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"FORMULATION AND CHARACTERIZATION OF ALMOND GUM LOADED CEFOPODOXIME PROXETIL FLOATING MICROBEADS"

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ABSTRACT

The objective of the research work highlights site specific delivery of cefopodoxime proxetil in acidic P_H values of stomach to improve bioavailability. Gastro retentive microbeads of Cefopodoxime proxetil by Ionotropic gelation technique was formulated in two different Combinations of sodium alginate along with almond gum and sodium alginate with HPMCE15M. The FTIR was applied to investigate drug-polymer interaction. The formulated beads were then evaluated for particle size, percentage drug entrapment efficiency, micromeritic properties, swelling property, surface topography, buoyancy properties and invitro dissolution. The best optimized formulation FC_4which is more suitable for sustained release upto 12hrs, follows first order kinetics (R^2 0.9537), best fitted with korsemeyer –Peppas (R^2 0.9895) model showing an n value from 0.80 to 0.87 which indicate the release mechanism follows anomalous transport.

KEYWORDS: Microbeads, almond gum, Ionotropic gelation, korsemeyer –Peppas, anomalous transport.

INTRODUCTION

The oral administration of Gastro-retentive drug delivery system (GRDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment.[1] In order to obtain local and sustained drug delivery in the stomach and proximal parts of the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also results in the reduction in dosing frequency of the dosage form.[2,3] The diminished efficacy of the administered dose may be observed due to intersubject variability and short time of gastric emptying which may results because of incomplete drug release from the drug delivery system above the absorption zone (stomach, upper part of small intestine). Moreover, it has been reported that drug delivery system is one of the commercial system which is attributed to obtain the higher bioavailability than that of the non-floating system.[4]

Almond gum is obtained from the tree Prunus communis which is a water soluble gum extrudes from the wounds on almond trees. The constitution of almond gum includes aldobionic acid, L-arabinose, L-galactose, D-mannose etc. It contains different components which have emulsifier, thickener, suspending pharmaceutical, adhesive, glazing agent and stabilizer. Gum is a bye product obtained as a result of metabolic mechanism of plants. Natural gums are either water soluble or absorb water to form a viscous solution. Natural gums are economic, easily available and found useful as tablet binder.[5]

Cefpodoxime Proxetil (CP) is 3rd generation broad spectrum ß-lactam cephalosporin class of antibiotic administered orally having absorption in upper GIT (stomach). It has the better solubility in acidic p_H. Among the various reasons for its low bioavailability, poor solubility and premature conversion of Cefpodoxime Proxetil to Cefpodoxime by intestinal esterase enzyme are important. Floating dosage form of Cefpodoxime proxetil will offer better bioavailability as drug will remain in absorption window for long duration and it will also inhibit premature conversion of Cefpodoxime Proxetil to Cefpodoxime by intestinal esterase enzyme. Hence Cefpodoxime Proxetil has all the ideal characteristics required for gastro retentive drug delivery system.[6,7]

In human, the absolute bioavailability of cefpodoxime Proxetil administered as a 130mg tablet (equivalent to 100mg of cefpodoxime) is about 50%. Also the drug has only 2 to 3 hours halflife.[8]

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad. Almond gum obtained as a gift sample from Signet chemicals, Mumbai. All other reagent were of Analytical grade

Method[9]

Floating microbeads were prepared by Ionotropic gelation technique. Almond gum solution of different concentrations were prepared by dissolving almond gum in deionized water at 90°C with stirring at 200 rpm. The drug, Cefpodoxime proxetil and Calcium carbonate were dissolved/dispersed uniformly in the almond gum solution at or just below 40°C with continuous stirring (200 rpm) until a uniform dispersion was obtained. The bubble-free slurry (dispersion) was added drop wise into the gelation medium consisting of 100ml cross linking medium of different concentration (calcium chloride) with a 25 ml hypodermic syringe through a 22 G needle into the gelation medium with continuous stirring (200 rpm). The medium was continuously stirred during bead formation to enhance the mechanical strength of the beads and also to prevent their aggregation. The beads were cured for 10 min, separated by filtration, and dried at 40°C for 24 hours as shown in Table.1, Fig.1 and Fig.2.

