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Research Article

FORMULATION AND EVALUATION OF FLOATING TABLETS OF CEFUROXIME AXETIL

UMASANKAR MUKHI*, SMIATAPADMA MOHANTY

School of Pharmaceutical Education and Research, Berhampur University,Bhanja Bihar, Odisha, India, 760007.
Email: umasankar.mukhi@gmail.com

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ABSTRACT

Rate controlled oral dosage form is the frontier area among novel drug delivery systems. Among all the intragastric drug delivery systems, floating drug delivery systems (FDDS) appears to be one of the most effective and rational approaches for the controlled oral drug deliveries. This FDDS appears to have a distinct advantage in delivering the drugs that are absorbed mainly in the upper part of the GI tract and drugs having stability & solubility problem in the lower part of the intestine.

Cefuroxime is a broad spectrum antibiotic. It is a second generation Cephalosporin which is less susceptible to Beta-lactamase. It is absorbed from the gastrointestinal tract. Pro-drug of Cefuroxime is Cefuroxime axetil which is acetoxy ester form. bioavailability of the drug is 30% to 40% when taken on fasting and 5 to 60 % when taken with food.

From the above mentioned charcteristesitists of Cefuroxime axetil. It is clear that it (C.A.) had saturated kinetics that could be overcome by slow release of drug from the formulation by incorporation Cefuroxime axetil in controlled release drug delivery system. As Cefuroxime axetil has higher absorption in the proximal region of GI tracts and when a larger amount of Cefuroxime axetil enters to the colon associated with colitis, suggests it is an ideal condition for gastro retentive drug delivery system which will prolong drug release in the GI tract, where absorption of Cefuroxime is good.

The present research describes formulation development of an intragastric floating drug delivery system of Cefuroxime axetil using Guar gum with HPMC k4M. All formulations showed acceptable specifications for weight variation, thickness, hardness and friability. The dissolution studies showed release of drug over a period of 12 hours.

Keywords: Floating tablets**,** Rate controlled oral dosage form, Cefuroxime axetil, Guar gum, HPMC k4M

INTRODUCTION

Cefuroxime is a broad-spectrum/Mactamase stable, second generation cephalosporin antibiotic with a proven record of efficacy and safety in the parenteral management of various infections including urinary tract infections [1]. Since cefuroxime is not absorbed orally, cefuroxime axetil (CA) (1-acetoxyethyl ester of a β-lactamase-stable cephalosporin), an orally absorbed pro-drug of cefuroxime is used in the treatment of common community acquired infections because of its in-vitro antibacterial activity against several gram-positive and gram-negative organisms [2**]**. Cefuroxime is a β-lactam type of antibiotic. More specifically, it is a second-generation cephalosporin[3,4]. Cephalosporins work the same way as penicillins: they interfere with the peptidoglycan synthesis of the bacterial wall by inhibiting the final transpeptidation needed for the cross-links[5]. This effect is bactericidal. Cefuroxime is effective against the following organisms: Aerobic gram-positive microorganisms: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*. Aerobic gram-negative microorganisms: *Escherichia coli*, *Haemophilus influenzae* (including beta-lactamase-producing strains), *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis* (including beta-lactamase-producing strains), *Neisseria gonorrhoeae* (including beta-lactamase-producing strains). Spirochetes: *Borrelia burgdorferi*[6**]**. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [7**]**. Controlled release tablet is prepared by using guar gum as polymer. Guar gum (Galactomannan) is a high molecular weight carbohydrate derived from the natural seed of guar plant (Cyampopis tetragonolobus) [8]. The seed is composed of the hull (14-17%), the endosperm (35-42%), and the germ (43-47%). Structurally, Guar gum is a polysaccharide consisting of a mannose backbone with a galactose side chain. The galactose is randomly placed on the mannose backbone with an average ratio of 1:2 galactose to mannose. Guar gum has a polymeric structure containing numerous hydroxyl groups [9]. The most important property of guar gum is its ability to hydrate rapidly in cold water to attain uniform and very high viscosity at relatively low concentrations. Another advantage associated with guar gum is that it is a soluble in hot & cold water and provides full viscosity in even cold water. Apart from being the most cost-effective stabilizer and emulsifier it provides texture improvement, and water-binding; enhances mouth feel; and controls crystal formation. It is inert in nature. It is resistant to oil, greases, and solvents [10].

