

*Full Length Research Paper*

# Novel buccoadhesive delivery system of hydrochlorothiazide formulated with ethyl cellulose-hydroxypropyl methylcellulose interpolymer complex

A. A. Attama, P. A. Akpa\*, L. E. Onugwu and G. Igwilo

Drug Delivery Research Unit, Department of Pharmaceutics, University of Nigeria, Nsukka 410001, Enugu State Nigeria.

Accepted 11 June, 2008

The buccoadhesive and *in vitro* release properties of patches formulated with ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) interpolymer complexes of different ratios were studied. The patches containing hydrochlorothiazide (HCTZ) were prepared by casting and thereafter, evaluated using the following parameters: diameter, thickness, swelling behaviour, buccoadhesive strength, drug content analysis and *in vitro* release studies. An adapted Lecomte Du Nouy tensiometer was used to assess the buccoadhesion of the patches on freshly excised buccal mucosa of a pig. The release of HCTZ from the patches was studied in phosphate buffer (pH 7.5). The result of the study indicated that 1:2 ratio of EC and HPMC gave the highest buccoadhesive strength. All the patches had uniform diameters but varied thicknesses with their areas ranging from 2.06 to 2.16 cm<sup>2</sup>. The area swelling ratio (ASR) indicated that the patches did not swell up to two times their initial areas, with the batch containing 3:2 ratio of EC and HPMC possessing the highest ASR. Higuchi's analysis of the release mechanism indicated that the release of HCTZ from the patches formulated with 1:1 and 2:1 ratios of EC and HPMC predominantly occurred by a diffusional process. This method could be used as an effective alternative delivery system for HCTZ compared with conventional tablet formulations.

**Key words:** Hydrochlorothiazide, ethylcellulose, hydroxypropyl methylcellulose, interpolymer complex, area swelling ratio, buccoadhesive delivery.

## INTRODUCTION

Bioadhesive delivery systems have received considerable attention as absorption promoters due to their ability to adhere to the mucin/epithelial cell surface and thereby anchor a dosage form at the site for optimum drug absorption and lead to an overall increase in bioavailability (Hui and Robinson, 1985; Longer et al., 1985; Mortazavi and Smart, 1994; Magi et al., 1994; Caramela et al., 1994). Mucoadhesion utilizes the property of bioadhesion of certain water soluble or swellable polymers which become adhesive on hydration and hence can be used for targeting a drug to particular regions of the body where mucus or receptive epithelial cells are present e.g. nasal, buccal, GIT, cervical and vaginal. The formulation can re-

main attached for extended period of time and this may reduce toxic side effects and increase the therapeutic efficacy of the incorporated drug (Kamath and Park, 1994; Attama et al., 2003). There are several types of controlled- release bioadhesive dosage forms in use, some of which include oral, buccal and nasal bioadhesive controlled- release devices (Ishida et al., 1983). Buccal delivery is the administration of drug via the membranes of the buccal cavity to the systemic circulation in a way to enhance absorption and overall bioavailability (Kamath and Park, 1994; Guptar et al., 1992; Desai and Pramod-Kumar, 2004). This delivery system has been an area of increased interest by drug delivery pharmaceutical scientists (Martin et al., 2003; Salamat-Miller et al., 2005; Cafaggi et al., 2005; Perioli et al., 2004).

Ethylcellulose (EC) is one of the most widely used water-insoluble polymers in pharmaceutical film coating due

\*Corresponding author. E-mail: [aakpa@alumni.unav.es](mailto:aakpa@alumni.unav.es). Tel: +234-42-771911. Fax: +234-42-771709.

**Table 1.** Quantities of the polymers and the HCTZ used for the formulation of the patches.

Batch	Polymer composition (g)		HCTZ (g)
	EC	HPMC	
1	1.0	1.0	0.25
2	0.7	1.4	0.25
3	1.4	0.7	0.25
4	0.8	1.2	0.25
5	1.2	0.8	0.25

