Research Article

Formulation and Evaluation of Bioadhesive Cyproheptadine Tablets

V Chandrakala V\textsuperscript{2*}, MS Srinath\textsuperscript{1}, Saral A Mary\textsuperscript{2} and Kumar S Utpal\textsuperscript{2}

\textsuperscript{1}Department of Pharmaceutics, Government College of Pharmacy, Bangalore, Pharmaceutical Chemistry Division, \textsuperscript{2}School of Science and Humanities, Vellore Institute of Technology, Vellore, Tamil Nadu, India

Abstract

\textbf{Purpose:} To evaluate the effect of formulation variables on the bioadhesion and release properties of bioadhesive cyproheptadine hydrochloride tablets.

\textbf{Methods:} Screening of polymers - hydroxypropyl methylcellulose, (HPMC), sodium carboxy methyl cellulose (CMC), and Carbopol 974p and 934p - in solution form were carried out by shear stress and detachment force measurement, based on Taguchi model, in order to determine their bioadhesion properties. Central composite design (CCD) was applied to optimize the combined effects of the polymers on release rate constant (K), diffusion coefficient (n), regression coefficient (R\textsuperscript{2}) and detachment force of a sustained release tablet formulation of cyproheptadine hydrochloride containing also a prompt dose of the drug.

\textbf{Results:} The shear stress of 3 % solution of HPMC was greater than that of an equivalent concentration of Carbopol 934P. The values of K, n, R\textsuperscript{2} and detachment force for the optimized formulation (F0) were 0.269, 0.696, 0.964 and 0.066 Newton (N), respectively, and showed good correlation with the predicted values, thus confirming the practicability and validity of the model.

\textbf{Conclusion:} Gastric retention time can be increased for cyproheptadine hydrochloride by formulating it as a bioadhesive tablet that enhances the retention of the dosage form in the stomach and hence gastric absorption of the drug.

\textbf{Keywords:} Cyproheptadine hydrochloride, Bioadhesive core tablet, Detachment force, Taguchi design, Central composite design

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*Corresponding author: \textbf{E-mail:} chandra_kalav@yahoo.com, \textbf{Tel:} +91-8025456581
INTRODUCTION

Oral ingestion is the most convenient and commonly used route of drug administration. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of ease of administration and patient acceptance [1,2].

Bioadhesion is an adhesive interaction between an oral pharmaceutical system and biological surface. It has been suggested that delay in gastrointestinal (GI) transit, brought about by intimate and extended contact between bioadhesive system and mucus/mucosal lining, will improve drug bioavailability and duration of action. Though the oral route is the most commonly employed route of drug administration, it is not suitable for drugs which are susceptible to gut and/or hepatic metabolism as well as drugs which cause gastrointestinal side effects [3].

Mucous membranes are the moist surfaces lining the walls of various body cavities. They consist of a connective tissue upper layer (epithelial layer), the surface of which is made moist usually by the presence of mucus. The major components of all mucus gels are mucin glycoprotein. Mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. It is as thick as 1mm in humans [4].

Although various selective antihistaminic drugs are available in the market, their delivery systems may cause various hazards and patient inconvenience. Conventional dosage forms of these drugs, such as tablets, capsules, lotions, suspensions and syrups, often fail to achieve effective management of these diseases due to peak level-associated disadvantages such as drowsiness, dry mouth, confusion and weight gain. In spite of their anti-allergic properties, they may produce allergic manifestations and also cause patient inconvenience [5].

Gastro-retentive dosage forms remain in the stomach for several hours due to their modified gastric retention time (GRT). Prolongation of GRT may sustain drug release behavior and provide a better alternative for maintenance of systemic drug concentration within the therapeutic window [6-9].

Cyproheptadine hydrochloride is well absorbed after oral administration. It has a short half life of 3 h and hence require frequent administration to maintain optimum plasma concentration which cause patients' non-compliance. These characteristics make it a good candidate for the formulation of an extended-release dosage form to minimize patients non-compliance and maximum utilization of drug within the therapeutic range [10,11].

