and here no batch variation > 5% of average weight which indicates that consistency in the preparation of the tablet having minimum batch to batch variation. There was proper distribution of the drug in the floating matrix tablets according to results of drug content analysis and well within the range of 95.95 -102.39 % of the total amount of the drug added in floating matrix tablets. Total floating time required by tablet was > 12 hrs and floating lag time was noted within 2-4 hr. It was concluded that formulation of cefpodoxime proxetil had potential application as antibiotic for sustained delivery of drug following in oral administration.

Keywords: Floating drug delivery system, Total floating time, Cefpodoxime proxetil, Floating lag time, Floating matrix tablets

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve and maintain therapeutic concentration within range and to show pharmacological action with minimum incidence of adverse effects. To achieve this goal one should maintain dosing frequency and suitable route of administration. There are so many routes used including oral, nasal, topical, parenteral, vaginal, rectal, ocular etc. Out of these routes, oral administration is the most convenient from any of drug delivery to the systematic circulation. It achieves improved therapeutic advantages, such as ease of dosing administration, patient compliance. The development process is affected by several physiological difficulties, such as highly variable nature of gastric emptying process. Improved bioavailability.[1,2] Oral sustain release dosage forms deliver drug for longer period of time and help to produce therapeutic effect for more than 12hr for those drugs which are having low plasma halflife.[3] Drugs that have narrow absorption window in the GIT (gastro intestinal tract) will have poor poor absorption.[4,5] The FDDS is advantageous for these drugs, gastroretentive dosage forms help in maintenance

of constant therapeutic levels for prolong period, increase therapeutic efficacy and decrease dose administration. FDDS has low density than gastric fluid so remain float in gastric fluid and show sustained drug release.[6] The FDDS is advantageous for drugs meant for local action in the stomach, E.g. Antacids. Patients should not take floating dosage forms just before going to bed because there are chances of gastric reflux.[7, 8] Cefpodoxime proxetil is a broad spectrum third-generation cephalosporin, which reveals potent antibacterial activity against both Gram-positive and Gram-negative bacteria, and high stability in the presence of beta-lactamase. Low concentrations of cefpodoxime inhibit most respiratory pathogens. This drug has very good in vitro activity against Enterobacteriaceae, Hemophilus spp. and Moraxella spp., including beta-lactamase producers and many strains resistant to other oral agents. It also has activity against Gram-positive bacteria, especially against streptococci. It has no activity against enterococci. It is one of the first third-generation cephalosporins to be available in oral form. It is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections.[9,10] Cefpodoxime proxetil have short half life and will have poor absorption. By formulating with floating drug delivery system, it remains longer time in gastro intestinal tract and improves bioavailability of drug.[11]

MATERIALS AND METHODS

Materials

Materials used in present investigation were Cefpodoxime proxetil (Zenith Pharma, Ahmedabad, India), Plasdone S630 (Ashland India limited, Kondapur, Hyderabad), Poloxamer 188 (BASF, India), WSR 303 (Dow Chemicals India, Mumbai, Maharashtra), Microcrystalline Cellulose (FML biopolymer India), Talc and Magnesium stearate (Signet Chemical Corporation, Mumbai, Maharashtra).

Preparation of Floating Tablets

Direct compression technique used to prepared tablet. Cefpodoxime proxetil was mixed with different excipient according to formulation. Then powder blend was lubricated by adding mg (magnesium) stearate and compressed on tablet punching machine. To maintain constant tablet weight as well as to counter balance the poor water solubility of drug, water soluble filler micro crystalline cellulose (MCC) was used. Prepared tablets were compressed to get hardness within range of 5-7 Kg/cm^2.

