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Development and evaluation of Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive Agent obtained from the Fruits of *Ficus carica* L.

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ABSTRACT

Buccal delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs. The paper describes formulation of buccal mucoadhesive gel from *Ficus carica* mucilage using prorpranolol hyderochloride. Propranolol, a nonselective beta adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. It is highly lipophilic and is almost completely absorbed after oral administration. However, much of the drug is metabolized by the liver during its first passage through the portal circulation; on average, only about 25% reaches the systemic circulation. The conventional oral dosage form of this drug has low bioavailability due to high first pass metabolism, so it is modified as buccal drug dosage form to improve bioavailability and for the localized drug release because of high vascularity and drugs diffusing across the membrane have easy access to the systemic circulation via internal jugular vein. In present research mucilage is extracted from *Ficus carica* and studeuied for there mucoadhesive properties. The gel were evaluated by different parameters such as zeta potential, viscosity, Gel strength, Drug Release, Mechanism of drug release & histological study.

Keyword: Buccal delivery, mucoadhesive, *Ficus carica* mucilage,

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INTRODUCTION

Buccal drug delivery system has emerged to be an important area in the field of pharmaceutical research. The buccal mucosa is considered to be a promising site for the systemic delivery of drugs where a rapid onset of action is required and for drugs that are not easily administered via other routes than by injection[1]. This route thus, serves as an excellent needle-free alternative which may improve patient compliance and allows extended use of self medication for many chronic diseases. The buccal mucosa being a highly vascularised area helps in rapid systemic absorption of the drug, thereby avoiding hepatic "first-pass effect" of drugs leading to quicker onset of action, which could be especially important in the management of crisis situations like cardiac arrest, epileptic seizures, severe nausea and vomiting[2].

Propranolol hydrochloride, one of the most widely prescribed b-blockers in the long-term treatment of hypertension and in psychotherapy is usually taken orally, although an intravenous form is available for acute administration[3-4]. Following oral administration, Propranolol hydrochloride is rapidly and completely absorbed from gastrointestinal tract (less than 5% recovered in feces), still the oral bioavailability is low (30%) because of significant first pass hepatic metabolism by CYP2C19 and 2D6 (urinary recovery as unchanged Propranolol hydrochloride is less than 1% of the administered dose)[5-6]. Moreover, in healthy individuals and in patients with various disease states, plasma concentration varies as much as 10–20-fold following oral and not intravenous administration due to difference in the first pass effect. Available sustained release dosage of oral Propranolol hydrochloride is not as effective as the equivalent amount of single dosages because slower oral absorption leads to greater hepatic metabolism. Administration of drugs via buccal route effectively bypasses first pass metabolism, along with providing sustained delivery.

In the present investigation, mucilage isolated from fig fruits (Ficus carica) was used as a mucoadhesive agent to prepare buccal mucoadhesive microspheres containing Propranolol hydrochloride and to characterize them accordingly. This mucilage is biocompatible and biodegradable since it is edible in nature[7]. The Ficus carica grows well in Warm temperate or sub-tropical climates. The Ficus carica is a small trees or shrubs, typically to a height of 10 - 30 ft. Wavy-margined leaves are usually 5 lobed with 4 or 3 lobes. Ficus carica leaves are conspicuously palmately veined. Their branches are large and twisting, which spread wider than they are tall. The wood is weak hence decays rapidly. Ficus carica trunk has large nodal tumors, where branches have been shed. Sap of Ficus carica contains milky latex. Ficus carica coat

consists of 6-8 % mucilage. The mucilage shows weak gelling nature in 3 % w/w of the concentration. Numerous bioactive compounds are present in *Ficus carica* which includes Mucilages, nicotinic acid, vitamins, flavonoids, enzymes, and tyrosin. Ficusin, bergaptene, stigmasterol, beta-sitosterol, psoralen, taraxasterol, rutin, sapogenin, Calotropenyl acetate, lepeolacetate and oleanolic acid sistosterol are obtained from leaf. The plant of ficyus carica also contains arabinose, β-amyrins, β- carotines, glycosides, β-setosterols and xanthotoxol16-18. Umbelliferone19,20, campesterol, , fucosterol, fatty acids21, 6-(2- methoxy- Z-vinyl)-7-methyl-pyranocoumarin and 9,19-cycloarlane riterpenoid as an anticancer22 and 6-Oacyl-β-Dglucosyl - β-sitosterol 23, lupeol acetate 24, and calotropenyl acetate as an antiproliferative agent[8-10].