EXPERIMENTAL

Materials

Cyproheptadine Hydrochloride (Indian Pharmacopoeia, IP) was procured from Mederich Pharmaceuticals, Bangalore, India. Hydroxypropyl methylcellulose (HPMC), Carbomer (Carbopol) 974P, and sodium carboxymethylcellulose (CMC) were obtained from Apotex Research Pvt Ltd, Bangalore, India. Carbomer (Carbopol) 934p (Strides Acrolabs, Bangalore, India) and microcrystalline cellulose (MCC) (Maple Biotech Pvt Ltd, Pune, India) were also used. All other chemicals and reagents used were of analytical grade.

Shear stress measurement

Screening of the various polymers - HPMC, CMC, and Carbopol 974p and 934p - was carried out by shear stress measurement. [12,13]. Two smooth, polished glass slides were selected, one of which was fixed with an adhesive onto a fixed surface. The second (upper) slide was tied with a thread, which was then passed over a pulley and tied to a pan. The weight of the pan and frictional force of the upper slide was nullified by
putting a weight on the pan such that the upper slide moves freely after infinitesimal small increase of weight in the pan. One drop of each polymer (3% aqueous solution) was placed at the center of the fixed slide and then a second slide was pressed down with a weight (100g) for fixed intervals of 5, 10, 15 and 30 min, after which weights were added to the pan. The load required to pull the upper slide or cause it to slide down from the fixed slide represents the adhesion strength. Taguchi design was applied for further screening of the polymers for use in tablet formulations based on the measurement of the detachment force.

Following this screening, the best two bioadhesive polymers, HPMC and Carbopol 934P, were selected for the formulation of tablets. Various ratios of these two polymers, with respect to the weight of the drug, were then optimized by Central composite design (CCD).

**Formulation of Cyproheptadine tablets**

The cyproheptadine hydrochloride (HCl) tablets prepared consisted of a sustained release dose as the tablet core, and an outer prompt dose component. The sustained release core was prepared by wet granulation method and optimized by CCD. An accurately weighed quantity of cyproheptadine HCl and polymer were blended together. The ingredients were mixed in geometric proportion, after first grinding separately in a mortar with a pestle, to form a homogenous mixture. The powder mixture was granulated with sufficient ethanol to make a damp mass. The damp mass was then passed through a 1 mm sieve and dried in an oven at 40 °C for 30 min. The granules were then successively passed through sieves with aperture size of 250 and 90 µm, respectively.

The resulting granules were mixed with magnesium stearate, talc and remaining quantity of MCC, and compressed in a tablet machine, using 8 mm flat punches, to make the core tablets. Various concentrations of polymers, based on the Taguchi design (Table 1), were screened for detachment force in core tablet formulations. Selection of the polymers, using the Taguchi OA design, was based on maximum detachment force.

The best two polymers obtained from the Taguchi OA design were subjected to CCD, as in Table 2, using different ratio of HPMC.

### Table 1: Composition of various tablet core formulations based on Taguchi Orthogonal Array (OA) Design

| Ingredient          | HPMC | Carbopol 934P | Carbopol 974P | CMC  | Lactose |
|---------------------|------|---------------|---------------|------|---------|
| A1                  | 15   | -             | -             | -    | 101     |
| A2                  | 30   | -             | -             | -    | 86      |
| A3                  | 45   | -             | -             | -    | 71      |
| A4                  | -    | 7.5           | -             | -    | 108.5   |
| A5                  | -    | 15            | -             | -    | 101     |
| A6                  | -    | 22.5          | -             | -    | 93.5    |
| A7                  | -    | -             | 7.5           | -    | 108.5   |
| A8                  | -    | -             | 15            | -    | 101     |
| A9                  | -    | -             | 22.5          | -    | 93.5    |
| A10                 | -    | -             | -             | 60   | 56      |
| A11                 | -    | -             | -             | 75   | 41      |
| A12                 | -    | -             | -             | 9    | 26      |

