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DESIGN AND EVALUATION OF FLOATING MATRIX TABLETS OF CEFIXIME TRIHYDRATE USING ALOE VERA GEL POWDER FOR TREATMENT OF GASTRIC ULCERS

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ABSTRACT

Cefixime trihydrate floating matrix tablets were developed to improve patient compliance, extend the drug's stomach residence duration, and improve its bioavailability. Fast gastrointestinal transit may cause partial drug release from the drug delivery system above the absorption zone, which would reduce the effectiveness of the dosage that is given. The tablets were made using the direct compression method. Citric acid was utilized as a floating agent, sodium bicarbonate was added as a gas producing agent, and HPMC K100M and powdered aloe vera gel were added to increase the release rate. The thickness, hardness, friability, drug content, floating lag time, floating time, in-vitro drug release tests, and release kinetics of the produced matrix floating tablets were assessed. When compared to the other optimized formulations, F5, which ranges from F1 to F9, exhibits a higher release rate in contrast to alternative formulations. The improved formulation (F5) fit into the kinetic model, which displays the Higuchi model and the R2value of 0.956, according to the drug release kinetic data. To examine the drug's release mechanism from the polymeric system, the outcomes of the in-vitro release data were fitted to the Korsmeyer-Peppas equation. The drug release is thought to follow a non-Fickian release mechanism, as indicated by the found "n" value of 0.995.

KEYWORDS: *cefixime trihydrate, floating matrix tablets, in-vitro drug release, floating lag time, non- fickian release.*

INTRODUCTION

Helicobacter pylori are helical, gram-negative, flagellar bacteria that regularly infect people; the global infection rate is estimated to be 4.4 billion.(Hooi JKY et al, 2017) Gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer are all brought on by H. pylori infection (McColl KE et al, 2010). These bacteria invade the stomach and duodenum by penetrating the mucosa due to their unique morphology.

Because of its extended gastric residence period, FDDS is mostly used for gastro retentive issues. Low density systems known as floating systems have enough buoyancy to pass over the contents of the stomach and stay afloat there for an extended amount of time without reducing the rate at which the stomach empties.(Trop J et al, 2015)

Floating, swelling, high density, and bioadhesive systems are a few of the gastroretentive strategies that have been investigated to improve dosage form gastro retention. These retention systems are crucial for drugs that are broken down in the intestine, such as antacids, some antibiotics, and stomach-acting enzymes. The device floats over the contents of the stomach and releases the drug slowly and at the desired rate, increasing the gastric retentive time and reducing fluctuations in plasma drug concentration.(Anilkumar J Shind et al 2010)

Cephalosporins are the preferred medication in this case because of their wide range of antimicrobial activity. A wide range of action is exhibited by third-generation cephalosporins, which also exhibit enhanced activity against gram-negative bacteria. There are members of this category whose activity against gram-positive organisms has reduced. Parenterally administered third-generation cephalosporins provide superior efficacy against the majority of streptococcus pneumonia isolates, including those that possess intermediate and high levels of penicillin resistance. By directly interacting with the cells that produce acid or perhaps through engagement with the H2 receptors on the parietal cells, aloe vera gel demonstrated concentration-dependent suppression of gastric acid discharges. It has been shown that aloe vera gel prevents stomach ulcers in both rats and humans. Its

anti-inflammatory, cytoprotective, healing, and mucus-stimulating properties account for its antiulcer action (Hamman JH et al, 2008). Because lectins are present, aloe vera exhibits gastroprotective action at lower concentrations. Proteins called lectins, also known as glycoproteins, have the ability to recognize and bind to carbohydrate moieties. It has been demonstrated that lectins prevent parietal cells from absorbing aminopyrine. Therefore, direct impact on the acid-producing cells may account for gel powder's capacity to limit stomach acid secretion (Sadiq Y et al, 2004). By preserving the effective drug concentration, keeping amoxicillin and aloe vera gel in the stomach might improve its effectiveness in treating peptic ulcers. Therefore, the goal of this study is to create and test a bilayer gastroretentive floating tablet containing powdered aloe vera gel and amoxicillin for the treatment of peptic ulcers. Here, aloe vera gel powder will have a local effect whereas amoxicillin will be taken systemically. Utilizing a direct compression method, sodium bicarbonate was added as a gas-generating agent, citric acid served as a floating agent, and HPMC K100M and powdered aloe vera gel were utilized to increase the release rate of the tablets. The thickness, hardness, friability, drug content, floating lag time, floating time, in-vitro drug release tests, and release kinetics of the produced matrix floating tablets were assessed.