Solubility Enhancement Techniques of Cefpodoxime Proxetil

- As such drugs: Weighed 100 mg of cefpodoxime proxetil and transferred in 250 ml beaker. Add 250 ml 0.1N HCL. Than sample was kept in sonicator for 12 hrs.
- Micronization: Reduction in particle size of drug by passing it through 100# having 149 micron particle size. Weighed 100 mg drug and dissolved in 0.1 N HCL using sonicator.
- Using surfactant: Weighed equal amount of SLS and drug. Weighed 100 mg of drug and add 100 mg of SLS. Transferred it in 250 ml beaker and mixed it well. Add 250 ml of 0.1N HCL and kept it into sonicator.
- Using Solid dispersion: Poloxamer was used as a carrier for solid dispersion with the different ratio of drug and poloxamer like 1:0.5, 1:1, 1:2.

According to results of solubility of these all techniques, solid dispersion gave better solubility so it was taken further for formulation development.

Evaluation of Prepared Tablets

a) Thickness

Tablet thickness was measured using vernier caliper. Ii is expressed in millimeter.[12]

b) Hardness

The hardness of core tablets was measured using Monsanto Pfizer.[12]

c) Friability

6.8 gm weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed.[12]

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

% F = {1-(Wt/W)} ×100

Where, % F is friability in percentage, W is the initial weight of tablet and Wt is the final weight of tablets after revolutions. Values of friability of 1 % are considered as an acceptable.

d) In Vitro Buoyancy Study

Floating lag time is the time taken by the tablet to emerge onto the surface of the dissolution medium after adding to simulated gastric fluid. The time taken by the tablet to raise to the surface of the dissolution media and time taken for it to sink was noted, the difference of which gives the duration of buoyancy.[13]

e) In Vitro Drug Release Study

In vitro release study of cefpodoxime Proxetil were evaluated using a USP dissolution testing apparatus type 2 (paddle method) at 37±0.5 °C with rotation speed of 75 rpm in 900 ml of 0.1 N hydrochloric acid buffer for 12 hr. From this, 5 ml of the dissolution medium were withdrawn at regular time intervals, replaced with an equal volume of fresh dissolution fluid then analyzed for the drug content using UV-Vis spectrophotometer at 254 nm.[14]

f) Drug Content

Equivalent to 100 mg of cefpodoxime Proxetil was taken and transferred to 100 ml volumetric flask, dissolved and diluted with pH 0.1 HCl buffer. The absorbance of the resulting solution was measured at the λmax of 254 nm using a UV spectrophotometer after filtration through whatmann filter paper. The drug content was calculated using equation given below[12]:

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

g) Weight Variation

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight.[12]

% Deviation = Avg. weight of tablet–Individual tablet weight/Avg. weight of tablet×100

h) Stability Study

To determine the change in performance of dosage form on storage, stability study was carried out for 1 month at 40° C in a humidity jar having 75% RH according to ICH.[15]

RESULTS

1) Drug-Excipient Compatibility Study

IR analysis of pure drug and drug mixed with excipients of all were done on IR. It was found that all the prominent functional group picks [Alkenes C=C stretching (1669), Aromatic C-C stretching (1527), Aromatic C-C stretching (1373), Aromatic amines CN stretching (1276), Aromatic CH stretching (735)] were observed in physical mixture. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

Table 1: Formulation chart of each Cefpodoxime proxetil floating tablet

Batches	Drug (mg)	Plasdone S 630 (mg)	WSR 303 (mg)	MCC 102 (mg)	Talc (mg)	Mg. stearate (mg)	Total (mg)
F-1	200	112.5	45	83.5	4.5	4.5	450
F-2	200	90	45	106	4.5	4.5	450
F-3	200	67.5	45	128.5	4.5	4.5	450
F-4	200	112.5	67.5	61	4.5	4.5	450
F-5	200	90	67.5	83.5	4.5	4.5	450
F-6	200	67.5	67.5	106	4.5	4.5	450
F-7	200	112.5	90	38.5	4.5	4.5	450
F-8	200	90	90	61	4.5	4.5	450
F-9	200	67.5	90	83.5	4.5	4.5	450