Composition is given in terms of mg per tablet. Each formulation contained 11, 4, 4 and 15 mg of cyproheptadine hydrochloride, magnesium stearate, talc and microcrystalline cellulose (MCC), respectively; CMC = sodium carboxymethyl cellulose.
and Carbopol 934p with respect to the weight of the drug at an \( \alpha \) (star point or distance from the centre calculated by the formula \( 2^{\frac{2}{4}} \)) value of 1.414 with three centre point to formulate bioadhesive core tablets. The resultant core formulations were evaluated for detachment force, dissolution (n value, which characterizes release mechanism of the drug, with \( n \leq 0.45 \) corresponding to Fickian diffusion mechanism; \( 0.45 < n < 0.89 \) to non-Fickian diffusion; \( n = 0.89 \) to case II transport; and \( n > 0.89 \) to supercase II transport), as well as for release rate constant (K), variability of % drug release (\( R^2 \)) in a given concentration of the polymer, assay, and % drug release, as response variables. These response variables were subjected to multiple regression analysis and ANOVA to find out the relation between the independent variables and response. The final formula, \( F_0 \), was then prepared by optimization based on the release rate and detachment force of the formulations obtained by CCD. Around this final formulation, the loading (prompt) dose (consisting of drug along with superdisintegrant, cross carmellose sodium) was directly compressed to completely surround the core tablet core using 10 mm concave punches.

**Table 2:** Application of Central composite design (CCD) to optimize polymer combination for the formulation of optimized bioadhesive core tablets

| Ingredient  | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  | F10 | F11 |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| HPMC        | 20  | 20  | 10  | 30  | 5.86| 20  | 34.14| 30  | 10  | 20  | 20  |
| Carbopol 934p| 3.96| 7.5 | 5   | 10  | 7.5 | 11  | 7.5 | 5   | 10  | 7.5 | 7.5 |
| Lactose     | 92  | 88.5| 101 | 76  | 102.6| 85  | 74.36| 81  | 96  | 88.5| 88.5|

Composition is given as mg per tablet. Each formulation contained 11, 4, 4 and 15 mg of cyproheptadine hydrochloride, talc, magnesium stearate and microcrystalline cellulose (MCC), respectively; HPMC = hydroxypropyl methylcellulose

**Measurement of detachment force of tablets**

This test was carried out using the tablet core (i.e., the sustained release dose component) to measure in-vitro bioadhesive capacity of the bioadhesive polymers to the mucosa of rat stomach. The animals were sacrificed by cervical dislocation. The stomach mucosa was collected and stored in a deep freezer at -21 °C. During the experiment, Tyrode solution was added to the vial, the brim of which was tied with rat mucosa and the other end was fixed to a glass mortar on a hot plate maintained at 37 °C. The adhesion force of the tablets was then measured (\( n = 6 \)) as follows. A hole was drilled in centre of the tablet to be tested. One end of the thread was passed through it and tied and the other end was passed through the pulley and tied to a pan on which a beaker was placed. The weight of the pan was nullified by suspending the weight. Water was added to the beaker using a burette. The tablet was allowed to stay in contact with the tissue for 30 min. Water was then added to the beaker from a burette. The quantity of water required to separate the tablet from the tissue surface was noted and this value was converted to detachment force (in newtons) using Eq 1.13.

\[
\text{Detachment force} = \frac{(0.00981 \times w)}{2} \quad \text{………(1)}
\]

where \( w \) is the mean weight of the added water.

**Optimization procedure**

Taguchi design was applied to reduce the number of experiments to optimize the range of variable concentrations needed to obtain maximum bioadhesion. The same optimized levels of the variable (polymer concentration) were used for further optimization of core tablets by central composite design.
Statistical experimental design of two factors at three different levels was used to evaluate the influence and interactions of the three levels to the final responses tested. Such three level-CCD requires a minimum number of tests for each variable. The fact that the expected responses do not vary in a linear manner with the selected variable and to enable the quantification of the prediction of the responses, a central composite plan was selected, where the response could be modeled in a quadratic manner since the error in predicting the response increases with the distance from the centre of the modeled region. It is advisable to limit the use of the models to an area bound by values corresponding to \(-\alpha\) to \(+\alpha\) limits.

The parameters were carefully selected to carry out composite factorial design (one of the forms of CCD where the effect of each factor is evaluated at five different levels) based on codified values of \(-\alpha\), -1, 0, +1, +\alpha. The value of alpha is chosen such that the variance of the response predicted by the model would depend only on the distance from the centre of the modeled region. The value of alpha was taken here as 1.414. Three replicate central point were prepared to estimate the degree of experimental error for the modeled responses.

