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FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF CEFPODOXIME PROXETIL

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ABSTRACT
In the present research work, floating matrix tablets of Cefpodoxime proxetil were developed to prolong gastric residence time and increase drug absorption further increasing the bioavailability. Cefpodoxime proxetil was chosen as a model drug because it is well absorbed from stomach and upper part of small intestine. Absorption profiles in acidic pH make this drug a suitable candidate for formulating it as gastro retentive dosage form for improved bioavailability. Preformulation studies were carried out to optimize the required quantity for HPMC-E15, Locust Bean Gum, Xanthan Gum. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. A total of nine batches of floating tablets of Cefpodoxime proxetil were prepared by direct compression technique, using polymers such as Hydroxypropylmethyl Cellulose (HPMC-E15), Locust bean gum, Xanthan gum in different combinations with other standard excipients like Sodium bicarbonate, Citric acid, Magnesium Stearate and Talc. Tablets were evaluated for physical parameters viz. hardness, friability, swelling index, floating capacity, thickness and weight variation. Further, tablets were evaluated *in-vitro* for drug release up to 9 hr. The effect of polymer concentrations on buoyancy and drug release pattern was also studied. All the matrix tablets showed significantly greater swelling index and exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than 12 hr. The paddle speed had a negative effect on the floating lag time and floating duration. The optimized formulation followed the Higuchi release model and showed non-Fickian diffusion mechanism.

KEYWORDS: Cefpodoxime proxetil, Swelling index, Floating capacity, Locust bean gum, Xanthan gum, HPMC, Controlled release formulation.

1. INTRODUCTION

ORAL DRUG DELIVERY

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Oral delivery can be classified into three categories, immediate release is designed for immediate release of drug for rapid absorption, sustained release pharmaceutical products which are designed on the basis of spansule coating technology for extended absorption and sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained (Vyas and Khar, 2002; Aulton, 2007).

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 (Chien, 2002; Brahmankar and Jaiswal, 2005).

GASTRO-RETENTIVE DOSAGE FORMS

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro-retentive dosage forms (GRDFs). GRDFs can remain in the gastric region for several hours and hence prolong the gastric residence time of drug. GRDFs offer several advantages over immediate release dosage form, including the minimization of fluctuations in drug concentration in plasma, and at the site of action over prolonged periods of time (Chawla et al 2004; Jain, 2004).

Cefpodoxime proxetil is a third generation Cephalosporin prodrug, very slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in

acetonitrile and 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. 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 (Kawashima, 2000; Rao et al 2012).

2. MATERIALS AND METHODS

Materials: The active drug Cefpodoxime proxetil and Xanthan gum obtained from Zeneca Healthcare Haridwar, India. Locust bean gum was purchased from Advance Inorganic, Delhi. All other solvents and ingredients used were of analytical grade.

Methods

Formulation of Floating Tablets: Floating tablets containing 200 mg Cefpodoxime Proxetil were prepared by direct compression method (Lachman et al, 1991). Cefpodoxime was mixed with required quantity of locust bean gum (LBG), xanthan gum, HPMC E15, sodium bicarbonate, citric acid 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 2 min. The lubricated blend was compressed into tablets using single punch. A total of nine batches were prepared with varying composition of excipients (Table 1).

Pre-Compression Parameters

Angle of repose

The angle of repose of Cefpodoxime proxetil was determined by fixed funnel method. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder (Sinko, 2006).

Carr's index: The Carr's index or Carr's Compressibility Index is an indication of the compressibility of a powder. It can be calculated by formula

$$\text{Carr's Index} = \frac{(\text{tapped density} - \text{bulk density}) \times 100}{\text{tapped density}}$$

Hausner's ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It can be calculated by formula

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Thickness: Thickness of tablets was determined using Vernier calipers. Three tablets from each batch were used, and average values were calculated (Indian Pharmacopoeia, 2014).

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 (Borkar et al, 2010).

