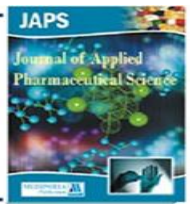
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 05-12-2011
Revised on: 10:12:2011
Accepted on: 28-12-2011

Gastro-Retentive Floating Matrix Tablets of Cefpodoxime Proxetil

K. Sreenivasa Rao, Rakesh R. Vairagkar, Dattatreya B. Udgirkar, Praveen S. Patil and Karnakumar V. Biradar

ABSTRACT

The present work aims at the development and evaluation of Floating matrix tablets of Cefpodoxime Proxetil were undertaken to prolong gastric residence time. A visible Spectrophotometric method has been employed for the estimation of Cefpodoxime Proxetil at 263 nm and Beer's law is obeyed in the concentration range of 5-40 µg/ml. Total 7 formulations (B1-B7) were prepared using guargum with carbopol 934P was used in different concentrations. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as hydroxy propyl methyl cellulose (HPMC K4M), guargum and carbopol 934P in different combinations with other standard excipients like sodium bicarbonate and lactose. Tablets were evaluated for physical characterization viz. hardness, friability, swelling index, floating capacity, thickness and weight variation. Further tablets were evaluated *in-vitro* drug release for 12 hr. The effect of polymer concentrations on buoyancy and drug release pattern was also studied. *In-vitro* drug release mechanism was evaluated by PCP V-3 software. Carbopol 934P had a negative effect on the floating properties also decreased the drug release. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer concentrations. The entire matrix tablets showed significantly greater swelling index, exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than12 hr. The paddle speed affected the floating lag time and floating duration it had a negative effect on the floating properties. The optimized formulation followed the higuchi release model and showed non-fickian diffusion mechanism. It also showed no significant change in physical appearance, drug content, floatability or *in-vitro* dissolution pattern after storage at 45 ^{o}C at 75 % RH for three months.

Keywords: Cefpodoxime Proxetil; swelling index; floating capacity; Guargum; HPMC, Carbopol 934P

K. Sreenivasa Rao, Rakesh R.Vairagkar, Dattatreya B. Udgirkar, Praveen S.Patil and Karnakumar V.Biradar
Department of Pharmaceutics, RRKS,s College of Pharmacy, Bidar-585401,(Karnataka), India

For Correspondence
K. Sreenivasa Rao, Rakesh R.Vairagkar, Dattatreya B. Udgirkar, Praveen S.Patil and Karnakumar V.Biradar
Department of Pharmaceutics, RRKS,s College of Pharmacy, Bidar-585401,(Karnataka), India.

INTRODUCTION

Oral route is the most convinient and extensively used route for drug administration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS). Controlled release drug delivery system release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This helps in achieving predictable drug plasma concentration required for therapeutic effect. A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation (Chawla et al, 2004 and Kawashima et al.200). Cefpodoxime proxetil is a third generation cephalosporin prodrug, having a white to light brownish white powder, odourless, slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in acetonitrile & in methyl alcohol which is administered orally. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%.

Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil (Arora et al., 2005) The half life of cefpodoxime proxetil is 2.2 hours. Cefpodoxime proxetil is a β lactum antibiotic. Its action is by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes.

MATERIALS AND METHODS

Cefpodoxime proxetil was procured as gift sample from Okasa Pharmaceuticals, Satara. HPMC obtained by Colorcon Asia Ltd, Goa. Guar gum, NaCMC was purchased from S.D. fine chemicals Mumbai. All other solvents and reagents were used of analytical grade.

Formulation of Floating Tablet

Each floating tablets containing 200 mg Cefpodoxime Proxetil were prepared by direct compression method. Cefpodoxime pure drug was mixed with required quantity of HPMC K4M, guargum, carbopol 934P, sodium bicarbonate and lactose by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2min.The lubricated blend was compressed into tablets using 12 mm flat-face round tooling on CLIT Pilot Press rotary tablet machine (Rowe et al.2003). Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4.0 mm tablet thickness (Table no.1).

Table 1: Composition of floating tablets of cefpodoxime proxetil.

