

Development and *In-Vitro* Evaluation of Cefpodoxime Proxetil Gastro-Retentive Floating Tablets

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ABSTRACT:

The present study was undertaken with the aim to develop and evaluate Gastro retentive floating tablets of Cefpodoxime proxetil to get drug release up to 12hrs. These tablets were prepared by direct compression method using various bioadhesive polymers like HPMC K4M, HPMC K100M. The formulated gastro retentive floating tablets were evaluated for different parameters such as drug excipient compatibility studies, weight variation, thickness, hardness, content uniformity, *In vitro* Buoyancy studies, *In vitro* drug release studies performed in 0.1N HCl for 12hrs and the data was subjected to zero order, first order, Higuchi release kinetics and Korsmeyer Peppas graph. All pre and post compression parameters were found to be within limits. From the drug release data among formulations, F8 formulation was found to be optimized when compared with standard/marketted.

INTRODUCTION:

Oral administration is the most convenient and preferred mean of drug delivery to the systemic circulation. Many attempts have been made to develop sustained-release preparations with extended clinical effects and reduced dosing frequency. In order to develop oral drug delivery systems, it is necessary to optimize both the release rate of the drug and the residence time of the system within the gastrointestinal tract. Various approaches have been used to retain the dosage forms in the stomach (Moes et al., 1993; Deshpande et al., 1996; Hwang et al., 1998), as a way of increasing the gastric residence time (GRT) including floating (Yuasa et al., 1996; Rouge et al., 1998; Lee et al., 1999; Tripathi et al., 2010), high density (Hwang et al., 1998), mucoadhesive (Akiyama et al., 1995), magnetic (Groning et al., 1998),

unfoldable, extendible, or swellable (Fix et al., 1993), and superporous hydrogel systems (Park et al 1988).

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (Kaza et al., 2009).

Cefpodoxime proxetil (CP) is a prodrug of the third generation cephalosporins, which is broad-spectrum antibiotic and is administered orally. In human, the absolute bioavailability of cefpodoxime proxetil administered as a 130mg tablet (equivalent to 100mg of cefpodoxime) is about 50% (Borin et al., 1991). Reported studies have pointed possible reasons for low bioavailability as: low solubility, typical gelation behavior of CP particularly in acidic environments (Hamamura et al., 1995a; Hamamura

et al., 1995b; Hamamura et al., 1995c), and pre-absorption of luminal metabolism into cefpodoxime acid by the action of digestive enzymes (Manciet et al., 1997; kakumanu et al., 2006). It has been reported that the absorption of cefpodoxime proxetil is optimum at low pH (Hughes et al., 1989).

MATERIAL AND METHODS

Materials

Cefpodoxime proxetil was obtained from SURA LABS. Citric acid, HPMC k 4M, HPMC K 100M, Sodium bicarbonate, Magnesium stearate, Micro crystalline cellulose and talc was purchased from Merck Specialities Pvt Ltd, Mumbai, India. All chemicals/reagents used were of analytical grade.

Methods

Analytical method development

a. Determination of absorption maxima

For a solution containing the concentration of 10 μ g/ml of 0.1N HCl, a UV Spectrum was taken using Double beam UV/ visible spectrophotometer. The solution was scanned in the range of 200– 400nm.

b. Preparation calibration curve

100mg of cefpodoxime proxetil pure drug was dissolved in 100ml of 0.1N HCl (stock solution) and then 10ml of solution was taken and make up with 100ml of 0.1N HCl (100 μ g/ml). From this 10ml was taken and made up with 100 ml of 0.1N HCl(10 μ g/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 2, 4, 6, 8, 10 and 0.1 μ g /ml of per ml of solution. The absorbance of the above dilutions was measured at 277 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line. Linearity of standard curve was assessed from the square of correlation coefficient (R^2)

which is determined by least-square linear regression analysis.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples were mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm^{-1} to 500 cm^{-1} . The resultant spectrum was compared for any spectrum changes.

Pre formulation parameters

The quality of tablet, once formulated by rule is generally dictated by the quality of physicochemical properties of blends. The granules were evaluated for flow property i.e. angle of repose, bulk density, tapped density and compressibility index (Carr's index) using standard procedures (Indian Pharmacopeia, 1996; Lachman et al., 1990).

Formulation development of Tablets

All the formulations were prepared by direct compression. The tablets were prepared as per the procedure given below and aim is to prolong the release of Cefpodoxime proxetil. Total weight of the tablet was considered as 600 mg.

