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FORMULATION AND EVALUATION OF STOMACH SPECIFIC DRUG DELIVERY SYSTEM FOR CEFPODOXIME PROXETIL

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ABSTRACT

The objective of the present study was to formulation and evaluation of stomach specific drug delivery system for Cefpodoxime Proxetil. Cefpodoxime Proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of cephalosporin class. Cefpodoxime Proxetil has a short elimination half-life & also possesses high solubility, chemical, enzymatic stability and absorption profile in acidic pH. Cefpodoxime Proxetil floating insitu gel drug delivery system were prepared using Sodium alginate as gelling polymer, HPMC K100M as release retarding (sustained release) polymer and calcium carbonate (CaCo3) as complexing agent using ion sensitive hydrogel approach. A 32 full factorial design was applied to systematically optimize the drug release profile. The concentration of sodium alginate (X1) and concentration of HPMC K100M (X2) were selected as independent variable and gelling strength, floating lag time & time required for complete release (T100) were selected as dependent variable. The optimize batch was obtained is F9 showed statisfactory results with respect to viscosity, floating lag time, total floating duration & sustained drug release properties.

KEYWORDS: Floating in situ gel, sustained release, Cepfodoxime Proxetil, Ion sensitive hydrogel, sodium alginate, HPMC, 32 Full factorial design.

MATERIALS AND METHOD

List of chemicals used

Table: 1

SI. No	Materials	Property	Supplier
1	Cefpodoxime Proxetil	Antibioctic	Nibin Pharmaceutical
2	Sodium alginate	Gelling agent	ACS Chemicals Ltd, Ahmedabad
3	HPMC	Release retarding polymer	Colorcon Asia Pvt Ltd-Goa
4	Calcium carbonate	Complexing agent	Astron chemicals Ltd
5	Sodium citrate	Stabilizer	Astron chemicals Ltd
6	Methyl parabin	Preservative	Astron chemicals Ltd
7	Sucralose	Sweetening agent	Astron chemicals Ltd

List of instruments

Table No: 2

SI. NO	Instruments	Manufacturer
1	Weighing balance	Wenser
2	UV spectrophotometer	Shimadzu
3	FT-IR	Shimadzu
4	Magnetic stirrer	Patel Scientific
5	pH Meter	Patel Scientific
6	Dissolution apparatus	Veego
7	Viscometer	Brookfield Eng. Lab, US.

METHODOLOGY

Preformulation study

Following are the tests performed for the preformulation study:

1. **Drug Identification Study**

- Organoleptic properties
- Melting point
- FT-IR spectrum of drug
- Solubility study
- UV Scanning

2. **Calibration curve**
3. **Drug-excipient compatibility study (FT-IR and DSC)**

Post formulation study

Following are the tests performed for the post formulation study:

1. Gelation Studies.
2. Viscosity Measurement.

3. Gel Strength Determination (Modified method).
4. pH Measurement.
5. Drug Content Determination.
6. In-vitro Buoyancy Study.
7. In-vitro Drug Release Study.
8. Stability Study of Optimized Formulation.

For optimization of final formulation, 3^2 factorial design has been used. From the design response surface plots and contour plot has been drawn.

METHOD OF PREPARATION OF IN SITU GEL

Specified quantity of Cefpodoxime Proxetil, Sodium citrate, Calcium carbonate, methyl paraben, sucralose, and different polymers such as Sodium alginate and HPMC were weighed accurately. Heat deionized water containing Sodium citrate at 60ºC (Solution A). In A solution add Sodium alginate and cool at below 40ºC with stirring. The solution B of HPMC was prepared in deionized water. Calcium carbonate and solid dispersion complexes were added and dispersed properly with continuous stirring in HPMC solution. After cooling to below 40ºC, both solutions A and B were mixed with continuous stirring. Solution of methy paraben and sucralose was added and mixed properly.

COMPOSITION OF OPTIMIZATION FORMULATION F-1 TO F-9 USING 3^2 FULL FACTORIAL DESIGN.