due to its convenient film formability, good physicochemical property and minimal toxicity (Porter, 1984). Hydroxypropyl methylcellulose (HPMC) swells in water and produces a clear to opalescent viscous colloidal dispersion. It is used as a dispersing and thickening agent (Hjartstam et al., 1990). Buccoadhesive delivery systems make use of polymers that are highly bioadhesive and do not dissolve before releasing the incorporated drug, rather drug leaches out of the physiologically inert matrix on absorption of minimum amount of aqueous fluid. Hydrochlorothiazide (HCTZ) is a thiazide diuretic (water pill). It decreases the amount of fluid in the body by increasing the amount of salt and water lost in urine and is used to lower blood pressure and to decrease edema (swelling). HCTZ is not metabolized but is eliminated rapidly by the kidney. It is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension (Hardman et al., 2001). Orthostatic hypotension may occur as a side effect of HCTZ therapy and this may be aggravated by alcohol or antihypertensive drugs. It is also easy to become dangerously dehydrated while taking HCTZ in hot weather. Formulating HCTZ as a buccal patch may help the patient terminate the therapy when serious side effects are noticed especially in ambulatory patients in the tropics where hot weather is common and patient monitoring is low. Mixture of these two polymers may help control the release of HCTZ from the formulation and possibly prevent dehydration and orthostatic hypotension that may occur with burst release characteristic of immediate release dosage forms during thiazide therapy. In this study, the hydrophilicity of HPMC was modified with hydrophobic EC to reduce the area swelling ratio of the formulated buccal patches when administered in the buccal cavity. The hydrophobic nature of the EC is also expected to moderate the imbibition of aqueous fluid in the buccal cavity as excessive uptake of fluid will lead to loss of bioadhesive strength of the patches and surge in release of HCTZ. This work is aimed at assessing the *in vitro* availability of hydrochlorothiazide from a novel buccoadhesive delivery system formulated with interpolymer complex of HPMC and EC.

## EXPERIMENTAL METHODS

### Materials

The following materials were sourced locally and used without further purification: hydrochlorothiazide (MSD, U.S.A), ethyl cellulose (Dow-Chemical Co. USA), hydroxypropyl methylcellulose (Shin ETSU, Japan) and dichloromethane (Carlo-Erba, Italy). All other reagents and solvents were of analytical grade and were used as such. Distilled water was obtained from a glass still.

### Preparation of HCTZ buccoadhesive patches

The patches were prepared using the quantities of the components as stated in Table 1. Appropriate quantity of HCTZ was weighed and dispersed in a dispersion of the polymers in dichloromethane. The dispersion was poured into circular metal wells (moulds) of uniform diameter and thickness. This was left for 24 h at 28°C for the organic solvent to completely evaporate. The patches formed from inter-complexation of the two polymers during solvent drying and were thereafter manually removed and stored in a desiccator until used.

### Evaluation of HCTZ patches

Five patches from each batch were randomly selected and the diameters and thickness were measured with a vernier calliper and micrometer screw gauge respectively. The averages and standard deviations were calculated.

### Porosity

Five patches were selected at random from each batch and observed with a microscope for homogeneity, brittle fracture and presence or absence of pores.

### Swelling studies

The swelling studies were carried out on the five batches of the patches using phosphate buffer (pH 7.5) as the swelling fluid. Each of the patches was placed in a Petri dish and a 100 ml quantity of phosphate buffer (pH 7.5) was poured into it. The diameter of the patch was measured at 5 min intervals for 60 min. The respective area swelling ratios (ASR) were calculated from the average of three measurements using equation 1 (Attama and Adikwu, 1999).

$$ASR = \frac{A_t}{A_o} \quad \dots \quad \dots \quad \dots \quad (1)$$

Where  $A_t$  is area of the patch at  $t$ , and  $A_o$  is area of the patch at time zero.

### Ex vivo buccoadhesive test

The Lecomte Du Nouy tensiometer (model Nr. 3124, A. Kruss Hamburg, Germany) was used for the study. A freshly excised pig buccal mucosa was rinsed with chilled normal saline and used within 2 h post mortem. The mucus surface (3 x 3 cm) cut off from buccal mucosa was each time used for the test. The tissue was pinned on a polythene support of the instrument placed on a metal