MATERIALS AND METHODS

Materials

Cefixime trihydrate was purchased from Yarrow chem. Products, Mumbai. HPMC K100M was purchased from Precision chemicals Coimbatore. Aloe vera gel powder was purchased from praacheen vidhaan, Bangalore. $NaHco_3$ and Citric acid were purchased from Modern Scientifics, Coimbatore. Avicel pH (102) was purchased from Nice Chemicals Pvt. Ltd., KeralAloe Magnesium stearate and Talc were purchased from Loba ChemiePvt. Ltd., Mumbai.

FTIR spectra

The compatibility study was performed to find out any possible drug-drug and drug-excipient interaction by ATR method using FTIR spectrophotometer at scanning range of 4000-400 cm^{-1}. The resultant spectrum was compared for any spectral changes and observed for the presence of characteristic peaks for respective functional group in the compound (Thumma S et al, 2009).

Solubility of cefixime trihydrate

100 mg of Cefixime trihydrate was dissolved in 20 ml of methanol and made up to 100 ml with 0.1N HCL solution in a100 ml volumetric flask, so as to get a stock solution of 1000 µg/ml.

METHOD OF PREPARATION OF FLOATING MATRIX TABLETS

Floating Matrix tablets of Cefixime trihydrate were prepared by direct compression technique using variable concentrations of HPMC K100M, aloe vera gel powder and avicel pH 102. Sodium bicarbonate and Citric acid are used as gas generating agents. HPMC K100M is used as matrix forming layer. The drug was passed through the sieve no.40. The drug and all other ingredients except Magnesium stearate were taken in poly bag and mixed thoroughly for nearly about 10 minutes. Finally, the powder blend was lubricated with magnesium stearate and the blend then compressed by direct compression technique using 8mm flat punch on a 10 Stationary punching.

Table 1: Composition of different formulation for floating tablets of cefixime trihydrate.

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime trihydrate	200	200	200	200	200	200	200	200	200
HPMC K 100M	80	100	120	80	100	120	80	100	120
Aloe vera gel powder	0	0	0	30	40	50	30	40	50
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Citric acid	20	30	40	20	30	40	30	20	10
Avicel pH(102)	100	70	40	70	30	00	60	40	20
Magnesium stearate	15	15	15	15	15	10	15	15	15
Talc	10	10	10	10	10	5	10	10	10
Total	500	500	500	500	500	500	500	500	500

Optimization by 2^2 Factorial Designs

The 22 Factorial Design was utilized to optimize cefixime trihydrate floating matrix tablets (Design-Expert Software 13). Aloe vera gel powder (designated as Y) and (HPMC) [designated as X] were selected as formulation factors. Studies on in vitro dissolution and floating time were regarded as the dependent variables. CCD was a potential involved approach since it investigates the complex problems with optimal exploratory runs. The exams in CCD were finished in a randomized manner (Gonzalez Mira et al, 2011).

Bulk density

It is calculated by using the formula,

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume of powder}}$$

Tapped density

It is calculated by using the formula,

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped volume of powder}}$$

Hausner's ratio

Hausner's ratio is calculated by using the formula as,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's Index or Compressibility Index

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in % and is given by, (Subramanyam et al, 2001)

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Angle of Repose

It is calculated by fixed funnel method using the formula given below (Lachman L et al, 1991)

$\theta = \tan^{-1} (h / r)$

where,

h= height of the pile

r = average radius of the powder cone

Post-Compression parameters of tablets

Weight variation test

20 tablets were randomly chosen from each tablet formulation and individually weighed to check for the weight variation. According to IP, not more than 2 of individual weight of tablets out from the average weight by more than the percentage deviation and none deviate by more than twice the percentage.

Hardness test

Tablet hardness was determined for each formulation by Pfizer hardness tester. It was expressed in kg/cm^2.

Thickness test

The thickness of the prepared tablets was determined for 3 pre weighed tablets from each formulation utilizing Vernier caliper, expressed as average thickness in mm. Tablet thickness must be within ±5% variation of the standard (Joshi R et al, 2020)

Friability test

The friability test was performed employing Roche friabilator. A prior weighed sample of tablets was taken in the plastic chamber of friabilator that revolves at a speed of 25 rpm for 4 mins and the tablets were dropped at a distance of 6 inches with each revolution. Tablets after the friability test were de-dusted and re-weighed. The core tablets must not lose >1% of their weight (Sarfraz RM et al, 2014)

$$\text{Drug content: \% friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Drug Content uniformity