MATERIALS AND METHODS

Materials

The drug Cefuroxime axetil was received as a gift sample from Zorex pharmaceutical ltd. (Ahmadabad, India), Guar gum was supplied by Meghna products Mumbai. HPMC was obtained from Colorcon asia Pvt. Ltd (Goa, India), , Di-calcium phosphate, Sodium Bicarbonate, Magnesium Stearates, Sodium lauryl sulfate, Citric acid were obtained from Ranbaxy Fine Chemicals Ltd.New Delhi, Qualiges fine chemicals,limited, Hi Media , Mumbai, SD Fine chemicals Mumbai, Merk ltd. Mumbai respectively. Methanol and Conc.HCl were of analytical grade.

Formulation of floating tablets of cefuroxime axetil using guar gum & HPMC k4M

Floating tablets of Cefuroxime axetil was prepared by direct compression method [11]. Cefuroxime axetil (300mg equivalent to 250mg of cefuroxime base) was mixed with the required quantities of polymer blend (Guar gum & HPMC k4M), sodium lauryl sulphate, $NaHCO_3$ & Di calcium phosphate by geometric mixing .The powder blend was then lubricated with Mg. stearate (1%) & compressed on a single punch machine (Rimek mini press, Ahmedabad) using 12mm standard flat punch. Di calcium phosphate, a water soluble filler, was used to maintain constant tablet weight as well as counter balance the poor water solubility of the drug.

Table 1: Composition of tablets of cefuroxime axetil with guar gum given in the table (in mgs)

Ingredients (mgs)	FORMULATIONS					
	F1	F2	F3	F4	F5	F6
Drug	300	300	300	300	300	300
Guar gum	100	110	120	100	125	130
HPMC k4M	25	25	25	25	10	5
$NaHCO_3$	72	72	72	72	72	90
Mg stearate	6	6	6	6	6	6
Sodium Lauryl Sulphate	6	6	6	6	6	6
Di-calcium Phosphate	31	28	11	21	21	13
Citric acid	60	60	60	60	60	60

* Weight of each tablet equals 600 mg

Evaluation Of Powder Blends [12, 13]

Angle of repose

Angle of Repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way that tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan α= h/r

Bulk density and tapped density

An accurately weighed quantity of the blend **(W)**, was carefully poured into the measuring cylinder and the volume **(V_0)** was measured. Then the cylinder was tapped for a fixed time. The minimum volume **(V_f)** occupiedin the cylinder was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas

Bulk density = W/ V_0

Tapped density = W/ V_f

Compressibility index (CI)/ Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula

$$CI = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Hausner's ratio

Hausner's ratio is a number that is correlated to the flowability of a powder. It is measured by ratio of tapped density to bulk density.

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

Table 2: Evaluation of physical properties of powder blend of all formulations

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Angle of Repose	25.05	22.37	24.23	22.65	20.83	18.91
Compressibility Index %	20.38	18.38	19.73	18.75	16.43	15.43
Hausner's Ratio	1.26	1.21	1.17	1.23	1.18	1.2

Evaluation of Tablets [11, 12, 14, 15]

Thickness

Thickness of the tablets was determined using a digital vernier caliper MITUOTYO.

Weight variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance Aqua and the test was performed according to the official method.

Drug content (assay)

Drug content of the tablets was determined spectrophotometrically.

Hardness

Hardness of the tablets was determined using a Monsanto tablet hardness tester. A tablet hardness of about 3 to 5 kg/cm^2 is considered adequate for mechanical stability.

Friability

Friability of the tablets was measured in a friabilator (Roche). 20 tablets were accurately weighed (W0) and placed in friability test apparatus. They were observed for 100 rotations. After 100 rotations they were weighed again (W). The weight loss should not be more than 1% w/w.