Drug content: Twenty tablets were crushed and powder equivalent to weight of tablets was dissolved in 0.1 N hydrochloric acid. Then suitable dilutions were made and absorbance at 236 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 236 nm (Indian Pharmacopoeia, 2014).

Hardness: The ability of tablets to resist breakage, under conditions of shipping or 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 (Banerjee and Singh, 2013).

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 (Indian Pharmacopoeia, 2014).

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

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°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 (Deshpande et al, 2014).

$$WU\ \% = \frac{\text{Wt of swollen tablet} - \text{Initial wt of the tablet}}{\text{Initial wt of the tablet}} \times 100$$

Buoyancy determination

The buoyancy test of tablets was studied by placing them in 500 ml beaker containing 0.1 N hydrochloric acid, and then tablets from same batch were placed in dissolution test apparatus containing 900 ml 0.1N hydrochloric acid, 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 (Hilton and Deasy, 1992; Jain et al, 2012).

***In vitro* Release Studies**

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 900 ml of 0.1 N hydrochloric acid for 12 hours. Dissolution medium was 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 236 nm.

3. RESULT AND DISCUSSION

The reported melting point values for Cefpodoxime proxetil was in the range of 112°C-113°C which was in agreement with literature. The absorption maxima of the standard solution was scanned between 200-350 nm regions on Shimadzu 1800 spectrophotometer. The absorption maxima was found to be 236 nm. FTIR study was performed with the supplied sample of Cefpodoxime proxetil. This FTIR spectrum was found concordant with the FTIR of Cefpodoxime proxetil reported in official monograph and the peaks matched with the standard peaks of pure Cefpodoxime proxetil. The infrared spectrum of physical mixture of polymers (Locust bean gum, Xanthan gum) and Cefpodoxime proxetil was studied and confirmed that there was no interaction with each other. The spectra exhibited all the prominent peaks of drug as well as polymer. Hence, it can be concluded that there were no significant changes in the physical mixture of Cefpodoxime proxetil, Locust bean gum and Xanthan gum.

The powder mixtures of all the formulations were tested by various studies including angle of repose (ranging from 26.52° to 39.08°), bulk density (ranging from 0.336 to 0.648 gm/cm^3), tapped density (ranging from 0.484 to 0.797 gm/cm^3), Hausner's ratio (ranging from 1.23 to 1.44) and Carr's index (ranging from 18.69 to 30.57 %). All the results showed moderate flow property (Table 2). The thickness of prepared tablet batches from F1 to F9 was measured by Vernier calipers and was found to vary between 5.68±0.04 to 5.7±0.06 mm. The hardness of formulations F1 to F9 was measured by Monsanto tester and was found to assume values between 5.33±0.47 and 4.66±0.47 kg/cm^2. The friability of all the formulations was measured by Roche friabilator and was found to be in the range of 0.67±0.08 to 0.54±0.07, well within the permissible limits.

The weight variation for different formulations (F1 to F9) was found to be ranging in between 498 to 500 mg, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. Drug content was in the range of 97.18±0.90 to 98.99±0.80. The results of physicochemical characterizations are given in Table 3.

Studies to determine the floating lag time and duration of floating of various formulations were carried out and the results indicated that floating lag time which was observed for all the tablets was within 0-1 minute after immersion into gastric media and duration of floating was greater than 12 hours for all batches (Figure 1, Table 4).

Swelling study was performed on all the batches (F1 to F9) for 9 hours. The results of swelling index are given in Table 5 and the graph between swelling indices against time is plotted in Figure 2. Cefpodoxime floating tablets showed higher swelling index in the first 3 hours but could not maintain up to 9 hours due to continuous erosion of the polymer. Tablets of F4 and F6 formulation showed constant increase in swelling index. Tablets of formulation F9 showed less swelling index at the beginning but was found higher at the end of 8 hours. Among all formulations F1 and F4 showed less swelling index in comparison to other formulations. Formulation F2 showed highest swelling index. From the results, it was concluded that swelling increases as the time passes because the polymer gradually absorbs water due to its hydrophilicity. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

The results of *in-vitro* dissolution studies are given in Table 6. All the tablet formulations showed more than 12 % release within 1 hour, but F6 formulation showed maximum 21.07% drug release within 1 hour. After 9 hours study, drug release for formulations F2, F3, and F6 (with Locust bean gum > Xanthan gum) were found to be 50.51%, 62.05%, and 70.10% respectively.