In present research work buccal mucoadhesive gels are formulated. The minimal use of synthetic polymer is done to achieve desired results

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was received as a kind gift from Alkem laboratory (Mumbai, India), Ficus carica was procured from a local market. Chitosan was obtained as a gift from Central Institute of Fisheries Technology, Cochin (India). Carbopol & PVP were obtained from S.D. Fine Chemicals Ltd, Mumbai, India. Ethyl alcohol was procured form Sun Pharma Ltd. (Vadodora, Gujarat). CMC was received as a gift sample from M/s Natco Pharma Ltd (Hyderabad, India).

Methods

Extraction of mucoadhesive material from Ficus carica fruit

FC fruit was washed with double distilled water to remove any adherent material attached to fruit. About three times its volume distilled water was taken and hated for 4 hrs at 60±1°C on water bath to prepare slurry. The viscous slurry was then filtered and the filtrate was diluted with three times its volume with distilled water. The undissolved portion was allowed to settle down by keeping filtrate in refrigerator for 12 hrs. The clear solution was decanted concentrated at 60±1°C in rotary vacuum evaporator. The concentrate was cooled to room temperature and precipitated with ethyl alcohol. The precipitation of the mucilage took place immediately. The precipitated mucilage was separated and dried in the hot air oven at 50°C for 5 h. The yield of the dried mucilage was determined and was used to prepare the microspheres[11].

Zeta Potential of Ficus carica mucilage:

Zeta potential of the **Ficus carica** mucilage was determined using Malvern instruments (DTS

Ver 5.3). Distilled water was used as dispersant with a count rate of 1287.3 kcps by using clear disposable zeta cell[12].

Formulation of buccal mucoadhesive gel

Formulations of buccal mucoadhesive gel were prepared using minimum concentration of the Ficus carica mucilage and the synthetic polymer.

a) Formulation containing Ficus carica mucilage :

Accurately weighed drug was and dissolved in 50.0 ml water. Then Ficus carica mucilage was weighed accurately and added separately to 50.0 ml water and boiled for 30 min at 80 ^{0}C. Both these solutions were mixed and continuous stirring using mechanical stirrer (250 RPM).

b) Formulation containing Ficus carica mucilage with synthetic mucoadhesive agents:

Formulation F2 containing chitosan, drug was weighed and dissolved in 50 ml water. This solution was boiled at 80^0 C with weighed quantity of Ficus carica mucilage for 30 min. Weighed quantity of chitosan was dissolved in 50.0 ml of 0.15 % (v/v) glacial acetic acid in water. This solution of chitosan was mixed to the drug and Ficus carica mucilage solution with continuous stirring with mechanical stirrer (250 RPM). For formulation F3, F4 and F5, Propranolol hydrochloride was weighed accurately and dissolved in 50.0 ml water. Then Ficus carica was weighed accurately and added to the drug solution, boiled for 30 min at 80^{0}C. separately weighed quantity of carbopol, CMC and PVP was dissolved in 50.0 ml water which was mixed with 50.0 ml of drug and Ficus carica mucilage mixture separately, with continuous stirring using mechanical stirrer(250RPM). The compositions of the gels formulation were as per Table1.

Table 1. Composition of various formulations

Ingredients	F1	F 2	F3	F4	F5
Prop. HCl	1	1	1	1	1
Ficus Carica	3.0	3.0	3.0	3.0	3.0
Chitosan		0.5			
Carbopol			0.3		
CMC				0.5	
PVP					0.7

Evaluation of buccal mucoadhesive gel

Viscosity measurement and rheological behavior studies:

The viscosity of gel formulations was measured using Brookfield DV- E viscometer. Following equation was used to evaluate rheological behavior of buccal mucoadhesive gel[13].

$$\tau_i = K_{a\tau}\,\alpha \qquad (1)$$

Where τ_i = Shear stress

$K_{a\tau}$ = Conversion factor (0.279 for spindle # 3)

α = Torque dial

$$\gamma_i = K_{n\gamma}(n)N_i \quad (2)$$

Where γ_i = Shear rate

n = flow index of gel (computed from slope of log of τ_i vs. log N)

$K_{n\gamma}$ = Conversion factor (taken on the basis of obtained values of n)

N_i = Rotational speed

Gel strength measurement:

A plunger of weight 30 grams was used to measure gel strength. The time (in seconds) taken for plunger to move % cm down trough gel was used to measure gel strength (Figure 1). Additional weights were added on the plunger if time taken for the apparatus was more than 10 minutes to pass through gel[14].

