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FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF CEFPODOXIME PROXETIL

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ABSTRACT

In this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailability. Preformulation studies were carried out to optimize the required quantity for HPMC (K4M). (K15M). (K100M). Total 12 formulations were prepared. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as hydroxy propyl methyl cellulose HPMC (K4M). (K15M). (K100M) with other standard excipients like sodium bicarbonate, MCC and Magnesium stearate used as gas generating agent, as filler and as lubricant respectively. Tablets were evaluated for physical characterization. All the matrix tablets showed significantly greater swelling index and exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than12 hr. The optimized showed no significant change in physical appearance, drug content, floatability or *in-vitro* dissolution pattern after storage at 45^{o}C at 75% RH for three months.

KEYWORDS: Cefpodoxime Proxetil, swelling index, floating capacity, HPMC.

INTRODUCTION

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, due to ease of admistration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS). Controlled release drug delivery system release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration.

The CRDDS possessing ability of being retained in the stomach are called gastro retentive drug delivery system (GRDDS) and they can help in optimizing oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window, for prolonged period of time.[1] Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. The controlled gastric retention[2] of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying.[3]

Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions, fundus, body and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.[4]

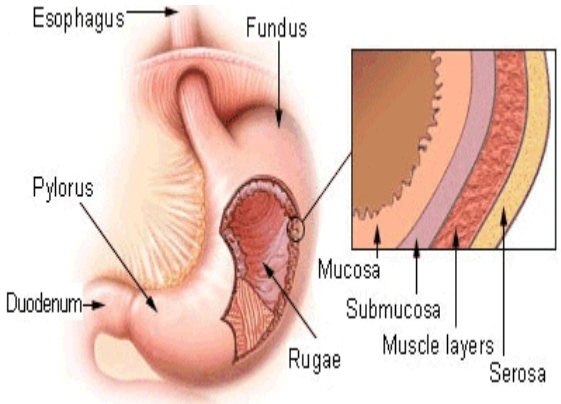


Figure 1.Physiology of stomach.

Gastric Emptying

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine.
Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises of continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form.

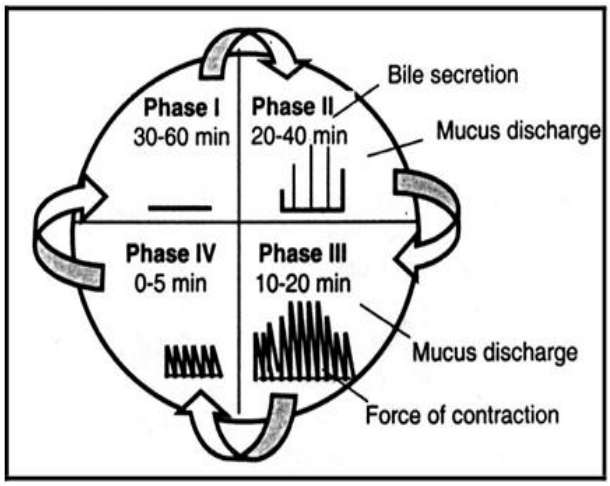
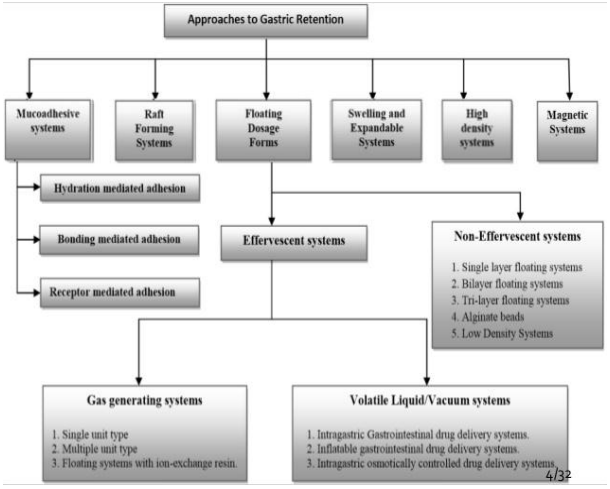


Figure 2. Typical motility patterns in fasting state

Need Of Grdds[5]

- Drugs required to exert local therapeutic action in the stomach: misoprostol, 5- fluorouracil, antacids and antireflux preparations, anti Helicobacter pylori agents and certain enzymes.
- Drugs exhibiting site-specific absorption in the stomach or upper parts of the small intestine: atenolol, furosemide, levodopa, p-aminobenzoic acid, piretanide, riboflavin- 50-phosphate, salbutamol (albuterol), sotalol, sulpiride and thiamine.
- Drugs unstable in lower part of GI tract: captopril.
- Drugs insoluble in intestinal fluids (acid soluble basic drugs): chlordiazepoxide, chlorpheniramine, cinnarizine, diazepam, diltiazem, metoprolol, propranolol, quinidine, salbutamol and verapamil.
- Drugs with variable bioavailability: sotalol hydrochloride and levodopa.



The various mechanisms used for development of gastroretentive drug delivery systems are shown in Figure 3.[6,7]

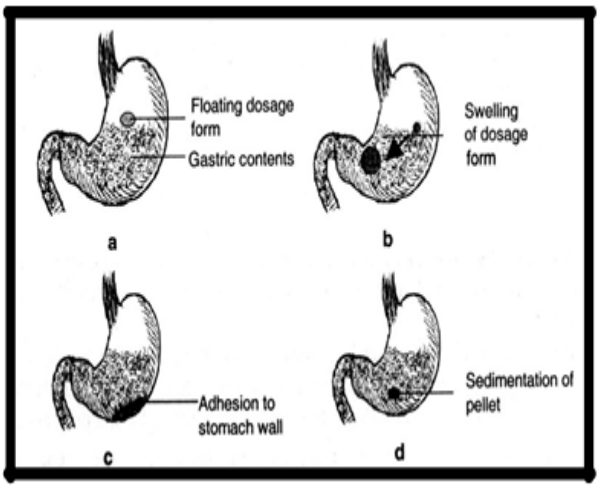


Figure 3. Various forms of gastroretentive systems; (a) Floating gastro-retentive drug delivery systems; (b) Swelling gastro-retentive drug delivery systems; (c) Bioadhesivegastroretentive drug delivery systems; (d) High-density gastro retentive drug delivery systems.

Floating drug delivery system

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach.[8] Floating drug delivery systems are classified depending on the use of two formulation variables, effervescent and non-effervescent systems.

Effervescent system[9,10]

A drug delivery system can be made to float in the stomach by incorporating a floating chamber which may be filled with vacuum, air or inert gas. The gas in the floating chamber can be introduced either by volatilization of an organic solvent or by the effervescent reaction between organic acid and bicarbonate salts.