Table No: 3

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefpodoxime Proxetil	1.617	1.617	1.617	1.617	1.617	1.617	1.617	1.617	1.617
Sodium Alginate (%w/v)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
HPMC K100M (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
$CaCo_3$ (% w/v)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Sodium citrate (%w/v)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Methyl paraben (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sucralose	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water (ml)	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml	Q.S to 30ml

Evaluation Parameters

1. Gelation Studies

Gelation studies were carried out using 0.1 N HCl. In these studies the gelling capacity (gelling speed and extent of gelation) for all formulations were determined. Gelation characteristics were assessed ranging between + (poor), ++ (good), +++ (very good)**.**

2. Viscosity Measurement

The viscosity value of prepared formulations were measured by using Brookfield viscometer with spindle LV 1 at 1.5, 3and 6 rpm at room temperature. The average of three readings was used to calculate the viscosity. Evaluations were conducted in triplicates.

3. Gel Strength Determination (Modified method)

A sample of 50 g of the gel was put in a 100 ml graduated cylinder. A weight of 35 g was placed onto the gelled form. The gel strength, which is an indicator for the viscosity of the gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel.

4. pH Measurement

The pH was measured in each of the sodium alginate based in situ solutions, using a calibrated digital pH meter at room temperature. The measurements of pH of each data were performed in triplicate**.**

5. Drug Content Determination

Formulation equivalent to 5 ml of Cefpodoxime Proxetil insitu gel was accurately taken. Transfer it to a 100 ml volumetric flask containing 100 ml 0.1 N HCl. Shaken vigorously for 30 min and then sonicated for min and filtered. Dilution of filtrate were made with 0.1 N HCl. Absorbance of this solution was made at 263 nm (λmax of Cefpodoxime Proxetil); values were substituted in the equation of calibration curve to obtain concentration**.**

6. In-vitro Buoyancy Study

The in vitro buoyancy study was performed using the USP dissolution apparatus II with 500 ml of simulated gastric fluid (pH = 1.2). The medium temperature was kept at 37ºC. A 10 ml sample of the prepared solution (in-situ gelling formulation) was drawn up with help of a disposable syringe and placed into petri dish. Then, the petri dish was placed in the dissolution vessel containing the medium without much turbulence. The time for gel to come

to surface (floating lag time) and the time the gel remained floating on the medium surface (total floating time) were recorded**.**

7. In-vitro Drug Release Study

The drug release study was carried out using USP (type-II) paddle apparatus at 37 ± 0.5ºC and at 50 rpm using 500 ml of pH 1.2 HCL as a dissolution medium (n = 3). Formulations each containing 10 ml were used for the study. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. % drug dissolved at different time intervals was calculated using the simultaneous equation method**.**

8. Stability Study of Optimized Formulation

The optimized final formulation was kept at controlled conditions of 40±2ºC/75±5% RH for stability studies for a period of 1 months* according to ICH guideline Q1C. Samples were removed and characterized by gelation studies, viscosity, gel strength, pH, Drug content, floating lag time, total floating time and in vitro drug release study.

(*optimized formulations are kept for further stability study.)

EVALUATION OF INVITRO RELEASE KINECTICS

Dissolution Profile Modeling By Kinetic Study.

a) Zero order kinetics [Graph : Q Vs t]

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms, release (those dosage forms that release the drug in planned, predictable and slower than the normal manner), is zero-order kinetic.

$$\mathbf{Q = k_0\, t}$$

Where Q is the amount of drug released at time t

K_0 is the release rate

b) First order kinetics [Graph : log Qt Vs t]

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern.

$$\mathbf{Log\ Qt = \log Q_0 + K_1\, t/2.303}$$

Where, Qt is the percent of drug release at time t

Q_0 is the initial amount of drug in the solution

K_1 is the first order release rate constant

c) Higuchi model: [Graph: Q Vs √t]

A large number of modified release dosage form contain some sort of matrix system. In such instance, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies:

$$\mathbf{Q = k_2 t^{½}}$$

Where Q is the percent of drug release at time t

k_2 is the diffusion rate constant.

d) Hixson–crowell model

Hixson and crowell recognize that the particle regular area is proportional to the cubic root of its volume.

$$\mathbf{W_0^{⅓} - W_t^{⅓} = K_0 t}$$

Where, W_0 is the initial amount of drug in the pharmaceutical dosage form,

Wt is the remaining amount of drug in the pharmaceutical dosage form at time t

K is a constant for the surface volume relation.