**Table 2.** Properties of the patches evaluated.

Batch	Parameter					
	Polymer ratio EC/HPMC	D (cm ± SD)	T (cm ± SD)	CT (Nm <sup>-2</sup> × 10 <sup>-2</sup> ± SD)	ADC (mg ± SD)	CA (cm <sup>2</sup> ± SD)
1	1:1	1.63 ± 0.09	0.22 ± 0.04	6.87 ± 1.22	24.8 ± 2.3	2.09 ± 0.13
2	1:2	1.65 ± 0.11	0.61 ± 0.02	7.21 ± 1.15	24.9 ± 3.8	2.14 ± 0.18
3	2:1	1.66 ± 0.08	0.67 ± 0.03	6.80 ± 0.98	24.9 ± 4.1	2.16 ± 0.05
4	2:3	1.66 ± 0.12	0.51 ± 0.06	6.62 ± 1.05	25.0 ± 4.2	2.16 ± 0.12
5	3:2	1.62 ± 0.10	0.69 ± 0.05	6.98 ± 1.21	25.1 ± 3.9	2.06 ± 0.14

D = diameter; T = Thickness; CT = calculated tension; ADC = absolute drug content; CA = calculated area.

support. The instrument was zeroed and the buccoadhesion of the clean plastic plate (3 x 3 cm suspended on the lever arm of the tensiometer) determined in degrees. For the determination of the buccoadhesive strengths of the patches, a patch was glued to the plastic plate using a cyanoacrylate adhesive. The patch was then made to contact with the everted buccal mucosa by raising the lower platform of the tensiometer. A 1µl quantity of phosphate buffer was added at the interface to activate buccoadhesive interaction. A time interval of 7 min was allowed for buccoadhesive interaction to take place. The patch was then raised by means of a screw until it just detached from the tissue. The tension required to detach the patch was recorded in degrees and the appropriate conversion to detachment force equivalent to buccoadhesive strength was done using equation 2, the modified equation of Harkins and Jordan (Harkins and Jordan, 1930). Average of five determinations on a fresh buccal mucosa for each batch was taken as the buccoadhesive strength.

$$T = \frac{Mg}{2L} \cdot F \quad \dots \quad \dots \quad \dots \quad (2)$$

Where *T* is the tension equivalent to buccoadhesive strength, *M* is the mass required to re-zero the lever after each experiment, *g* is the acceleration due to gravity, *F* is the instrument constant and *L* is the area of the buccoadhesive interface. This area is equal to the area of the patch.

#### Absolute drug content

Five patches were selected at random from each batch and allowed to hydrate in 80 ml of phosphate buffer (pH 7.5) contained in a 100 ml volumetric flask for 24 h. The solution was filtered and made up to 100 ml with the phosphate buffer through the filter. The absorbance of the solution was determined in a spectrophotometer (SP 6-450 UV/VIS Pye Unicam) at 273 nm after proper dilution. The absolute drug content for each batch of the patches was calculated by reference to a Beer's plot.

#### Release studies

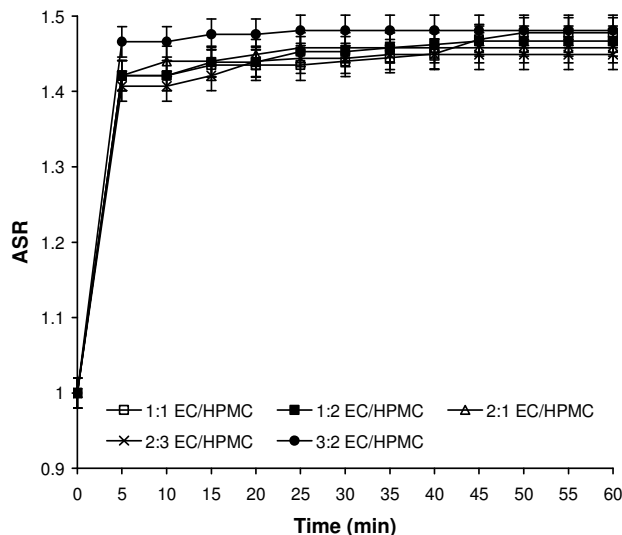
The magnetic stirrer assembly (Model LR11 Mettler, England) with an attached hot plate was adopted for the study. The dissolution medium consisted of 500 ml of phosphate buffer (pH 7.5) maintained at 37 ± 1°C by means of a thermo-regulated hot plate. A patch from each batch was placed into the appropriate chamber of the assembly separated from the medium by a micropore membrane, and the magnetic stirrer set at a speed of 100 rpm. One-

milliliter samples were withdrawn at predetermined time intervals for all the batches. For each sample withdrawn, an equivalent volume of phosphate buffer was added to the dissolution medium to ensure sink condition was maintained throughout. A ten-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 273 nm. Average of three absorbance values at each time interval was converted to amount released by reference to a Beer's plot.