A. Volatile liquid containing system

The gastric retention time of a drug delivery system can be sustained by incorporating floatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasify at body temperature to cause inflation of chamber in the stomach. These devices are osmotically controlled floating system.[11] Intragastric osmotically controlled drug delivery systemconsist of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In stomach water is absorbed through the semipermeable membrane into the osmotic compartment to dissolve the salt. An osmotic pressure is thus created, which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce it's volume and release the drug solution through the delivery orifice(Figure 4).[12]

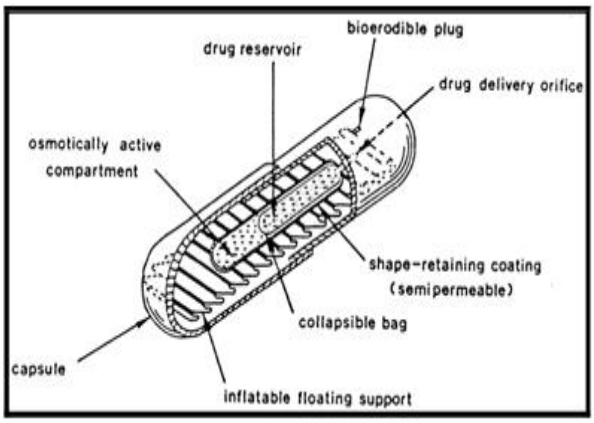


Figure 4.Osmotically controlled drug delivery system.

B. Gas generating system

These are matrix types of systems prepared with swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastriccontents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which providesbuoyancy to the dosage forms. A decrease in in specific gravity causes the dosage form to float on the chyme.[13] In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer and CO_2 bubbles are trapped in the swollen matrix (Figure 5a). Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (Figure 5b). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2 (Figure 5c). The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of polymer. Its difficult to control in situ acid base reaction and in turn drug release.[14]

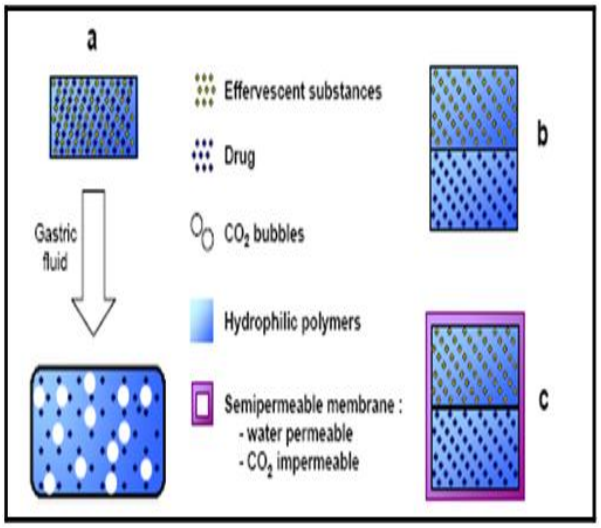


Figure 5. Gas generating system: Schematic monolayer drug delivery system(a) Bilayer gas generating system, with (c) or without (b)semipermeable membrane.

Raft-forming system

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles (Figure 6) on contact with gastric fluid. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.[15]

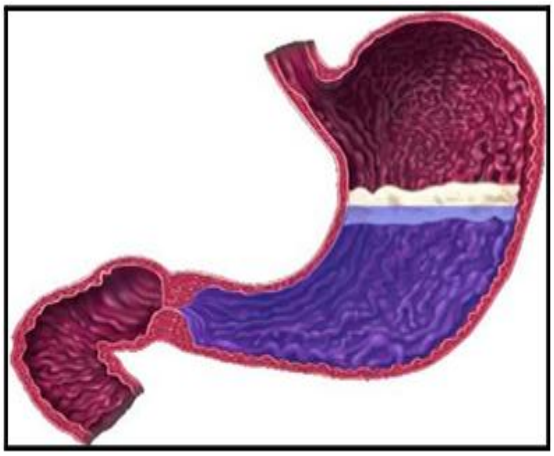


Figure 6.Schematic illustration of the barrier formed by a raft-forming system.

Non-effervescent floating dosage form

The most commonly used excipients in non-effervescent FDDS are gel-forming or highly swellablecellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration.

Hydrodynamically balanced system

On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug. As the exterior suface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air trapped in by swollen polymer maintainsadensityless than unityand confersbuoyancy to these dosageforms (Figure 7).

The hydrodynamically balanced system must comply with three major criteria-

- It must have sufficint structure to form cohesive gel barrier
- It must maintain an overall specific density lower than that of gastric content.[16]

The main drawback of HBS is pasivity of operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence on the characteristics and amount of polymer. Effective drug delivery depends upon the balance between drug loading and effect of polymer on it's release profile.

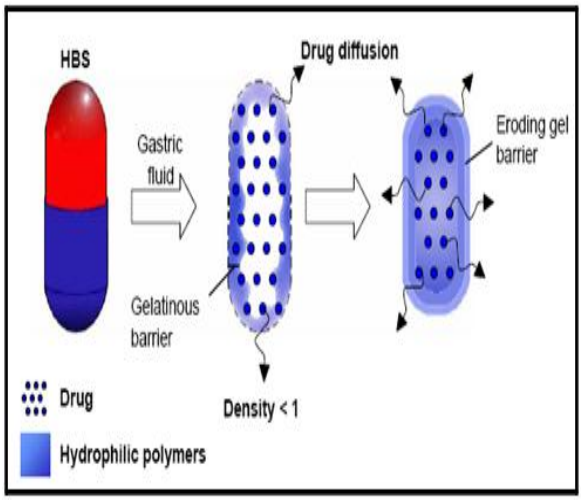


Figure 7.Hydrodynamically balanced system (HBS).

Expandable gastroretentive dosage forms

- A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. The expandable GRDFs are usually based on three configurations-Small (‘collapsed’) configuration which enables convenient oral intake
- Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.
- Another small form that is achieved in the stomach when retention is no longer required i.e. after the gastroretentive dosage form hasreleased its active ingredient, there by enabling evacuation.

Swellable system[17]

Swelling usually occurs because of osmosis. These are dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type systems”. On coming in contact with gastric fluids, the polymers imbibe water and swells. The extensive swelling of these polymers is due to the presence of physical and chemical crosslinks in the hydrophilic polymer network. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains.

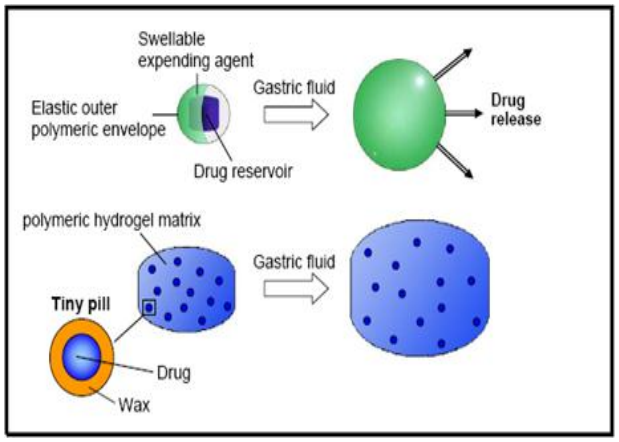


Figure 8.Swellable system.

Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10 nm and 10 µm, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state, during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.[18]

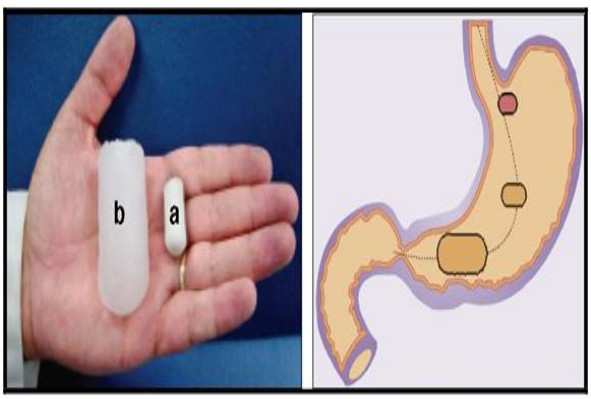


Figure 9.Superporous hydrogels.

Unfolding system

Unfolding takes place due to mechanical shape memory i.e. the gastroretentive dosage form (GRDF) is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrierdissolves and the GRDF unfolds or opens out, to achieve extended configuration. The unfolding occurs when polymeric matrices, known or designed to have suitable mechanical properties, are used with some emphasis on appropriate storage conditions of the GRDF. The storage should maintain unfoldable properties for extended time spans.

Bio/muco adhesive systems

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastric retention time of drug delivery systemin the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GI tract. Mucus secreted continuously by the specialized goblet cells located throughout the GI tract plays a cytoprotective role. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.[19]

The major challenge for bioadhesive drug delivery system is the high turnover rate of the gastric mucus and resulting limited retention times. Furthermore, it is difficult to target specifically the gastric mucus with bioadhesive polymers.

High density system

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Systems with a threshold density of 2.6-2.8 g/cm^3 can be retained in the lower part of the stomach.

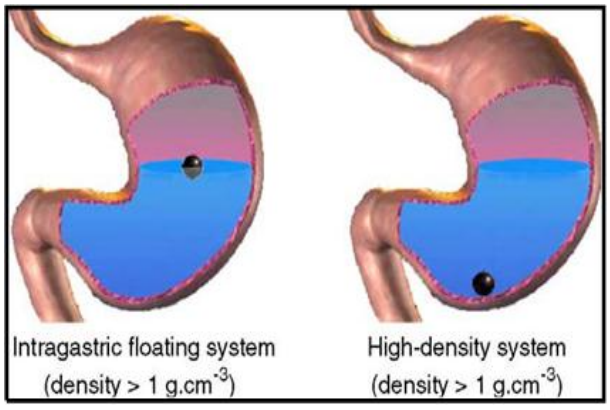


Figure 10. Schematic localization of an intragastric floating and high density system in the stomach

The only major drawback with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8. It is necessary to use diluents like barium sulphate (d=4.9), zinc oxide, titanium dioxide, iron powder, etc. to manufacture such high density formulations.

Magnetic systems

This system is based on a simple idea: the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. This technique has been used in rabbits with bioadhesive granules containing ultrafine ferrite (Fe_2O_3). These bioadhesive granules were guided to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h.[20]

LIMITATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

GRDDS have potential in improving bioavailability of drugs exhibiting ‘absorption window’, however, they have certain limitations.

- 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 for delaying their gastric emptying.
- There are limitations to the applicability of GRDDS for drugs that have solubility or stability problems in the highly acidic gastric environment and are irritant to the gastric mucosa.

DRUG RELEASE MECHANISM

When hydrophilic dosage forms come in contact with aqueous medium, various events that take place are:

1. Partial hydration of the polymer followed by the dissolution of the drug at the surface, resulting in an immediate release.
2. Penetration of solvent molecules into free spaces present on surface between macromolecular chains.
3. Water continuously penetrates the matrix, the gel expands and dissolution of soluble solute inside the matrix and after that dissolution of drug through the gel layer takes place.
4. Simultaneously attrition/erosion of outermost layer and release of insoluble particles occurs.

Therefore, release of active principle by a matrix system is produced by 2 simultaneous mechanisms.[21]

1. Erosion or attrition of the outermost, least consistent gel layers.
2. Dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed. The mechanism that dominates is directly related to the hydrosolubility of the active principle. When this is very low, the possibility of release by diffusion is practically zero and the release is almost all by surface erosion, giving characteristic zero- order profile.

Table no. 1: Examples of various FDDS

Sl.No	Dosage Form	Examples **Drugs Uses**
1	Tablets	Acetoaminophene, Acetylsalicylic acid, Ampicillin, Atenolol, Chlorpheniramine, Cinnarazine, Diltiazem Sotalol, Theophylline
2	Capsules	Chordiazepoxide HCL, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid.
3	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
4	Granules	Diclofenac Sodium, Indomethacin, Prednisolone.

MATERIALS AND METHODOLOGY

Cefpodoxime Proxetil, HPMC K4M, K15M, K100M, Chitosan, Guar gum, Sodium CMC, Ghatti gum, xanthane gum, Carbopol 971(p), 974(p), Mg stearate, Talc.

Methods: Analysis of Excipients used in the formulation

The following excipients HPMCK100M, HPMCK15M as polymers, Sodium bicarbonate as effervescent mixture, Magnesium Stearate as lubricant, Talc as glidant, Lactose as diluent are selected for formulating GFDDS and these have been evaluated and analyzed for the physico-chemical character.

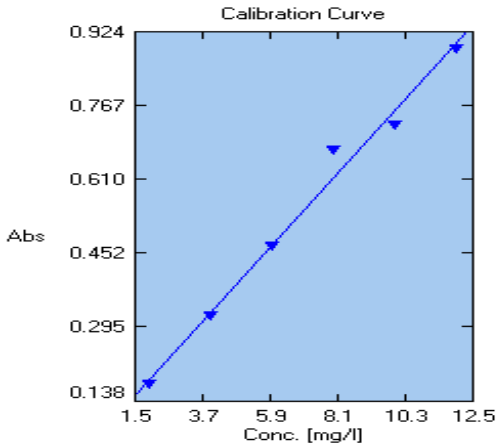


Fig 11: CALIBRATION CURVE

Table no: 2: Formulations containing HPMC K15M, HPMC K100M

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4 M	12.5	25	-	-	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	12.5	25	50	75	100	-	-	-	-	-
HPMC K100 M	-	-	-	-	-	-	-	12.5	25	50	75	100
NaHCO3	60	60	60	60	60	60	60	60	60	60	60	60
Mg Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
AEROSIL	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
MCC	121	108	121	108	83	58	33	121	108	83	58	33
TOTAL TAB. WT.	300	300	300	300	300	300	300	300	300	300	300	300