e) Korsmeyer peppas model

Korsmeyer peppas equation is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{Mt / M\infty = K t^n}$$

Where, Mt is the amount of drug release at time t

M∞ is the amount of drug release after infinite time

K is a release rate constant incorporating structural and geometric characteristics of the dosage form n is the diffusional exponent indicative of the mechanism of drug release. The log value of percent drug dissolved is plotted against log time for each formulation according to the above equation. For drug release from a cylindrical or that swellable polymer, if the value of $n \leq 0.45$ indicates fickian (case I) release; on the other hand if $0.45 < n < 0.89$ non-fickian (anomalous) transport could be obtained; and if n approaches 0.89, the release mechanism could be super case II type of release. Case II generally refers to a combination of

both diffusion and erosion controlled drug release. Release kinetics models were applied to optimized formulation (F9).

RESULTS

Preformulation Studies

Solubility Analysis

The solubility of API (drug) was determined as per BCS class.

Weighed amount of pure drug were added to 250 ml conical flask containing 25 ml distilled water. The sealed flask was shaken for 24hrs at 37±0.5ºC. Then aliquots were filtered through whatman filter paper. The sample were filtered, diluted and analyze by UV at λmax. Same way for different Medias listed below were checked

- 0.1 N HCL
- Methanol

Table 4: Solubility of API in different media

Sr No.	Media	Conc. (mg/ml)	Absorbance* (Mean ± S.D.)	Remarks
1	Water	10	0.083±0.002	Sparingly Soluble
2	0.1 N HCl	10	0.154±0.004	Soluble
3	Methanol	10	0.244±0.003	Highly soluble

DRUG- EXCIPIENT COMPATIBILITY STUDIES

Drug – excipient compatibility study was carried out by FT-IR Spectroscopy study. Method of performing FT-IR was prescribed in experimental work.

FTIR spectrum of:

- Cefpodoxime Proxetil
- Cefpodoxime Proxetil + Sodium Alginate
- Cefpodoxime Proxetil + HPMC
- Cefpodoxime Proxetil + Calcium Carbonate
- Cefpodoxime Proxetil + Sodium Alginate + HPMC + Calcium Carbonate + Sodium citrate + Methyl Paraben

