

Full Length Research Paper

## “Development and evaluation of gastro-retentive drug delivery systems of cefuroxime axetil”

A. S. Gudigennavar<sup>1\*</sup>, L. S. Vijapur<sup>1</sup>, C. C. Patil<sup>2</sup> and R. V. Kulkarni<sup>2</sup>

<sup>1</sup>Department of Pharmaceutics, H.S.K College of Pharmacy, Bagalkot-587101, India.

<sup>2</sup>Department of Pharmaceutics, B.L.D.E.A's College of Pharmacy, Bijapur-586103, India.

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The aim of the present investigation was to increase the gastric residence time of cefuroxime axetil by preparing gastro retentive mucoadhesive tablet, thereby improving bioavailability of cefuroxime axetil. Tablets were prepared using different mucoadhesive polymers such as hydroxypropylmethyl cellulose K4M, carbopol 974P, sodium alginate, and chitosan in combination ratios by wet granulation method. All the batches were subjected to various evaluation parameters such as physicochemical properties, swelling index, *in vitro* residence time, and *in vitro* drug release. Optimized formulation containing carbopol 974P and chitosan in combination (F6) exhibited maximum *in vitro* residence time of 10.05 h and *in vitro* release up to 45.89% in 10 h. The F6 formulation was further subjected to *in vitro* permeation, scanning electron microscope (SEM), stability studies and *in vivo* residence time. SEM revealed smooth surface characteristics with increasing pore diameter, indicating the diffusion mechanism of release. Stability was conducted as per International Conference on Harmonisation (ICH) guidelines at  $40 \pm 20^\circ\text{C}/75 \pm 5\%$  relative humidity (RH) and the values were within permissible limits. *In vivo* X-ray photographs taken during the experiment showed mucoadhesion to the gastric mucosa up to 10 h.

**Key words:** Cefuroxime axetil, gastro retentive, mucoadhesive polymers, X-ray study.

### INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have been considered for their therapeutic advantages. However, these approaches not been suitable for certain drugs, are characterized by a narrow absorption window in the upper part of the gastrointestinal tract that is, stomach. This is due to the relatively short transit time of the DF in the stomach. This results in a short absorption phase that is often accompanied by lesser bioavailability (Rajput et al., 2010). However, the oral dosage forms for gastric retentions have drawn more attention for their therapeutic advantages in permitting control over the time and site of drug release. The challenge in the development of controlled drug delivery system is not just

sustained drug release but also to prolong the presence of a dosage form in the stomach (Patil et al., 2006).

The term mucoadhesive describes material that bind to biological substrate, such as mucosal layer. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This increased residence time can result in enhanced absorption and in combination with a controlled release of drug also improve patient compliance by reducing the frequency of administration (Uddhav et al., 2009). Cefuroxime axetil is a  $\beta$ -lactum antibiotic. More specifically, it is a second generation cephalosporin.

\*Corresponding author. E-mail: [aa\\_sg7@rediffmail.com](mailto:aa_sg7@rediffmail.com). Tel: +919986537166.

Cefuroxime axetil (CFA) is acid stable and completely absorbed in gastrointestinal tract and is rapidly hydrolyzed in the intestinal mucosa and blood to cefuroxime, absorption is increased by the presence of food. Peak plasma concentration is about 2 to 3 h after oral dose. The biological half life is 80 min and bioavailability is 37%. In the present study we tried to enhance the bioavailability of cefuroxime axetil by formulating it in the form of gastro retentive mucoadhesive drug delivery system for controlled release which is expected to be a better dosage form when compared to conventional or immediate dosage form (William, 2006; Shelke et al., 2009). Therefore, the aim of the present work was to formulate gastro-retentive mucoadhesive tablets for cefuroxime axetil.