## RESULTS AND DISCUSSION

The result indicated that batches 2 and 4 containing 1:2 and 2:3 of EC and HPMC respectively, were more porous when observed with a microscope. The pores may be due to the interspersed EC which may not have inter-complexed with HPMC or HCTZ particles since the drug was insoluble in the solvent used. These pores may be advantageous in that they may allow penetration of aqueous fluid for buccoadhesion and drug release to take place. Table 2 shows the diameters and thicknesses of the patches. The patches had uniform diameters with low standard deviations as moulds of uniform diameters were used. The little difference observed may be due to statistics or slight diametric contraction on drying. The thicknesses of the patches were not very uniform. This may have probably arisen from the different degrees of inter-complexation of the two polymers and was higher in batches 2 and 4 with the higher quantity of HPMC probably due to its higher swelling tendency.

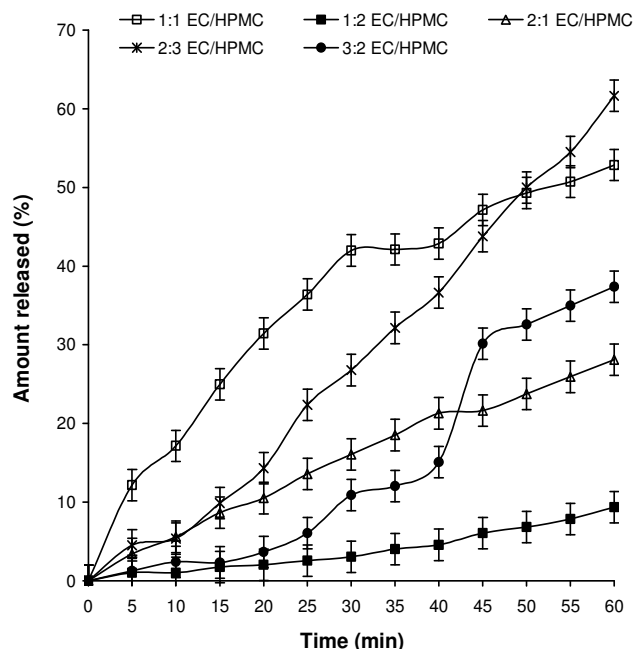
The result of the swelling studies carried out on the patches is presented in Figure 1 showing the variation of the area-swelling ratio (ASR) with time, while the areas of the patches calculated at the outset are presented in Table 2. Figure 1 reveals that the patches had different ASR with time when in contact with aqueous fluid. This is expected since they contained different amounts of the hydrophobic modifier. However, all the patches almost reached maximum swelling after 5 min which may signify that they would not swell to the extent that the patient will become uncomfortable. The patches also had different initial areas as presented in Table 2. Ultimately, the patch containing 3:2 ratio of EC and HPMC had the lowest area but higher ASR since it also had the lowest initial area.



**Figure 1.** Swelling profiles of the patches containing HCTZ in phosphate buffer (pH 7.5).

The study of EC polymer alone revealed no volume expansion at all in the medium due to its hydrophobic nature. This implies that the swelling of the patches may probably be due to the HPMC content. The water permeability increased as the quantity of HPMC increased in the patch and the rate of swelling is favoured by increasing content of HPMC (Cafaggi et al., 2005). ASR is important since the formulation is intended to be attached unto the buccal cavity, where minimal swelling is required so as not to make the patient uncomfortable. The ASR for all the batches were found to be slightly above 1 indicating that these patches may not swell excessively. The water retention capacity of EC blends with hydrophilic polymers has been studied (Sakllariou et al., 1988) and the result obtained in this study conforms to the earlier report.