Four key responses as mentioned earlier in the text were selected to derive the mathematical models for evaluating relevant factors. The experimental levels of the variables (maximum and minimum) boundary of each response variables are defined in the optimization techniques. The quadratic model test for the CCD is as shown in Eq 2.

\[
Y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2 + b_{11}x_1^2 + b_{22}x_2^2 \ldots \ldots (2)
\]

where \(Y\) = response, \(x_1\) = drug: polymer ratio, \(x_2\) = polymer : polymer ratio, \(b_0\) is the intercept for the regression line, \(x_1x_2\) is the interaction and other \(b\)’s stands = for coefficients.

\textbf{In vitro dissolution studies}

Drug release studies on the tablets were performed using a United States Pharmacopoeia dissolution rate test apparatus (type 1, 100 rpm, 37 \(^\circ\)C) in 900 ml simulated gastric fluid (0.1M HCl) without enzymes. A 5 ml aliquot was withdrawn at different time intervals, filtered through 0.45 \(\mu\) filter and the dissolution medium replenished with 5 ml of fresh dissolution fluid. The drug content of the sample was determined by Elico UV-Visible Spectrophotometer (model SL-159) at 290 nm after suitable dilution of the sample. The experiments were conducted in triplicate.

\textbf{Data analysis}

To analyze the mechanism of drug release and release rate kinetics from the dosage form, the responses obtained from formulations F1 to F11 and F0 were subjected to zero order, first order, Korsmeyer and Peppas release models using Prism\textsuperscript{®} and Sigma plot\textsuperscript{®} software, for curve fitting and statistical data analysis, respectively. Finally all the response, viz, n, K, R\textsuperscript{2}, %Assay, %drug release and time of maximum drug release were fitted to the quadratic regression model as shown in Eq 2 to determine the coefficients and intercept for the factors tested at each response. The optimum formulation was constructed using this regression line and to predict the responses form the response boundary, ANOVA was performed to ascertain statistical significance of the model at 95 % confidence limit.

\textbf{RESULTS}

The shear stress of the four polymer tested is depicted in Fig 1. As the time of contact with mucus is increased the shear force of the polymers also increased almost linearly except for Carbopol 974p which initially showed a rapid increase of shear stress and thereafter a steady state or plateau was observed.
Drug dissolution and release kinetics

In vitro parameters for the various tablet formulations are listed in Table 3. Drug release throughout the study period ranged from 80 to 98% while diffusion coefficient (n) ranged from 0.3 to 0.7, K from 0.3 to 0.5 and $R^2$ from 0.8 to 0.9. The curve-fitting results for drug release from the formulations gave an insight into the release rate and release mechanism [8].

The final optimized composition of the core tablet (sustain release dose component), F0, is as follows: cyproheptadine HCl 11 mg, HPMC 28 mg, Carbopol 934p 4.65 mg, magnesium stearate 4 mg, talc 4 mg, MCC 15 mg, and lactose 82.97 mg. The composition of the loading (prompt) dose, which was coated around the core tablet, is: cyproheptadine HCl 4 mg, MCC 30 mg, lactose 184 mg, magnesium stearate 10 mg, talc 10 mg, and cross-carmellose sodium 12 mg.

**DISCUSSION**

The bioadhesive cyproheptadine HCl tablet formulation was designed to increase bioavailability and prolong therapeutic action. The bioadhesive nature and controlling characteristics of certain polymers can be attributed to shear stress, detachment force and release.[13]

