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GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF CEFPODOXIME PROXETIL

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ABSTRACT

Gastric emptying is a complex process, one that is highly variable and that makes in vivo performance of drug delivery systems uncertain. A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter and intra subject variability of gastro-intestinal (GI) transit time and to the non-uniformity of drug absorption throughout the alimentary canal. Floating or hydro dynamically controlled drug delivery systems are useful in such applications. Various gastro retentive dosage forms are available, including tablets, capsules, and pills, laminated films, floating microspheres, granules and powders. Floating system have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms. The present work briefly addresses the physiology of the gastric emptying process with respect to floating drug delivery systems. The purpose of this review is to bring together the recent literature with respect to the method of preparation, and various parameters affecting the performance and characterization of floating system.

KEYWORDS: Gastro retentive, floating drug delivery system, cefpodoxime proxetil.

INTRODUCTION

Oral delivery of drugs is the most preferable route among all the drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration Garg. Technological attempts have been made in the pharmaceutical research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times and unpredictable gastric emptying times (GET). Dosage forms that can be retained in the stomach are called Gastro retentive drug delivery systems. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal Bioavailability. Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve.[1]

Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems provide drug release at predetermined, predictable, and controlled rate. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract preferably by passive diffusion, to ensure continuous absorption of the released drug. The average time required for a dosage unit to traverse the GIT is 3-4 hrs, although slight variations exist among various dosage forms orally administered drugs are absorbed by passive diffusion processes and by no passive means. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity because of the prevalence of these mechanisms in only certain regions of the GIT. Many drugs show poor BA because of the presence of enzymes and efflux pumps. Intestinal metabolic enzymes primarily, Phase I metabolizes such as cytochrome are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon.[2]

In addition, carriers like secretary transporter is P-glycoprotein may affect drug absorption. An example of such a, which is present in the tip of entrecotes and has the capacity to interact with a vast variety of drugs. P-gp sends the absorbed drug from the cytoplasm of the entrecotes back to the intestinal lumen, thus reducing the drug's bioavailability.

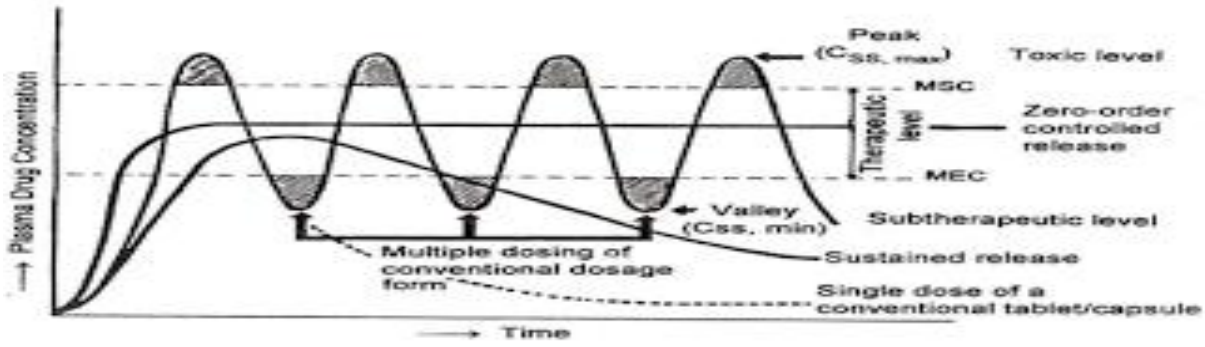

Figure: 1 Plasma level profile fallowing conventional and controlled released dosing form