Table: 1 FORMULATION OF CEFOPODOXIME PROXETIL MICRO BEADS

S.NO	INGREDIENTS	FC_1	FC_2	FC_3	FC_4	FC_5	FC_6	FC_7
1	CEFOPODOXIME PROXETIL (DRUG) (mg)	200	200	200	200	200	200	200
2	SODIUM ALGINATE (%W/V)	4%	-	4%	4%	4%	4%	4%
3	ALMOND GUM (%W/V)	-	4%	400	600	-	-	-
4	HPMC E15M (mg)	-	-	-	-	400	600	600
5	$CaCO_3$ (%W/V)	1	1	1	1	1	1	-
6	$CaCL_2$ (%W/V)	5	5	5	5	5	5	5

Fig.1: PHOTOGRAPH OF ALMOND GUM.

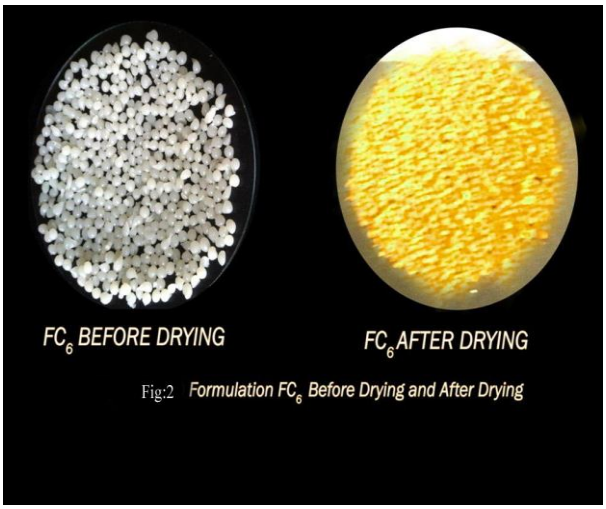


Fig: 2 FORMULATION OF CEFOPODOXIME PROXETIL MICRO BEADS.

Characterization of floating almond gum loaded cefpodoxime proxetil beads

Prepared beads were evaluated for particle size, drug content, % yield, floating ability, entrapment efficiency, surface morphology, FTIR studies, In-vitro drug release study and swelling studies.

Drug-polymer interaction studies

Drug-polymer interaction studies were carried out by FT-IR.

Micromeritics properties[9]

The beads are characterized by their micromeritic properties such as particle size, bulk density, tapped density, Carr's index, Hausner ratio and flow property.

Particles size

Particle size analysis was carried out by using optical microscopy. About 1000 micro beads randomly selected and their sizes were determined by using optical microscope fitted with standard micrometer scale. The surface morphology of the microbeads for formulation FC_4 & FC_6 were examined by means of scanning electron microscope **(**Model JSM 5400**,** Jeol, and Tokyo, Japan). The microbeads were previously fixed on a brass stub using double-sided adhesive tape and then were made electrically conductive by coating, in a vacuum, with a thin layer of platinum (3–5 nm), for 100 s and at 30 W.

Percentage yield[9]

The prepared beads were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of drug and polymer.[12]The production yield of beads was calculated as follows.

% Production yield = Total mass of beads / Total mass of drug and polymer *100

Determination of drug content and Entrapment efficiency

Accurately weighed (100 mg) grounded powder of beads was soaked in 100 ml 0.1 N HCl and allowed to disintegrate completely for 4 hr. The resulting dispersion was sonicated using a sonicator for 30 min and then filtered through a whatman filter paper. The polymeric debris was washed twice with fresh 0.1 N HCl to extract any adhered drug and drug content was determined spectrophotometrically at 262 nm against constructed a calibration curve. The drug content (DC) and % Entrapment efficiency was calculated by using following formula.

% Drug content = (Amount of drug in beads /Amount of beads) × 100 %

Entrapment efficiency = A_Q/ T_Q × 100

Where

$A_{Q=}$ Actual quantity of drug in beads

T_Q =Theoretical quantity of drug present in beads

Swelling index[9]

50 mg of microspheres were allowed for swelling in SGF (pH 1.2) for 4 h, the excess adhered liquid was removed by blotting with filter paper and weighed.[11,12] Swelling index (SI) ¼ W_s_W_o/W_o, where, W_o initial weight of the dry microspheres, W_s final weight of swollen microspheres, results were shown in Table 3.