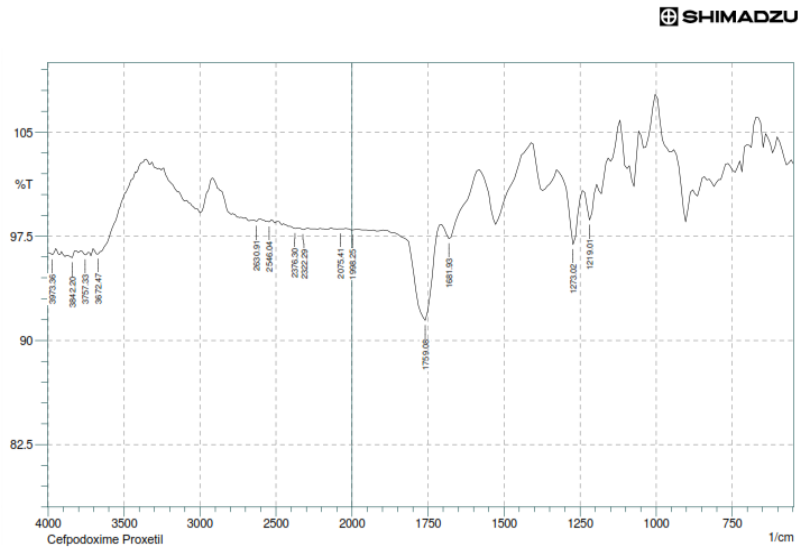

Figure 1 FT-IR spectrum of pure drug Cefpodoxime Proxetil

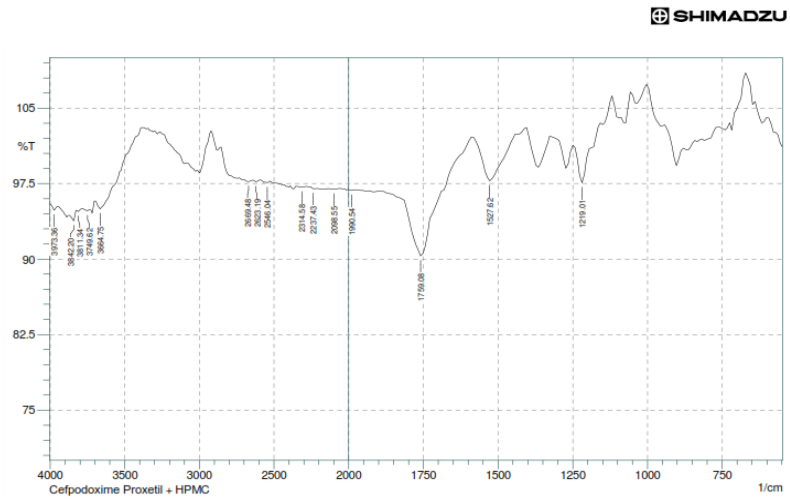

Figure 2: FT-IR spectrum of pure drug Cefpodoxime Proxetil and HPMC

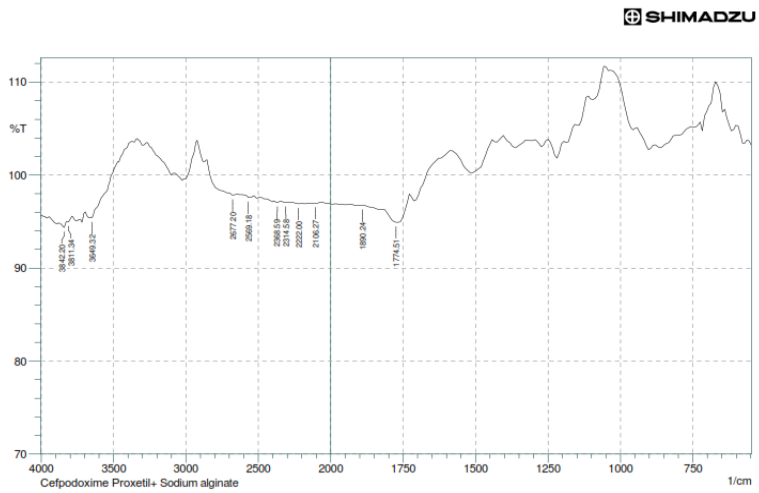

Figure 3: FT-IR spectrum of pure drug Cefpodoxime Proxetil and Sodium alginate

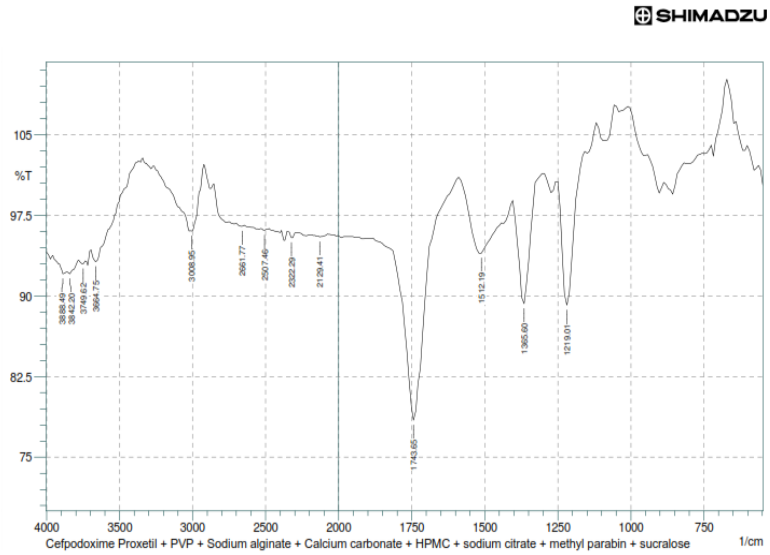

Figure 4: FT-IR spectrum of pure drug Cefpodoxime Proxetil, Sodium alginate and HPMC (Final formulation)

EVALUATION OF PARAMETERS

Table 5: Evaluation of factorial batches (n=3)