Twenty tablets were randomly selected from each batch and was finely powdered with a mortar and a portion of the resulting powder equal to the weight the respective tablets was solubilized in 0.1N HCL IN 100ml of volumetric flash and further diluted to with 0.1N HCL to make a solution of cefixime trihydrate as per the standard concentration of the calibration curve and assayed spectrophotometrically at 285 nm. Each measurement was carried out in triplicate and all the results are averaged. A blank solution containing all the components except for the drug was also prepared corresponding concentration were calculated from the standard curve.(Manish P et al, 2009)

Floating lag time

The floating lag time was carried out in a beaker containing 100 ml of 0.1 N HCl as a testing medium maintained at 37° C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Floating Time

Floating time was the time, during which the tablet floats in 0.1 N HCI dissolution medium (including floating lag time).

***In-vitro* dissolution studies**

Procedure

The above-mentioned conditions applied to the dissolving test apparatus. After putting one tablet in each basket, the device was operated. One milliliter of liquid was taken out of the zone halfway between the surface of the dissolving medium and the top of the rotating paddle after the predetermined amount of time. With the dissolving media, 1 milliliter of the extracted sample is diluted to 10 milliliters and thoroughly mixed. After turning on, the instrument was stabilized. Using UV spectrophotometry at 285 nm, the withdrawal solution was further diluted and the amount of medication discharged was measured.(Manish P et al, 2009)

Kinetic Analysis of In-Vitro Release Study

By applying the drug release data through a variety of kinetic equations, including Zero-order (cumulative percentage of drug released vs. time), First-order (log cumulative percentage of drug unreleased vs. time), Higuchi (cumulative percentage of drug released vs. square root of time), and Korsmeyer-Peppas (log cumulative percentage of drug released vs. log time), the release mechanism of the drug from formulations F1–F9 was identified. For every model, the values of the regression coefficients were ascertained for the various formulations F1–F9.

RESULTS AND DISCUSSION

DRUG-POLYMER INTERACTION (FTIR) STUDY

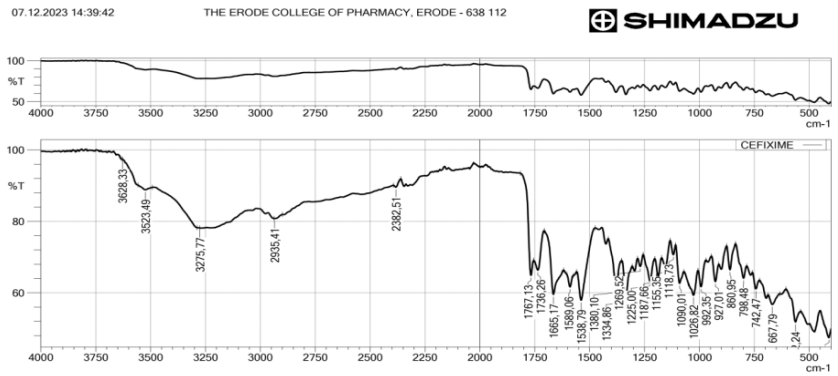

Fig. 1: FTIR of cefexime trihydrate.

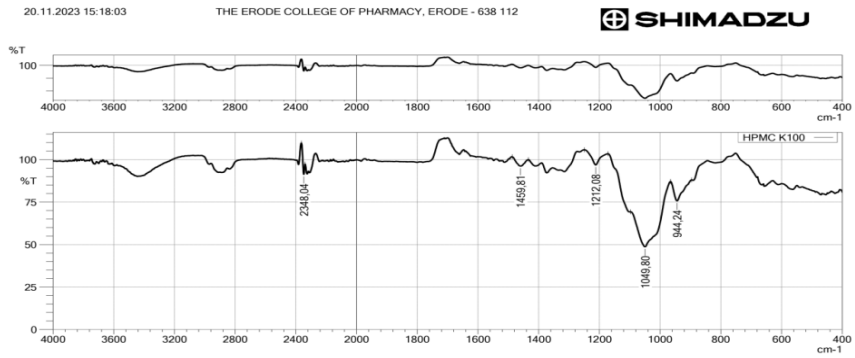

Fig. 2: FTIR of HPMC K100M.