Formulations F4, F7 and F8 (with Xanthan gum > Locust bean gum) exhibited drug release of 44.01%, 47.00% and 56.60% respectively. Formulations F1, F5 and F9 (with Locust bean gum and Xanthan gum in equal amount) showed drug release of 55.49%, 65.69% and 57.40% respectively. Formulations containing hydroxypropyl methyl cellulose showed decrease in the rate of drug release with increase in concentrations. The formulation containing maximum amount of Locust bean gum and minimum amount of HPMC-E15 (F6) showed maximum drug release of 70.10% compared to other formulations whereas from the marketed formulation, about 55% drug was released within first 5 hours.

Table 1: Composition of Floating tablets of Cefpodoxime proxetil

Batch code	Cefpodoxime proxetil (mg)	Xanthan gum (mg)	Locust bean gum (mg)	HPMC E15 (mg)	Sodium bicarbonate (mg)	Citric acid (mg)	Magnesium stearate (mg)	Talc (mg)
F1	200	45	45	100	80	20	5	5
F2	200	45	55	90	80	20	5	5
F3	200	45	65	80	80	20	5	5
F4	200	55	45	90	80	20	5	5
F5	200	55	55	80	80	20	5	5
F6	200	55	65	70	80	20	5	5
F7	200	65	45	80	80	20	5	5
F8	200	65	55	70	80	20	5	5
F9	200	65	65	60	80	20	5	5

Table 2: Precompression parameters

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratios	Angle of repose (θ)	Flow property
F1	0.336	0.484	30.57	1.44	26.52	Good
F2	0.416	0.564	26.24	1.35	27.41	Good
F3	0.343	0.490	30	1.42	28.24	Good
F4	0.635	0.736	19.21	1.23	32.49	Passable
F5	0.501	0.63	23.27	1.30	27.16	Good
F6	0.498	0.558	24.31	1.32	24.87	Excellent
F7	0.523	0.671	22.05	1.28	38.47	Passable
F8	0.549	0.690	20.43	1.25	29.04	Good
F9	0.648	0.797	18.69	1.23	39.08	Passable

Table 3: Postcompression parameters

Batch code	Tablet hardness (kg/cm^2)	Tablet thickness (mm)	Tablet Weight (mg)	Drug content (%)	Tablet friability (%)
F1	5.33±0.47	5.68±0.04	499.5±1.28	98.43±0.42	0.67±0.08
F2	5.00±0.81	5.71±0.06	498.7±1.35	97.66±1.38	0.57±0.09
F3	5.33±0.47	5.69±0.05	500.5±1.23	97.18±0.90	0.56±0.07
F4	5.00±0.81	5.69±0.05	500.2±1.98	98.12±0.42	0.58±0.03
F5	5.66±0.47	5.71±0.06	499.1±1.56	98.99±0.80	0.61±0.06
F6	5.66±0.47	5.7±0.05	500.5±1.55	97.62±0.74	0.5±0.05
F7	5.33±0.94	5.69±0.05	499.5±1.25	97.27±0.62	0.67±0.07
F8	4.66±0.94	5.7±0.06	500.1±1.95	97.67±1.54	0.65±0.03
F9	4.66±0.47	5.7±0.06	499.7±1.24	98.05±0.84	0.54±0.07

Table 4: Floating lag time and Duration of floating of various formulations

Batch code	Floating lag time (sec)	Floating duration (hour)
F1	55	12
F2	30	12
F3	25	12
F4	25	12
F5	45	12
F6	30	12
F7	27	12
F8	49	12
F9	30	12