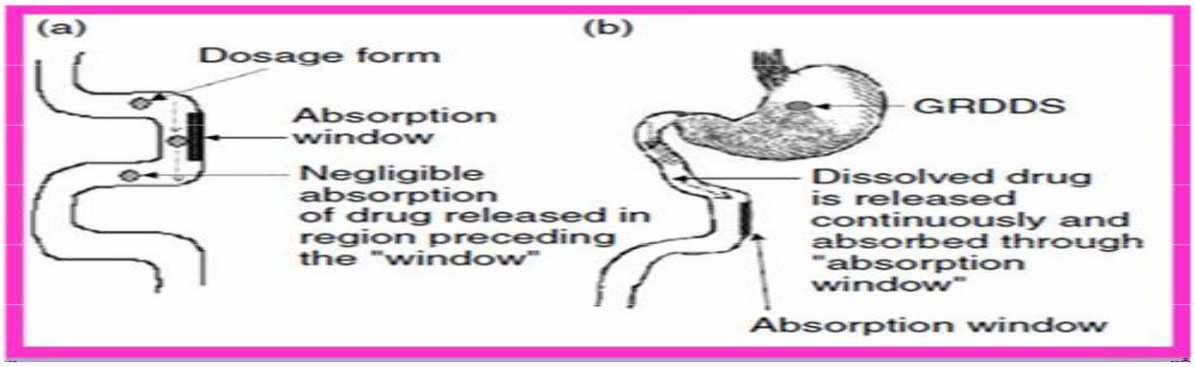

Figure: 2 Drug absorption in case of (a)conventional dosage form(b)Gastroretentive drug delivery system

Advantages of gastro retentive drug delivery system[3]

Bioavailability enhances, despite first pass effect, because fluctuations in plasma drug concentration are avoided, and a desirable plasma drug concentration is maintained by continuous drug release. Superior to single-unit floating dosage forms, as such microspheres release drugs uniformly and there is no risk of dose dumping.

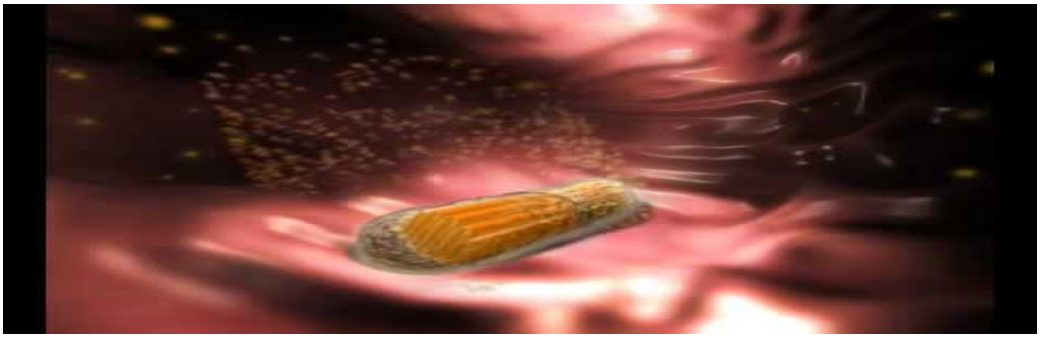

Figure: 3.Gastro retentive drug delivery system

Gastrointestinal Motility Patterns Affecting Dosage Form Retention

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage.

Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. The fasted state is associated with various cyclic events, commonly referred to as the Migrating Myoelectric Complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal.[4]

(Phase I), preburst, (Phase II), and burst, (Phase III) intervals.

Figure4.Gastric motility pattern

Approaches to increased gastric retention: Several techniques, including swelling, floating and muco adhesion, have been explored to increase the gastro retention of dosage forms.