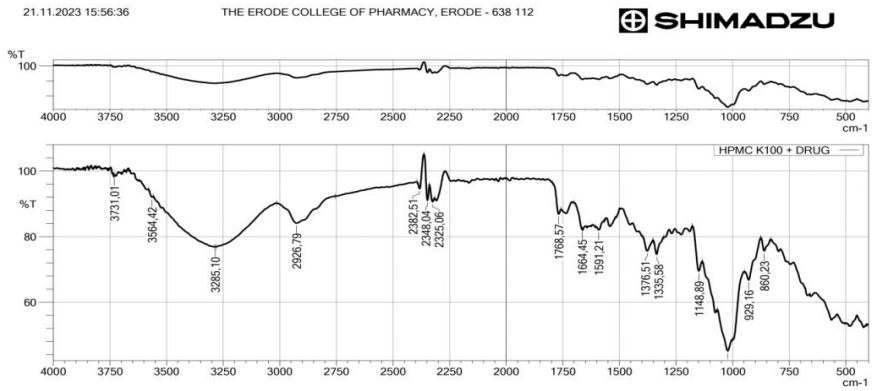

Fig 3. FTIR of Drug + HPMC K100M.

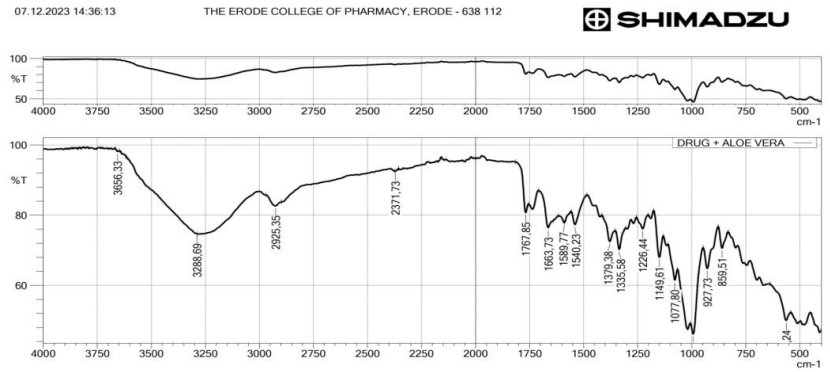

Fig. 4: FTIR of Drug + Aloe vera.

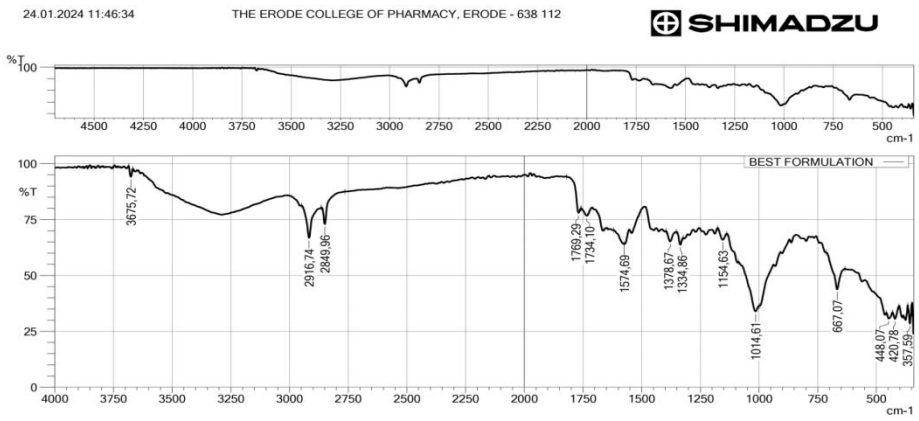

Fig. 5: FTIR of optimized formulation (F5).

Standard calibration curve by UV spectroscopy

Cefixime trihydrate

Table 2: Concentration and Absorbance of Cefixime trihydrate.