Buoyancy Test[9]

The obtained beads were studied for buoyancy and floating time using USP type II dissolution test apparatus (Lab India, Chennai). 100 beads of each batch were placed in 900ml of 0.1N HCl (pH 1.2) containing 0.02%w/v Tween 80 and agitated at 100 rpm at 37ºC ± 2 C. The number of sinking beads was observed visually.

In vitro dissolution studies[10]

The in vitro studies was carried out in 900 ml of Acid buffer, pH 1.2 maintained in 37ºC ± 0.5ºC and 50 rpm by using United States Pharmacopoeia paddle type dissolution test apparatus (Testing Instruments, Kolkata) under sink conditions, 100 mg of drug's equivalent to micro beads were added to dissolution medium and at present time intervals, 5 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium. After suitable concentration of cefodopoxime proxetil in test samples was corrected and calculated by following formula:

([Test absorbance\ Standard absorbance] x Standard concentration/Test concentration]) x 100.

Release kinetics[10]

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into, zero order, the first order, Higuchi matrix, and Peppas model. The 'r' values obtained were compared to judge the best fit model.

Stability studies[10]

The success of an effective formulation was evaluated only through the stability studies. The purpose of stability testing was to obtain a stable product which assures its safety and efficacy up to the end of shelf life. The optimized formulation of FC4 packed in PVC blister pack then, they were stored at three different temperatures 4ºC±2ºC, 27 ºC±2ºC and 45ºC ±2ºC for 45 days at RH 75±5%. The micro beads were evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time, in-vitro buoyancy studies, drug entrapment efficiency etc.

RESULT AND DISCUSSION

Drug –Polymer Interaction study using FTIR

Infrared spectrum shows all prominent peaks of cefpodoxime proxetil. IR spectrum indicated that characteristics peaks belonging to measure functional group such as principle peak at wave number 2937.04, 2984.39, 3330.81, 1618.05 and 1638.19cm-1. The major IR peaks observed cefopodoxime proxetil were 2937.04(C-H), 3330.81(N-H), 1638.19(C=N), 1074(C-O), 1761(C=O), 1274(C-N), 1375(C-H) (Fig.1).The spectra showed all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional group such as principle peaks at wave no. 2941.53, 2984.33, 3332.64, 1623.67 and 1628.19 as shown in (Fig.3,4,5,6). Hence it can be concluded that there were no any significant changes and interaction in the physical mixture of cefopodoxime proxetil and HPMC E15M used for micro beads formulation.