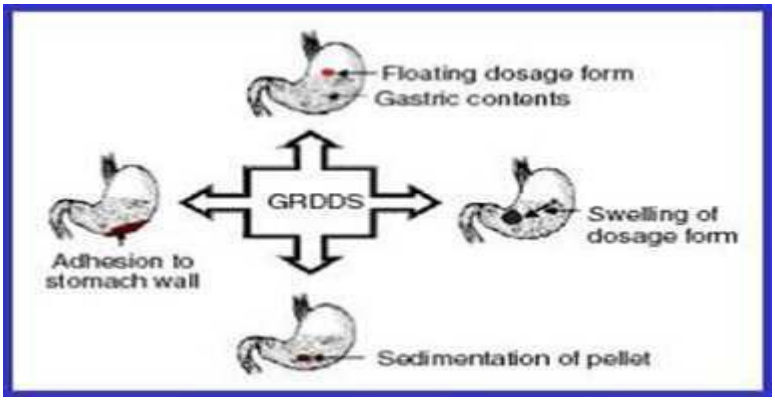

Figure: 5 Types of gastric retention

Floating systems: Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period without affecting the gastric emptying rate. The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier. Floating systems can be classified as Effervescent and Non Effervescent Systems.

(a) Effervescent Systems: The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Floatability can be achieved by generation of gas bubbles. CO2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid either the natural gastric acid entrapped of liquid, which forms a gas at body temperature. The approach has been used for single and multiple unit systems.

(b) Non - effervescent Systems: Hydro dynamically Balanced System (HBS) was first designed by Sheath and Tossounian in 1984. Such systems contain drugs with gel-forming hydrocolloids meant to remain buoyant on the stomach contents. These systems incorporate a high level20-75% w/w of one or more gel-forming; highly swell able, cellulose-type hydrocolloids [e.g. Hydroxyethyl cellulose, Hydroxypropyl cellulose.

Factors affecting gastric retention time of the dosage form[5]

Gastric residence time: An oral dosage forms is affected by several factors. The pH of stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. The rate of Gastric emptying depends mainly on viscosity, volume, and caloric content of meal. Biological factors such as age, body mass index, gender, posture, and diseased state.

Volume of Stomach: The resulting volume of stomach is 25 to 30 ml. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

Density: GRT is a function of dosage form buoyancy that is dependent on the density. The density of dosage forms affects the gastric emptying rate. Floating dosage form having density less than that of gastric fluids therefore it will float on gastric contents. Since it is away from the pyloric sphincter, the dosage units are retained in the stomach for a prolonged period. Size- Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.[6]

Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better GRT ≈90 % to 100 % retention at 24 hours compared with other shapes.

Limitations of floating GRDDS

One of the major disadvantages of floating systems is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently. These systems also require the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating systems for drugs that have solubility or stability problems in the highly acidic gastric environment or that are irritants to the gastric mucosa.[7]

Cefpodoxime proxetil

Cefpodoxime proxetil is an orally absorbed broad spectrum third generation cephalosporin antibacterial. It is a prodrug that is de-esterified *in vivo* to its active metabolite, cefpodoxime. After single- and multiple-dose (12-hourly) administration of cefpodoxime proxetil in the therapeutic dose range of 100 to 400mg of cefpodoxime equivalents, average peak plasma concentrations of cefpodoxime range from 1.0 to 4.5 mg/L and occur between 1.9 and 3.1 hours after administration. The half-life of cefpodoxime ranges from 1.9 to 2.8 hours.

MATERIALS AND METHODS

Materials: The following drug, excipients and chemicals were used for the formulation and evaluation of Gastroretentive drug delivery system.

Drug: Cefpodoxime Proxetil.

Polymers and Excipients: HPMC (K100 LV), Xanthan gum, Microcrystalline cellulose (MCC KG 100), Sodium bicarbonate, Anhydrous citric acid, Magnesium stearate, Talc.

Standard calibration curve

Standard calibration curve of Cefpodoxime Proxetil in pH 3 buffer Stock standard solution was prepared by dissolving accurately weighed 100 mg Cefpodoxime Proxetil in volumetric flasks, dissolved in methanol and diluted to 100 ml with freshly prepared in glycine buffer (pH 3.0). The stock solution was filtered through a 0.45 µm membrane filter. A standard curve was prepared by withdrawing appropriate aliquots from stock solution into a series of 10 ml of volumetric flasks.