S. No	Concentration (µg/ml)	Absorbance at 285 nm
1.	0	0
2.	2	0.075
3.	4	0.148
4.	6	0.226
5.	8	0.291
6.	10	0.368

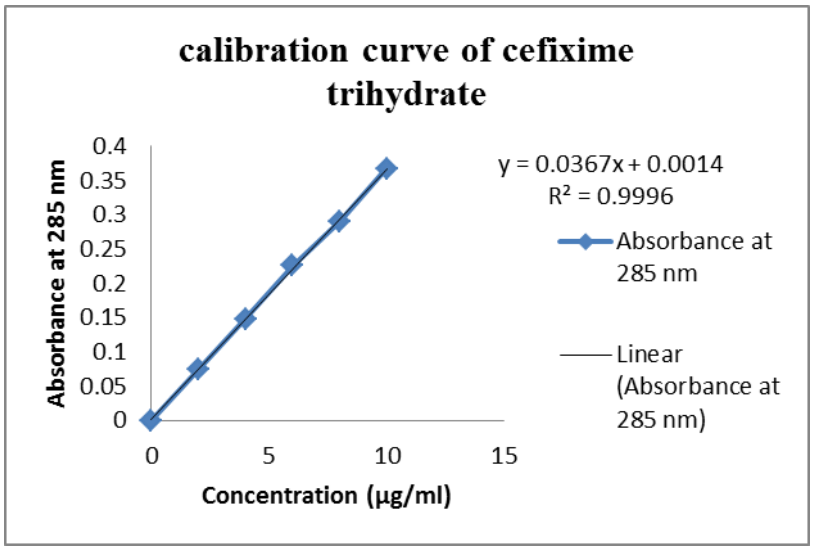

Fig. 6: Calibration curve of cefixime trihydrate.

The calibration curve showed linearity in a particular range and the regression coefficient (R^2) value of cefixime trihydrate was found to be 0.9996 at 285 nm.

Pre-Compression study of tablet blend

Table 3: Pre-Compression Parameters.

Formulations	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.55	0.65	15.38	1.18	24.92
F2	0.53	0.62	14.51	1.16	26.07
F3	0.54	0.63	14.28	1.16	29.38
F4	0.57	0.62	8.06	1.08	30.40
F5	0.58	0.65	10.76	1.12	28.53
F6	0.52	0.62	16.12	1.19	22.98

F7	0.59	0.68	13.23	1.19	24.63
F8	0.58	0.69	15.94	1.15	29.59
F9	0.59	0.69	14.49	1.16	30.61

ANOVA for Reduced Linear model

Response 1: IVD

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	201.42	1	201.42	5.44	0.0420	significant
B-Aloe Vera Powder	201.42	1	201.42	5.44	0.0420	
Residual	370.58	10	37.06			
Lack of Fit	159.58	7	22.80	0.3241	0.9007	not significar
Pure Error	211.00	3	70.33			
Cor Total	572.00	11				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 5.44 implies the model is significant. There is only a 4.20% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case

ANOVA for Reduced Linear model

Response 2: Floating time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	5035.60	1	5035.60	5.44	0.0420	significant
B-Aloe Vera Powder	5035.60	1	5035.60	5.44	0.0420	
Residual	9264.40	10	926.44			
Lack of Fit	3989.40	7	569.91	0.3241	0.9007	not signific
Pure Error	5275.00	3	1758.33			
Cor Total	14300.00	11				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 5.44 implies the model is significant. There is only a 4.20% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case is a significant model term. Values greater than 0.1000 indicate the model

Fig. 7: ANOVA of 2 Responses (In Vitro Drug Release & Flosting Time).

2 Solutions found

	Number	HMPC	Aloe Vera Powder	IVD	StdErr(IVD)	Floating time	StdErr(Floating time)	Desirability	
	1	***100.000***	**35.427**	**95.429**	**1.767**	**117.144**	**8.835**	**0.897**	**Selected**
	2	*100.000*	35.303	95.304	1.762	116.522	8.811	0.897	

Fig. 8: Optimized Formulation Selected by StatEase Software.

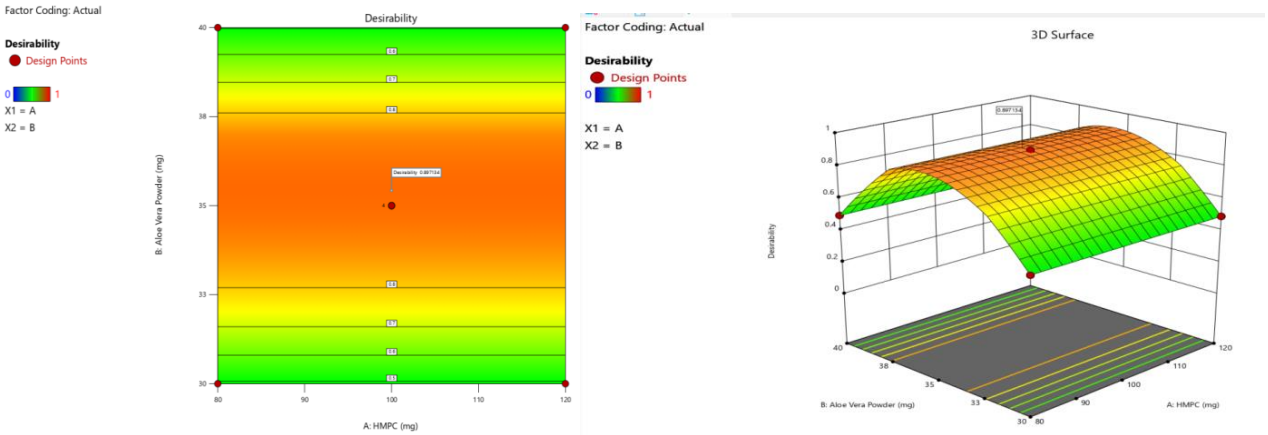

Fig. 9: Contour Plot – Desirability & 3D Response Curve.