Ingredient (mg)	B1	B2	B3	B4	B5	B6	B7
Proxetil	200	200	200	200	200	200	200
HPMC K4M	100	100	100	100	100	100	100
Guar Gum	45	40	35	30	25	20	15
Carbopol 934P	20	20	20	20	20	20	20
Lactose	94	99	104	109	114	119	124
Sodium bicarbonate	85	85	85	85	85	85	85
Magnesium stearate	6	6	6	6	6	6	6
Total weight of tablets	550	550	550	550	550	550	550

Evaluation of Granules

The angle of repose of Cefpodoxime Proxetil was determined by fixed funnel method (Banker GS et al., 1990).The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder**.**

Compressibility Index

The Carr's index (%) and the Hausner ratio were calculated using following equations (Chavanpatil.M.D ey al 2006).

$$Carr's\ Index = \frac{TBD - LBD}{TBD} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{TBD}}{\text{LBD}} \times 100$$

Evaluation of Tablets

Physical properties like Weight variation, Hardness, Thickness, Friability and Drug content of tablet performed (Table No.2).

Thickness

Thickness of tablets was determined using Vernier caliper. Three tablets from each batch were used, and average values were calculated.

Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

Drug content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 263 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 263 nm (Borkar et al., 2010).

Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets} \times 100}{\text{Initial wt. of tablets}}$$

Determination of swelling index

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37 ± 0.5 ^{0}C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain.Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation shows relationship between swelling index and time (Anilkumar et al., 2010).

$$WU\ \% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet} \times 100}{\text{nitial weight of the tablet}}$$

In Vitro drug Release

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for 12 h in 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Cefpodoxime Proxetil was measured spectrophotometrically at 263 nm.

Buoyancy determination

The buoyancy test of tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at 37±0.5°C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation (Sangekar et al., 1987).

RESULTS AND DISCUSSION

The reported melting point values for cefpodoxime proxetil was in the range of 160^0c.The observed melting point ranged between 155-160^0c. The absorption maxima of the standard solution were scanned between 200-400 nm regions on shimazdu 1800 spectrophotometer. The absorption maxima were found to be 263 nm. Infrared spectrum shows all prominent peaks of cefpodoxime proxetil.IR spectrum indicated that characteristics peaks belonging to measure functional group such as principle peak at wave number 2937.04,2984.39,3330.81,1618.05 and 1638.19cm^{-1}.The major IR peaks observed cefpodoxime proxetil were 2937.04(C-H), 3330.81(N-H), 1638.19(C=N),1074(C-O), 1761(C=O), 1274(C-N), 1375(C-H) (Fig.1).

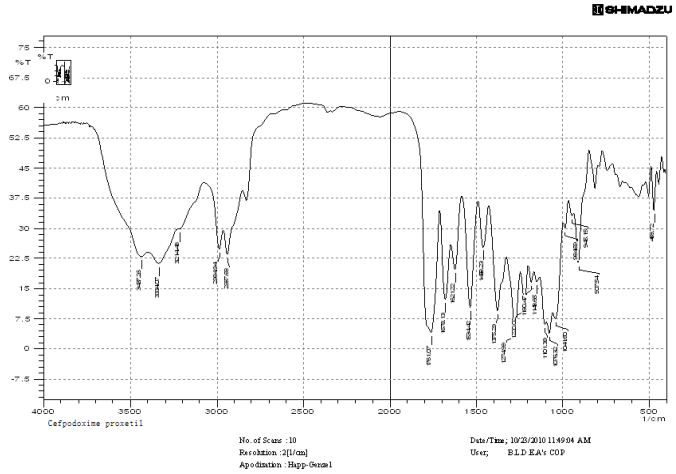


Fig.1: IR spectrum of cefpodoxime proxetil.

The infrared spectrum of physical mixture of polymers (HPMC K4M) and cefpodoxime proxetil was studied and confirmed that there is no interaction with each other. The spectra showed all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional group such as principle peaks at wave no. 2941.53, 2984.33, 3332.64, 1623.67 and 1628.19. (Fig.2).

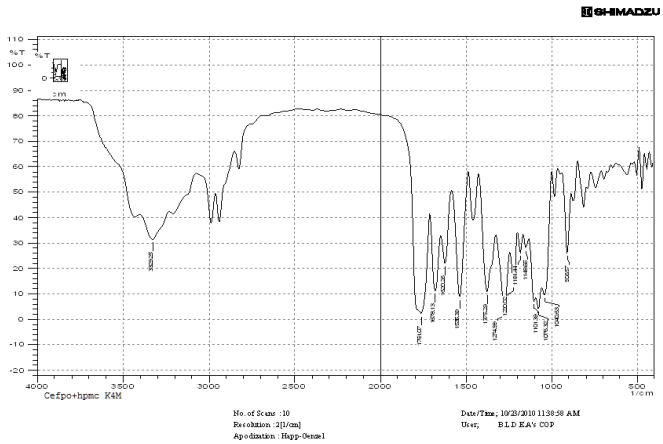


Fig.2: IR spectra of mixture of Cefpodoxime proxetil + HPMC K4M (2:1).