Flow properties[8]

Angle of Repose: The flow characteristics are measured by angle of repose. Flow constrains due to frictional forces between the particles were quantified by angle of repose.

Angle of repose was calculated from the average radius using the following formula

$\theta = \tan^{-1} (h/r)$ Where, θ = Angle of repose, h = Height of the pile, r = Average radius

Table 1: Specifications of Angle of Repose

Angle of Repose	Type of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Hausner's ratio & Carr's compressibility index: Hausner ratio is an indirect index of ease of power flow. The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index = (Tapped density – bulk density / Tapped density) X 100

Table 2: Specifications of Flow Pro

% Compressibility	Flow Description
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

perties Corresponding to Compressibility Index

Hausner's ratio= Tapped density/ Bulk density

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Particle size determination: Particle size determination of Cefpodoxime Proxetil was determined.

Drug excipients compatibility study: The drug excipients interaction study was carried out by using Fourier transform infrared spectroscopy**.**

FTIR spectroscopy study: IR spectroscopy was used to determine the molecular interaction between drug and excipients. The above (as per DSC study) all physical mixtures and drug sample were mixed with dried KBr in ratio 1:100. The mixture was compressed to a 12 mm semi-transparent disk by applying a pressure of 10 tons for 2 min. The FTIR spectra over the wavelength range 4000-400 cm^{-1}were recorded using a FTIR.[9]

Preparation of Gastro retentive tablets of CefpodoximeProxetil: CefpodoximeProxetil tablets were prepared by the direct compression method. Eachtablet contained about 250 mg of the drug. All the ingredients were sifted throughsieve no. 40 and magnesium stearate was passed through sieve no 60. The requiredquantities of the materials were mixed thoroughly for 15 minutes in polybag andlubricated with magnesium stearate for 3 minutes.

Table 3: Composition of Cefpodoxime Proxetil floating tablets(X1-X9)

Ingredients (inmg)	X1	X2	X3	X4	X5	X6	X7	X8	X9
Cefpodoxime Proxetil	330	330	330	330	330	330	330	330	330
Xanthangum	16.5	21.45	26.40	16.5	21.45	26.40	16.50	21.45	26.40
HPMC K100 LV	26.40	26.40	26.40	33.0	33.0	33.0	39.60	39.60	39.60
MCCKG-100	21.55	16.60	11.65	14.95	10.0	5.05	8.35	3.40	3.45
Sodium lauryl Sulphate	4.90	4.90	4.90	4.90	4.90	4.90	4.90	4.90	4.90
Citricacid	14.70	14.70	14.70	14.70	14.70	14.70	14.70	14.70	14.70
Sodium bicarbonate	73.50	73.50	73.50	73.50	73.50	73.50	73.50	73.50	73.50
Magnesium stearate	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45
Totalweight	490	490	490	490	490	490	490	490	490

Evaluation parameters of tablets

Weight Variation test

Twenty tablets were taken from each formulation and weighed individually to check fo r weight variation. Calculated average weight and compared the individual tablet weight to the average.[10]

Table 4: Weight variation tolerance for tablets

Averageweightoftablets(mg)	Maximum%differenceallowed
80orless	10
80–250	7.5
Morethan250	5

b) Thickness: Thickness of tablets was measured by using digital Venire calliper.

c) Hardness: Tablets were selected at random from individual formulation and hardness was measured and expressed inKg/cm^2or Newton's (N).

d) Friability: Twenty tablets werer and omlyselected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100times in4min. The tablets were removed, deducted and accurately weighed. The percent weight loss was calculated. Results are expressed as mean values±SD.