%Friability = (W0-W)/ W0 X100

Table 3: Physical Properties of tablets of different formulations (F1 to F6)

Batches	Weight Variation(mg)	Diameter(mm)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Drug Content
F1	599.296 ±7.6355	11.946 ±0.0496	5.033 ±0.1011	4.219 ±0.3590	0.96	99.64 ±1.9911
F2	598.401 ±9.8533	11.941 ±0.0544	5.028 ±0.095	4.179 ±0.3463	0.95	99.8192 ±2.0082
F3	599.5 ±7.451	11.936 ±0.0515	5.033 ±0.0966	4.180 ±0.345	0.78	99.729 ±2.0248
F4	598.55 ±7.277	11.926 ±0.057	5.045 ±0.0956	4.25 ±0.3308	0.89	99.53 +2.105
F5	598.87 ±7.0972	11.915 ±0.0552	5.039 ±0.0936	4.280 ±0.319	0.94	100.4092 ±1.9438
F6	598.86 ±7.0913	11.921 ±0.0567	5.031 ±0.0912	4.282 ±0.3241	0.91	99.538 ±2.1072

Table 4: Floating Properties of prepared formulations

Batches	FloatingLag time(Seconds)	TotalFloating Time(hrs)
F1	30	0.5
F2	25	10
F3	30	0.5
F4	28	24
F5	20	12
F6	30	12

In-vitro drug release study [16]

In-vitro dissolution studies were designed to carryout in such a way that they simulate in vivo conditions. Dissolution was carried out in USP XX (Electrolab, Mumbai) test apparatus using paddles. 900 ml of 0.1 N HCl water was taken as dissolution medium. Dissolution was performed at 37 ± 0.5ºC with 100 rpm for 12 hours. A specified aliquot was withdrawn at specific intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours) and replaced with fresh dissolution medium of same quantity. Samples were diluted suitably, filtered 0.45µm filter paper and analyzed spectrophotometrically for drug content at 278nm [17].

Kinetics of drug release [18]:

Various models such as Zero order kinetics (cumulative percentage amount of drug release versus time), First order kinetics (log cumulative percentage of drug remaining to release versus time), Higuchi (fraction of drug release, Mt/Mi, versus square root of time) and Korsermeyer-Peppas (log fraction of drug released, log Mt/Mi, versus log time) were applied to assess the kinetics of drug release from prepared tablets. Most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism.

