Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2014, 4(4), 385-390
doi: 10.5681/apb.2014.057
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Research Article

Formulation and Characterization of Cetylpyridinium Chloride Bioadhesive Tablets

Jafar Akbari[1]*, Majid Saeedi[1], Katayoun Morteza-Semnani[2], Hamidreza Kelidari[3], Maryam Lashkari[1]

[1] *Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.*
[2] *Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.*
[3] *Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran.*

Article info

Article History:
Received: 15 December 2013
Revised: 26 February 2014
Accepted: 15 March 2014
ePublished: 10 August 2014

Keywords:
· Cetylpyridinium Chloride
· HPMC K100M
· Carbopol 974P
· Polycarbophill
· Bioadhesive

Abstract

Purpose: Bioadhesive polymers play an important role in biomedical and drug delivery applications. The aim of this study is to develop a sustained- release tablet for local application of Cetylpyridinium Chloride (CPC). This delivery system would supply the drug at an effective level for a long period of time, and thereby overcome the problem of the short retention time of CPC and could be used for buccal delivery as a topical anti-infective agent.

Methods: CPC bioadhesive tablets were directly prepared using 7 mm flat-faced punches on a hydraulic press. The materials for each tablet were weighted, introduced into the die and compacted at constant compression pressure. The dissolution tests were performed to the rotation paddle method and the bioadhesive strength of the tablets were measured.

Results: The results showed that as the concentration of polymer increased, the drug release rate was decreased. Also the type and ratio of polymers altered the release kinetic of Cetylpyridinium Chloride from investigated tablets. The bioadhesion strength increased with increasing the concentration of polymer and maximum bioadhesion strength was observed with HPMC K100M.

Conclusion: The selected formulation of CPC bioadhesive tablet can be used as a suitable preparation for continuous release of CPC with appropriate bioadhesion strength.

Introduction

Bioadhesive polymers play an important role in biomedical and drug delivery applications. Good adhesion and intimate contact between polymer carrier and tissue are desirable for use in these applications. Mucoadhesive systems are advantageous over conventional drug delivery systems due to their ability to increase the contact time of drug with the biological substrate, thus increasing drug absorption. Various bioadhesive mucosal dosage forms have been developed, which included adhesive tablets, gels, ointments, patches, and more recently films.[1] Mucoadhesion is provided by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers. Mediated by mucoadhesive polymers, the residence time of dosage forms on the GI- mucosa should be prolonged, which allows a sustained drug release at a given target site to maximize the therapeutic effect.[2]

A major difficulty for the successful eradication of infections of oral cavity is the dilution and rapid elimination of topically applied drugs due to the flushing action of saliva. The delivery system in which the drug is incorporated is therefore an important consideration and should be formulated to prolong retention of the drug in the oral cavity. Efficient local delivery of actives such as dental bleaches and antimicrobials to the oral cavity is compromised by a number of factors that dramatically reduce residence time, most notably the shear forces associated with speaking, swallowing and mastication, as well as dilution and washout caused by continuous saliva production.[3]

Typical polymers that have been used as mucoadhesive drug carriers are poly (acrylic acid), poly (methacrylate acid), cellulose derivatives, poly (ethylene oxide), lectin and chitosan.[4] The PAA and its cross-linked commercial forms, Carbopol and polycarbophil exhibit strong mucoadhesive properties.[5] Many attempts have been undertaken to improve the mucoadhesive properties of polymers by preparing copolymers, polymer conjugates or interpolymer complexes.[6,7]

CPC, an amphiphilic quaternary compound, has been used extensively in oral hygiene formulations.[8] Valuable properties of CPC include solubility in water and alcohol, as well as its ability to reduce surface tension. A number of laboratory studies are available in the literature that report the broad spectrum activity of CPC on a range of organisms, including bacteria and yeast found in dental plaque.[9-11] Bonesvoll and Gjermo have shown that a moderate plaque inhibition was obtained

***Corresponding author:** Jafar Akbari, Tel Tel/Fax: +98 (151) 3543084, Email: JAkbari@mazums.ac.ir

when CPC was applied twice daily as a mouthwash. Only when the frequency was increased to 4 times daily did the plaque inhibitory effect approach that of chlorhexidine. The differences in clinical effect could be explained from the retention time of the drug: the quaternary ammonium compounds were cleared from the mouth more rapidly than was chlorhexidine.[12] Fridman et al. prepared the cast film composed of ethylcellulose and CPC. The films exhibited sustained inhibition of *Streptococcus mutans* growth *in vitro*. The results of the clinical study proved that a single application of cetylpyridinium films decreased plaque accumulation for a period of 3 days. No changes in the total salivary flora were observed during the study.[13]

The aim of this study is to develop a sustained- release tablet for local application of CPC. This delivery system would supply the drug at an effective level for a long period of time, and thereby overcome the problem of the short retention time of CPC and could be used for buccal delivery as a topical anti-infective agent.