## MATERIALS AND METHODS

Cefuroxime axetil was obtained as a gift sample from Cipla Pvt. Ltd Pune., carbopol 974P was obtained as a gift sample from Kemwell Ltd., Bangalore, hydroxypropylmethyl cellulose (HPMC) K4M was obtained from Arihant trading co. Mumbai. Chitosan was obtained from Fisheries' Ltd Kocchin. Sodium alginate, magnesium stearate, methanol barium sulphate, sodium chloride, magnesium stearate, potassium dihydro ortho phosphate was procured from S.D. Fine Chem. Ltd Mumbai.

### Preparation of mucoadhesive tablets

The composition of bioadhesive CFA tablets prepared by wet granulation technique is shown in Table 1. All the ingredients were weighed as per the formulations (F1 to F9) required, were passed through sieve no. 60# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder (15% of starch paste). The blend wet mass was passed through sieve no. 16# and dried at 45 to 55°C for 2 h. Dried granules were sized by sieve no. 40# and finally magnesium stearate and talc were added. Flat 500 mg tablets were prepared by 12.5 mm flat punches in Rimek mini press 1 tablet compression machine (Saravanan et al., 2006).

### Physicochemical evaluation of formulations

#### Physicochemical parameters for tablets

The thickness of the five tablets of each formulation was measured using digital vernier caliper in mm. Hardness was determined using a Monsanto hardness tester. Pressure required to break the tablet was determined in kg/cm<sup>2</sup>. Friability was tested by taking 10 dedusted tablets and the percentage friability was calculated. The percentage friability was measured using formula according to Saravanan et al. (2002) and Banker and Anderson, (1990).

**Weight variation:** Ten tablets were randomly selected from each batch and weighed individually. The average weight and standard deviation of 20 tablets was calculated and tabulated (Banker and Anderson, 1990).

**Drug content uniformity:** Twenty tablets were weighed and powdered. The quantity equivalent to 100 mg of cefuroxime axetil was weighed accurately and taken in 100 ml volumetric flask. 50 ml

of 1.2 pH buffer was added and stirred for 5 min, the volume was made up to 100 ml with 1.2 pH (SS-I) and filter. From the above solution, 25 ml aliquot was pipetted into 100 ml volumetric flask and volume was made with 1.2 pH (SS-II). From this, 2 ml was pipetted into 25 ml volumetric flask with 1.2 pH buffer. The absorbance was measured at 280 nm. The content uniformity was calculated (Banker and Anderson, 1990).

**Swelling index:** The tablets were coated on the lower side with ethyl cellulose then weighed ( $W_1$ ) and placed separately in Petri dishes containing 20 ml of pH 1.2 hydrochloric acid buffer. The dishes were stored at room temperature. After 2, 4, 6 and 24 h, the tablets were removed and the excess liquid on the surface was carefully removed using filter paper. The swollen tablets were reweighed ( $W_2$ ) and the index of swelling was calculated by the formula.

$$\text{Swelling index} = W_2 - W_1 / W_1 \times 100$$

For each formulation, three tablets were tested (El-Samaligy et al., 2004).

### In vitro dissolution studies

Dissolution of the tablet of each batch was carried out using U.S. Pharmacopeial (USP) XXIII dissolution type II apparatus using paddle, and fixing the tablet to the paddle. 900 ml of pH 1.2 hydrochloric acid dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at  $37 \pm 0.5^\circ\text{C}$ . The rotation speed of the paddle was set at 50 rpm. 1 ml of sample was withdrawn at predetermined time interval of 1 h and same volume of fresh medium was replaced. The samples withdrawn were diluted to 10 ml volumetric flask with 1.2 pH buffer, filtered and analyzed by an ultra violet (UV) spectrophotometer at 280 nm using buffer as blank. The drug content was calculated using the equation generated from standard calibration curve. The percentage cumulative drug release was calculated (Cilurzo et al., 2003).