POST COMPRESSION PARAMETER

Table 4: Post Compression Parameters.

Formulation	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Swelling index (%)
F1	485	3.7	4.1	0.49	96.06	87.25
F2	500	4.1	4.1	0.47	97.35	91.36
F3	490	3.9	3.9	0.58	94.22	93.87
F4	490	3.8	4	0.65	97.59	89.12
F5	500	3.5	4.1	0.63	99.65	95.65
F6	480	4.1	4	0.52	96.98	90.87
F7	485	3.9	4	0.61	97.80	89.90
F8	490	3.5	3.9	0.47	98.35	93.54
F9	500	3.8	4	0.67	98.73	92.00

IN-VITRO DISSOLUTION STUDIES

Cefexime trihydrate

The invitro drug release study of cefexime trihydrate a 285 nm using 0.1N HCL as follows

Table 5: *Invitro* release profile of cefexime trihydrate.

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	6.48	7.86	7.41	9.36	10.48	11.53	10.58	10.36	8.96
2	12.16	13.4	13.62	18.78	28.48	22.56	28.37	20.78	19.41
3	18.34	17.43	19.49	25.11	35.5	29	36.41	29.14	26.82
4	24.68	20.41	21.15	30.52	42.38	39.45	43.61	38.76	39.06
5	30.41	28.32	27.34	39.34	54.45	46.11	56.82	46.81	48.75
6	36.38	34.5	36.82	45.68	62.26	57.34	63.36	54.43	57.3
7	40.57	39.64	42.68	54.93	70.1	64.67	71.47	60.04	64.59
8	46.77	44.71	50.31	61.42	83.46	71.21	80.68	69.5	69.86
9	49.04	47.8	59.83	69.64	90.65	79.18	84.18	75.31	76.43
10	52.18	50.17	64.21	78.68	94.64	85.42	89.41	84.12	80.27
11	67.61	59.95	69.63	84.71	95.96	89.62	90.93	89.95	86.7
12	74.35	65.19	72.46	89.56	96.03	92.51	94.64	94.57	92.61

The Optimized formulation (F5) showed the maximum drug release of 96.03% at the end of 12hrs.

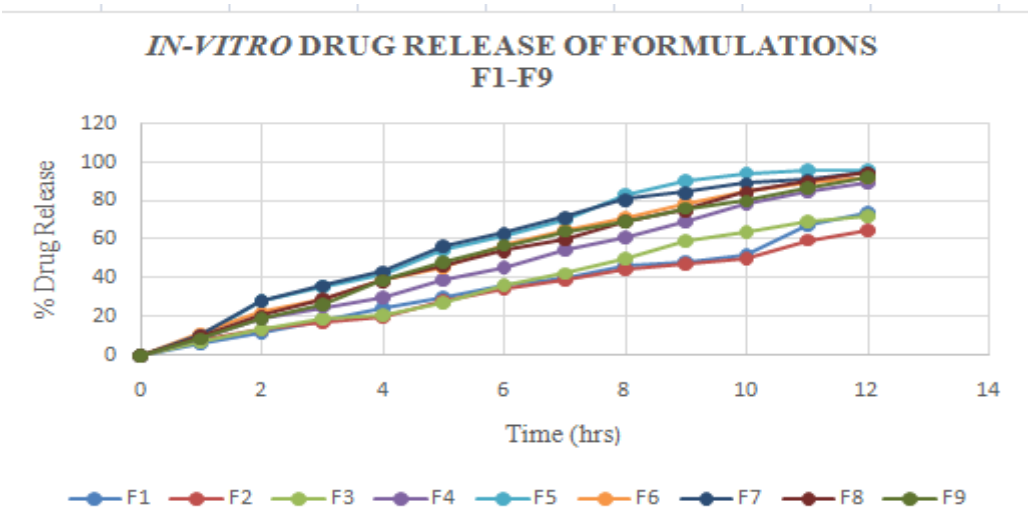

Fig. 10: *In-vitro* drug release of Cefixime Trihydrate.

Table 6: *In- vitro* buoyancy and lag time study.

