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Formulation and optimization of controlled released floating matrix tablets of cefixime

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ABSTRACT

The purpose of this research was to prepare a floating drug delivery system of Cefixime trihydrate (Cefixime). Floating matrix tablets of Cefixime were developed to prolong gastric residence time, increase its bioavailability and patient compliance. Rapid gastro-intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as HPMC K 100 LV, HPMC K4M, HPMC K15M and HPMC K100M, alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas generating agent and citric acid was incorporated as a release rate enhancer. The effect of Sodium bicarbonate, tablet hardness and content of citric acid on drug release profile and floating properties were investigated. A 3^2 full factorial design was applied to systematically optimize the drug release profile. The ratio of HPMC K4M to HPMC K100 LV (X_1) and content of citric acid (X_2) were selected as independent variables. The time required for 50 % (t_{50}), percentage drug release at 12 hr (Q_{12}), release rate constant (k) and diffusion exponent (n) were selected as dependent variables. The results of factorial design indicated that ratio of HPMC K4M to HPMC K100LV had dominant role on drug release from floating matrix tablets compared to citric acid, although the presence of later component in formulation with optimum concentration is essential to improve the drug release of hydrophobic molecules of drug. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r).

Keywords: Cefixime, HPMC K 100 LV, HPMC K4M, HPMC K15M and HPMC K100M

INTRODUCTION

Retention of dosage forms in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site specific absorption from the stomach or upper part of the small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling and expanding systems, floating systems, and delayed gastric emptying devices. the principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustain drug release. Cefixime is orally active third generation cephalosporin active against enterobacteriaceae, Haemofilia influenzae, Streptococcus pyogenes, Streptococcus pneumoniae, Moraxella, E. coli, Protease, Neisseria gonorrhea and is resistant to many b- lactamases. The absolute bioavailability of all newer oral cephalosporin is below 50-60%, which suggests an absorption mechanism through the mucosa with limited capacity. The biological half life of Cefixime is 3.0 ± 0.4 and dosing of Cefixime is 200 mg twice a day for 7-10 days. Considering the wide range of activity of Cefixime, the objective of this study was to decrease the dose frequency and increase the speed of recovery from the indications by increasing the rate of bacterial killing and thereby increasing patient compliance. Aim of present work is to develop, optimize and characterize gastroretentive tablet of Cefixime to reduce the frequency of dosing and to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing the uniform drug delivery and patient compliance.

In context of the above principles, a strong need is felt to develop a dosage form that would increase in the efficiency of the drug, providing sustains action. Thus in the present investigation, a systematic approach will be applied for the formulation and development of gastroretentive Cefixime dosage forms.

In context to above intention, following criteria were aimed to achieve.

1. Floating lag time of drug delivery system should be less than 15 min.
2. Total floating time of drug delivery system should be approx. 12 hours.
3. The first hour drug release should be around 32 %, which is calculated based on the pharmacokinetic parameters of Cefixime.
4. More than 90% of drug should be released within 12 hours.

The gastroretentive drug delivery system can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have and absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These

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include floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high –density systems and other delayed gastric-emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for dosage form and sustained drug release. The present investigation describes the formulation development of an intragastric floating drug delivery system of Cefixime.

MATERIALS AND METHODS

Materials

Cefixime was received as generous gift from Lincoln Pharmaceuticals Limited, Ahmedabad, India, HPMC K100LV, HPMCK4M, HPMCK15M and HPMCK100M were received from Zydus-Cadila Healthcare Limited, Ahmedabad, India, Sodium bicarbonate, citric acid and magnesium Stearate were received from S.D. Fine-Chem. Limited, India. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Methods

Preparation of Cefixime trihydrate floating tablets:

Tablets were prepared by direct compression technique. Cefixime trihydrate (479 mg equivalent to 400 mg of Cefixime anhydrous) was mixed with required components except magnesium stearate by geometric mixing. The powder blend was then lubricated with magnesium stearate (1%w/w) and manually compressed on single punch tablet machine using 5 mm standard round punch. The lactose being water soluble filler was used to maintain constant tablet weight as well as to counter balance the poor water solubility of drug. The tablets were compressed to obtain hardness in a range of 5-7 Kg/cm^2.