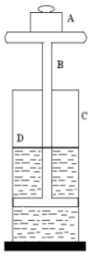

Figure1: Gel strength measuring apparatus

(A)Weight; (B) Shaft; (C) measuring cylinder; (D) Gel formulation

Drug Release study:

In vitro drug diffusion study:

Franz diffusion cell was used to perform *in vitro* drug diffusion study. A dialysis membrane was used to perform (mol. wt. cut-off 12000- 14000, 2.5 cm^2) *in vitro* drug diffusion study. Phosphate buffer solution pH 6.8 (15.0 ml) was added in receptor compartment maintained at 37 ± 1^0 C. The membrane was equilibrated with 1.0 ml of phosphate buffer pH 6.8 before application of gel in donor compartment. After an equilibration of membrane formulation of Propranolol hydrochloride (equivalent to 2 g) was placed in the donor compartment. Samples (0.5 ml) were periodically (at 15, 30, 60, 90, 120, 180, 240, 300 and 360 min) withdrawn from the receptor compartment and replaced with the same amount of fresh buffer solution. Withdrawn samples were diluted appropriately with phosphate buffer pH 6.8, filtered and assayed spectrophotometrically by UV 1700 Shimadzu ®, Japan.

Drug diffusion kinetics:

Data obtained from in vitro diffusion studies were transformed in various kinetic models: zero

order as cumulative amount of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time and Higuchi's model as cumulative percentage of drug released vs. square root of time.

Mechanism of drug release:

To evaluate the mechanism of drug release from the Propranolol hydrochloride gel, in vitro drug release data was plotted in Korsmeyer-Peppas equation as a log cumulative percentage of drug release Vs log time. The release exponent *n* and *k* values were calculated through the slope of the straight line[15].

$$Kt^n = M_t/M_\infty$$

Where M_t represents amount of the drug released at time t, M_∞ is the total amount of the drug released after an infinite time, K is the diffusional characteristic of drug/mucilage system constant, and n is an exponent that characterizes the mechanism of drug release. The value of n indicates the drug release mechanism from the delivery system. If the exponent n = 0.43 then the drug release mechanism is Fickian diffusion, if n < 0.43 the mechanism is quasi-Fickian diffusion, if n = 0.43–1.0 then it is non-Fickian or anomalous diffusion, if n = 1.0 the mechanism is non-Fickian case II diffusion and if n > 0.43 the mechanism is non-Fickian super case II.

In vitro permeation study:

Fresh buccal mucosa was carefully removed from the buccal cavity of sheep obtained from the local slaughterhouse. Tissue samples were placed in Franz diffusion cells displaying a permeation area of 0.785 cm^2. Receiver compartment containing 16.0 ml of phosphate buffer (PBS) pH 6.8 maintained at 37 ^{0}C. After pre incubation for 20 minutes, pure drug solution or formulation equivalent to 2.0 mg of Propranolol hydrochloride was placed in the donor chamber containing 1.0 ml of phosphate buffer pH 6.8. At predetermined time interval samples were withdrawn from the receiver compartment, replacing the sampled volume with PBS pH 6.8 after each sampling, for a period of 6 hrs. The samples withdrawn were filtered and used for analysis. The amount of permeated drug was determined using a UV-visible spectrophotometer.

Permeability coefficient (P) was calculated by following formula

$$P = \frac{\frac{dQ}{dt}}{C_o \times A} \qquad (3)$$

Where, dQ/dt -: Flux or Permeability rate (mg/ hr),

Co - Initial concentration in donor compartment,

A - Effective surface area of nasal mucosa.