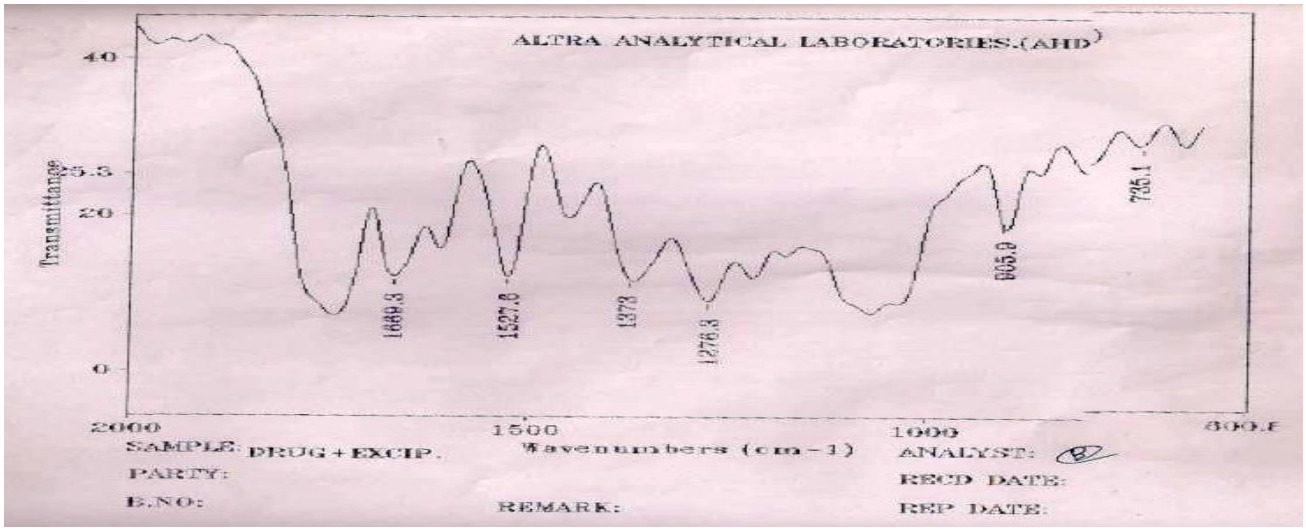

Figure 1: IR spectrum of Drug + Excipients

2) Physico Chemical Characterization of Prepared Tablets

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

Batch code	Hardness (KPascal)	Friability (%)	Thickness (mm)	Weight variation (mg)	Drug content (%)	Duration of buoyancy (h)	Floating lag time (second)
F1	7.83±0.06	0.25±0.03	3.38±0.15	446±0.3	95.95±0.72	>12	3
F2	7.83±0.06	0.22±0.06	3.37±0..12	452±0.4	97.21±0.62	>12	4
F3	7.86±0.06	0.25±0.05	3.39±0.31	448±0.2	98.46±0.88	>12	3
F4	7.87±0.1	0.20±0.04	3.39±0.31	446±0.3	102.39±0.69	>12	3
F5	7.86±0.05	0.26±0.07	3.37±0.21	449±0.2	100.65±0.77	>12	2
F6	7.86±0.05	0.30±0.04	3.38±0.15	451±0.3	98.20±0.73	>12	4
F7	7.90±0.04	0.26±0.05	3.40±0.37	452±0.5	96.47±0.79	>12	2
F8	7.89±0.06	0.30±0.07	3.37±0.25	447±0.4	96.53±0.68	>12	3
F9	7.90±0.05	0.25±0.02	3.38±0.31	445±0.3	98.34±0.62	>12	3

(n = 3*)

3) In Vitro Buoyancy Study

Time taken by the tablet to emerge onto the surface of the dissolution medium after adding to simulated gastric fluid was noted within 2 to 4 seconds. And total floating time required by tablet was > 12 hr.