Formulation	Floating lag time (sec)	Total floating duration (hrs)
F1	36	6.30
F2	31	8.00
F3	29	12.00
F4	34	8.00
F5	32	12.00
F6	40	9.00
F7	38	12.00
F8	42	12.00
F9	31	7.00

KINETIC ANALYSIS OF *IN-VITRO* DRUG RELEASE OF F5

Release kinetics of Cefixime Trihydrate

Table 7: Determination of release kinetics of Cefixime trihydrate in F5.

Time (mins)	% Drug release	% Drug remaining	Log % drug remaining	SQRT 't'	Log 't'	Log % drug release
0	0	100	2	0	0	0
1	10.48	89.52	1.95	1	0	1.02
2	28.48	71.52	1.85	1.41	0.30	1.45

3	35.50	64.50	1.80	1.73	0.47	1.55
4	42.38	57.62	1.76	2	0.60	1.62
5	54.45	45.55	1.65	2.23	0.69	1.73
6	62.26	37.74	1.57	2.44	0.77	1.79
7	70.10	29.90	1.47	2.64	0.84	1.84
8	83.46	16.54	1.21	2.82	0.90	1.92
9	90.65	9.35	0.97	3	0.95	1.95
10	94.64	5.36	0.72	3.16	1	1.97
11	95.96	4.04	0.60	3.31	1.04	1.98
12	96.03	3.97	0.59	3.46	1.07	1.98

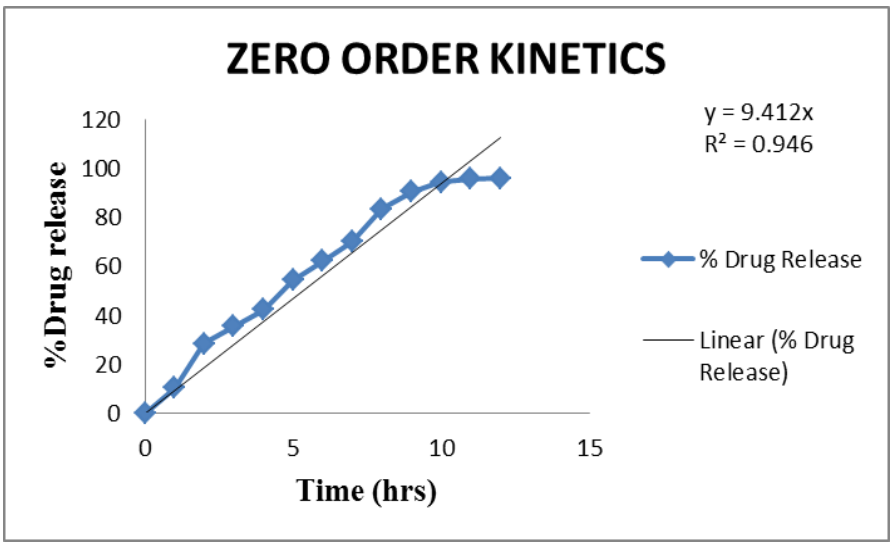

Fig. 11: Zero Order Release Kinetics.

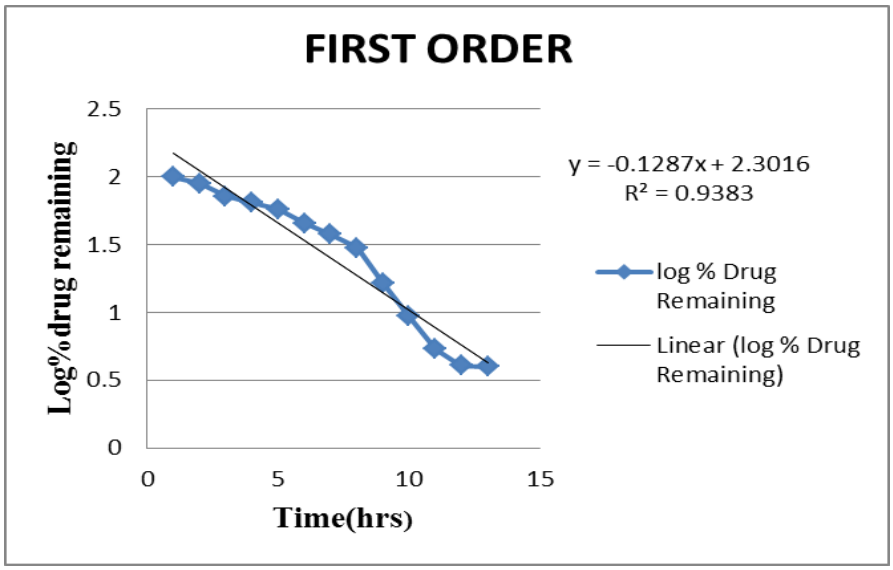

Fig. 12: First order release kinetics.