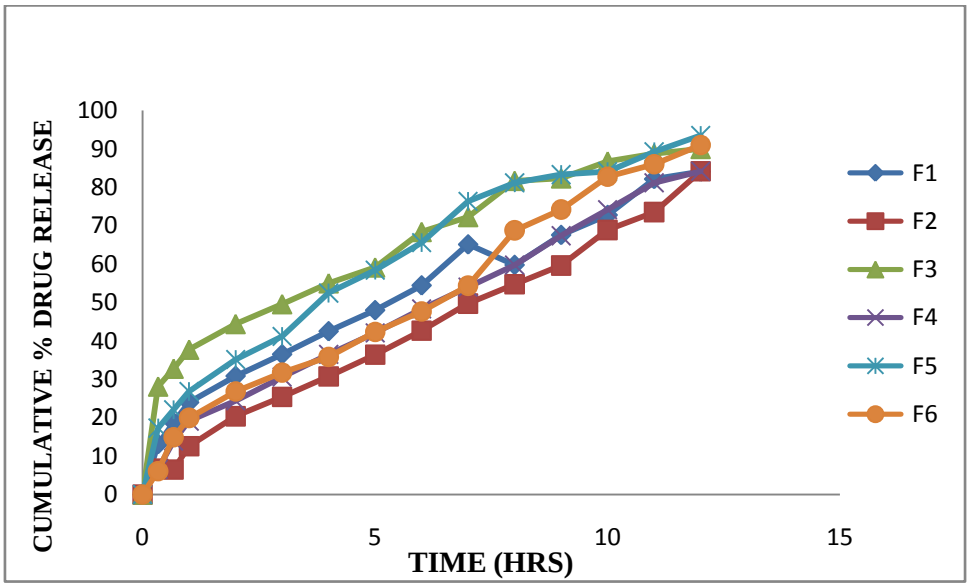

Fig. 1: Zero order plot of different formulations

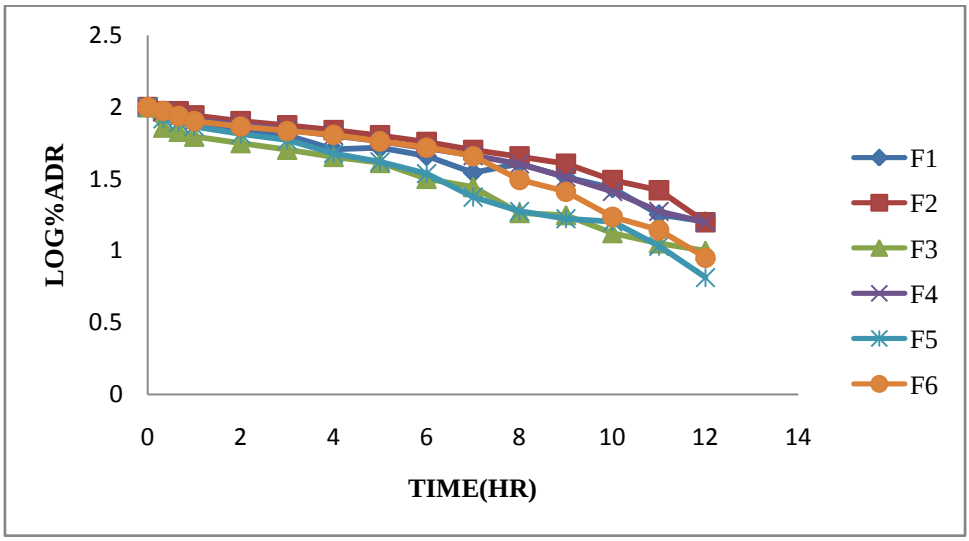

Fig. 2: First order plot of different formulations

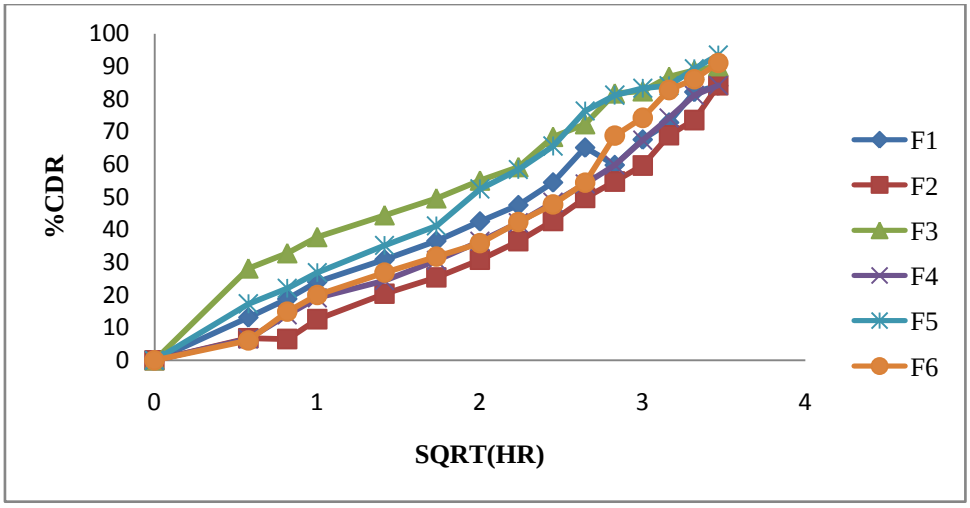

Fig. 3: Higuchi's plot of different formulations

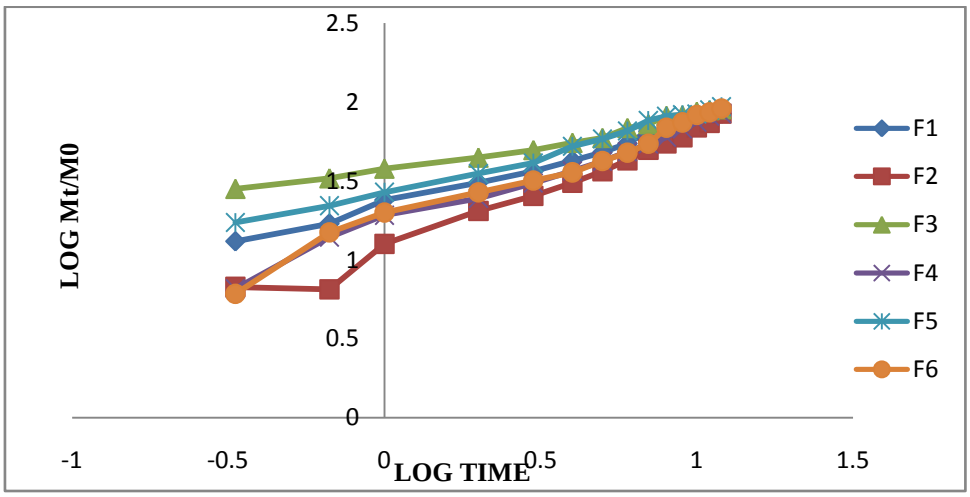

Fig. 4: Korsemeyer-Peppas plot of different formulations

Table 5: kinetic study of different formulations

Formulation No.	Cumulative % Drug Release	Zero order R^2	First order R^2	Higuchi R^2	Hixson Crowell R^2	Korsemeyer-Peppas	
						R^2	n
F1	84.06	0.957	0.958	0.985	0.975	0.989	0.637
F2	84.18	0.994	0.929	0.951	0.967	0.979	0.665
F3	90.03	0.897	0.977	0.979	0.974	0.975	0.78
F4	84.18	0.986	0.957	0.971	0.982	0.984	0.652
F5	93.48	0.942	0.977	0.991	0.989	0.989	0.68
F6	91.04	0.984	0.926	0.954	0.964	0.967	0.82