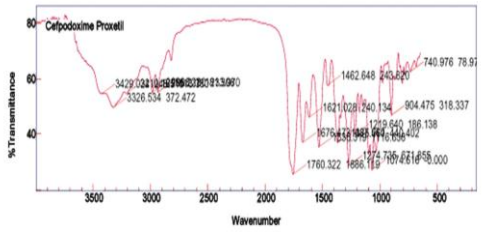


Fig.No:3 FTIR SPECTRUM OF CEFOPODOXIME PROXETIL

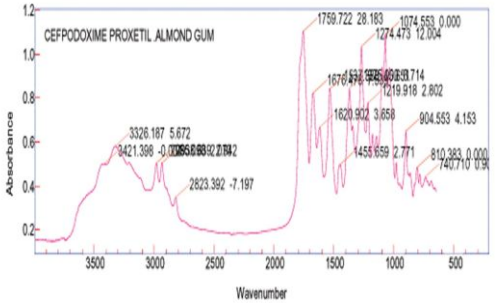


Fig.No:4 FTIR SPECTRUM OF CEFOPODOXIME PROXETIL + SODIUM ALMOND GUM

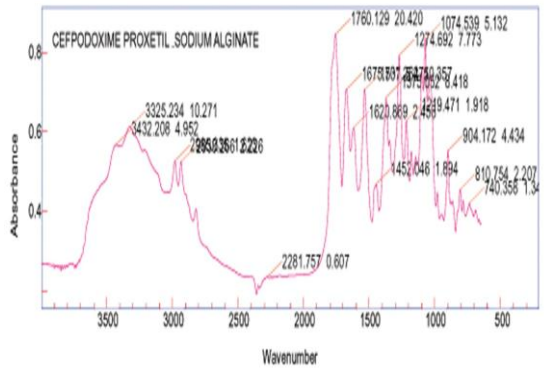


Fig.No:5 FTIR SPECTRUM OF CEFOPODOXIME PROXETIL + SODIUM ALGINATE

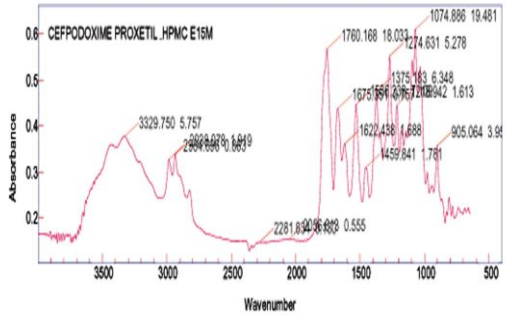


Fig.No:6 FTIR SPECTRUM OF CEFOPODOXIME PROXETIL + HPMC E15M

Micrometric properties of beads

It was found angle of repose was in the range of. 20.49 ^{o} to 24.46^{o}. Bulk density and the tapped density were found in the range of 0.37±0.004 0g/ml to 0.48±0.001g/ml respectively which inferred that powder is loosely packed. The compressibility index of all the prepared formulation lies in the range of 7.50±0.017 to12.72±0.012**%** inferring the blend possessed excellent flow in all formulations. The Hausner's ratio was obtained in the range of 1.08±0.04 to 1.14±0.16 revealing good flow ability as well as good compaction properties depicted in Table: 2. Hence that required dose quality can be dispensed through capsule bodies.

Table: 2 MICROMETRIC PROPERTIES OF BEADS

FORMULATIONCODE	BEADS SIZE (mm)	ANGLE OF REPOSE (ɵ)DEGREE	BULK DENSITY (g|Cm3)	TAPPED DENSITY (g|Cm3)	CARR'S INDEX	HAUSNER RATIO
Fc1	1.05±0.01	24.49^{o}	0.38±0.006	0.42±0.015	9.52±0.01	1.10±0.75
Fc2	1.09±0.04	23.26^{o}	0.37±0.004	0.40±0.012	7.50±0.017	1.08±0.04
Fc3	0.95±0.016	21.41 ^{o}	0.44±0.008	0.50±0.002	12.01±0.08	1.13±0.001
Fc4	0.93±0.012	20.49 ^{o}	0.46±0.009	0.52±0.004	11.53±0.017	1.13±0.018
Fc5	0.97±0.03	22.24 ^{o}	0.43±0.005	0.48±0.006	10.41±0.04	1.11±0.012
Fc6	0.99± 0.01	24.46^{o}	0.46±0.019	0.51±0.01	10.86±0.09	1.10±0.12
Fc7	1.02±0.008	23.64^{o}	0.48±0.001	0.55 ±0.03	12.72±0.012	1.14±0.16

Drug Entrapment and content Uniformity studies

Results showed that entrapment efficiency is dependent upon polymer concentration. This may be because of increase in viscosity of polymeric solution, in turn increases the cross linking of polymer and prevent drug diffusion out of the system as shown in Table: 3.

Table: 3 EVALUATION TEST OF CEFOPODOXIME FLOATING MICROBEADS.

FORMULATION CODE	PERCENTAGE PRACTICAL EFFICIENCY	PERCENTAGE DRUG ENTRAPMENT EFFICIENCY	SWELLING INDEX (gms)
FC1	89.50	37.28	1.18±0.26
FC2	86.92	45.72	1.29±0.21
FC3	94.64	85.76	1.59±0.42

FC4	91.03	87.58	2.40±0.65
FC5	92.28	64.86	1.48±0.32
FC6	95.13	67.84	1.86±0.24
FC7	88.12	67.26	1.84±0.12

Surface morphology and SEM Study

The particle size of micro beads determined by using optical microscope fitted with standard micrometer scale was in the range of 0 .93±0.012mm to 1.09±0.04mm (Table.2), showed good flow properties, the micro beads were with smooth surface and lightly porous in nature as revealed by the SEM studies and thus exhibiting excellent buoyancies in simulated gastric fluid because of low density as shown in Fig.8 and 9.