### In vitro bioadhesion

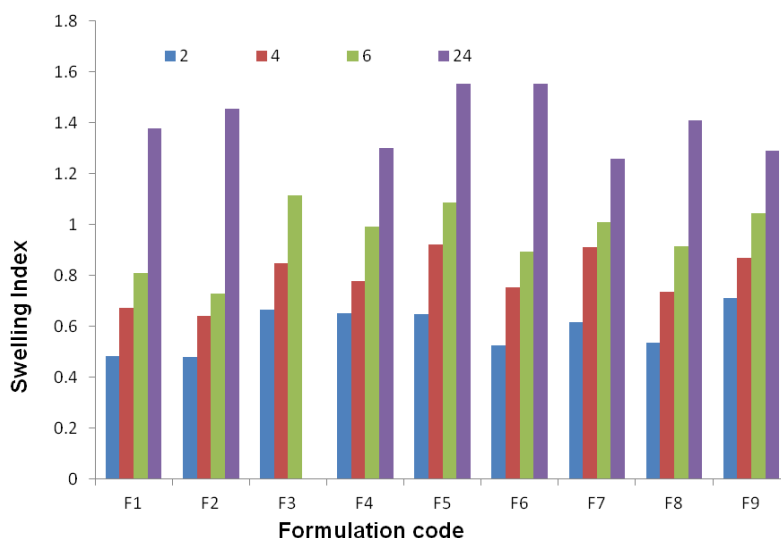
The measurement of bioadhesive strength was done as reported by Mortazavi. Rat stomach mucosa was used as a model mucosal surface for bioadhesion testing. In order to evaluate the bioadhesive strength of the prepared tablets, the apparatus shown in Figure 1 was used. The upper stationary platform was linked to a digital balance of 0.01 g sensitivity, measuring the force needed to break contact between the tablet and mucosa. The test cell was filled with pH 1.2 hydrochloric acid buffer maintained at 37°C, and the sections of rat stomach placed and fixed in place over the lower platform with cyanoacrylate glue and allowed to equilibrate in this solution for 2 min. Similarly, the tablets from each formulation were glued to the upper platform. The lower platform was elevated until the mucosal surface came in contact with the surface of tablet attached to the upper platform and it was allowed to remain in contact for 3 min. Then, a constantly increasing force was applied on the adhesive joint formed between mucosa and the test tablet by gradually lowering the lower platform. This process was continued until the contact between the test tablet and mucosa was broken and the maximum detachment force measured was recorded by the formula:  $F = WG / A$ , where  $F$  = force,  $W$  = weight,  $G$  = gravity and  $A$  = surface area of tablet (Mortazavi, 2002; Ali, 2002).

### In vitro permeation studies for the optimized formulation (F6)

This test was carried out using a Franz diffusion cell. The inferior

**Table 1.** Formulation design of mucoadhesive CFA tablets.

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefuroxime axetil	250	250	250	250	250	250	250	250	250
HPMC K4M	109	109	109	109	-	-	-	-	86.9
Lactose	64.8	34.8	64.8	34.8	64.8	34.8	64.8	34.8	-
Carbopol 934	70	100	-	-	70	100	-	-	70
Chitosan	-	-	-	-	109	109	109	109	86.9
Sodium alginate	-	-	70	100	-	-	70	100	-
Magnesium Sterate	5	5	5	5	5	5	5	5	5
Propyl paraben	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08
Methyl paraben	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12

**Figure 1.** Swelling index.

compartment, filled with 54 ml of pH 1.2 phosphate buffer simulated the blood circulation while the superior compartment, filled with 5 ml of a pH 1.2 hydrochloric acid buffer simulated the gastric pH. A rat stomach mucosa was clamped with the external surface turned versus the superior compartment. The tablet adhered to the external mucosal surface into the superior compartment. This system was placed on a thermostatic cum magnetic stirrer to generate stirring in the inferior compartment at a temperature of  $37 \pm 0.5^\circ\text{C}$ . 1 ml of solution was withdrawn from inferior compartment and replaced with equal volume of fresh buffer at 1 h intervals for a period of up to 10 h. The samples were withdrawn and diluted to 50 ml with buffer, filtered and analyzed by an UV spectrophotometer at 280 nm using 1.2 pH buffer as a blank. The concentration of cefuroxime axetil in the samples was calculated on the basis of the equation generated from standard calibration curve. Then, cumulative (%) drug release was calculated.