Materials and Methods

Materials

Cetyl pyridinium Chloride, magnesium stearate, potassium hydrogen phosphate and lactose were purchased from Merck Co. (Germany). Carbopol 934P and polycarbophill from BF Goodrich Co. (USA), and HPMC K100M were prepared from Colorcon Co. (UK). All chemicals and solvents were of analytical grade. Freshly double distilled water was used in the experiments.

Preparation of bioadhesive tablets

Six formulations (F1-F6) were directly prepared using 7 mm flat-faced punches on a hydraulic press. The materials for each tablet (Table 1) were weighed, mixed and introduced into the die and compacted at constant compression pressure using 1% (w/w) magnesium stearate.

Table 1. Formulation composition of cetylpyridinium chloride mucoadhesive tablets

Formulation code	Formulation Composition (mg)					
	Drug	Carbopol 974P	Poly carbophill	HPMC K100M	Lactose	Mg stearate
F1	30	30	-	-	-	0.6
F2	30	15	-	-	15	0.6
F3	30	-	30	-	-	0.6
F4	30	-	15	-	15	0.6
F5	30	-	-	30	-	0.6
F6	30	-	-	15	15	0.6

In vitro dissolution

The dissolution tests were performed to the rotation paddle method (USP pharmacopoeia 24). A dissolution apparatus (Caleva 8ST, Germany) was employed with a stirring rate of 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH: 6.8). Samples of the solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was passed through a filter and then the concentration of CPC in solution was measured with an ultraviolet spectrophotometer (Varian, Australia) at a wavelength of 258 nm after suitable dilution with the dissolution medium when necessary. The experiment was carried out in triplicate.[14]

Kinetic analysis

In order to describe the kinetics of drug release from mucoadhesive tablets, various mathematical equation models (zero-order, first-order, Higuchi) were tested

$Q_t = k_0 t$

$\ln Q_t = \ln Q_0 - k_1 t$

$Q_t = k_H t^{1/2}$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the tablet and k_0, k_1 and k_H are the respective release rate constants for zero-order, first-order and Higuchi models. In order to define a model, that will represent a better fit for the formulations, dissolution data can be further analyzed by the Ritger and peppas and Korsmeyer equation

$M_t/M_\infty = k_p t^n$

Where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, k_p is a constant and 'n' is the release exponent indicating the type of drug release mechanism.[15]

Determination of bioadhesive strength

To evaluate the bioadhesion strength, a tensile tester apparatus was designed similar to a tensile tester apparatus (Instron model 4301) and the bioadhesive strength of the tablets was measured according to previously published method by a tensile tester apparatus. After isolation of hairless abdominal skin of the rat, the dorsal section of abdominal skin of rat (mucosa part) was fixed on the head of diffusion cell and filled with phosphate buffer with pH 6.8. The same conditions were exactly used according to previously published method.[16]

Statistical analysis

Statistical analysis was carried out by using the analysis of variance (ANOVA) with computer software SPSS 10. Tukey-Kramers multiple comparison tests were used to compare the group data.

Results and Discussion

Bioadhesive preparations are preferred for treatment of diseases of oral cavity because they can adhere to the mucosa, protect the diseased part, and retain the drug for the desired period. Examples of oral cavity diseases for which buccal dosage forms have been designed include: aphthous stomatitis, oral candidiasis, and periodontal disease. In the buccal region, a tablet may be adhered either to the buccal tissue (cheek) or the gingival. For local drug delivery, the highly keratinized epidermis of the gingival will present a barrier to systemic absorption. The buccal tablet must be sufficiently thin (1-2 mm) and of small diameter (6-8 mm), so as to be comfortable and not obtrusive when placed into the oral cavity. Bioadhesion is the phenomenon between two materials, which are held together for extended periods of time by interfacial forces. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface, mucoadhesion when occurs with the mucus layer covering a tissue.

The adhesion force of mucoadhesive tablets are shown in Figure 1. The bioadhesion strength of mucoadhesive tablets were evaluated by method that described by Akbari et al. The results of this study clearly demonstrate that the changing the type of polymer can also change the bioadhesive strength of tablets. Maximum bioadhesive strength was seen with F3 (HPMC K100M). Also the results showed that the bioadhesion strength decreased with incorporation of lactose in formulations.