| Table 3: Dependent variables used for optimization by CCD. |
|-----------------------------------------------------------|
| **Formulation** | **Detachment force (N)** | **Assay (%)** | **Drug release (%)** | **Time for drug release (h)** | **Korsmeyer-Peppas model** |
|                |                            |               |                     |                               | K | n  | $R^2$ |
| F1             | 0.0228                      | 89.32         | 91.41               | 11                            | 0.3217 | 0.412 | 0.9826 |
| F2             | 0.0299                      | 92.75         | 97.14               | 10                            | 0.3902 | 0.401 | 0.980  |
| F3             | 0.011                       | 92.37         | 98.56               | 5                             | 0.510  | 0.342 | 0.887  |
| F4             | 0.0214                      | 90.79         | 89.65               | 13                            | 0.3406 | 0.335 | 0.928  |
| F5             | 0.0548                      | 88.22         | 94.59               | 7                             | 0.4286 | 0.375 | 0.965  |
| F6             | 0.0166                      | 94.08         | 97.89               | 10                            | 0.365  | 0.423 | 0.984  |
| F7             | 0.0263                      | 94.70         | 81.96               | 10                            | 0.3008 | 0.4   | 0.980  |
| F8             | 0.0276                      | 95.67         | 91.24               | 12                            | 0.363  | 0.372 | 0.968  |
| F9             | 0.0251                      | 95.31         | 96.84               | 9                             | 0.3756 | 0.4    | 0.979  |
| F10            | 0.0246                      | 90.79         | 91.22               | 10                            | 0.2749 | 0.496 | 0.950  |
| F11            | 0.0584                      | 98.00         | 93.91               | 9                             | 0.4029 | 0.403 | 0.962  |
| F0             | 0.066                       | 91.15         | 93.92               | 16                            | 0.1269 | 0.696 | 0.964  |
Shear stress

The highest shear stress was shown by 3% solutions of HPMC and Carbopol 934P. This may be attributed to the swelling of the polymers which leads to greater entanglement of polymeric chains due to controlled hydration. Thus, shear stress increases with time as a result of the controlled rate of hydration. On the other hand, CMC and Carbopol 974P showed uncontrolled hydration and swelling with time which resulted in less increase in shear stress.

Detachment force

Tablet cores containing either HPMC or Carbopol 934p showed higher detachment force than the other two polymers, leading to the exclusion of the latter from further studies. The combination of HPMC and Carbopol 934p exhibited higher rate of swelling, higher chain entanglement and higher friction than the individual polymers; thus, the polymer combination yielded a higher detachment force. The exact ratio of the polymer combination that exhibited the highest bioadhesive strength was obtained by optimization using Central Composite Design (CCD).

Assay

Formulation F11 (HPMC:Carbopol 934p in the ratio 20:7.5) showed the highest drug content (98%) due probably to uniform mixing of the polymers and the drug. However, uniformity in mixing can be also achieved for the other formulations if the formulation conditions are appropriately modified.

Kinetic release mechanism (curve fitting)

Based on the dissolution profile, the drug release data were best fitted to the Korsmeyer - Peppas model for all the formulations as they showed high correlation coefficient ($R^2 = 0.98$) Thus, drug release occurred via non-Fickian diffusion. The response dependant variables - K, n, $R^2$ and detachment force - were examined by subjecting these responses to multiple regression analysis of variance, and the following observations were made.

Effect of formulation variables on release kinetics (K)

The model term, K, for cyproheptadine hydrochloride release was significant ($p = 0.0478$), indicating adequate fit to the surface linear model. In this model, as the concentration of HPMC increased, K value also increased, and this may be attributed to the swelling of the polymers which in turn increased the influx of water leading to increased drug diffusion. Carbopol 934p similarly caused an increase in the value of K.

Effect of formulation variables on diffusion coefficient (n)

The model term for n was highly significant ($F = 12.98$), indicating adequate fit to the quadratic model. At low concentrations of HPMC, n decreased while at higher concentrations, n increased; similarly, with increase in Carbopol 934p concentration n also increased. Thus, the optimum concentration of this two-polymer combination exhibited the desired predetermined controlled release and bioadhesive property.

Effect of formulation variables on detachment force

Detachment force was not important for the design chosen. As HPMC increased, detachment force also increased while for Carbopol 934P, detachment force first increased and then decreased. However, the optimized mixture of these two polymers in the tablet core showed sustained increase in detachment force over time. This is probably due to the fact that the rate-limiting hydration
interaction of Carbopol 934p was controlled by HPMC.

**Effect of formulation variables on $R^2$**

The model term for $R^2$ was significant ($F = 1.1572$), indicating adequate fit to the quadratic model. As HPMC concentration increased, $R^2$ also increased; a similar observation was made for Carbopol 934P.