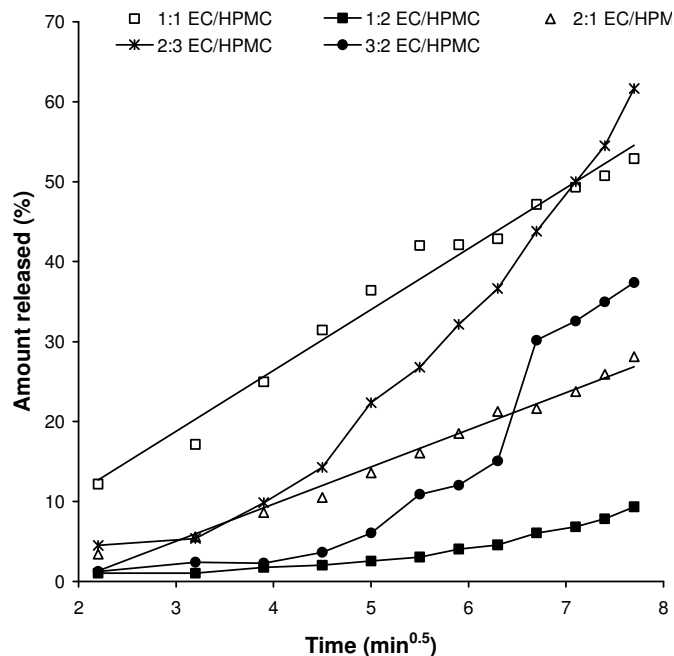
Batch 2 patches gave higher buccoadhesive strength than others as seen in Table 2. This is in line since it is the adhesive component. EC was included to modify the hydrophilicity of HPMC, reduce ASR and prolong drug release. This behaviour could possibly be attributed to the amount and nature of the polymer particles. The HPMC particles were finer and higher in quantity and so provided greater surface area for contact with the mucus membrane. The patch had higher buccoadhesive strength because the moisture absorbed may just be the maximum required to produce maximum buccoadhesive interaction in the swollen patch. As a result, buccoadhesion was enhanced since the patch contained higher amount of HPMC. HPMC have been shown to produce membranes with higher modulus of elasticity (Cafaggi et al., 2005). Buccoadhesive interaction may result from hydrogen bonding or other types of bonding made possi-



**Figure 2.** Release profile of HCTZ from the buccoadhesive patches in phosphate buffer (pH 7.5).

ble by the hydrophilic nature of HPMC. Table 2 shows the result of absolute drug content analysis of the patches. The small content variations indicated good formulation. Drug content variation may arise from lack of uniformity in weight which may be as a result of drug sedimentation before drying.

The result of the release studies carried out on the patches is presented in Figure 2. This reveals a delayed release of HCTZ in some of the patches probably as a result of combined effect of the EC hydrophobicity and gel-forming property of HPMC. Polymers retard drug release because increase in tortuosity as a result of swelling in contact with aqueous fluid increases the path length available for the drug to diffuse out from the swollen matrix (Hjærtstam et al., 1990). Batch 4 patches which contained 2:3 ratio of EC and HPMC had the highest release which may be attributed to the nature of the network within the patch which may be loose with consequent ease of penetration of the dissolution medium and diffusion of the HCTZ from the patch matrix. The release of HCTZ was as a result of swelling of the matrices with batches containing 2:1 and 2:3 of EC and HPMC almost conforming to zero order release (Figure 2). Batches containing 1:2 and 2:1 ratios of EC and HPMC may be employed in sustained release of HCTZ since not up to half of the incorporated drug was released within 60 min. The initial delay in release of drug from batch 5 patches containing 3:2 ratio of EC and HPMC may be due to a hydrophobic coating layer of EC due to



**Figure 3.** Square root plots of amount of HCTZ released from the patches.

its large amount and penetration of aqueous fluid may be very slow. This delay suggests that delivery of HCTZ as a sustained release formulation may be possible with patches formulated with interpolymer complexes of EC and HPMC. One major advantage of buccal delivery systems is that it is possible to interrupt the medication by removal when the patient wants to eat food or other things and reattaching it in the buccal cavity thereafter. Drug release from buccoadhesive patches of HCTZ may offer advantages over conventional tablet formulations. HCTZ is rapidly eliminated and constant blood level is required for maintenance of blood pressure within tolerable limit. Administration of such formulation may result in controlled and prolonged release of HCTZ without initial burst that may cause orthostatic hypotension especially in ambulatory patients. The release result was further analyzed using Higuchi's diffusion model (Higuchi, 1963). A plot of the amount of drug released against the square root of time when linear, indicates that diffusion is the predominant process of release (Higuchi, 1963). The film batches containing 1:1 and 2:1 ratios of EC and HPMC showed linear plots indicated by their high correlation coefficient ( $r^2 = 0.9777$  and  $0.9849$  respectively) (Figure 3). This indicated that diffusion was the predominant mechanism of HCTZ release from these patches. Other patches showed non-diffusional release mechanisms as their plots were non-linear.