Friability(%)=Initial weight-Final weight/InitialweightX100

Swelling index: The tablets were weighed individually (weightdesignatedasW1), placed separately in glass beaker containing 200ml of 0.1NHCl and incubated at37±1°C. The mucoadhesive tablets were removed from the beakersat1-hourintervals (over total of12h), and the liquid was removed carefully from the surface using paper. The swollen tablets were then weighed (W2). The swelling index (SI) was calculated using the following formula

$$\%\text{Swelling Index} = (W_2 - W_1)/W_1 X100$$

WhereW1-Initialweightoftablet, W2-Weightoftheswollentablet.

Mucoadhesive strength and mucoadhesion time: These were measured by modified balance method, a balance left pan was replaced with a weight to the bottom of which a tablet was attached and both sides were balanced with weight. Porcine gastric mucosa having a thick layer of mucus was fixed to a rubber cork, which was previously attached to the bottom of the beaker containing related medium with a level slightly above the mucosa. The weight was attached to the tablet brought into contact with the porcine mucosa, kept undisturbed for 5minutes and then the pan was raised. Weights were continuously added on the right side pan in small increments and the weight at which the tablet detached from the mucosa was recorded as the Mucoadhesive strength and the force of adhesion was calculated using following formula.[11]

Force of adhesion (N) =MucoadhesivestrengthX9.81/100

In vitro drug released study: The drug release of various formulationsX1-X9 was studied *invitro* using USP typeII apparatus setat100rpm.A buffer medium with pH3.0(900ml) at37.5±0.5°Cwas used.A10ml sample was withdrawn at1,2,4,6,8,10h time intervals over a period of 12h and replaced with the same dissolution media. The withdrawn samples were analyzed using HPLCat236nm.

Stability study: Stability studies were performed to check the effects of environmental conditions and storage conditions on the formulation. Optimized batch was maintained at40^{O}C/75±5%RHover a period of 3months to study the stability according to ICH guidelines.

RESULTS AND DISCUSSION

Standard calibration curve of Cefpodoxime Proxetilin pH 3.0

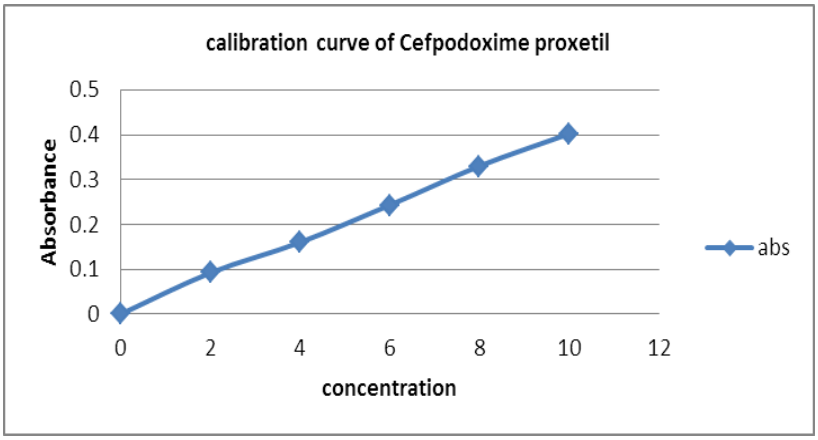

Fig.6: Calibration curve of Cefpodoxime Proxetil in glycine buffer (pH3)

Pre-formulation Study

Table 05: Evaluation of pre compression parameters of drug, polymers and excipients

Ingredients	Angleof repose(θ)	Bulk density gm/ml	Tapped density gm/ml	ausner'sratio	Compressi -bilityindex (%)
Cefpodoxime Proxetil	39.00±1.52	0.129±0.20	0.209±0.10	1.67±0.16	40.00±0.69
HPMCK100 LV	30.00±1.20	0.220±0.03	0.260±0.04	1.18±0.30	15.38±0.54
Sodiumalginate	32.32±1.52	0.230±0.03	0.310±0.04	1.34±0.30	25.80±1.76
Xanthangum	30.00±1.30	0.240±0.04	0.330±0.06	1.37±0.26	27.27±1.16