Factorial Design:

A 3^2 randomized full factorial design was utilized in the present study for development of dosage form. In this design two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations. The ratio of HPMC K4M to HPMC K100LV (X_1) and the amount of citric acid (X_2) were selected as independent variables. The time required for 50% of drug release ($t_{50\%}$), percentage drug release at 12 hr (Q_{12}), release rate constant (k) and diffusion exponent (n) were selected as dependent variables. Content of polymer blend was kept constant at 12.85 % of total tablet weight. The ratio of HPMC K4M and HPMC K100 LV was evaluated at 80:20, 70:30 and 60:40 while the content of citric acid was evaluated at 0%, 1% and 2% of total tablet weight. The experimental design with corresponding formulations is outlined in Table 1.

Drug content and physical evaluation:

Compressed tablets were evaluated for assay, weight variation and friability according USP 28. For assay, the 20 tablets were crushed and the powder equivalent of 400 mg of drug was transferred to 1000 ml of 0.1 N HCl in volumetric flask. The solution was analyzed at 285 nm using double beam UV/Vis spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve. The results shown in Table 2.

In vitro buoyancy study:

The *in vitro* buoyancy was characterized by floating lag time (FLG) and total floating time(TFT).The test was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HCl at 100 rpm at 37 ± 0.5^{o}C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as FLG and TFT , respectively (n=3).

In vitro drug release study:

The *in vitro* drug release was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HCl at 100 rpm at 37$\pm$ 0.5^o C. The samples were withdrawn at predetermined time intervals for period of 12 hr and replaced with the fresh medium. The samples were filtered through 0.45 µm membrane filter, suitably diluted and analyzed at 285 nm using double beam UV/Vis spectrophotometer. The content of drug was calculated using calibration curve. The results of dependent variables are shown in Table 3 and in vitro drug release profile is shown in figure 1.

Statistical analysis:

The statistical analysis of the factorial design batches were performed by multiple regression analysis using Microsoft Excel®. To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) followed by Tukey test was performed using Sigma Stat software (Sigma Stat 3.0, SPSS, USA). To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Sigma Plot software (Sigma Plot software 11.0, SPSS, USA). The value of $P < 0.05$ was considered to be significant.

RESULTS AND DISCUSSION

From preliminary investigation it was found that the ratio of HPMC K4 M to HPMC K100LV and addition of citric acid had desirable influence on drug release. Therefore, the influence of the ratio of HPMC K4M to HPMC K100LV and content of citric acid on drug release from floating matrix tablets was studied using 3^2 full factorial design. Tablets of each batch had complied the assay, weight variation and friability test according to USP 28 .Tablets of each batch had floating lag time below 2 min in (55 sec to 118 sec) regardless of ratio HPMC K4M to HPMC K100 LV and content of citric acid. Tablets of each batch constantly floated on dissolution medium for more than 12 hr except the tablets of batch A11 which might be due to lower strength of hydrophilic matrices as well as presence of citric acid increased the influx of dissolution medium subsequently leads to weakening of the strength of the matrices. From the results of in vitro drug release studies it was found that addition of more amount of lower viscosity grade of HPMC at all levels of content of citric acid, the drug release was increased might be due to the lowering of the viscosity of the hydrophilic matrices which opened up the channels for faster penetration of dissolution medium inside the swelled matrices leads to more availability of fresh dissolution medium inside the matrix leads to increased dissolution of un-dissolved particle of the drug and it may leads to increased in diffusion of drug out of the matrices due to weaker gel layer formed. It was observed that addition of citric acid improved the drug release at 1% of total tablet weight compared to tablets without citric acid but further increase in content of citric acid to 2 % of total tablet weight did not gave significant improvement in drug release in tablets containing higher fraction of HPMC K100LV might be due the attainment of agglomeration at higher level which may entrapped the molecule of drug inside the agglomeration formed. There has been considerable interest in using different grades of HPMC in controlled release drug

Table 1: Formulation of factorial design batches

Batch code	Coded level		Actual value(mg)	
	X_1	X_2	X_1	X_2
A10	+1	+1	54:36	14
A11	+1	0	54:36	7
A12	+1	-1	54:36	0
A13	0	+1	63:27	14
A14	0	0	63:27	7
A15	0	-1	63:27	0
A16	-1	+1	72:18	14
A17	-1	0	72:18	7
A18	-1	-1	72:18	0

X_1 is ratio of HPMC K4M: HPMC K100 LV and X_2 is amount of citric acid. All batches contained 479 mg Cefixime trihydrate [equivalent to 400 mg of Cefixime (Anhydrous)], 50 mg sodium bicarbonate, 12.85 % of polymer blends, 1% of magnesium stearate and quantity sufficient of lactose.