Batches	Gelling in 0.1N HCl*	Viscosity (cps)	Gelling strength (sec)	pH	Drug content (%)	FLT (Sec)	TFT (hr)
F1	+	162±1	21±1	7.29±0.01	99.55±0.49	30±0.5	3
F2	++	177.33±0.57	25±0.57	7.49±0.001	97.73±0.25	28±1.2	4
F3	++	190.33±1.15	29±0.57	7.69±0.05	99.84	25±1	4
F4	++	213±0.1	41±1	8.2±0.01	99.14±0.12	21±1	5
F5	+++	240.67±0.57	44±1	7.40±0.05	99.16±0.53	19±0.76	8
F6	+++	271.67±1.15	47±1.15	7.87±0.01	98.16±0.04	15±0.57	10
F7	+++	327.67±0.57	54±0.57	7.3±0.01	99.84±0.02	12±0	7
F8	+++	346.33±0.57	59±1.15	8.13±0.02	99.89±0.02	10±0.85	10
F9	+++	410.67±1.15	67±1.15	7.83±0.05	99.45±0.40	7±0.01	12

*+poor, ++good, +++very good

Table 6: Release profile of Cefpodoxime Proxetil in factorial batches (n=3)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	77.5078±1.036	72.246±0.598	77.931±0.52	66.125±0.48	46.253±0.34	24.842±0.05	52.652± 0.98	33.120±0.001	17.607±0.012
2hr	87.0886±1.19	79.183±0.56	84.061±0.54	74.102±0.29	51.654±0.51	30.246±0.02	59.0541±0.02	39.685±0.011	23.800±0.01
3hr	99.4962±1.36	89.12±0.78	92.041±0.89	83.312±0.91	62.853±0.25	39.153±0.99	64.673 ±1.9	46.308±0.01	35.460±0.01
4hr		98.761±0.52	99.771 ±0.52	90.677 ±0.52	69.757±0.29	51.744±0.79	76.875 ±0.004	52.953±0.005	40.119±0.006
5hr				98.766 ±0.79	80.671±0.91	59.783±0.85	82.55 ±0.01	64.199±1.57	48.821±0.002
6hr					84.809±0.29	63.043±0.825	93.334 ±0.04	71.853±0.01	55.816±0.004
7hr					86.012±0.29	72.385±0.29	99.923 ±0.01	76.82 ±0.02	63.2±0.001
8hr					99.032±0.05	84.169±0.29		83.62±0.02	71.021±0.002
9hr						93.213±0.21		91.43±0.001	79.188±0.004
10hr						99.806±0.05		99.02±0.01	86.421±0.002
11hr									95.215±0.01
12hr									101.09±0.373

In *vitro* drug release of different formulations

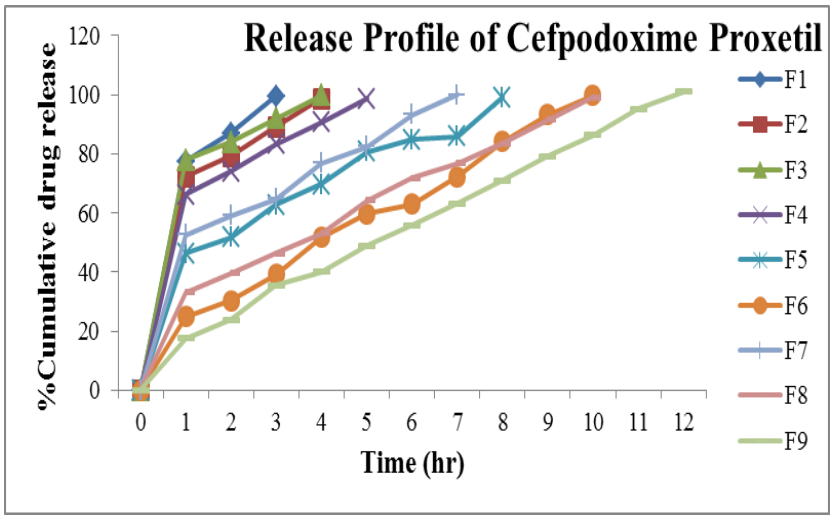

Figure 5: In vitro dissolution of Cefpodoxime Proxetil for factorial batches in 0.1N HCl

RELEASE KINETICS MODELS WERE APPLIED TO OPTIMIZE FORMULATION (F9).