Table no: 3: Formulations containing combination of polymers

Ingredients (mg)	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22
Drug	100	100	100	100	100	100	100	100	100	100
HPMC K4 M	37.5	-	-	25	-	-	-	-	-	25
HPMC K15 M	37.5	25	37.5	-	-	-	-	25	25	25
HPMC K100 M	-	25	-	-		-	25	-	25	25
XANNTHAN GUM	-	-	37.5	-	38	38	-	-	-	-
Sodium CMC	-	-	-	-	-	-	25	25	25	-
CARBOPOL 971	-	-	-	25	-	38	25	25	-	-
CARBOPOL 974	-	-	-	-	38	-	-		-	-
NaHCO3	60	60	60	60	60	60	60	70	70	70
Mg Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
AEROSIL	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
MCC	58	83	58	83	58	58	58	48	48	48
TOTAL TAB. WT.	300	300	300	300	300	300	300	300	300	300

Evaluation

Tablets are evaluated for its parameters like various quality control tests such as Tablet thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for GFDDS like floating lag time and total floating time & Release rate of drug.

RESULTS: Determination of solubility

The solubility of cefpodoxime proxetil as observed in buffers of various pH values 1.2, 5.4 and 6.8 are presented in table 6. Cefpodoxime proxetil exhibited a pH dependent solubility phenomenon in various aqueous buffers. Very high solubility of cefpodoxime proxetil was observed in acidic pH values, while the solubility dropped rapidly as the pH increased.

Table 4. Solubility data of cefpodoxime proxetil.

Solvent	Solubility (mg/ml)
pH 1.2	5.8
pH 5.4	0.45
pH 6.8	0.38

IR spectroscopy

IR spectrum of cefpodoxime proxetil showed all the peaks corresponding to the functional groups present in the structure of cefpodoxime Proxetil.

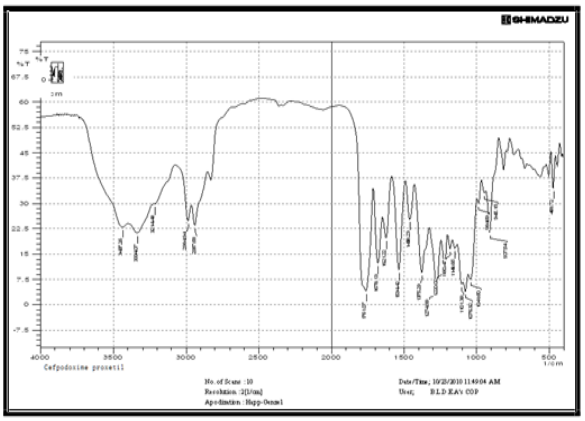


Fig.12 IR spectrum of cefpodoxime proxetil

Table.5 Interpretation of IR spectrum of cefpodoxime proxetil.

Peak observed (cm-^{1})	Interpretation	Peak observed (cm-^{1})	Interpretation
2937	C-H stretching(aliphatic)	1074, 1099	C-O stretching
2984	C-H stretching(aromatic)	1761	C=O stretching
3330	N-H stretching	674	C-S-C stretching
1618	N-H bending	1274	C-N stretching
1638	C=N stretching	1375	C-H bending

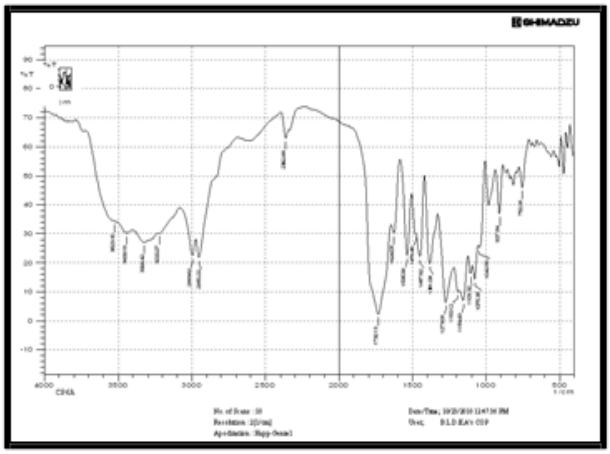


Fig: 13: IR spectra of F7

Excipient Compatibility study

The possible interaction between the drug and the polymers was studied by IR spectroscopy. The possible interaction between the drug and the polymers was studied by IR spectroscopy. The IR spectra's of pure Cefpodoxime, HPMC K4M, Sodium CMC, Guargum, Carbopol 934P and physical mixture of Cefpodoxime with HPMC K4M, Sodium CMC, Guargum, Carbopol 934P in F7 and F14. Pure Cefpodoxime showed 2937.04, 2984.33, 3330.81, 1618.05, 1638.19 cm-^{1} wave number as major peaks.

Table 6: Comparison of major IR peaks of drug polymer mixture with pure Cefpodoxime

Major peaks cm-^{1} wave number of			
Cefpodoxime	**Cefpodoxime: HPMC K4M (2:1)**	**F7**	**F14**
2937.04	2941.53	2941.53	2941.53
2984.39	2984.33	2976.61	2976.61
3330.81	3332.64	3330.71	3330.71
1618.05	1623.67	1625.60	1625.60
1638.19	1628.19	1630.02	1630.02

HPMC K4M= Hydroxypropyl methylcellulose (K4M), F=formulation codes.

UV Spectroscopy

Standard Calibration Curves

Spectrum of Cefpodoxime was obtained in 0.1 N HCl and methanol solutions, observed wavelength maxima was 263.10 nm and 264.00 nm respectively. At this particular wavelength absorbance of Cefpodoxime in 0.1 N HCl and methanol solution was taken, a linear curve was obtained with co-relation regression value was 0.9993 and 0.998 respectively, shown in **Figure 7.**