**Flux calculation:** The cumulative amount of permeated drug ( $\mu\text{g}/\text{cm}^2$ ) was plotted versus (h), and the flux ( $\mu\text{g}/\text{cm}^2 \text{h}^{-1}$ ) was calculated from the slope of the line using the following equation:

$$J = dQ / dt$$

Where J = flux, dQ = concentration of drug in receptor compartment

and dt = time (Ali, 2002).

#### ***In vitro* residence time**

The *in vitro* residence time was determined using a locally modified USP disintegration apparatus. The medium was composed of 800 ml pH 1.2 hydrochloric acid buffer maintained at  $37^\circ\text{C}$ . A segment of rat stomach mucosa was glued to the surface of a glass slab, and attached vertically to the apparatus. The mucoadhesive tablet was hydrated from one surface using pH 1.2 and then the hydrated surface was brought into contact with the mucosal layer of the stomach. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the highest point. The time necessary for erosion or detachment of the tablet from the mucosal layer of the stomach was recorded (Nafee et al., 2004).

#### ***In vivo* gastric retention time**

*In vivo* gastric retention time was determined by X-ray technique in rabbits. For *in vivo* study, barium sulphate containing mucoadhesive tablets were prepared by the same method, cefuroxime axetil was replaced by barium sulphate. For *in vivo*

**Table 2.** Evaluation parameters of formulations mucoadhesive CFA tablets.

Formulation code	Evaluation parameters						
	Thickness $\pm$ SD (mm) (n = 5)	Hardness $\pm$ SD (kg/cm <sup>2</sup> ) (n = 5)	% Friability	Weight variation (%) (n=10)	Drug content (%)	Residence time (h)	Force of adhesion (N) (n=3)
F1	4.52 $\pm$ 0.04	6.58 $\pm$ 0.381	0.024	0.505 $\pm$ 0.011	83.83	8.1	1.0767
F2	4.67 $\pm$ 0.05	6.25 $\pm$ 0.433	0.279	0.503 $\pm$ 0.010	87.37	8.9	1.4167
F3	4.65 $\pm$ 0.08	6.5 $\pm$ 0.5	0.184	0.498 $\pm$ 0.010	92.01	6.5	0.6903
F4	4.69 $\pm$ 0.06	6.91 $\pm$ 0.144	0.041	0.502 $\pm$ 0.135	94.83	7.8	0.9039
F5	4.52 $\pm$ 0.05	6.16 $\pm$ 0.288	0.008	0.503 $\pm$ 0.009	81.62	9.8	1.1243
F6	4.51 $\pm$ 0.04	6.75 $\pm$ 0.433	0.016	0.504 $\pm$ 0.010	89.02	12.5	1.4901
F7	4.49 $\pm$ 0.02	6.33 $\pm$ 0.144	0.008	0.504 $\pm$ 0.008	96.80	7.6	0.2581
F8	4.46 $\pm$ 0.03	6.75 $\pm$ 0.433	0.040	0.503 $\pm$ 0.008	95.53	7.1	1.0007
F9	4.60 $\pm$ 0.02	6.5 $\pm$ 0.25	0.115	0.504 $\pm$ 0.008	87.85	10.5	0.9696

retention study, albino rabbit of 3 months age and 2.5 kg weight was used. It was fasted overnight and on the next day morning, the tablet was administered orally through gastric tube, followed by giving 10 ml of water. X-ray photograph was taken immediately after administration of tablet and also at different time intervals of 2, 4, 6 and 10th h. X-ray photograph revealed the nature and position of the tablet up to 10 h after tablet administration. The experiment was carried out at veterinary hospital (Rao et al., 1998).

#### Accelerated stability studies of the optimized formulation (F6)

Stability studies were carried out as per ICH guidelines using Thermolab TH 90S stability chamber. The temperature and relative humidity value selected was 40  $\pm$  2°C/75  $\pm$  5% RH for a period of 6 months, where formulations were monitored for the hardness, drug content and *In vitro* drug release.