The findings in these studies give a clue that it may be possible to formulate buccoadhesive delivery systems of

hydrochlorothiazide with interpolymer complex derived from ethylcellulose and hydroxypropyl methylcellulose.

## REFERENCES

- Attama AA, Adikwu MU (1999). Bioadhesive delivery of hydrochlorothiazide using tacca starch/SCMC and tacca starch/Carbopols 940 and 941 admixtures. *Boll Chim Farm.* 138: 343-350.
- Attama AA, Adikwu MU, Nnamani PO (2003). Delivery of diclofenac sodium via non-disintegrating bioadhesive tablets of paraffin wax. *STP Pharm. Sci.* 13: 147-150.
- Cafaggi S, Leardi R, Parodi B, Caviglioli G, Russo E, Bignardi G (2005). Preparation and evaluation of a chitosan salt-poloxamer 407 based matrix for buccal drug delivery. *J. Control Rel.* 102: 159-169.
- Caramela C, Bonferoni MC, Rossi S, Ferrari F (1994). Rheological and tensile tests for the assessment of polymer mucin interaction. *Eur. J. Pharm. Biopharm.* 40: 213-217.
- Desai KGH, Pramod-Kumar TM (2004). Preparation and evaluation of a novel buccal adhesive system. *AAPS Pharm. Sci. Tech.* 5: 1-9.
- Guptar A, Gary S, Khar RK (1992). Measurement of bioadhesive strength of mucoadhesive buccal tablets: design of an *in vitro* assembly. *Indian Drugs* 30: 152-155.
- Hardman JG, Limbird LE, Gilman AG (2001). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10<sup>th</sup> edition, McGraw-Hill, New York, pp. 774-905.
- Harkins WD, Jordan HF (1930). A method for determination of surface and interfacial tension from the maximum pull on a ring. *J. Am. Chem. Soc.* 52:1751.
- Higuchi T (1963). Mechanism of sustained action medication: Theoretical analysis of the rate of release of solid drug dispersed in solid matrices. *J. Pharm. Sci.* 52:1145-1149.
- Hjartstam J, Borg K, Lindstedt B (1990). The effect of tensile stress on permeability of free films of ethyl cellulose containing hydroxypropyl methylcellulose. *Int. J. Pharm.* 61:101-107.
- Hui HW, Robinson JR (1985). Ocular delivery of progesterone using a bioadhesive polymer. *Int. J. Pharm.* 26: 203-213.
- Ishida MM, Nambu N, Nagai T (1983). Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and Carbopol. *Chem. Pharm. Bull.* 30: 986.
- Kamath KR, Park K (1994). Mucosal adhesive preparation In: Swarbrick J, Boylan JC (Eds.) *Ency. Pharm. Tech.* 10: 133.
- Longer MA, Robinson JR, Ch'ng HS (1985). Bioadhesive polymers as platforms for oral controlled drug delivery III: oral delivery of chlorothiazide using bioadhesive polymer. *J Pharm Sci.* 74: 406-411.
- Magi L, Carena E, Torre ML, Giunchedi P, Conte U (1994). *In vitro/in vivo* methods for the evaluation of bioadhesive polymers: a preliminary study. *STP Pharma. Sci.* 4: 343-348.
- Martin L, Wilson CG, Koosha F, Uchegbu IF (2003). Sustained buccal delivery of the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels. *Eur. J. Pharm. Biopharm.* 55:35-45.
- Mortazavi A, Smart JD (1994). An *in vitro* method for assessing the duration of mucoadhesion. *J. Control Rel.* 31: 207-212.
- Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, Rossi C (2004). Development of mucoadhesive patches for buccal administration of ibuprofen. *J. Control Rel.* 99:73-82.
- Porter SC (1984). Controlled release film coatings based on ethylcellulose. *Drug Dev. Ind. Pharm.* 15: 1495-1521.
- Saklariou P, Rowe RC, White EFT (1988). A study of the leaching/retention of water soluble polymers in blends with ethylcellulose using torsional brand analysis. *J. Control Rel.* 7: 147-157.
- Salamat-Miller N, Chittchang M, Johnston TP (2005). The use of mucoadhesive polymers in buccal drug delivery. *Adv. Drug Deliv. Rev.* 57: 1666-1691.