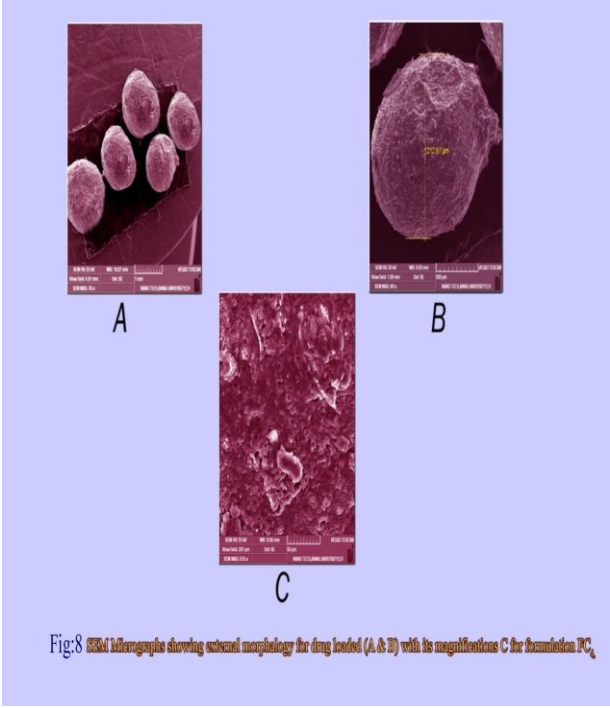


Fig:8 SEM Micrographs showing external morphology for drug loaded (A & B) with its magnifications C for formulation FC4

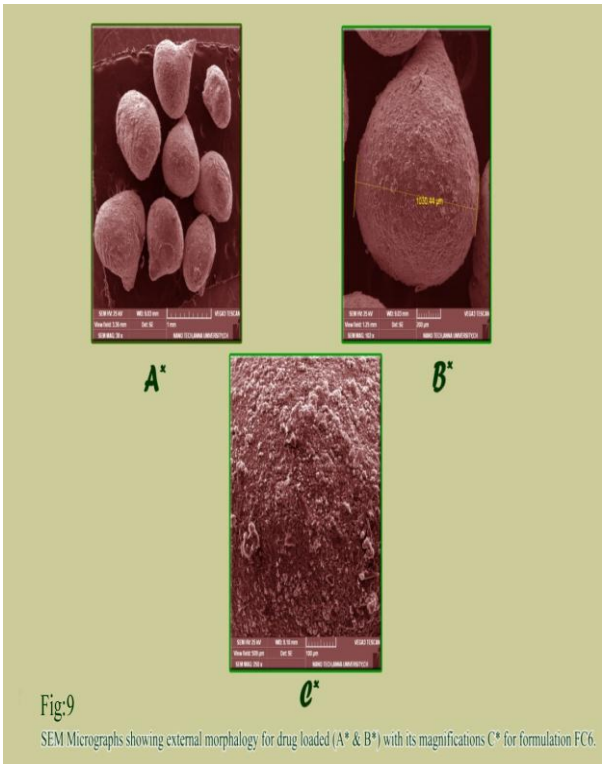


Fig:9
SEM Micrographs showing external morphology for drug loaded (A* & B*) with its magnifications C* for formulation FC6.

Determination of swelling ratio

The swelling behavior of alginate and almond polymer is also an important factor controlling the release of the drugs from the bead systems. Alginate and almond beads can swell when hydrated. For this reason, the swelling behavior of Cefopodoxime proxetil loaded beads was determined in SGF (pH-1.2). The extent of swelling of the beads prepared using different concentrations of alginate and almond polymer was followed in SGF (pH 1.2) and the results showed that the swelling was related to the polymer concentration with swelling being more significant for beads containing high polymer content. The swelling index was found to be in the range between1.18±0.26 to 2.40±0.65 as shown in the Table.no.3.