Procedure

1. Cefpodoxime proxetil and all other ingredients were individually passed through sieve no \neq 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc.
4. The tablets were prepared by using direct compression method.

Table 1: Formulation composition for floating tablets

Formulation	Cefpodoxime proxetil (mg)	HPMC K 4M (mg)	HPMC K100M (mg)	NaHCO ₃ (mg)	Citric acid (mg)	Mg. Stearate (mg)	Talc (mg)	MCC PH102 (mg)
F1	200	60	-----	20	10	6	6	298
F2	200	120	-----	40	20	6	6	228
F3	200	180	-----	60	30	6	6	118
F4	200	-----	60	20	10	6	6	298
F5	200	-----	120	40	20	6	6	208
F6	200	-----	180	60	60	6	6	88
F7	200	30	30	15	15	6	6	298
F8	200	60	60	30	30	6	6	208
F9	200	90	90	30	30	6	6	148

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content (Indian Pharmacopeia, 1996; Lachman et al., 1990).

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance and the test was performed. Thickness of tablet was determined using Vernier calipers. Ten tablets from each batch were used, and their average values calculated. Hardness of ten tablets of each formulation was determined using Monsanto hardness tester.

Friability is a measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

At the end of test, the tablets were re- weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\text{Percentage Friability (\%)} = [(W1-W2) / W1] \times 100$$

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content

Compression-coated tablets were tested for their drug content. Ten tablets were finely powdered. The quantities of the powder equivalent to one tablet weight of cefpodoxime proxetil were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies

The in vitro buoyancy was determined by floating lag time, and total floating time [As per the method described by Rosa et al (Rosa et al., 1994; Abdul and Lila., 2011)]. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time that the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

In vitro drug release studies

Dissolution parameters

Apparatus	-- USP-II, Paddle Method
Dissolution Medium	-- 0.1 N HCl
Rotations per minute	-- 50
Sampling intervals(hrs)	-- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	-- 37°C ± 0.5°C

As the preparation was for floating drug release given through oral route of administration, different receptor fluids are used for evaluating the dissolution profile.

Procedure

900ml Of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals, 5 ml of the receptor fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 277 nm using UV-spectrophotometer (Hareesh et al., 2015).

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics, the release rate data are fitted to the following equation.

$$F = K_0 t$$

Where, ‘F’ is the drug release at time ‘t’, and ‘K₀’ is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data were fitted to the following equation

$$\text{Log (100-F)} = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k t^{1/2}$$

Where, ‘k’ is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear

Kors meyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Kors meyer- Peppas equation. The exponent ‘n’ indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t/ M_∞ is fraction of drug released at time ‘t’, k represents a constant, and ‘n’ is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets) (B. Ramu et al., 2015).

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC} \cdot t$$

Where, k is the Hixson-Crowell rate constant.

RESULTS

The present study was aimed to develop gastro retentive floating tablets of cefpodoxime proxetil using various HPMC polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Evaluation of physical parameters of cefpodoxime proxetil

It was determined as per standard operating procedures

Table: 2 Organoleptic properties

Test	Specification /Limits	Observations
Colour	White to light brownish white powder	white powder
Taste	Bitter	Bitter
Odour	Faint	Faint

Table: 3 Properties of Cefpodoxime proxetil

Properties	Cefpodoxime proxetil
Angle of repose(Flow properties)	24 ⁰ ± 0.4
Bulk Density (gm/ml)	0.5±0.02
Tapped Density(gm/ml)	0.57±0.03
Compressibility index	5-15%
Hausner ratio	1-09%

Table:4 Solubility

Test	Specification	Result
Solubility in water,	Practically insoluble in water	Complies
Acetonitrile& Methanol	Practically very soluble	Complies

Table 5: Pre-formulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25 ⁰ ±0.5	0.52±0.03	0.57±0.04	8.7	1.09
F2	24 ⁰ ±0.3	0.58±0.05	0.62±0.08	6.45	1.06
F3	26 ⁰ ±0.2	0.56±0.06	0.68±0.03	17.6	1.21
F4	25 ⁰ ±0.4	0.51±0.04	0.62±0.01	17.7	1.21
F5	23 ⁰ ±0.3	0.56±0.02	0.67±0.05	16.4	1.19
F6	28 ⁰ ±0.2	0.55±0.08	0.66±0.02	16.66	1.2
F7	29 ⁰ ±0.1	0.54±0.07	0.63±0.04	14.2	1.16
F8	24 ⁰ ±0.4	0.52±0.02	0.57±0.03	8.77	1.09
F9	26 ⁰ ±0.4	0.57±0.03	0.62±0.09	8.06	1.08