Table 7: Standard Calibration Curves

Concentration	Absorbance
2	0.174
4	0.319
6	0.467
8	0.672
10	0.726
12	0.888

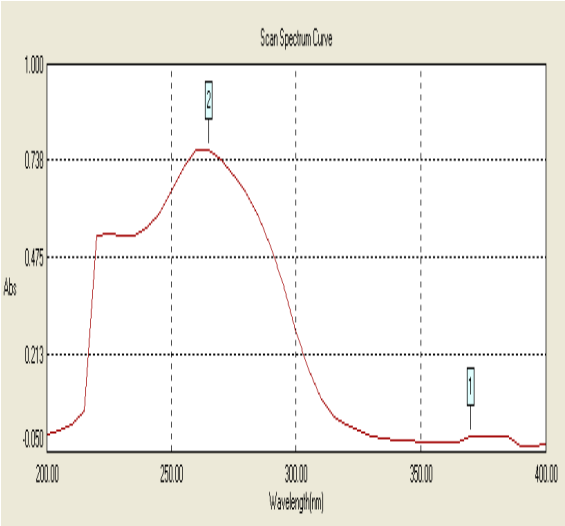


FIG 14: Cefpodoxime Proxetil floating tablets standardization of by UV method

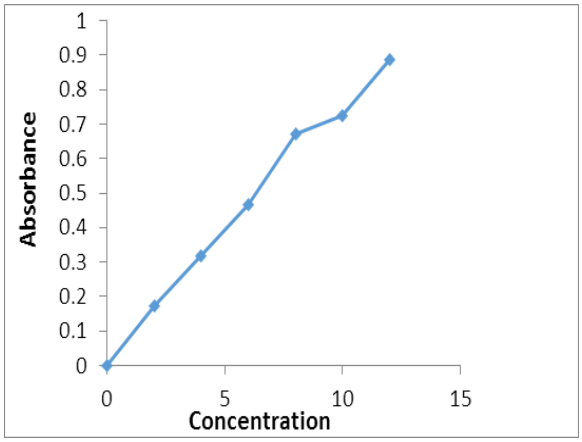


FIG 15: Standard Graph of Cefpodoxime Proxetil in 0.1N HCl

Differential scanning calorimetry study

Differential Scanning Calorimetry studies indicated a sharp endothermic peak at 159°C for pure cefpodoxime proxetil. There was no significant change in the position of this peak in the thermograms of drug and excipients mixture. So it can be concluded that the excipients and drug do not interact with each other.

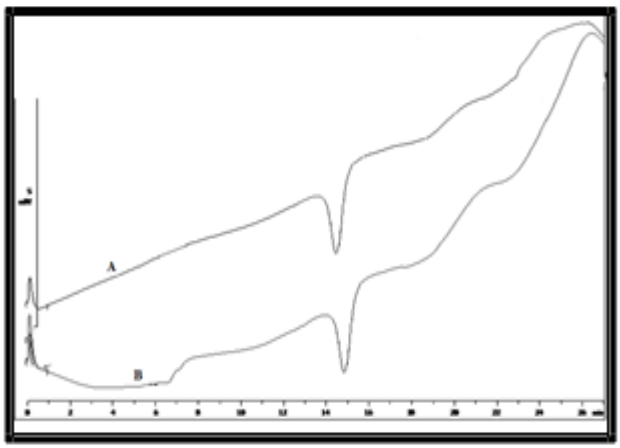


Figure 16. DSC thermograms (A) cefpodoxime proxetil (F) (B) F+HPMC K4M + sodium bicarbonate.

Micromeritic properties

The results of micromeritic properties are presented in table 8.

Table 8: Micromeritic properties of Cefpodoxime and mixtures of Cefpodoxime with excipients

Excipients	Angle of Repose	Carr's Index (%)	Hausner Ratio	Flow pattern
Pure Cefpodoxime	53.30^0±0.541	29.67±0.212	1.40±0.095	Poor
FX+LCT	44.92^0±0.292	22.±0.291	1.34±0.067	Poor
FX+LCT+HPMC+ MGS	24.22^0±0.225	13.10±0.099	1.24±0.002	Very good

All values are expressed as mean ± SD, n=3, FX= Cefpodoxime, LCT=Lactose, HPMC=Hydroxy Propyl Methyl celluloseK4M, MGS=Magnesium Stearate.

Formulation development

Floating tablets, containing drug and polymer, are one of the simplest approaches for controlled release of a drug. Among the different types of hydrophilic polymers reported, HPMC was used because of its associated advantages. In addition, HPMC is a pH independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables, such as compaction pressure, drug particle size and incorporation of lubricant.

Direct compression

Oral solid dosage forms which are commonly used today because of it various advantages to patients. Under the heading of oral solid dosage form, tablet is one of the dosage forms which have a global market. Today direct compression preferred over wet granulation and dry granulation because of its well known advantages.

Evaluation of Tablet characteristics

Physicochemical properties of tablet

The floating tablets of Cefpodoxime were prepared by effervescent technique. The tablets were evaluated for average weight, thickness, hardness, friability and drug content.

Table 9: Physicochemical properties of Cefpodoxime floating tablets

Batch Code	Average weight	Thickness (mm)	Hardness (kg/cm2)	Diameter (mm)	Friability (%)	Drug content (%)
F1	330	4.23 ± 0.04	12.03± 0.07	7.7± 0.06	0.70±0.063	102.48 ± 0.20
F2	340	4.00 ± 0.03	12.02 ± 0.03	7.0± 0.02	0.91±0.044	101.38 ± 0.20
F3	333	3.90 ± 0.03	12.04 ± 0.06	8.3± 0.03	0.71±0.080	99.38 ± 0.21
F4	363	4.20 ± 0.06	12.21 ± 0.04	8.1± 0.06	0.72±0.042	98.68 ± 0.20
F3	330	4.10 ± 0.03	12.01 ± 0.07	7.6± 0.07	0.80±0.066	102.28 ± 0.10
F6	343	3.90 ± 0.04	12.07 ± 0.03	7.6± 0.07	0.76±0.034	102.73 ± 0.13
F7	360	3.83 ± 0.07	12.10 ± 0.03	9.2± 0.03	0.73±0.043	103.36 ± 0.14
F8	333	3.90 ± 0.03	12.04 ± 0.06	8.3± 0.03	0.71±0.080	99.38 ± 0.21
F9	363	4.20 ± 0.06	12.21 ± 0.04	8.1± 0.06	0.72±0.042	98.68 ± 0.20
F10	330	4.10 ± 0.03	12.01 ± 0.07	7.6± 0.07	0.80±0.066	102.28 ± 0.10
F11	343	3.90 ± 0.04	12.07 ± 0.03	7.6± 0.07	0.76±0.034	103.73 ± 0.13
F12	360	3.83 ± 0.07	12.10 ± 0.03	9.2± 0.03	0.73±0.043	103.36 ± 0.14
F13	330	4.13 ± 0.04	12.11 ± 0.03	7.30± 0.02	0.64±0.083	102.08 ± 0.13
F14	343	3.98 ± 0.02	12.07 ± 0.02	8.4± 0.04	0.78±0.041	99.63 ± 0.12
F13	330	4.03 ± 0.07	12.06 ± 0.04	9.0± 0.06	0.77±0.039	102.71 ± 0.22
F16	360	4.18 ± 0.02	12.07 ± 0.07	7.0± 0.03	0.93±0.073	103.91 ± 0.13
F17	330	4.10 ± 0.04	12.06 ± 0.02	7.8± 0.02	0.71±0.044	103.47 ± 0.10
F18	330	4.07 ± 0.02	12.03 ± 0.09	8.8± 0.04	0.66±0.039	103.44 ± 0.12
F19	343	4.20 ± 0.07	12.01 ± 0.03	7.4± 0.03	0.76±0.060	96.38 ± 0.12
F20	360	3.83 ± 0.07	12.10 ± 0.03	9.2± 0.03	0.73±0.043	103.36 ± 0.14
F21	343	3.90 ± 0.04	12.07 ± 0.03	7.1± 0.02	0.76±0.034	102.73 ± 0.13
F22	330	4.10 ± 0.03	12.01 ± 0.07	7.6± 0.07	0.80±0.066	103.28 ± 0.10