Histological study:

The histological evaluation of tissue incubated in phosphate buffer (pH 6.8) for 6 hrs after collection was compared with tissue incubated in diffusion chamber with formulation. Tissue was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Sections were cut on glass slides and stained with hematoxylin and eosin. Sections were examined under a light microscope to detect any damage to the tissue.

Stability study of buccal mucoadhesive gel:

Formulations showing optimum gel strength, mucoadhesive force and drug content were selected for stability studies. Stability studies were carried out for three months on gel formulation according to ICH (International Conference on Harmonization) guidelines. Sufficient quantities of formulations in glass vials were stored in stability chamber maintained at 25°C ± 2°C, 60% ± 5% RH. The physical stability of gel was observed periodically for the overall appearance and occurrence of turbidity. Formulations were evaluated at periodic intervals for the clarity, drug content, gel strength and mucoadhesion strength of formulation for period of three months.

RESULT AND DISCUSSION

Extraction of Ficus carica mucilage:

Results showed that yield of extract precipitated with ethyl alcohol was 8% where as yield of extract precipitated with methanol and acetone were 7.5 % and 6 % respectively. Therefore ethyl alcohol was selected for precipitation.

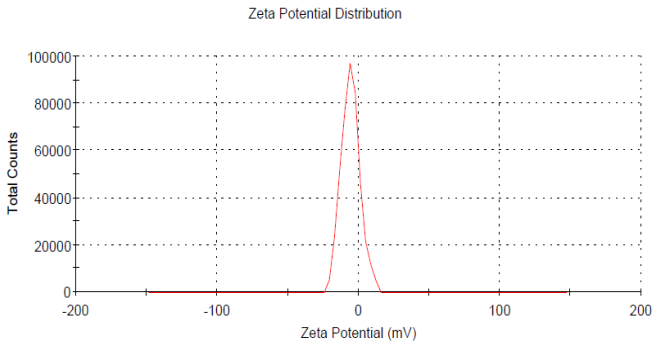

Figure 2: Zeta potential determination of Ficus carica mucilage

Zeta potential determination of F. Carica mucilage

Zeta potential of the mucilage was found as −20 mv which expressed anionic nature of mucilage (Figure 2).

Gel strength measurement:

In order to retain the buccal mucoadhesive gel for prolong duration at buccal mucosa the gel strength should be optimum. Gel strength less than 30 seconds eroded rapidly and lost its

integrity. The gel strength greater than 60 seconds caused discomfort to mucosal surface due to stiffness. The optimum gel strength values between 30-60 seconds were considered sufficient. Gel strength measured for mucoadhesive gel F1 formulated from FC mucilage showed 26.0 ± 1.52, formulation F2, F3, F4, & F5showed 49.0, 43.0, 37.0 & 36.0 (Table 2). It was observed from results that the gel strength of FC mucilage based gel increased with addition of chitosan, CP, CMC & PVP and. The highest gel strength was observed in combination with chitosan.

Table 2: Gel strength measurement of formulation batches

Formulation	Gel strength*(Sec)
F1	26.0 ± 1.5276
F2	49.0 ± 0.6800
F3	43.0 ± 2.1154
F4	37.0 ± 1.5967
F5	36.0 ± 1.2789

Mucoadhesive strength determination of Ficus carica based buccal mucoadhesive gel:

All formulations were subjected to in vitro mucoadhesion studies by the modified balance method. Carbopol is the synthetic polymer that has the highest mucoadhesion. The dosage form containing maximum concentration of carbopol is difficult to remove from the site of application therefore it is used in minimum concentration in buccal mucoadhesive dosage forms. Ficus carica showed the highest mucoadhesion in combination with chitosan among of all formulations. The formulations showed the mucoadhesion in following order F2>F3>F4>F5>F1 (Table 3). Five minutes of initial contact time gave optimum mucoadhesive strength; further increase in contact time did not affect the mucoadhesive strength.