In Vitro buoyancy studies of cefopodoxime Proxetil floating beads

The floating ability of prepared beads was evaluated using USP XXIII dissolution apparatus containing 500 ml SGF (pH 1.2). All the formulations showed good buoyancy range from 5 to 10 hrs. F1, F2 & F3 beads showed a longer lag time (51, 34, 21min) F4, F5 & F6 (26, 54 & 60 min) as shown in Table.4. This may be attributed to the decrease in density of the beads with an increase polymer.

In vitro dissolution studies of cefopodoxime proxetil from floating micro beads were performed in 0.1N HCl (pH 1.2) for 12 hours using USP Type II dissolution (paddle) test apparatus as shown in `fig.7. It was found that formulations FC3 to FC7 showed 96.12% to 68.21% of release at 12 hours.

It was observed that formulations FC1 showed 96.12% of drug release at the end of 8 hours. Formulations FC3 and FC4 showed 0% drug release at the end of 1 hour and 89.08% at the end of 12 hour and formulation FC4 showed 0% drug release even at the end of 2 hour and showed 68.21% drug release at the end of 12 hours. But formulations FC5 and FC6 showed initial burst release of 21.07% and 15.12% at the end of 1 hr and 96.10% and

90.75% at the end of 10 hrs and 12 hrs. It was observed that as the concentration of almond gum in Fc_4 was increased and as the concentration of HPMCE15 in Fc_6 increased, the % concentration drug release and initial burst release decreased as shown in Table.5 and Fig.10. The increased almond gum and HPMC E15 concentration leads to increased density of polymer matrix into the micro beads which results in an increased diffusional path length and consequent retardation in drug release.

In case of controlled or sustained release formulation, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling mechanisms, because in addition to diffusion includes relaxation of polymer chains, inhibition of water causing polymer to rubber state.

Furthermore, small, micro beads are formed at a lower polymer concentration (Fc_1 and Fc_4) have a large surface area exposed to dissolution medium, gives faster drug release and vice versa.

Table: 4 INVITRO BUOYANCY STUDIES OF CEFOPODOXIME PROXETIL FLOATING MICROBEADS

FORMULATION CODE	FLOATING LAG TIME (min)	TOTAL FLOATING TIME (hours)
FC_1	51	>5
FC_2	34	>7
FC_3	21	>9
FC_4	26	>12
FC_5	54	>8
FC_6	60	>8
FC_7	Nil	Nil

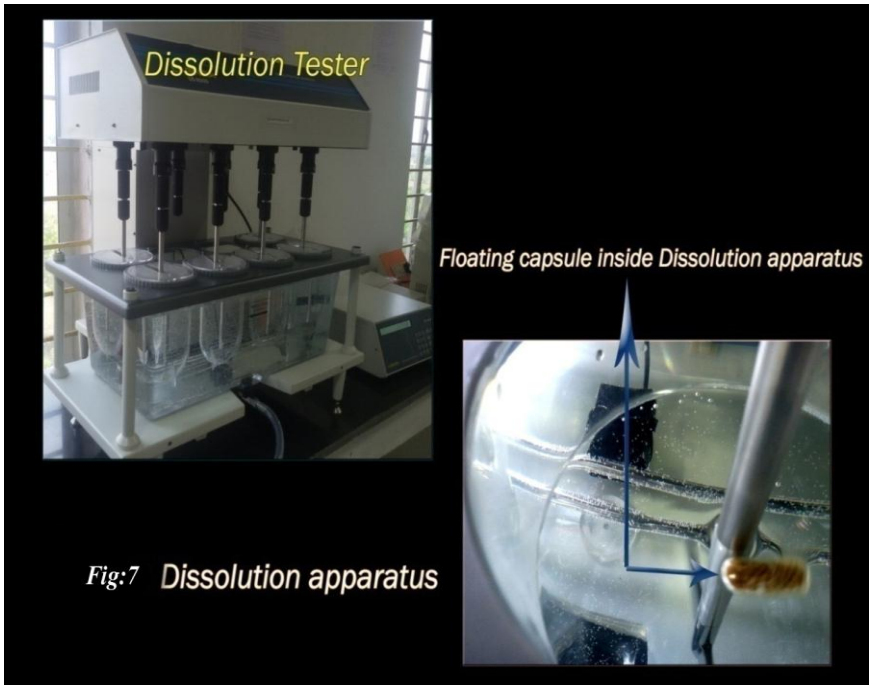


Table: 5 INVITRO DISSOLUTION STUDIES OF CEFOPODOXIME PROXETIL FLOATING MICROBEADS.