Table 10: LAG time of Cefpodoxime floating tablets

Batch Code	Floating Lag time (min)	Floating duration (min)	Integrity
F1	28	Float	Intact
F2	20	Float	Intact
F3	32	20	Intact
F4	28	40	Broken after 6-8Hrs
F3	20	60	Intact
F6	40	>720	Intact
F7	49 sec	>720	Intact
F8	28	Float	Intact
F9	20	Float	Intact
F10	Not float	Float	Intact
F11	40	>720	Intact
F12	Not float	Float	Intact
F13	3	43	Broken
F14	33 sec	>720	Intact

F13	49 sec	>720	Intact
F16	28	Float	Intact
F17	20	Float	Intact
F18	Not float	Float	Intact
F19	40	>720	Intact
F20	Not float	Float	Intact
F21	3	43	Broken
F22	33 sec	>720	Intact

Formulations from F1, F2, F8, F9, F10 and F12 did not float; this was due to the lower percentage of gas generating agent and high concentrations of carbopol934P polymer. The formulation F3, F4, F3, F6 and F11 floated but the lag time was more. F6 and F11 the duration was more than 12 h. It was seen that as carbopol934P concentration decreased, the floating capacity increased. F12 floated with less lag time due to high concentration of gas generating agent. F7 and F14 floating lag time was less due to high gas generating agent which were formulated later. It was observed that paddle speed affected the floating properties of tablet. In the study with 400 ml 0.1N HCL without paddle it was found that the floating lag time decreased and the duration increased for the same formulations.

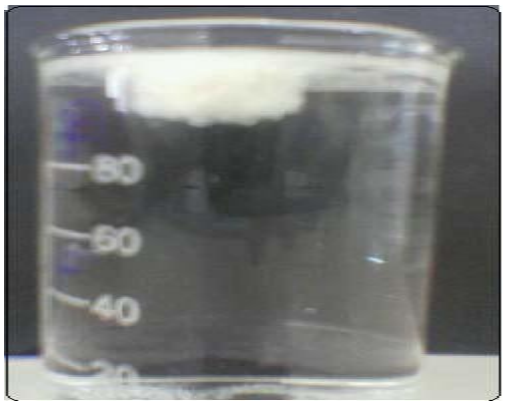


Fig 17: In vitro Dissolution Study

TABLE 11: Cumulative % drug release of Cefpodoxime Floating tablets

%DRUG RELEASE / TIME	F1	F2	F3	F4	F3	F6	F7	F8	F9	F10	F11
30	23	23.3	21.4	17.7	18.9	24	17.7	23.4	21.3	19	20
1	33.3	34.9	29.2	23.8	23.3	32.2	23.8	38.4	29.6	29.2	30.3
2	44.8	48.6	36.1	41.8	34.6	42.8	41.8	43.7	38.4	40.7	40
4	30	63.7	44.8	30.3	42.3	34.9	30.4	34.8	44.3	46.7	30.7
6	39.9	72.7	30.7	36	48.2	60.8	39.9	61.8	34.6	33.4	33.7
8	68.4	78.8	36.9	62.1	36.7	71.9	70	72.7	62.6	67.04	63.3
10	77.3	84.3	68.3	73.2	69.3	84.8	76.2	91.1	80.9	73.9	70.3
12	93.3	88.2	78.2	87.3	83.3	89.8	87	**98.1**	89.7	83.4	73.7

%DRUG RELEASE / TIME	F12	F13	F14	F13	F16	F17	F18	F19	F20	F21	F22
30	20	20.2	24.8	21.3	23.9	23.3	33.3	**21.57**	24.3	22	22
1	28.9	28.9	31.3	27.7	32.1	28.9	42.9	**38.69**	32.7	32.8	33.4
2	37	36.7	39.3	37.9	37.4	34	31.6	**49.58**	41.8	44.1	42
4	43.8	43.8	46.7	44.3	46.6	44.2	37.6	**56.57**	46.7	30.7	30
6	49.1	49.1	33.8	33.1	37.3	30.3	63.7	**64.57**	34.3	38.7	33.7
8	39.3	39.3	39.9	38.1	62.1	33.3	71.2	**77.58**	60.7	39.8	66.7
10	73	73	71.8	63.9	71.7	63.9	73.3	**85.39**	64.9	68.1	78.7
12	83.8	83.8	83.3	76.7	79.6	81.2	74.4	**97.38**	76.2	71.9	89.1

All the formulations were designed as dosage form for 12 hrs. Dissolution profile of all batches is shown in Figures 18-21.