Table 3: Mucoadhesive strength of formulation batches

Formulation	Mucoadhesion# (in weight as gram)
F1	4.90 ± 0.12
F2	11.25 ± 0.61
F3	6.65 ± 0.29
F4	5.20 ± 0.77
F5	4.70 ± 0.18

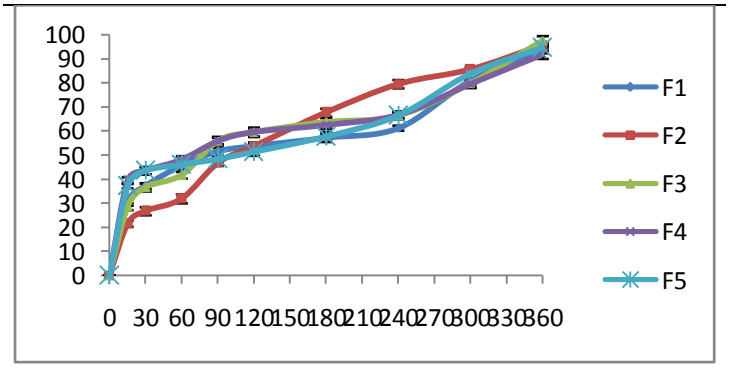

Figure 3: Drug release profile of formulation batches

In vitro drug diffusion study:

In vitro diffusion study of all gels showed sustained diffusion. All formulations showed almost complete diffusion in 6 hr. No bursting effect was observed. Release profiles of formulations are elaborated in Figure 3.

Viscosity Measurement:

Viscosity of mucoadhesive gel was measured using Brookfield DV- E viscometer at 10 r.p.m speed using a spindle No. 3. The gels exhibited shear-thinning behavior and non-Newtonian flow. It was found that synthetic polymers like carbopol, CMC, PVP and chitosan did not alter the shear thinning behavior of mucilage i.e. as the shear rate was increased the measured viscosity decreased Figure 4.

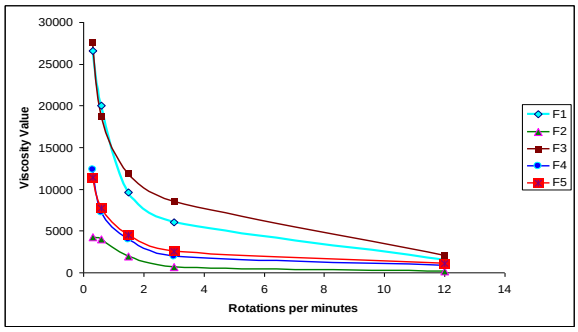

Figure 4: Viscosity measurement at various rotations per minute of formulation based on *Ficus carica* mucilage and various synthetic polymers

Mathematical treatment to in vitro drug diffusion data:

The graph between cumulative drug release and square root of time of all formulations showed almost linear relationship and followed Higuchi's equation. The drug transport mechanism of the same formulation was determined by using the Korrsemeyer exponential equation. From the plot of log ($t\ M / M$) vs. log of time, the kinetic parameter 'n' was calculated. The values of 'n' for the various formulations are shown in Table no.3. The formulation F1, F3, F4 and F5 showed Fickian diffusion, formulation F2 showed Anomalous (non-Fickian) diffusion.

Table 4: Model fitting of the release profile using different models of various Formulations

Formulation Code	Kinetic models					
	Zero order (R^2)	First order (R^2)	Higuchi matrix (R^2)	Best fit model order	Korsmeyer Peppa's 'n' value	Mechanism
F1	0.9170	0.6009	0.9661	Higuchi	0.3136	Fickian diffusion
F2	0.9665	0.6902	0.9967	Higuchi	0.4962	Anomalous diffusion
F3	0.9217	0.6132	0.9772	Higuchi	0.3522	Fickian diffusion
F4	0.8777	0.5589	0.9540	Higuchi	0.2448	Fickian diffusion
F5	0.9122	0.5837	0.9553	Higuchi	0.2624	Fickian diffusion

Histological study:

Histological study of buccal mucosa was done for control mucosa and test mucosa (formulation). Photomicrographs revealed no signs of necrosis or structural disturbance of buccal mucosa was observed. Hence it can be confirmed that FCM based buccal mucosa can be applied without any damage to mucous membrane of buccal cavity (Figure 5).