Hence it can be concluded that there were no any significant changes and behavior in the physical mixture of cefpodoxime proxetil and HPMC K4M. DSC thermogram of cefpodoxime shows endothermic peak at 159^0c.where as HPMC K4M shows melting endothermic at 34.40^0c.shown in (Fig.3).

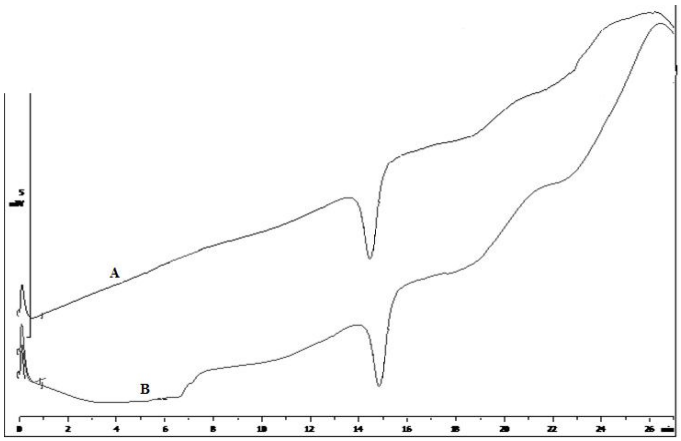


Fig.3: DSC thermograms (A) cefpodoxime proxetil (CP) (B) CP+HPMC K4M + sodium bicarbonate.

All formulation of tablets from batch B1 to B7 was evaluated for thickness and diameter by vernier caliper. Thickness and diameter was in range of 3.90 ±0.04 to 4.20±0.04.The hardness was in range of 7.0±0.23 to 9.2±0.40kg/cm^2,which was measured on Monsanto hardness tester. Drug content release was in the range of 96.38±0.12 to 107.73±0.13 shown in (Table 2). The percentage drug release was found 50% after 7 hrs. For all batch B1-B7 after 12 hrs. It shows 79% drug release (Table 3.)

The swelling index was calculated with respect to time. As time increase, the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration, later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed (Table no.4).

Table 2: Physiochemical Properties of Cefpodoxime Floating Tablets.

Batch code	Average wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
B1	560	3.85 ± 0.07	12.10 ± 0.03	9.2± 0.03	0.75±0.045	103.36 ± 0.14
B2	545	3.90 ± 0.04	12.07 ± 0.05	7.1± 0.02	0.76±0.054	107.73 ± 0.13
B3	550	4.10 ± 0.05	12.01 ± 0.07	7.6± 0.07	0.80±0.066	106.28 ± 0.10
B4	565	4.20 ± 0.06	12.21 ± 0.04	8.1± 0.06	0.72±0.042	98.68 ± 0.20
B5	555	3.90 ± 0.03	12.04 ± 0.06	8.3± 0.05	0.71±0.080	99.38 ± 0.21
B6	540	4.00 ± 0.05	12.02 ± 0.03	7.0± 0.02	0.91±0.044	101.58 ± 0.20
B7	550	4.25 ± 0.04	12.05± 0.07	7.7± 0.06	0.70±0.065	104.48 ± 0.20

All values are expressed as mean ± SD. F= Formulation code.

Table 3: Dissolution Drug Release Data Of B1 To B7 Formulations.

Time (min)	Cumulative % drug release					
	B1	B2	B3	B5	B6	B7
0	0.000	0.000	0.000	0.000	0.000	0.000
30	7.520	5.238	5.786	9.162	6.379	10.714
60	8.794	7.412	7.004	14.643	9.244	22.957
120	15.550	13.704	11.515	21.249	16.139	29.472
180	22.571	20.442	14.544	25.610	22.936	33.148
240	28.171	26.304	19.324	31.546	28.994	36.524
300	31.703	30.282	22.442	34.366	32.211	40.694
360	37.352	36.197	27.265	36.470	35.353	44.795
420	44.674	42.783	31.612	39.178	40.246	49.282
480	51.032	48.081	34.887	41.672	45.028	54.477
540	54.869	52.495	38.179	45.274	47.873	62.026
600	56.581	55.153	42.812	49.578	53.151	68.704
660	64.871	60.196	51.074	58.670	57.271	73.911
720	68.004	64.216	55.503	58.643	59.632	79.053

All values are expressed as mean ± SD, n=3, F=code of formulations.

Table 4: Swelling Index of B1 To B7 Formulation.