Table 6: Quality Control Parameters For tablets

Formulation code	Weight variation(mg)	Hardness(kg /cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Duration floating time (hr)
F1	598±0.1	5.1±0.1	0.56±0.5	4.6±0.3	98.24	4.20	1
F2	596±0.2	4.9±0.1	0.88±0.5	5.1±0.1	97.45	3.4	2
F3	602±0.3	5.3±0.5	0.57±0.1	4.8±0.1	97.51	2.2	4
F4	597±0.1	4.9±0.5	0.43±0.3	5.3±0.2	99.53	4.4	6
F5	599±0.1	4.6±0.1	0.43±0.2	4.9±0.1	98.55	2.8	12
F6	597±0.2	4.8±0.1	0.68±0.1	4.8±0.1	98.12	2.0	11
F7	598±0.4	5.2±0.5	0.59±0.5	4.7±0.2	97.47	3.1	10
F8	601±0.4	5.4±0.1	0.39±0.1	5.2±0.2	98.25	2.0	12
F9	598±0.1	4.9±0.5	0.57±0.1	5.1±0.1	97.25	3.3	12

Table 7: Observations for graph of cefpodoxime proxetil in 0.1N HCl (277nm)

Concentration [µg/ml]	Absorbance (nm)
2	0.221
4	0.391
6	0.573
8	0.765
10	0.955

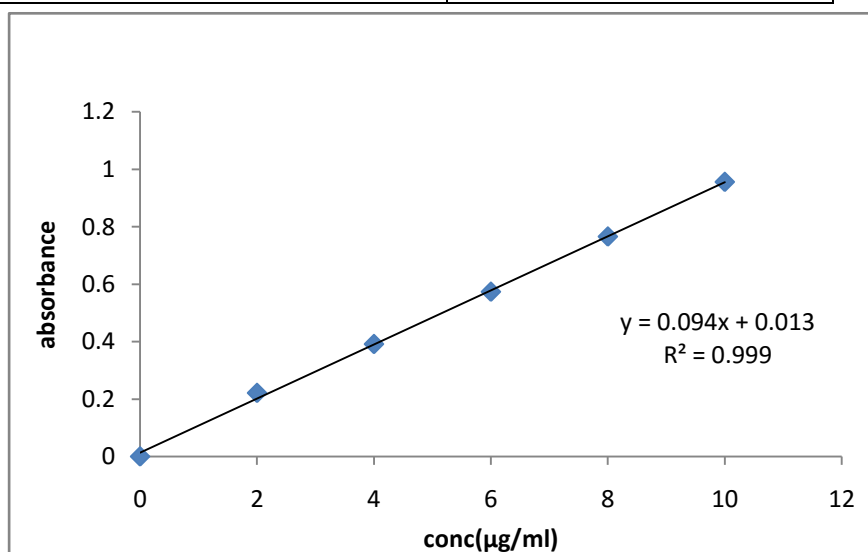


Figure 1: Standard graph of cefpodoximeproxetil in0.1N HCl

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

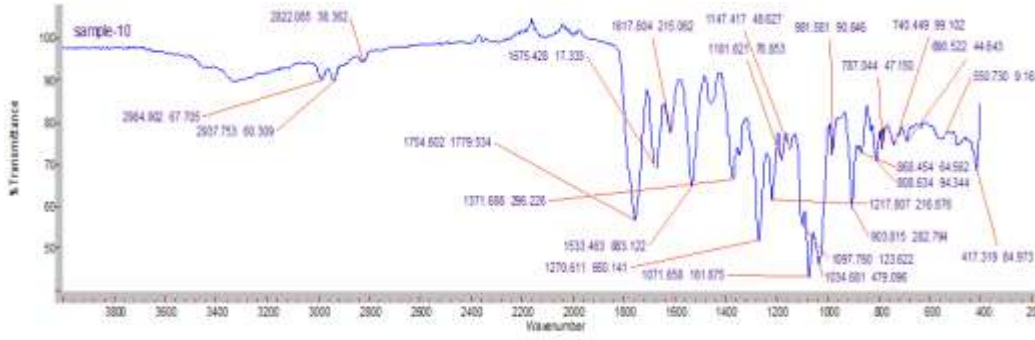


Figure 2: FT-IR Spectrum of cefpodoximeproxetilpure drug.