## RESULT AND DISCUSSION

In the present investigation, bioadhesive polymers such as carbopol 974P, HPMC K4M, sodium alginate and chitosan in different ratio were

employed (Table 1). Hence, the present research work was to study systematically the effect of formulation variables on the release and bioadhesive properties of cefuroxime axetil. Physical mixture of drug and polymer was characterized by fourier transform infrared spectroscopy (FTIR) spectra analysis. From the result, it was concluded that there was no interference in the functional group as the principle peaks of the cefuroxime axetil were found to be unaltered in the drug polymer physical mixture, indicating they were compatible chemically. The prepared tablets were subjected to preliminary characterization such as hardness, thickness, percentage weight variation, friability and drug content. Evaluation studies indicated that the values of various parameters were within the acceptable limits shown in Table 2. Swelling index study showed increase in weight, indicating that the polymers employed in the present investigation were having a capacity to swell. The swelling index was calculated with respect to time. As time increased, the swelling index was increased because weight by tablet was increased proportionally with rate of

hydration up to certain limit. Maximum water uptake and swelling of polymer was achieved up to 6 h and then gradually decreased due to erosion shown in Figure 1.

From the results, it was concluded that the F<sub>6</sub> formulation showed maximum swelling index (1.555  $\pm$  0.117) at 24 h as compared to other formulations. A trace of erosion was observed at 24 h of swelling in formulation F<sub>3</sub>. *In vitro* drug release was carried out for 10 h to all formulation. The data obtained from all formulation that is, from F1 to F9 were given in Figure 3. The *in vitro* dissolution showed that the formulation containing carbopol 974P and chitosan was found to retard the drug release, where drug release obeyed non-fickin diffusion controlled mechanism and was best fitted into Korsmeyer peppas equation. The mucoadhesive property of tablets was determined using transaction mechanism. The maximum bioadhesive strength was observed in tablet of formulation F<sub>6</sub> containing chitosan and carbopol 934P, and minimum strength was observed in tablet of formulation F<sub>3</sub> containing HPMC K4M and sodium alginate.

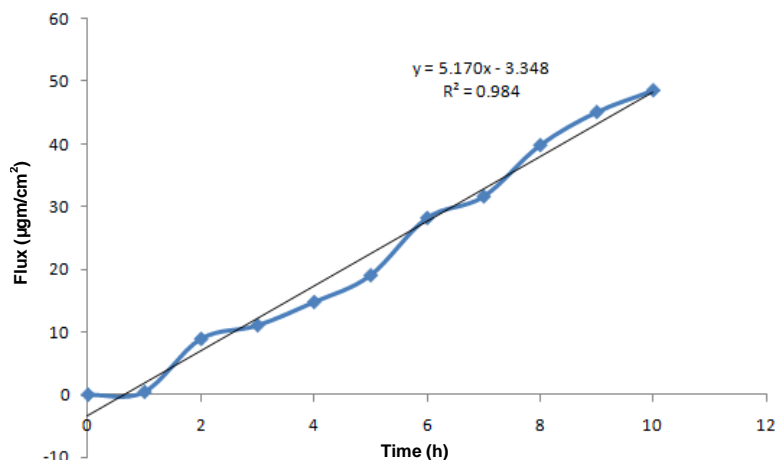


Figure 2. Flux calculation for *in vitro* permeation study of optimized F6.