Time (min)	% Swelling index						
	B1	B2	B3	B4	B5	B6	B7
0	0	0	0	0	0	0	0
15	44.4	49.01	42.3	47.16	50.98	42.3	38.18
30	51.85	54.9	53.84	56.6	58.82	55.76	52.72
60	66.66	72.54	76.92	73.58	82.35	75	74.5
120	85.16	94.11	92.3	100	103.9	96.15	96.36
180	109.25	113.7	111.53	107.54	127.45	109.61	116.36
240	116.66	127.45	126.92	128.3	147.05	123.07	143.63
300	118	139.21	140.38	141.5	152.94	134.61	147.27
360	127.77	141.17	146.15	145.28	160.78	136	160.45
420	138.88	152.94	151.9	152.8	164.7	150	176.36
480	141	159.33	160	158	172	152	185
540	144.44	168.62	171.15	167.92	180.39	150	188.22
600	151.85	166.66	167.3	150.94	182.23	140	190.72
660	150.64	165	167	147.16	182	135	192.54
720	140	155	150	137	170	130	195

The release rate can be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug. In view of these absorption characteristics, the hypothesis of current investigation is that, if the gastric residence time of cepfodoxime proxetil containing formulation is prolonged and allow floating in the stomach for a long period, the oral bioavailability might be increased. Hence the present research work was to study systematically the effect of formulation variable on the release and floating properties of cepfodoxime proxetil drug delivery system. For floating drug delivery system,the polymers used must be highly swellable in shortest time. Hence, HPMC was chosen as a main swellable polymeric material. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from the dosage form. In order to retain the dosage form in the stomach for a long period of time and to avoid gastric emptying dosage form carbopol 934P was included, the intention of adhering the dosage form to the inner wall of the stomach and also possibly to control the release of cepfodoxime proxetil from the dosage form. Physicochemical evaluation i.e. the prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations. Among all formulations, B7 given the highest floating time as compare to B6,B5,B2,B1,B3 and B4 (Table no.5).

Table 5: Floating ability of b1 to b7 cefpodoxime proxetil formulation.

Batch Code	Floating Lag time (min)	Floating duration (min)	Integrity
B1	Not float	Not float	Intact
B2	Not float	Not float	Intact
B3	Not float	Not float	Intact
B4	40	>720	Intact
B5	Not float	Not float	Intact
B6	5	45	broken
B7	55 sec	>720	Intact

All values are expressed as mean ± SD, n=3, CP= Formulation codes.

REFERENCES

Anilkumar J.Shinde et.al, 'Formulation and evaluation of an oral floating tablet of cephalexin:, International Journal of Pharmaceutical Education and Research. 2010;13:155-59

Arora S ey al. Floating drug delivery systems: A Review. AAPS PharmSciTech. 2005; 6: 47-49

Banker GS, Anderson NR. Tablets. In: Lachman L, Liberman HA, Kanig JL, editors. The theory and practice of industrial pharmacy. 3rd ed. Mumbai (India): Varghese Publishing House. (1990)296-302

Chawla G et al.Gastroretentive drug delivery systems. (2004) In: Jain NK, (eds). Progress in controlled and novel drug delivery system. 1st ed**. (**pp**.** 76-97). New Delhi (India): CBS Publishers and Distributors.

Chavanpatil.M.D, Jain.P, Chaudhari.S, Shear.R, Vavia. P. R. "Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for Ofloxacin". Int J.Pharm. 2006;316: 86–92.

Goodman & Gilman's The Pharmacological basis of therapeutics 10th edition; (1211) 255-57

Kawashima Y et al. Gastrointestinal retentive microparticulate system to improve oral drug delivery. In: Wise DL, editor. Handbook of pharmaceutical controlled release technology. New York: Marcell Dekker Inc (2000) 505-25

Indian Pharmacopoeia. Delhi (India): Controller of Publications 1996; 2:734-36.

Rowe RC, Sheskey PJ, Weller PJ, editors. Handbook of pharmaceutical excipients. 4th ed. New York: Pharmaceutical press; (2003) 354

S.N Borkar et. al, 'An approach to formulate bilayered gastroretentive floating drug delivery system of cefpodoxime proxetil' *International Journal of ChemTech Research* 2010;2: 1229-42

Sangekar S et al. Evaluation of effect of food and specific gravity on tablets on gastric retention time. Int J Pharm 1987; 35:187-91

Srivastava.A. et al,"Oral sustained delivery of Atenolol from floating Matrix tablets-formulatuion and evaluatuion",Drug Develop.and Industrial Pharm.2005;31:367-74.

Wells, J. Pharmaceutical preformulation. Pharmaceutics*: The Science of Dosage Form Design*. M. E. Aulton., Eds.; 3rd, Edinburgh London: Melbourne and New York, (1988) 235-236