FTIR Study

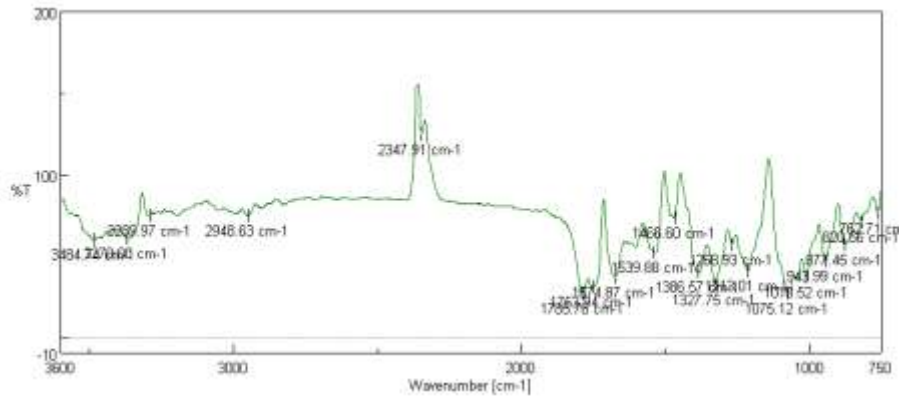

Fig. 5: FTIR Study of Cefuroxime axetil

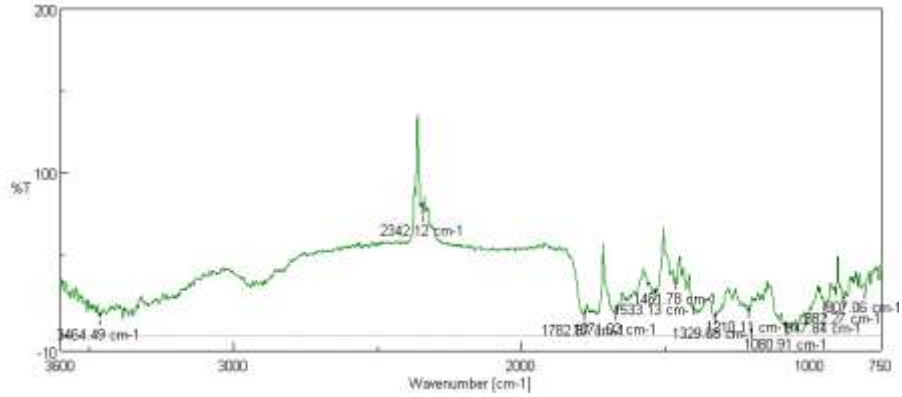

Fig. 6: FTIR Study Cefuroxime axetil + Guar gum & HPMC

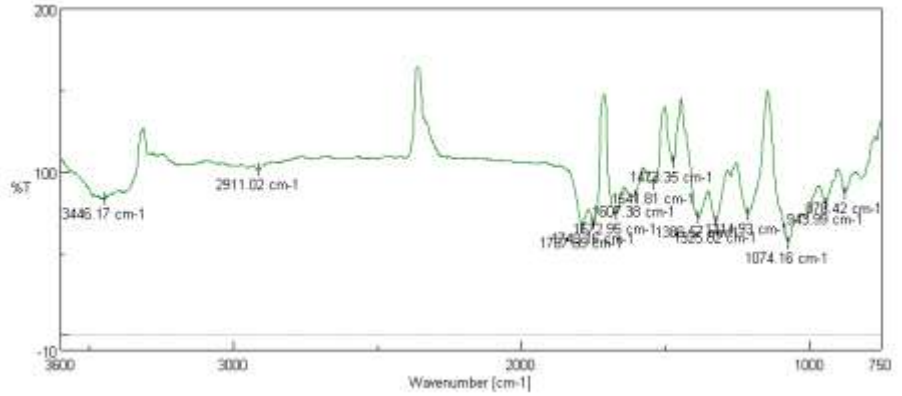

Fig. 7: FTIR Study Complete Cefuroxime axetil formulation

RESULT AND DISCUSSION

SEM Study

It is mainly done to determine the crystalline nature of drug & surface nature of formulation due to polymorphism.

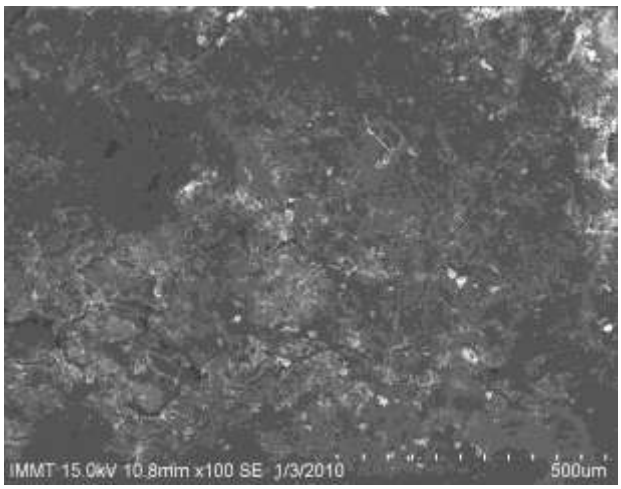

Fig. 8: SEM study of guar gum based formulation

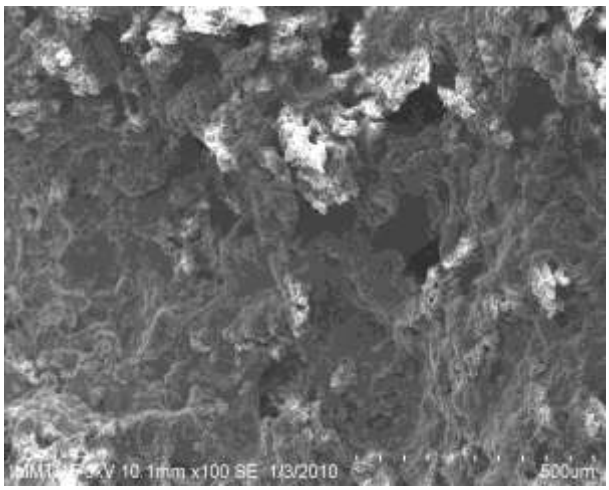

Fig. 9: SEM study of guar gum based formulation after 8hr wetting

The present study was aimed to make the formulation remain in the stomach for longer period of time and to release the drug (cefuroxime axetil) in controlled rate. Guar gum was selected as a hydrophobic meltable material to impart sufficient integrity to the tablets. Sodium bicarbonate generates carbon dioxide gas in the presence of hydrochloric acid present in gastric dissolution medium. The tablets were evaluated for, physical characteristics, weight variation, friability, hardness and dissolution studies. The hardness values were approximately 4.179 ± 0.3463 to 4.282 ± 0.3241 kg/cm^2. All formulations showed floating lag time in between 20 to 30 seconds and duration of buoyancy were more than 10 hours except F1 and F5 (0.5 hrs). All formulations showed more than 84 to 94% of drug release in 12hrs of dissolution study. The FTIR spectrum showed that both drug and polymer were not interacted with each. The data for stability studies were carried out for the optimized Formulation at 40°C ± 2°C/75%RH±5%RH for 6 months and it revealed that no considerable differences in drug content and dissolution rate and buoyancy were observed.

CONCLUSION

In the present study gastro-retentive floating tablets of cefuroxime axetil were successfully prepared by direct compression method using polymer HPMC k4M and natural gum like guar gum. From the study it is observed that formulation F5 was best in terms of drug release, floating time (12 hrs) and physicochemical properties. The developed tablets (F-5) were stable and retain their pharmaceutical properties and drug shows no degradation over a period of 6 month.

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