Table 5: Percent swelling index of batch F1-F9

Time (min)	Percent swelling index								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
15	33.16	40.36	38.86	32.12	32.55	34.66	35.48	36.45	36.32
30	48.32	59.50	52.16	47.23	46.12	45.42	52.16	46.70	45.42
60	60.06	75.84	64.15	54.42	62.66	70.43	64.44	60.45	70.43
120	82.45	95.45	85.62	80.12	74.78	86.34	75.99	88.57	86.34
180	105.32	106.65	104.37	107.25	96.61	109.56	97.52	107.60	109.56
240	120.09	125.21	115.35	121.37	111.53	124.90	117.45	125.55	124.90
300	134.36	130.54	120.15	132.33	123.92	132.61	127.4	133.36	132.33
360	138.75	138.38	130.68	137.75	134.80	138.20	135.24	139.64	138.20
420	141.25	143.83	140.39	141.45	138.74	142.60	138.90	142.80	142.60
480	148.50	150.09	146.84	145.66	144.37	148.64	142.67	148.39	148.64
540	151.47	158.72	156.86	148.65	150.82	152.36	152.75	154.51	154.68

Table 6: Cumulative percent drug release of batch F1-F9

Time (hr)	Cumulative percent drug release of formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	8.55	6.16	12.57	6.88	12.28	15.79	7.65	9.67	10.31
1	13.40	12.28	15.79	13.71	18.24	21.07	12.16	17.03	13.52
2	18.80	18.24	22.68	16.87	27.30	35.15	22.29	24.62	19.45
3	22.56	23.22	28.78	22.93	32.51	40.87	27.77	27.87	24.69
4	29.35	27.30	37.75	26.80	37.10	49.08	30.35	31.30	29.51
5	37.83	32.51	42.57	32.02	41.49	55.96	33.30	35.92	35.74
6	45.84	37.10	50.09	34.55	50.51	58.88	36.76	39.68	41.83
7	48.57	41.50	53.54	37.71	55.56	62.93	40.67	45.96	46.81
8	52.54	46.42	58.44	39.96	60.59	66.00	44.78	51.84	52.78
9	55.49	50.51	62.05	44.01	65.69	70.10	47.00	56.60	57.40

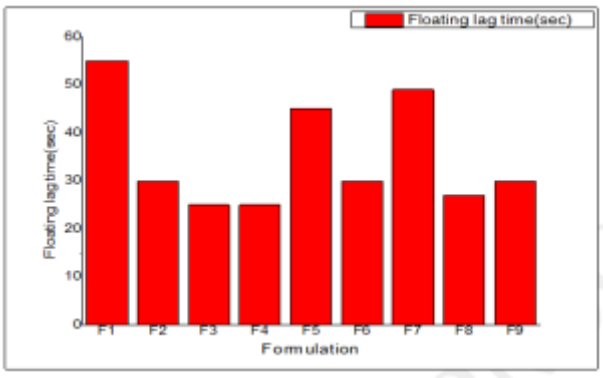

Figure 1: Floating lag time of various formulations

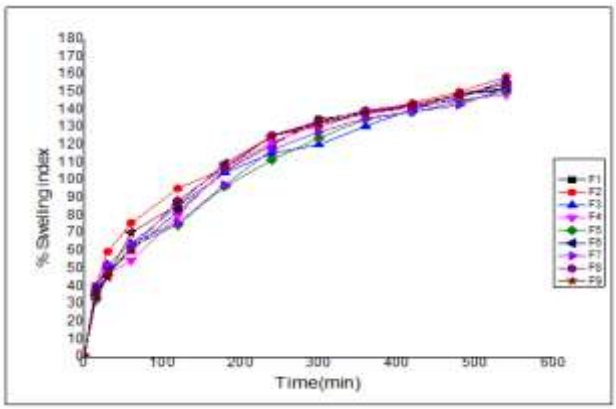

Figure 2: Comparison of percent swelling index of different formulations

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