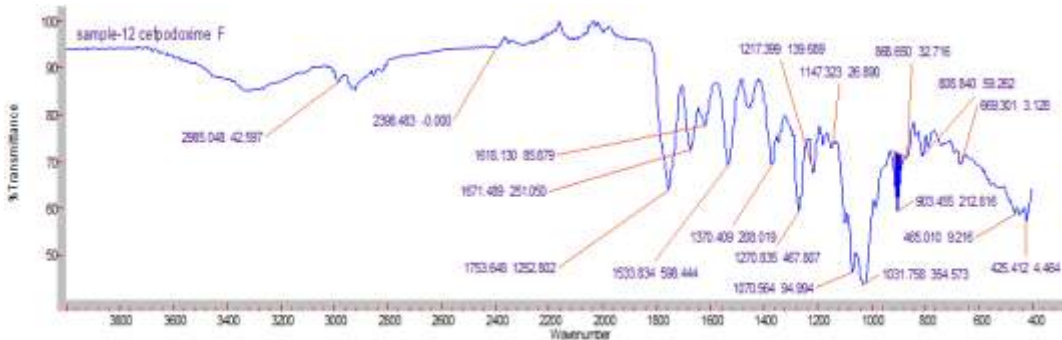


Figure 3: FT-IR Spectrum of Optimised Formulation

Table 8: Dissolution Data of Cefpodoxime proxetil Tablets Prepared with HPMC K 4 in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0	0	0	0
0.5	45.67	30.81	27.24
1	61.81	42.73	33.81
2	99.7	55.63	43.75
3		64.81	54.17
4		77.42	65.83
5		88.89	73.19
6		98.72	88.62
7			99.73

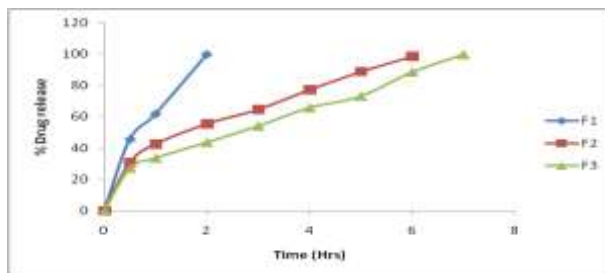


Fig 4: Dissolution profile of Cefpodoxime proxetil floating tablets (F7, F8, F9 formulations)

Table 9: Application of Release Rate Kinetics to Dissolution Data

CUMULATIVE RELEASE Q	TIME (T)	ROOT (T)	LOG % RELEASE	LOG (T)	LOG % REMAIN	RELEASE RATE (CUMULATIVE % RELEASE/t)	1/CUMULATIVE % RELEASE	PEPPAS log Q/100	%DRUG REMAINING
0	0	0			2.000				100
15.1	0.5	0.707	1.179	0.301	1.929	30.200	0.0662	-0.821	84.9
21.72	1	1.000	1.337	0.000	1.894	21.720	0.0460	-0.663	78.28
28.84	2	1.414	1.460	0.301	1.852	14.420	0.0347	-0.540	71.16
35.62	3	1.732	1.552	0.477	1.809	11.873	0.0281	-0.448	64.38
41.89	4	2.000	1.622	0.602	1.764	10.473	0.0239	-0.378	58.11
48.08	5	2.236	1.682	0.699	1.715	9.616	0.0208	-0.318	51.92
55.43	6	2.449	1.744	0.778	1.649	9.238	0.0180	-0.256	44.57
61.54	7	2.646	1.789	0.845	1.585	8.791	0.0162	-0.211	38.46
67.15	8	2.828	1.827	0.903	1.587	8.394	0.0149	-0.173	32.85
75.56	9	3.000	1.878	0.954	1.388	8.396	0.0132	-0.122	24.44
81.43	10	3.162	1.911	1.000	1.269	8.143	0.0123	-0.089	18.57
89.96	11	3.317	1.954	1.041	1.002	8.178	0.0111	-0.046	10.04
99.89	12	3.464	2.000	1.079	-0.959	8.324	0.0100	0.000	0.11

Table: 10 Dissolution data of optimized formulation and marketed brand

Time (hrs)	Mean cumulative % Drug Release	
	F8	Marketed product (Cifran OD)
15 min	15.1	13.9
1hr	21.72	18.69
2hrs	28.84	20.8
3hrs	35.62	29.6
4 hrs	41.89	35.63
5 hrs	48.08	40.05
6 hrs	55.43	49.34
7 hrs	61.54	52.45
8 hrs	67.15	59.15
9 hrs	75.56	60.44
10 hrs	81.43	72.33
11 hrs	89.96	79.69
12 hrs	99.89	82.98