Table 7: Release kinetics of optimized batch

DRUG RELEASE KINETIC DATA			OPTIMIZED BATCH (F9)
SR NO.	**KINETIC MODEL**	**PARAMETERS**	
1	Zero order	R^2	0.99635
		n	0.133006
		Intercept	7.3298
2	First order	R^2	0.78983
		n	0.00179
		Intercept	0.9451
3	Higuchi	R^2	0.97755524
		n	0.24468
		Intercept	3.9182
4	Hixon-crowell	R^2	0.926605
		n	0.010969527
		Intercept	2.9898
5	Korsmeyer and peppas	n	0.729489

SUMMARY

Cefpodoxime Proxetil is orally administered third generation, extended spectrum, semi synthetic antibiotic of cephalosporin class. Cefpodoxime Proxetil is a prodrug; its active metabolite is cefpodoxime. It has very good activity against *Enterobacteriance, Hemophilus species, Moraxella soecies, including lactamase* producers and many strains resistant to other oral agents. It is also active against many Gram-positive and Gram-negative bacteria. Cefpodoxime Proxetil is absorbed from the intestinal tract after oral administration and

hydrolysed to its parent moiety cefpodoxime acid by non-specific esterase in the intestinal wall/plasma. The bioavailability of Cefpodoxime Proxetil administered as tablet relative to Cefpodoxime sodium intravenous infusion is about 50% as drug having pH dependent solubility. It is stable and well absorbed within pH range 1-4. The drug shows relatively higher bioavailability in feb condition than fasted condition. Moreover drug have shorter half-life of 2-3 hr. Most of the conventional oral drug delivery systems have shown some limitations related to fast gastric-emptying time. It does not restain and locate the dosage form within the desired region of the gastrointestinal tract. Therefore, Short residence time so effective concentration in upper GIT cannot be achieved and thus fluctuation in plasma drug concentration occurs which does cure the disease effectively. To overcome the limitations of conventional therapy, a novel drug delivery system. In situ gel was selected not only to alleviate the shortcomings of conventional delivery vehicles but also provide stability and ease of administration. Floating drug delivery system is designed to prolong the residence time of the dosage form within the GI tract. It is the formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. Drug dissolution and release, from the gel floating in gastrointestinal fluid, occur in the stomach, under fairly controlled condition. FTIR study of drug along with excipients indicates absence of incompatibility between drug and excipients. In the preliminary studies, selection of floating polymer was done and then optimization of conc. of Sod. Alginate and HPMC K100M was done. Floating in situ gel was prepared by mixing using polymers such as Sodium alginate (floating agent), HMPC K100M (suspending agent) and sodium citrate and $CaCo_3$ (complexing agent). A 3^2 full factorial design was applied to investigate the combined effect of the two independent formulation variables (i.e. concentration of sodium alginate (X_1) and concentration of HPMC (X_2)) on the dependent variables (Gelling strength of suspension (Y_1), Floating lag time (Y_2) and Time required for complete release (T100) (Y_3)). Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables. Then optimum batch was identified. Then a check point batch was formulated using 0.98% sodium alginate and 0.97% HPMC K100M. It gave desired results in terms of time for 90% drug release almost equal to 12 hr. The model fitting of the optimized batch was carried out to find out the mechanism of drug release. Results showed that **korsmeyer and peppas** model was best fit for release of Cefpodoxime Proxetil from the dosage form. The stability study of optimized batch was carried out at room temperature for one month. It showed no statistically significant difference in in-vitro drug release profile before and after stability study.

CONCLUSION

Taken together, it is concluded that the floating in situ gel drug delivery system of Cefpodoxime Proxetil were successfully formulated by ion sensitive hydrogel approach. A 3^2 full factorial design was applied to systematically optimize the drug release profile. The concentration of Sodium alginate (X_1) and concentration of HPMC K100M (X_2) were selected as independent variable where as gelling strength, floating lag time & time required for complete release (T100) were selected as dependent variable. The optimize batch was obtained is F9 shows satisfactory results with respect to viscosity, floating lag time, total duration & Sustained drug release properties. Thus, ultimately Cefpodoxime Proxetil in situ floating gel was formulated with better & controlled delivery to stomach with an aim increasing the mean residence time in the stomach where the drug has higher solubility. Thus, better absorption, improved bioavailability, reduction in side effects, & therefore, a pediatric patient complaint product.

Future scope

The long term stability studies required to establish the stability data for these oral floating insitu gels.

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