TIME(Hours)	DRUG RELEASE (%)						
	FC_1	FC_2	FC_3	FC_4	FC_5	FC_6	FC_7
1	22.05	17.45	0	0	21.07	15.12	16.24
2	28.24	29.72	4.12	0	33.08	29.42	30.56
3	34.61	36.34	10.16	5.O9	40.25	36.47	35.04
4	45.19	49.03	25.64	14.52	52.24	42.18	46.52
5	59.03	52.15	34.83	21.46	65.94	57.04	59.49
6	72.14	73.78	41.68	36.49	76.15	64.25	64.52
8	96.12	88.05	65.52	44.26	84.24	72.62	79.14
10	Nil	92.86	76.26	53.20	96.10	85.14	82.68
12	Nil	Nil	89.08	68.21	Nil	90.75	92.26

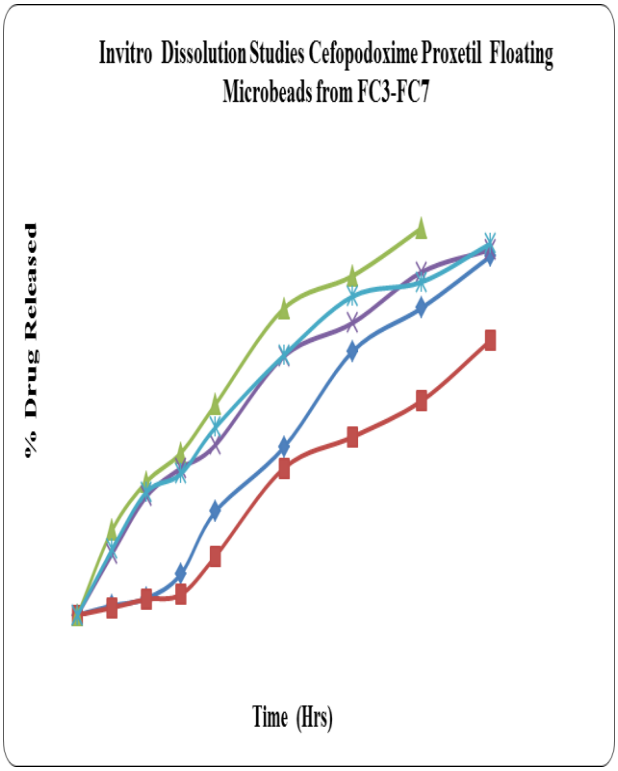
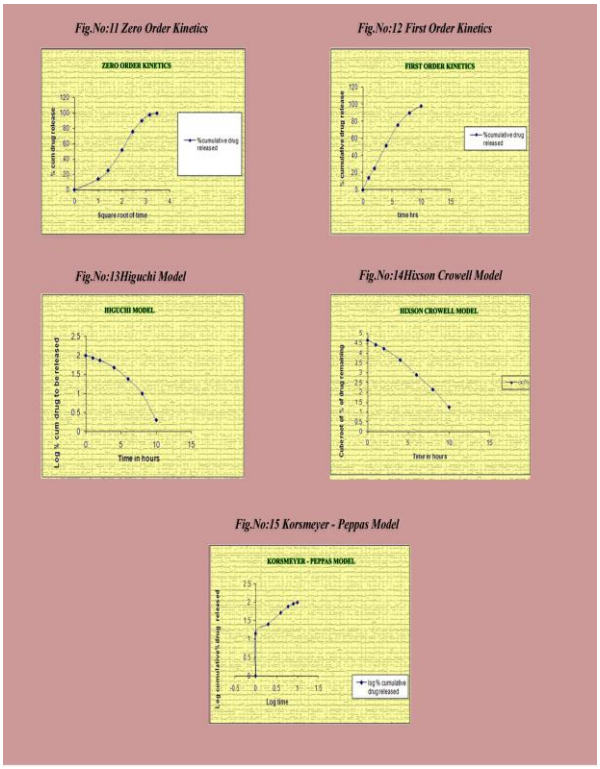


FIG NO: 10 PERCENTAGE DRUG RELEASE OF FORMULATED FLOATING MICROBEADS OF CEFOPODOXIME PROXETIL

DRUG RELEASE KINETICS

The data obtained for in-vitro release were fitted into equations for the zero order, first order and Higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients as shown in Fig no:11,12,13,14 & 15.