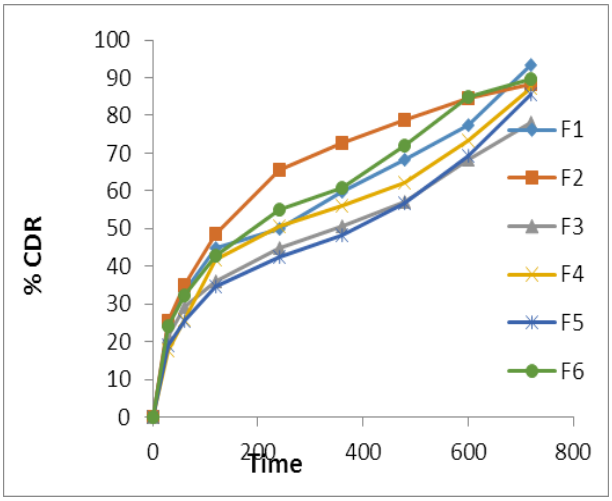


FIG 18: Dissolution graphs of F1, F2, F3, F4, F3 & F6 formulations

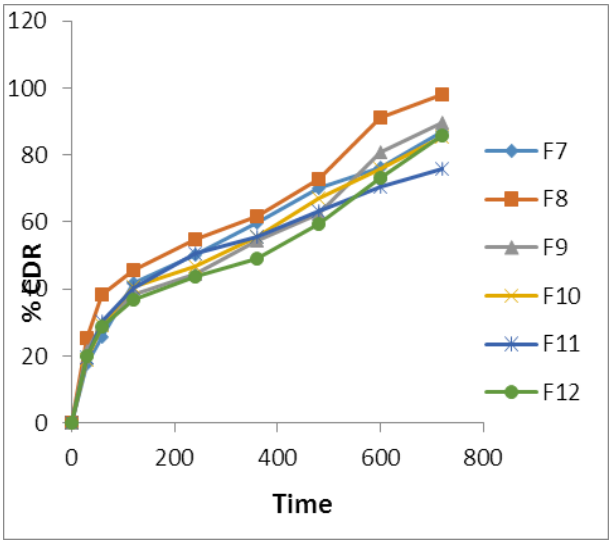


FIG 19: Dissolution graphs of F7, F8, F9, F10, F11 & F12 formulations

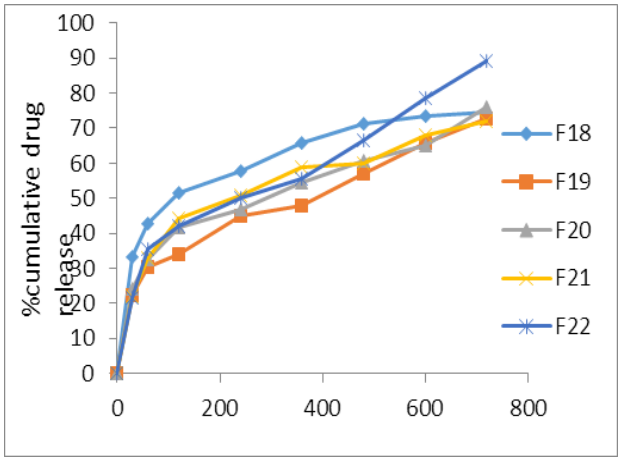


FIG 20: Dissolution graphs of F13-F17 formulations

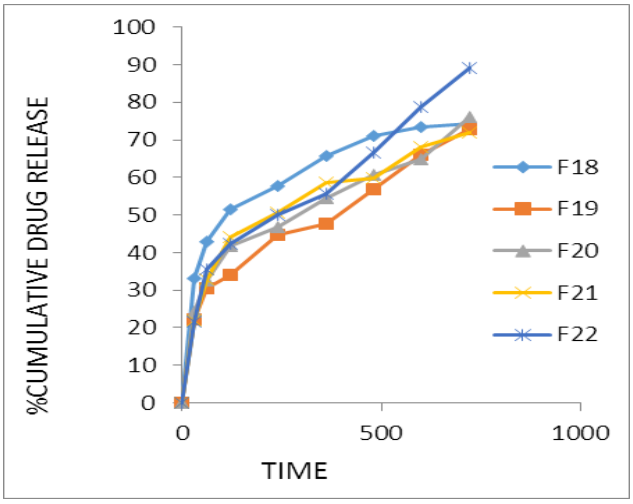


FIG 21: Dissolution graphs of F18-F22 formulations

Swelling index (water uptake) study

This mechanism gives the idea regarding the water uptake study of various grades of polymer. This phenomenon is attributes to that the swelling is maximum due to water uptake and then gradually decreased due to erosion. Swelling measurement was performed separately in order to collect on the basis of weight increase over time. The swelling is due to presence of hydrophilic polymer, which gets wetted and allows water uptake leads to increase in its weight.

Table 12: swelling index of batch F1-F12

TIME (MIN)	% SWELLING INDEX											
	F1	F2	F3	F4	F3	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
13	38	38	39.6	32.14	40.38	37	31.3	44.4	49.01	42.3	47.16	30.98
30	33.38	31.9	49	33.71	31.92	40	33.7	31.83	34.9	33.84	36.6	38.82
60	67.73	71.13	64.13	33.33	69.23	68.3	72.2	66.66	72.34	76.92	73.38	82.33
120	84.61	84.6	84.9	76.8	88.46	83.18	101.9	83.16	94.11	92.3	100	103.9
180	103	101.9	103.7	91.07	119.2	107.4	122.2	109.3	113.7	111.3	107.3	127.3
240	113.4	119.2	128.3	101.8	123.1	123.9	142.6	116.7	127.3	126.9	128.3	147.1
300	121.2	126.9	132	108.9	134.6	133.3	137.4	118	139.2	140.4	141.3	132.9
360	134.6	136.3	137.7	116	130	140.7	161.1	127.8	141.2	146.2	143.3	160.8
420	138.3	142.3	143.4	123.2	133.8	142.6	173.9	138.9	132.9	131.9	132.8	164.7

480	143.8	146.8	130.1	121.7	160.4	148	178.8	141	139.3	160	138	172
340	133.8	133.8	137.7	113.8	171.2	133.7	181.3	144.4	168.6	171.2	167.9	180.4
600	131.2	130	130.9	103.7	170	131.9	182.4	131.9	166.7	167.3	130.9	182.2
660	148	148	130.9	104.8	166	130	183.9	130.6	163	167	147.2	182
720	136	138	140	102.6	160	140	194.9	140	133	130	137	170

Table 13: swelling index of batch F13-F22

TIME (MIN)	% SWELLING INDEX									
	F13	F14	F13	F16	F17	F18	F19	F20	F21	F22
0	0	0	0	0	0	0	0	0	0	0
13	38	38	39.6	32.14	40.38	31.3	44.4	49.01	42.3	47.16
30	33.38	31.9	49	33.71	31.92	33.7	31.83	34.9	33.84	36.6
60	67.73	71.13	64.13	33.33	69.23	72.2	66.66	72.34	76.92	73.38
120	84.61	84.6	84.9	76.8	88.46	101.9	83.16	94.11	92.3	100
180	103	101.9	103.7	91.07	119.2	122.2	109.3	113.7	111.3	107.3
240	113.4	119.2	128.3	101.8	123.1	142.6	116.7	127.3	126.9	128.3
300	121.2	126.9	132	108.9	134.6	137.4	118	139.2	140.4	141.3
360	134.6	136.3	137.7	116	130	161.1	127.8	141.2	146.2	143.3
420	138.3	142.3	143.4	123.2	133.8	173.9	138.9	132.9	131.9	132.8
480	143.8	146.8	130.1	121.7	160.4	178.8	141	139.3	160	138
340	133.8	133.8	137.7	113.8	171.2	181.3	144.4	168.6	171.2	167.9
600	131.2	130	130.9	103.7	170	182.4	131.9	166.7	167.3	130.9
660	148	148	130.9	104.8	166	183.9	130.6	163	167	147.2
720	136	138	140	102.6	160	194.9	140	133	130	137