Table 2: Results of evaluation of tablets for factorial design batches

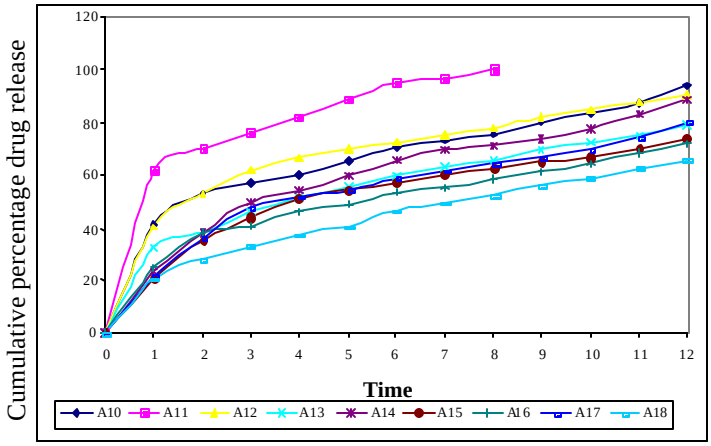
Batch	Assay	Average	Friability	Buoyancy Characteristics(n=3)	
Code	(%)(n=20)	weight	(%)	FLT(sec)	TFT(hr)
A10	98.85	700 (2.3)	0.48	60 (3)	>12
A11	98.36	698 (2.8)	0.54	55 (5)	*~8*
A12	100.35	700 (3.0)	0.49	65 (2)	>12
A13	100.86	699 (2.5)	0.56	80 (3)	>12
A14	99.90	699 (1.8)	0.65	92 (3)	>12
A15	101.28	700 (2.2)	0.64	100 (3)	>12
A16	102.39	700 (3.0)	0.52	85 (3)	>12
A17	100.29	700 (1.7)	0.47	98 (3)	>12
A18	101.86	699 (1.4)	0.37	118 (3)	>12

Value in parenthesis indicates standard deviation

Table 3: Results of dependent variables for factorial design batches

Batch	$t_{50\%}$	Q_{12}	Release rate constant(k)	Diffusional release exponent(n)
Code	(min)	(%)		
A10	100	94.80	40.93	0.309
A11	45	109.19	60.24	0.242
A12	110	90.67	42.29	0.307
A13	220	79.19	31.29	0.364
A14	185	89.04	26.41	0.490
A15	235	73.98	25.75	0.439
A16	310	72.02	26.60	0.388
A17	230	80.09	25.07	0.466
A18	440	66.12	20.39	0.459
A10	100	94.80	40.93	0.309

Figure 1: Dissolution profiles of tablets for factorial design batches



delivery system due to their hydrophilic nature and fast hydration. The release profiles appear to be bi-phasic with initial burst effect followed by a polymer-controlled slower release in the second phase. The difference in burst effect of the initial time is a result of difference in the viscosity of the polymeric mixtures as well as amount of citric acid which mainly contribute in dissolution of drug in initial period. The polymeric system with higher content of HPMC K100LV yielded a faster initial burst effect. On other hand, the apparent drug release rate observed in the second phase from different polymeric mixture are quite similar which describe that once the gel layer formed, there appears to be no difference in release rate.

CONCLUSION

For the development of controlled release dosage form for poorly soluble drug like Cefixime trihydrate, polymer blends of different viscosity grade of HPMC and presence of citric acid appears necessary, which imparts hydrophilic environment and to increase drug release, respectively .Tablets had desired buoyancy characteristics. It was found that ratio of HPMC K4M to HPMC K100LV had dominant role on drug release from floating matrix tablets compared to citric acid, although the presence of later component in formulation with optimum concentration is essential to improve the drug release of hydrophobic molecules of drug. The promising formulation (Batch A14) had desire drug release kinetics and found to be stable for 3 months under stability study.

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