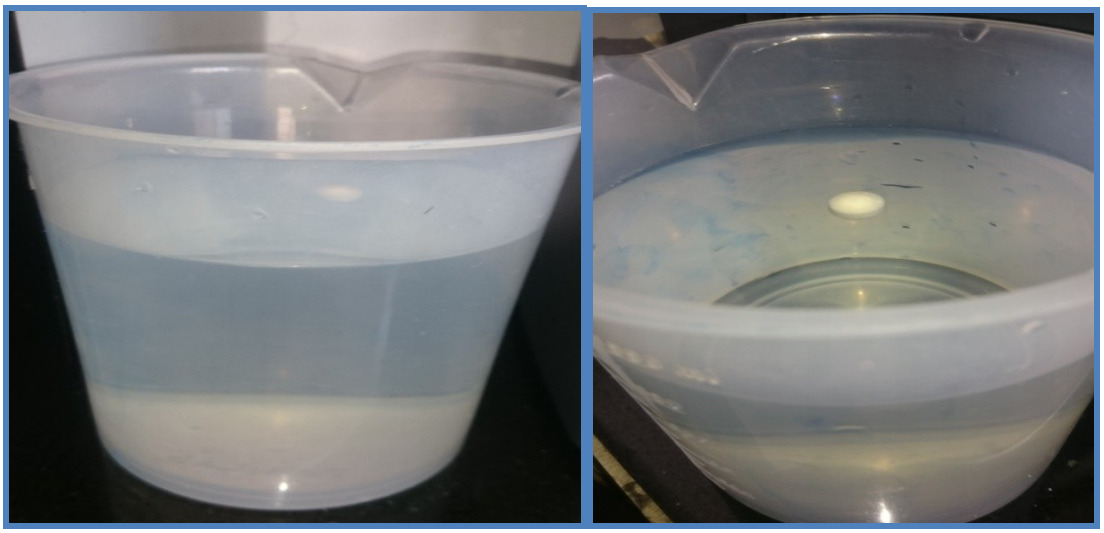

Figure 2: Photographs of in vitro floating behavior of floating tablet

4) In Vitro Release Study

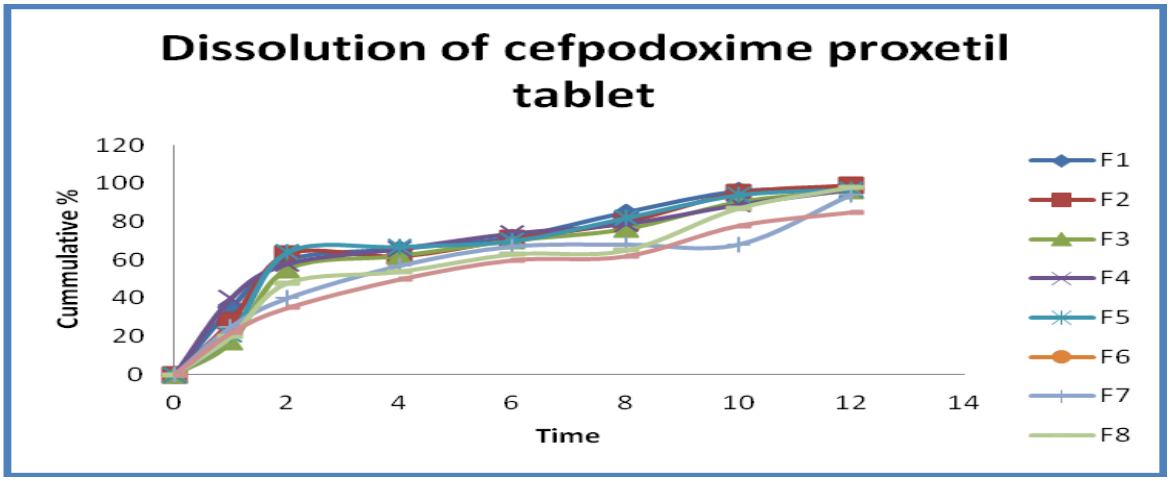

Figure 3: In vitro drug release profile of cefpodoxime proxetil from floating tablet formulations