**Optimization**

A numerical optimization technique by the desirability approach was used to generate the optimum setting for the formulation using maximum adhesive force as well as favorable drug release time, $K$, $n$ and $R^2$. When this was done, F0 showed drug release for up to 16 h. The optimized formulation was prepared using the various criteria mentioned earlier and the formulation was evaluated for various responses. The optimization results obtained are shown in Table 4.

The results showed a good relationship between the experimental and predicted values, which confirms the practicability and validity of the model. Furthermore, it can be stated that the mechanism of drug release from the bioadhesive drug delivery system was non-Fickian transport.

**CONCLUSION**

The final optimized cyproheptadine hydrochloride formulation, incorporating Carbopol 934p and HPMC, resulted in tablets with superior bioadhesion and prolonged release. It consisted of a sustained release tablet core around which was compressed a prompt release coat containing sodium carboxymethyl cellulose that would disintegrate within 5 min to provide immediate therapeutic effect. Furthermore, the application of optimization technique is a useful tool, particularly in evaluating several response variables as the observed variables were in close agreement with predicted values for the optimized formulation, thus demonstrating the feasibility of the optimization procedure used. Consequently, formulation of a bioadhesive tablet of cyproheptadine hydrochloride using optimization technique has been successfully achieved and the approach used holds promise for other drugs that have an absorption window in the stomach.

**REFERENCES**

1. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharm 1996; 22(6): 531-539.
2. John SD. The basics underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev 2005; 57: 1556-1568.
3. Chowdary KRP, Kamalakara RG, Bhaskara P. Mucoadhesive polymers - Promising excipients for controlled release. Int. J Pharm Excip 2001;2: 33-38.
4. Edith M, Chickering D. Bioadhesive drug delivery systems. in: Encyclopedia of Controlled Drug Delivery, Vol I, Patrick Aebscher, Roland Bodmeier, Nicholas Bodor, Clarissa Bonnahrn et al, Ed, Wiley and Sons, New York, 1999; pp 9-79.
5. Attama AA, Petra O. Melt extrusion bioadhesive drug delivery: a case of diclofenac contained in carbopol 940 matrices. Indian J Pharm Sci 2005; 67(1): 66-69.
6. Yanbin H, William L. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces J Control Rel 2000; 65: 63-71.
7. Mahesh CD, Paras J, Sachin C, Rajesh S, Pradeep VR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J Pharm 2006; 316: 86-92

**Table 4** Predicted and actual values for optimized formulation, F0

| K      | N     | $R^2$ | Detachment force |
|--------|-------|-------|------------------|
| Actual | Predicted | Actual | Predicted | Actual | Predicted | Actual | Predicted |
| 0.1269 | 0.1283 | 0.696 | 0.7          | 0.964 | 0.845 | 0.066 | 0.06 |

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8. Vanessa V, Evone SG. Fickian and relaxational contribution quantification of drug release in a swellable hydrophilic polymer matrix. Drug Dev Ind Pharm 1994;20(16):2519-2526.
9. Susana T, Pablo P, Paloma MD, Santiago T. Chitosan - poly(acrylic) acid polyionic complex: in vivo study to demonstrate prolonged gastric retention. Biomaterials 2004;25:917-923.
10. Klaus F, Harry GB, David JM, Gerald SB, Abdullah AG, William M, Edward Smith AB. Analytical profiles of drug substance, Vol 9, Academic Press, edn 1, 1991; pp 155-179.
11. Martindale, The Complete Drug Reference. A&C Black Publishers Ltd, Edn 33, 2000; pp 181-187.
12. Jaspreet KV, Kaustubh T, Sanjay G. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm 2003;255:13-32.
13. Vyas SP, Khar RK. Controlled Drug Delivery Concepts and Advances, CBS publishers New Delhi, 1st edition, 2002; pp 196-217.
14. Vjera G, Davide G, Andreas N. Comparison of mucoadhesive properties of various polymers. Adv Drug Deliv Rev 2005;57:1713-1723.
15. Owens TS, Dansereau RJ, Adel S. Development and evaluation of extended release bioadhesive sodium fluoride tablets, Int J Pharm 2005;288:109-122.