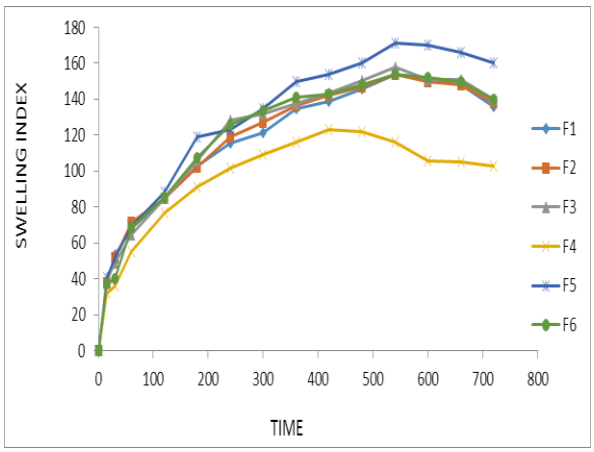


FIG 22: Relationship between swelling index and time of F1-F6

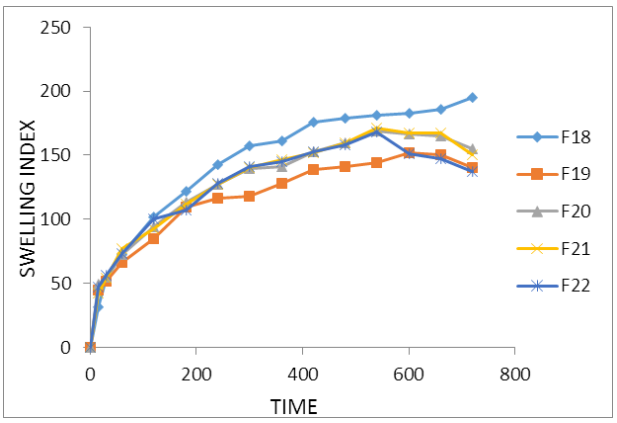


FIG 24: Relationship between swelling index and time of F13-F17

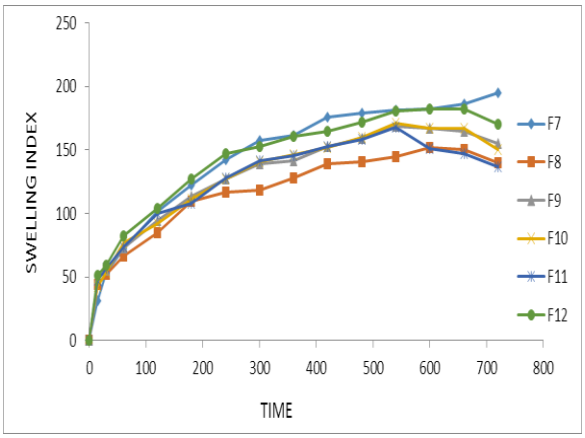


FIG 23: Relationship between swelling index and time of F7-F12

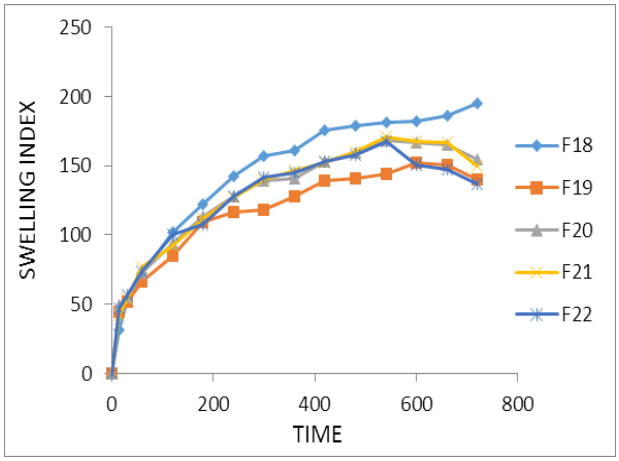


FIG 25: Relationship between swelling index and time of F18-F22

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The increase in concentrations of guargum and sodium CMC increases swelling indices and faster rate of swelling.

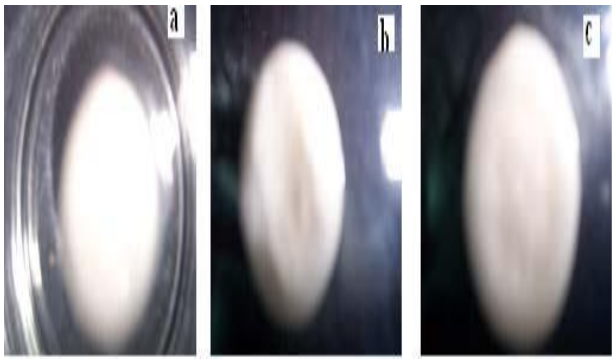


Fig: 26 Swelled tablet after 3h a) F3, b) F7 c) F10

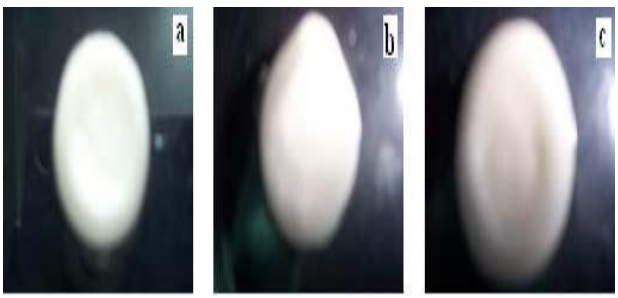


Fig: 27 Swelled tablet after 6 h a) F3, b) F7 c) F11

DISCUSSION

Floating drug delivery system belongs to oral controlled drug delivery system group that are capable of floating in the stomach by bypassing the gastric transit. These dosage forms are also defined as Gastro Retentive drug delivery system or hydrodynamically balanced dosage form or gastric floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged period. It is primarily absorbed from the stomach and upper part of intestine. To enhance bioavailability, an attempt was made to prepare the gastro retentive floating tablet of Cefpodoxime proxetil using polymers such as HPMC K4M (14.5-18%), Guargum (3-8%), Carbopol934P(2-11%), SCMC (4.5-11%), $NaHCO_3$ (10- 15%) and MCC as quantity sufficient.

Hence, the present research work was to study systematically the effect of formulation variables on the release and floating properties of Cefpodoxime proxetil.

CONCLUSION

From the above experimental results it can be concluded that,

- Formulated tablets gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity.
- Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K4M has predominant effect on total floating time and drug release. Carbopol also shows significant effect on drug release.
- Sodium CMC and Guargum has given extra adhesion property and helped to maintain the integrity of the tablet.
- Swelling index has a significant effect on the drug release. The formulations CP7 and CP14 showed higher swelling index compared to others.
- In-vitro release rate studies showed that the maximum drug release was observed in CP7 and CP14 formulations up to 12 hrs.
- Formulations CP7 found to be stable at 45^0C and 75% RH for a period of 3 month.
- FT-IR studies revealed that there was no interaction between Cefpodoxime proxetil and the polymers used.
- From the study it is evident that a promising controlled release floating tablets of Cefpodoxime proxetil can be developed to increase gastric residence time and there by increasing its bioavailability.

SUMMARY

In the present study gastro-retentive delivery systems of Cefpodoxime proxetil were successfully developed in the form of hydrodynamically balanced tablets to improve the local action and its bioavailability, which reduces the wastage of drug and ultimately improves the solubility for drugs that are less soluble in high pH environment. Cefpodoxime proxetil floating tablets were prepared by using HPMC K4M, sodium CMC, guargum and carbopol 934P polymers with excipients sodium bicarbonate and lactose. The prepared formulation can be used to perform in-vivo studies in animals.

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