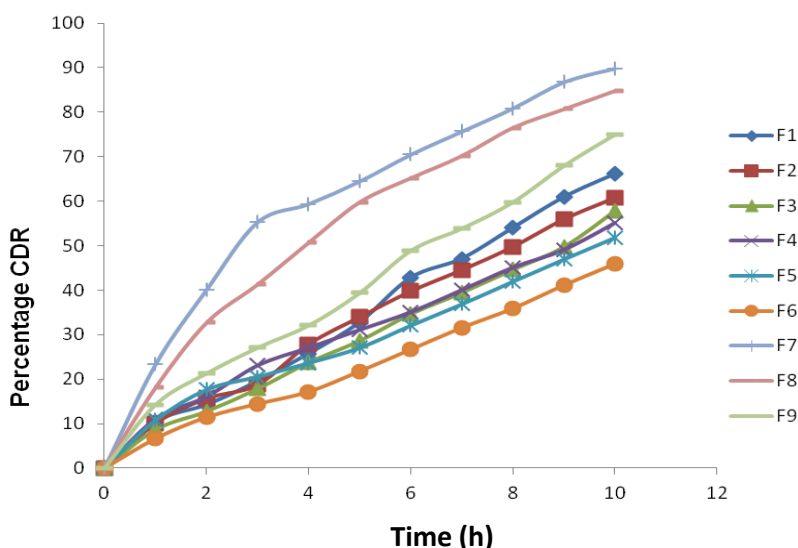
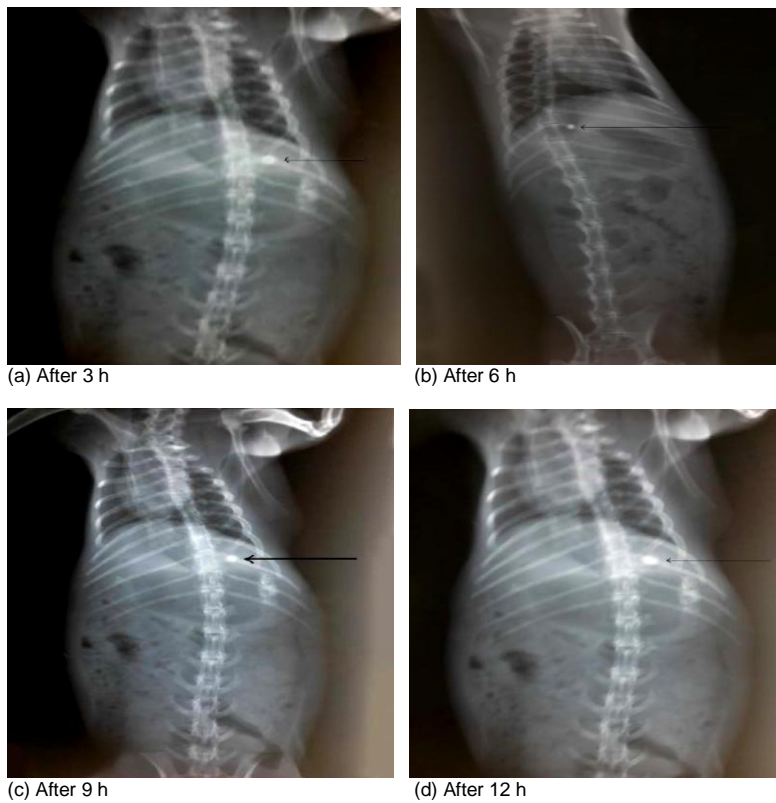


Figure 3. *In vitro* cumulative percentage drug release versus time for F1 to F9.