Table 3: Kinetic treatment of dissolution profile

Batch No.	Multiple R	Slope	Intercept
F1	0.980215693	27.37325415	8.038660821
F2	0.972676492	27.67536827	5.797404278
F3	0.972676492	27.67536827	5.797404278
F4	0.977661029	25.75511443	10.33936439
F5	0.96153187	28.05119789	4.655781878
F6	0.98155412	26.91584133	0.471697757
F7	0.977585702	24.50211294	2.395254023
F8	0.979124521	26.90430154	-0.50476322
F9	0.995421316	24.22751709	-0.41962159

Table 4: Results of tablet evaluation for the factorial design batches

Std	Run	Factors		Response	
		Plasdone S 630 (%)	WSR 303 (%)	Floating lag time (sec)	Dissolution (%)
1	2	15	10	3	85
2	3	20	10	4	80
3	8	25	10	3	76
4	4	15	15	3	79
5	1	20	15	2	82
6	6	25	15	4	71
7	9	15	20	2	68
8	5	20	20	5	65
9	7	25	20	9	62

Table 5: Result of optimized formula

Factor	Concentration(%)	Floating lag time(sec)	Dissolution at 8 hrs(%)
Plasdone S 630	16	2.5	71.155
WSR 303	19		

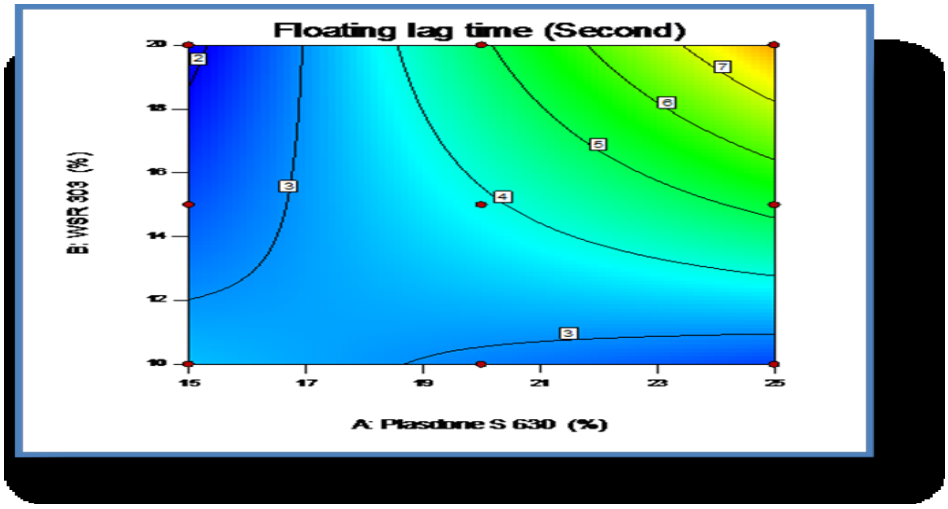

Figure 4: Contour plot for Floating lag time (R_1)