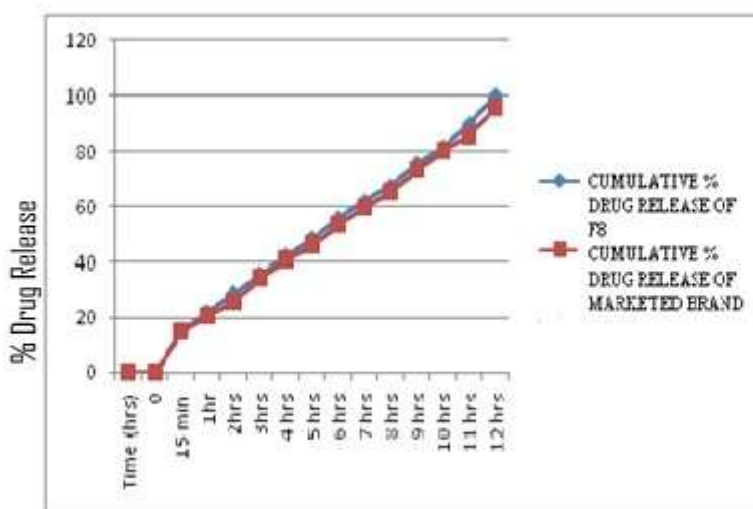


Figure 5 Dissolution data of optimized formulations and marketed brand

DISCUSSION

Development of Gastro retentive floating drug delivery of cefpodoxime proxetil tablets is to provide the drug action up to 12 hours.

The organoleptic properties, flow properties, bulk density, tapped density, solubility tests and powder compressibility properties of cefpodoxime proxetil were performed and the results were complied with the standards. The results were reported in the table 2,3 and 4.

Precompression parameters of the formulations were reported in the Table No.-5. Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values were in the range of 23.3 to 29.1. The bulk density of all the formulations was found to be in the range of 0.51 to 0.58(gm/cm³). The tapped density of all the formulations was varied from 0.57 to 0.68. The compressibility index of all the formulations was found to be in the range of 6 to 18. All the formulations have shown the hausner's ratio in the range of 1 to 1.2. Therefore, the results indicate that the powder blend has good flow properties.

The hardness of tablets was found to be in the range of 4.6 to 5.4 kg/cm². The friability values of all the formulations were less than 1% which was an indication of good mechanical resistance of the tablets. The thickness of the tablet was from 4.6mm to 5.3 mm. The percentage of drug content was in the range of 97% to 99% and the duration of floating time of tablets were in the range of 1 to 12 hours.

From the results of FTIR studies that are reported in the figure no.-2 and 3, it was evident that the drug and excipients does not have any interactions.

From the dissolution data which is reported in the table no.-8, 10 and figure no.-4 and 5, F1 to F6 formulations which contains single polymer either HPMC K4M or HPMC K100M did not hold the drug release up to 12 hrs therefore those drugs did not take into consideration. F7 to F8 formulations which contain two polymers (HPMC K4M and HPMC K100M) has

shown good release than single polymer used formulations. From those formulations, F7 and F9 also did not take into consideration because F7 did not hold the drug release up to 12hrs and F9 hold the drug release more than 12 hours. Among all formulations, F8 has taken as optimized formulation which was shown drug release upto 12hrs.

Gastro retentive floating tablets were prepared by direct compression method using various bio adhesive polymers like HPMC K4M, HPMC K100M. Sustained release bi-layered floating tablets of Cefpodoxime proxetil were prepared by direct compression method. All the formulated tablets met the pharmacopoeial standard of uniformity of weight variation, percentage friability, thickness and drug content. The results concluded that stable and persistent buoyancy was achieved by trapping the gas by the hydration of high viscosity grade HPMC K100M. This study showed that there is a potential for this novel intra gastric, floating Bi-layer tablet to remain in the stomach for a longer time. Moreover, the two distinct layers allow separate regulation of the floating ability and drug release kinetics. The floating drug delivery system becomes an additional advantage for drugs that are primarily in upper part of GIT.

CONCLUSION

The following conclusions could be drawn from the results of various experiments. The present study concludes that gastro retentive floating Cefpodoxime proxetil tablets, among the all formulations, F8 formulation has shown optimised results.

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