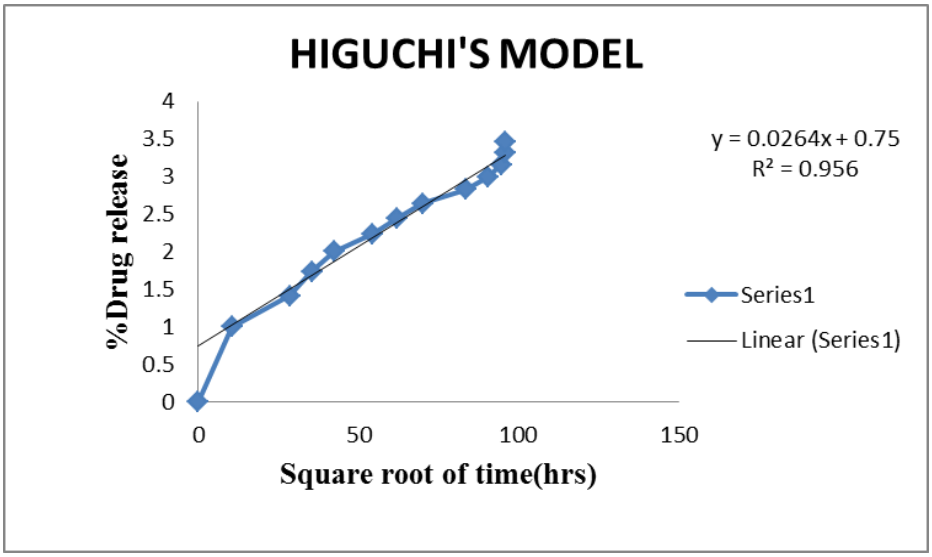

Fig. 13: Higuchi release model.

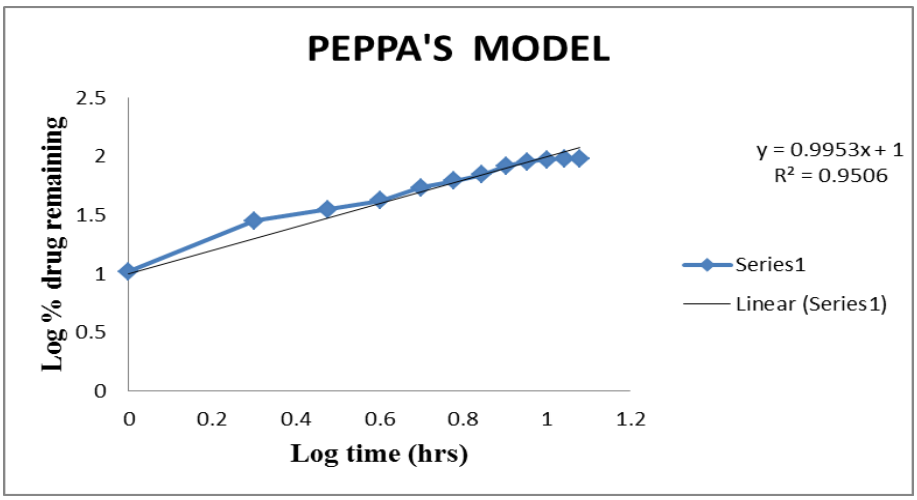

Fig. 14: Korsmeyer or Peppas release model.

Table 8: Kinetic value obtained from *In-vitro* release of Cefixime trihydrate in F5.

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2				n-value
F5	0.946	0.938	0.956	0.950	0.995

Based on the data analysis, the drug release for cefixime trihydrate was found to follow Higuchi release kinetics with highest linearity (R^2) of 0.956. The slope ('n') value was found to be 0.995 indicating that the release follows anomalous diffusion mechanism (non-Fickian transport).

CONCLUSION

The study was concluded that to develop a floating matrix tablet of cefixime trihydrate and aloe vera gel powder for prolonged gastric residence time and to increase the bioavailability of the drug. All the formulations (F1-F9) were optimized by using design expert software by CCD and the optimized batch was found to be F5. The formulated tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, friability, drug content, floating lag time, floating time and swelling index. The *in vitro* dissolution studies of F5 showed maximum drug release of 96.03%. The release kinetics of F5 showed highest linearity R2 of 0.956. The 'n' value (0.995) obtained by fitting into this peppas model, concluded that the mechanism of release to be non-Fickian anomalous diffusion mechanism.

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