Sodium bicarbonate	37.00±2.00	1.100±0.35	1.760±0.22	1.60±0.25	37.50±1.22
Citricacid	28.00±1.50	0.630±0.50	1.000±0.55	1.60±0.63	37.5±1.30
Magnesium stearate	30.00±1.12	0.400±0.07	0.600±0.06	1.50±0.50	33.33±1.20

Particle size analysis of Cefpodoxime Proxetil by Malvern

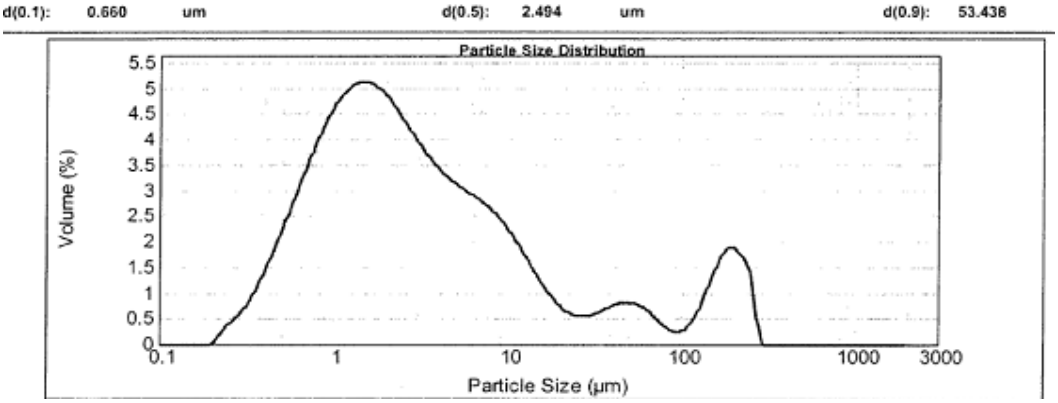

Fig.7: Particle size distribution of Cefpodoxime Proxetil by Malvern technique.

D (0.9): 53.438 µm (90 % of the particles were 53.438 µm or above)

D (0.5): 2.494 µm (50 % of the particles were 2.494 µm or above)

D(0.1):0.660µm (10%of the particles were 0.660 µm or above)

Drug excipients compatibility study

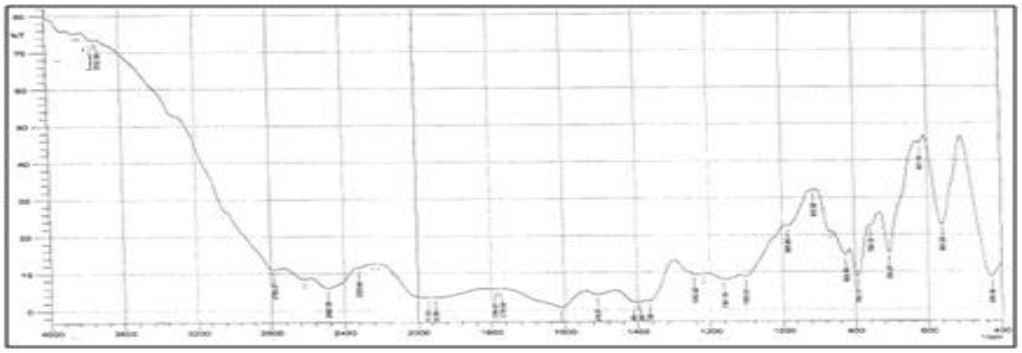

Fig.8: FTIR spectrum of Cefpodoxime Proxetil with Xanthan gum

Table-6: Physico chemical characterization of Floating tablets of Cefpodoxime Proxetil

Parameters	**X1**	**X2**	**X3**	**X4**	**X5**	**X6**	**X7**	**X8**	**X9**
Average weight(mg)*	490±3	490±3	490±3	490±3	490±3	490±3	490±3	490±3	495±3
Thickness (mm)*	5.83	5.82	5.82	5.83	5.84	5.84	5.83	5.8	5.86
Hardness (kg/cm^2)*	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5