The optimized formulation FC4 which is more suitable for sustained release upto 12 hours, follows First order kinetics (R^2 0.9537) model, best fitted with Korsemeyer peppas model (R^2 0.9895) model and non-fickian diffusion (n value 0.785) dominates the drug release through swellable matrix and hydrophilic pores as shown in Table no: 6.

The value of release exponent(n) for the proposed model was 0.785 indicating that the transport of the drug molecules across polymeric beads takes place through diffusion controlled and swelling controlled drug release (anomalous transport). The actual drug release mechanism includes two apparent Phenomenon: Penetration of the acidic medium inside the beads and hence, swelling of the almond gum network at early stage that moves drug molecules, and the diffusion of the drug molecules out of the alginate coat as solvent hydrates the beads.

Table. 6: RELEASE KINETICS STUDY OF OPTIMIZED FORMULATION (FC4)

FORMULATION CODE	ZERO ORDER EQUATION (R^2)	FIRST ORDER EQUATION (R^2)	HIGUCHI MODEL(R^2)	KORSE-MEYER PEPPAS MODEL(R^2)	HIXON CROWELL MODEL(R^2)
FC_4	0.9516	0.9537	0.8031	0.9895	0.9544

STABILITY STUDIES

According to ICH guidelines, stability study at $4^0C \pm 2^0C$, $27^0C \pm 2^0C$ and $45^0C \pm 2\ ^0C$ for 30 days at RH 75±5% of optimized formulation (FC_4) was carried out. It showed negligible change over time for parameters like Drug entrapment efficiency, floating behaviour and in vitro drug release etc., No significant difference in the drug content between initial and formulations stored at $4^0C \pm 2^0C$, $27^0C \pm 2^0C$ and $45^0C \pm 2^0C$ for 30 days at RH 75±5% as shown in table no.7.

Table. 7: STABILITY STUDY (40°C/75%RH) OF OPTIMIZED FORMULATION (FC4)

S.NO	PARAMETERS	AFTER 30 DAYS
1.	Size& shape	White, smooth and porous in appearance
2.	Drug entrapment efficiency	86.92%
3.	Swelling index	2.38±0.62
4.	Buoyancy lag time(sec)	29
5.	Total floating time(hrs)	12
6.	In vitro release (%)	70.35

CONCLUSION

The present study has been a satisfactory attempt to formulate floating micro beads of Cefopodoxime proxetil with concentration of sodium alginate and almond gum of natural polymers by the Ionotropic gelation technique. From the results it can be concluded that biocompatible and cost effective natural polymers like almond gum and sodium alginate can be used to formulate an efficient floating micro beads with good % entrapment efficiency practical yield and sustained release properties than the combination of synthetic and natural polymer.

Sodium alginate beads were prepared by dripping method using 26G needle. HPMC E15 M was used as swellable polymers for sustained release of the drug form the beads. The beads were formed due to the cross linking of sodium alginate with divalent calcium ions of the $CaCl_2$ solution. This mechanism is called Ionotropic gelation.

The surface topography reveals that the beads were highly porous because of the rapid escape of the carbon dioxide during curing process. The number of observed pores appears to be directly related to the amount of gas forming agent.

The particle size analysis revealed that the particles were of size range of 0.93±0.012mm to 1.09±0.04mm, showed good flow properties, the micro beads were with smooth surface and lightly porous in nature as revealed by the SEM studies and thus exihibiting excellent buoyancies in simulated gastric fluid because of low density.

Formulation FC_4 can be considered as an optimized formulation among all on the basis of drug entrapment efficiency, drug release study, floating behaviour and mechanical strengths for gastro retentive floating micro beads of cefopodoxime proxetil. The result of in vitro drug release studies showed that optimized formulation FC4 could sustain drug release (68.21%) for 12 hours and remain buoyant for more than 12 hours in improving its bioavailability.

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