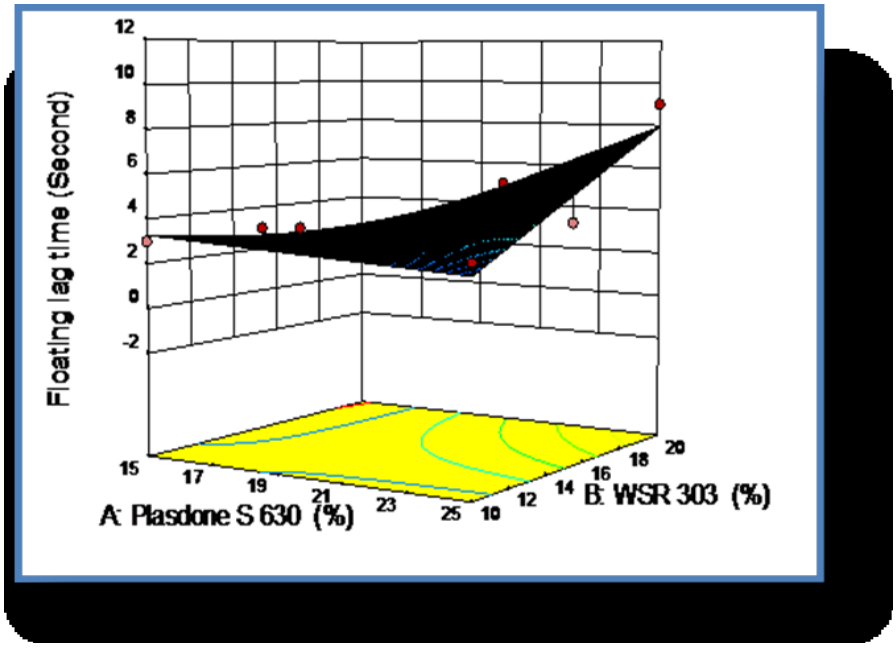

Figure 5: Response surface plot for Floating lag time (R_1)

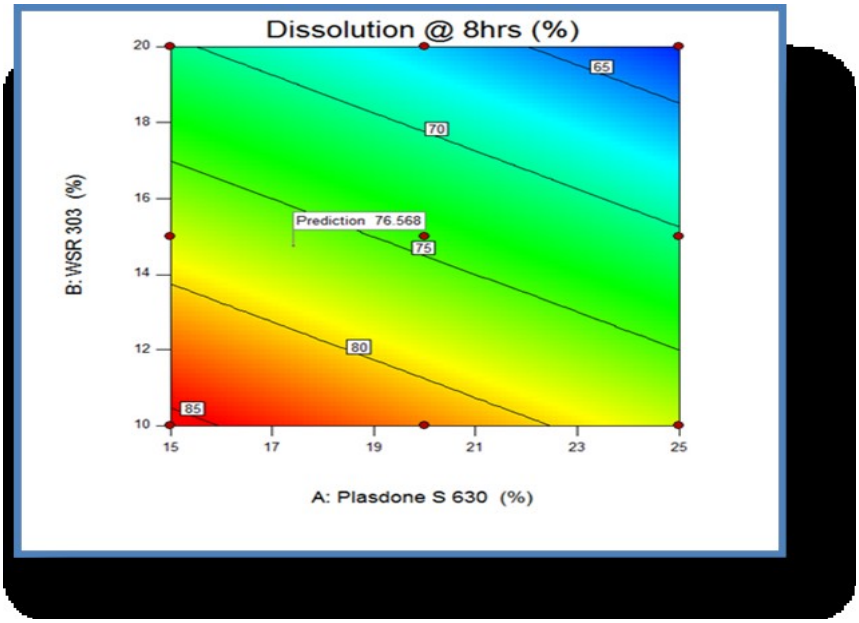

Figure 6: Contour plot for Dissolution at 8 hrs (R_2)

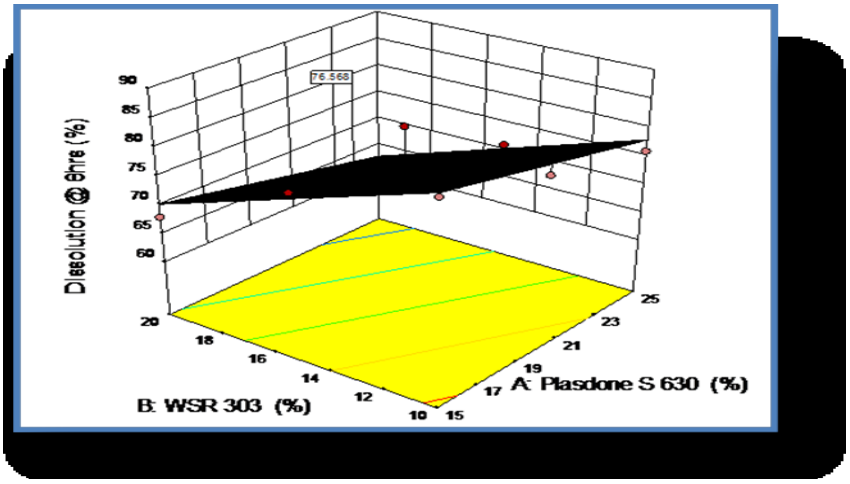

Figure 7: Response surface plot for Dissolution at 8 hrs (R_2)