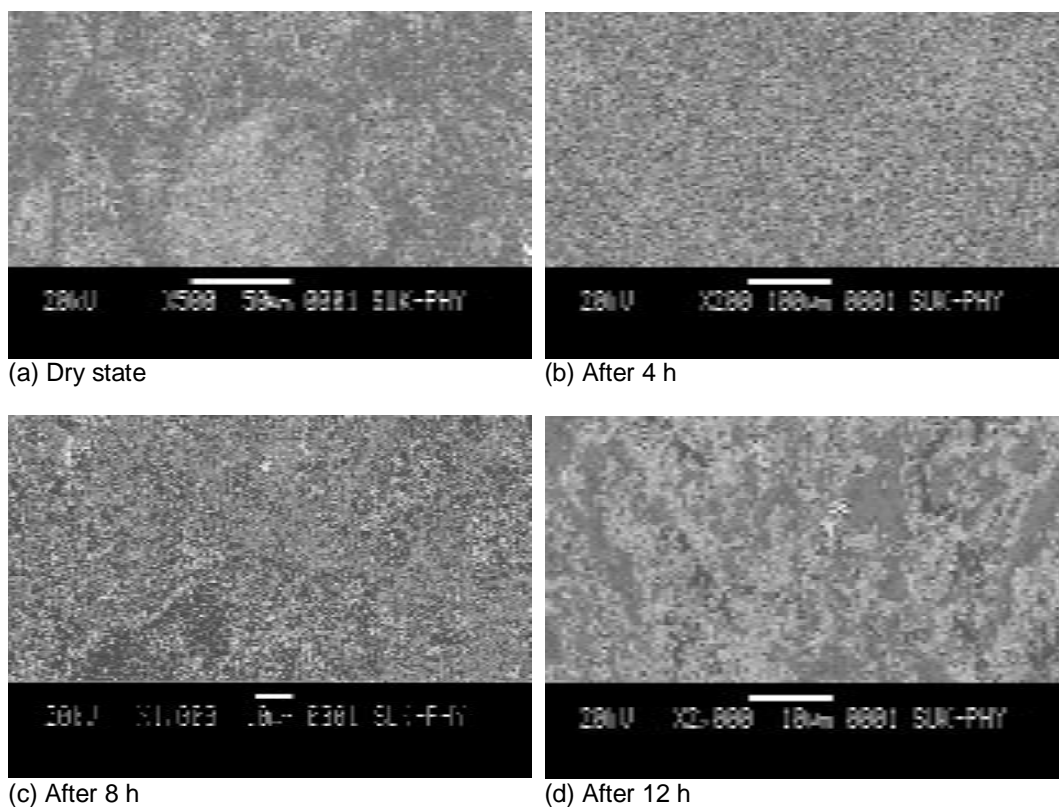
The *in vitro* residence time was determined by USP disintegration apparatus. Among the all formulation subjected for this study, F6 showed maximum residence time of 12.5 h and it was found that an increase in concentration of carbopol increased the residence time, and F<sub>3</sub> exhibited minimum *in vitro* residence time. This minimum residence time might be due to erosion of tablet during swelling because F<sub>3</sub> formulation exhibits erosion after 6 h in swelling studies. *In vitro* permeation study was carried out for optimized formulation F6 using Franz diffusion cell at  $37 \pm 20^\circ\text{C}$ , with rat mucosa results indicating that cefuroxime axetil showed a steady state flux of  $0.3189/\text{cm}^2$  with a slope value of 1518.0, and can exhibit  $1.060 \text{ mg}/\text{cm}^2 \text{ h}$ , which was sufficient for maintaining therapeutic concentration in systemic circulation as shown in Figure 2.

The results of the *in vivo* gastric retention time testing by X-ray studies on rabbit has shown that the tablet adhered in the stomach and could be seen at almost same place even after 10 h of administration, and this indicated that the mucoadhesion was so strong and were gastro retentive as shown in Figure 4. Stability studies were carried out for optimized formulation as per ICH and the results of stability study revealed that there was no significant change in color, drug content and *in vitro* drug release, with slight decrease in hardness on storage.

In SEM analysis, surface of the intact tablet without swelling was found to be rigid and more porous. As the swelling time increased, the surface was found to be smooth and the number of pores decreased following diffusion, with formation of matrix as shown in Figure 5.



**Figure 4.** *In vivo* gastric retention time of the optimized formulation (F6).



**Figure 5.** SEM of Formulation optimized formulation (F6).

## Conclusion

Gastroretentive mucoadhesive tablets were successfully developed using carbapol 974P, sodium alginate, chitosan and HPMC K4M for cefuroxime axetil. From the results of *in vitro* drug release, it can be concluded that combination of carbapol 974P and chitosan retarded drug release when compared to the combination of HPMC K4M and sodium alginate. The optimized formulation F6 showed enhanced mucoadhesion when it was subjected to *in vitro* bioadhesion studies and *in vivo* residence studies. So an optimized ratio of carbapol 974P and chitosan polymer will give a promising gastro retentive drug delivery for cefuroxime axetil.

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