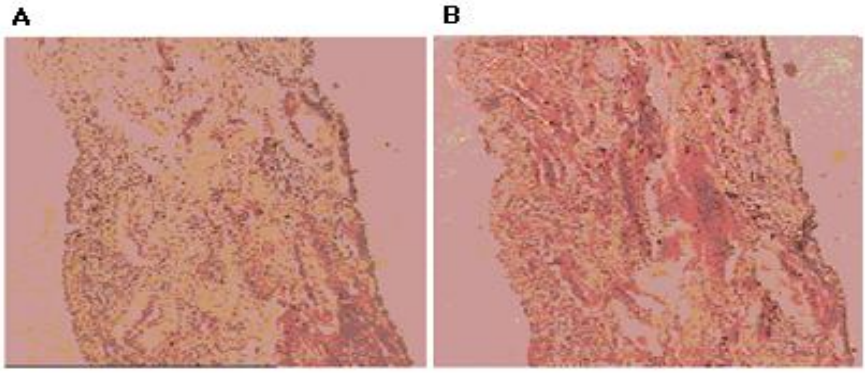

Figure 5: Photomicrograph of the normal buccal mucosa and, *Ficus carica* mucilage based gel.

Stability study of buccal mucoadhesive gel:

The stability studies were carried out on optimized formulations at 25°C ± 2°C / 60% RH ± 5% RH for 3 months. All formulations were exhibited good stability with no remarkable change in drug content, gel strength and mucoadhesive strength.

CONCLUSION:

The mucilage obtained from *Ficus carica* showed good mucoadhesion. It is clear from the study that buccal mucoadhesive gel can be formulated from ficus carica based mucilage. The buccal mucoadhesive gel provides alternative root for Propranolol hydrochloride which increases the bioavailability of drug.

REFERENCES

1. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: A Review, J Pharm Pharmaceut Sci 1998; 1(1): 15-30.
2. Aungst BJ, Rogers NJ, Shefter E. Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter. The J Pharmacol Exp Ther 1988; 244: 23-27.
3. Kazierad DJ, Schlanz KD, Bottorf MB. Beta blockers, in: W.E. Evans, J.J. Schlentag, W.J. Jusko (Eds.), Applied Pharmacokinetics, Principle of Therapeutic Drug Monitoring, 3rd Edition, Applied Therapeutics, Vancouver, 1992: 24–41.

4. Riddel JG, Harron DWG, Shanks RG. Clinical pharmacokinetics of b-adrenoceptor antagonists, Clin. Pharmacokin 1987; 12:305–320.
5. A. Parkinson, Biotransformation of xenobiotics, in: C.P. Klaassen (Ed.), Casarett and Doulls Toxicology, The Basic Science of Poisons, International Edition, 1st Edition, McGraw-Hill, New York, 1996: 152–153.
6. Shand DG, Nuckolls FM, Oates JA. Plasma Propranolol levels in adults with observations in four children. Clin Pharmacol Ther 1970; 11:112–120.
7. Luna LE. The concept of plants as teachers among four Mestizo shamans of Iquitos, northeastern Peru. J Ethnopharmacol 1984; 11: 135–56.
8. Gilani AH, Mehmood MH, Janbaz KH, Khan AU, Saeed SA. Ethnopharmacological studies on antispasmodic and antiplatelet activities of Ficus carica. J Ethnopharmacol, 2008; 119:1-5.
9. Vaya J, Mahmood S. Flavonoid content in leaf extracts of the fig (Ficus carica L.), carob (Ceratonia siliqua L.) and pistachio (Pistacia lentiscus L). Biofactors; 2006; 28:169-75.
10. Ross JA, Kasum CM. Dietary flavonoids, bioavailability, metabolic effects, and safety. Annu Rev Nutr. 2002; 22: 19-34.
11. Felter, Harvey Wickes & Lloyd, John Uri. "Hibiscus Esculentus.—Okra.", *King's American Dispensatory*, 1898, retrieved March 23:2007
12. Bandopadhyay AK, Sudhakar Y, Kuotsu K. Buccal bioadhesive drug delivery: A promising action for orally less efficient drugs. J Control Release 2006; 114: 15-40.
13. Mitchka P. Simple conversion of Brookfield R.V.T readings into viscosity functions. Rheol. Acta 1982; 21: 207-209.
14. Yong CS, Choi JS, Rhee JD. Effect of sodium chloride on the gelation, Gel strength and Bioadhesive force of poloxamer gels. Int J Pharm 2001; 275: 195-205.
15. Cartensen JT. Modeling and data treatment in the pharmaceutical sciences, Technomic Publishing Co. Inc., New York, Basel 1996.