5) Stability Study

The tablets were stored for 1 month at 40˚C/ 75% RH. The result do not show any significant change in physical appearance, buoyancy and dissolution behavior of floating tablets in comparison with initial values. Similarity factor f2 was found to be 83%.

DISCUSSION

The angle of repose was found to be in the range of 20.21 to 27.24 having excellent or good flow property. Bulk density were found to be in the range of 0.28 to 0.32 and tapped density were found to be in the range of 0.34 to 0.41. Hausner's ratios of preliminary trials were found to be in the range of 1.21 to 1.33 having moderate flow property. Carr's index were found to be in the range of 16.67 to 25 having passable flow property. The thickness all tablets was found to be in the range of 3.37 to 3.40mm. Sufficient strength of all tablets was also evident since the friability was less than 1%, indicating compliance with the requirements of Indian pharmacopeia. Hardness of tablets were found to be between 7.83 to 7.90 K Pascal indicated good strength. The average weight of the prepared tablets were in the range of from 445 to 452 mg. Tablets of all batches complied with the mass variation requirement of Indian Pharmacopoeia, here no batch variation > 5% of average weight which indicates that consistency in the preparation of the tablet having minimum batch to batch variation. There was proper distribution of the drug in the floating matrix tablets according to results of drug content analysis and well within the range of 95.95 -102.39 % of the total amount of the drug added in floating matrix tablets so, comply with the pharmacopoeial limit. Total floating time required by tablet was > 12 hrs and floating lag time was noted within 2-4 min. Compatibility study performed with various excipients, the physical attributes of the tablet were found to be satisfactory. Then the solubility enhancement of cefpodoxime proxetil was successfully done using solid dispersion technique with different ratio of poloxamer. Then the dosage form was formulated using direct compression technique. Results for other physical evaluations were also found to be within the limit. The release of the drug was found to be directly proportional to the concentration of WSR 303 and Plasdone S 630. It was found that drug release to be depending on equal concentration of Plasdone S 630 and WSR 303. Optimization of tablet formulation using 3^2 factorial designs was carried out. There were two response considered in factorial design, floating lag time and dissolution at 8 hr. Analysis of variance carried out for this 2 responses. 2 factor interaction model selected for response 1 and linear model selected for response 2. Contour graph and 3D surface graph of these two responses created after choosing model. Optimized batch find out using software design expert 10 and floating buoyancy study as well as dissolution study carried out of optimized batch. Stability study of optimized batch was carried out at 40Ċ in a humidity jar having 75% RH specified by ICH. The floating lag time was found to be 4

sec and total floating time was found to be more than 12 hr. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance of tablets

CONCLUSION

The present study was aimed to develop prolong release stable, pharmaceutically equivalent formulation of cefpodoxime proxetil using polymers Poloxamer 188 and WSR 303 and optimized by 3^2 full factorial design. Formulation of cefpodoxime proxetil had potential application as antibiotic for sustained delivery of drug following in oral administration. Cefpodoxime proxetil have short half life and will have poor absorption. By formulating with floating drug delivery system, it remains longer time in gastro intestinal tract and improves bioavailability of drug. Being class-IV drug, for successful formulation drug should get solubilized 1^{st} to get absorbed. So trial will be made to get solubilized in stomach, so that it can get absorb in stomach and can provide quick action for longer period of time. For this drug, different tools were used for solubility enhancement and will prove it. After improving solubility, it will be formulated as floating drug delivery system. So it can remain in stomach for longer period of time and sustain release can be achieved.

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