Friability (%)	0.25	0.43	0.33	0.46	0.56	0.49	0.51	0.46	0.52
Buoyancy lag time(sec)*	21±3	23±3	20±3	25±3	27±3	26±3	29±3	30±3	35±3
Total Buoyancy time (h)	12	12	12	8	12	10	12	12	12
Drug content (%)*	99.27 ±1.58	98.64 ±1.58	99.00 ±1.58	99.71 ±1.58	100.11 ±1.58	99.51 ±1.58	100.1 ±1.58	100.34 ±1.58	100.15 ±1.58

Swellingindex: Swelling is also a very important factor to ensure drug dissolution of the formulation. The hydration ability of the formulation influences; (I)tablet buoyancy (ii)adhesion ability of swellable polymers and(iii)drug release kinetics. Cefpodoxime Proxetil composed of polymeric matrices build age layer around the tablet core when they come in contact with water. The ability of hydro gel to absorb water is due to the presence of hydrophilic groups. The swelling index of mucoadhesive controlled release tablets of formulations X6andX9 were 125±10% and155±10% at10h.

Mucoadhesion: It can be seen that the microspheres had good mucoadhesive properties and could adequately adhere to intestinal mucosa. The results also showed that with change in polymer to drug ratio, the % mucoadhesion also varies. The maximum and prolonged mucoadhesion (87.11%) was observed with the formulation.

Table7. Percentage mucoadhesion

Formulation No.	Percentage Mucoadhesion
X1	74.30
X2	77.21
X3	79.80.
X4	80.12
X5	82.32
X6	84.11
X7	78.11
X8	83.40
X9	87.11

In vitro drug released for mucoadhesive gastro retentive drug delivery system

The tablets with formulations X1toX9, containing combinations of Xanthum gum with HPMCK100LV in different ratios were evaluated. The formulations X1, X2, X3, X4, X5, and X6 burst within 4h with cumulative drug release of 99.20±0.22, 99.30±2. 89, 99.50±3. 87, 98. 78±3. 87, 98.00±3.20, and 96.00±0.52 percent respectively. Formulations X8, X9 could maintain its matrix integrity for more than 8hwith release of 98.90±1.23 and

99.80±3.20 % of drug respectively.

Table8: Evaluation of Cefpodoxime Proxetil Floating Gastro retentive tablets (H9) kept for stability at40^{0}C/75%RH

Formulation	**Cefpodoxime Proxetil floating tablets(X9)**			
Parameters	**Initial**	**1Month**	**2Months**	**3Months**
Averageweight (mg)	495mg	495mg	495mg	495mg
Thickness(mm)	5.80±0.078	5.81±0.098	5.82±0.058	5.80±0.078
Hardness (kg/cm^2)	4-5	4-5	4-5	4-5
Buoyancy Lag time (sec)	13±3	15±4	16±4	18±4
Total buoyancy time (h)	12	12	12	12
Drugcontent (%)	100.13±2.10	99.93±4.10	99.90±0.95	99.97±0.81
%drug released	99.0±0.92	98.0±0.97	98.2±0.45	98.1±0.74

CONCLUSION

In conclusion, on the basis of the in vitro drug release studies, it may be concluded that formulation X9 is most stable. The Mucoadhesive tablets were maintained at 40 °C / 75 %relative humidity in closed high-density polyethylene bottles for 3 months. There were no changes in the physicochemical parameters and drug content of in the formulation X9. It may possibly concluded that increasing percentage of polymer in formulation the decreased drug release pattern, which was dependent on type of polymer used in the formulation. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of Cefpodoxime Proxetil for mucoadhesive tablets containing Xanthum gum with HPMC K100 LV which showed controlled drug release up to 12 h and may possibly be a better delivery system for drug like Cefpodoxime Proxetil.

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