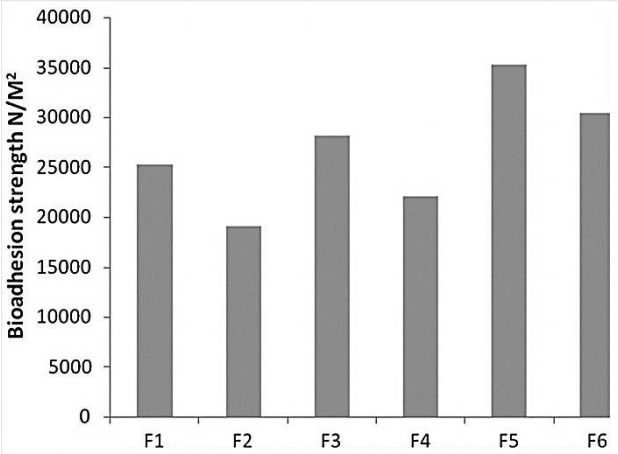

Figure 1. Comparison of the mucoadhesive force of investigated cetylpyridinium buccal tablets containing carbopol 974P, polycarbophyl, and HPMC K100M (n=3).

Bioadhesive force means the force with which tablets bind to buccal mucous membranes. The bioadhesive forces of the tablet are affected by the shape of the tablet, the swelling degree of the tablet and the nature of the tablet components.[17]

Various classes of polymers have been investigated in order to meet the requirements for a mucoadhesive polymer, such as proper hydrogen-bonding functional groups, suitable wetting properties, swelling/water load properties, and sufficient flexibility for entanglement with the tissue mucus network. The mucosal surface is covered with a mucus layer, in which mucins are the major component. Mucins are highly glucosylated glycoproteins with a large peptide backbone and oligosaccharides as side chains. As a result, mucins are negatively charged at physiological pH. Mechanisms of polymer attachment to mucosal surfaces are not yet fully understood. However, certain theories of bioadhesion have suggested that it might occur via physical entanglement (diffusion theory) and/or chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding, and Van der waals interactions (adsorption and electronic theories).[18]

Formulation F2 was having lowest bioadhesive force because the carbopol 974P has a lower viscosity than the other two polymers. While formulation F5 containing HPMC K100M shows higher bioadhesion force due to higher viscosity. HPMC is a long chained, nonionic polymer and so its mucoadhesion is attributable to the formation of physical bonds or hydrogen bonding with the mucus components. HPMC possesses a large number of hydroxyl groups that are responsible for adhesion. Formation of hydrogen bonds between the hydrophilic functional groups of the mucoadhesive polymers and the mucus layer or the mucosal surface is a prerequisite for extensive and longer mucoadhesion. The increased sites for bond formation can explain the increase in bioadhesion with an increase in concentration. The higher mucoadhesive potential observed with formulations containing only HPMC is probably due to the controlled rate of hydration of HPMC as a nonionic polymer. This could in turn prevent the tablet from quick over hydration and formation of slippery and weak mucilage, which could be easily removed from the mucosal surface.[19]

From the above results it was found that polymers having high molecular weight and high viscosity exhibited higher adhesion. Chandira et al. prepared the mucoadhesive tablets of Clarithromycin by using the Carbopol 974P, HPMC K15M and HPMC K4M. They found that polymers having high molecular weight and high viscosity exhibited higher adhesion. HPMC K15M and Carbopol 974P were found to be having good mucoadhesive strength. HPMC and carbopol possesses hydroxy and carboxy groups respectively required for bioadhesion.[20] Akbari et al evaluated the effect of fillers on the bucoadhesive propranolol hydrochloride tablets. The results that they obtained showed bioadhesion force increased with increasing the concentration of polycarbophil. It is clear that the formation of very thin and strong gel layer at the boundary might be necessary for adhesion. The viscosity of this layer is increased by adding polycarbophil and therefore the bioadhesion strength increases.[21]

Also Maniyar et al. stated that the strength of mucoadhesion can be influence by polymer concentration. Physical state of the delivery system defines the polymer concentration, with observational differences between semisolid and solid state platforms. In semisolid state, an optimum concentration exists for

each polymer beyond which reduced adhesion occurs because a lower number of polymer chains are available for interpenetration with mucus. On other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases.[22]

In vitro dissolution studies

The effect of polymer type and addition of lactose on release rate are shown in Figure 2. The initial percentage drug release after 2 hour for F1, F2, F3, F4, F5 and F6 were 14.20, 48.48, 14.63, 48.02, 16.12 and 25.52 respectively. The percentage drug release after 8 hour for F1, F2, F3, F4, F5 and F6 were 39.91, 70.66, 35.63, 67.41, 26.87 and 50.59 respectively. The lowest release rate was observed with formulation F5 containing HPMC K100M and the highest release rate was observed with formulation F2 containing Carbopol and Lactose (P<0.01). The significant difference was not observed between F1-F3 and F2-F4 but there were the significant differences between the release rate of formulations F1 - F3 with F5 (p<0.01) and F2-F4 with F6 (p<0.001).

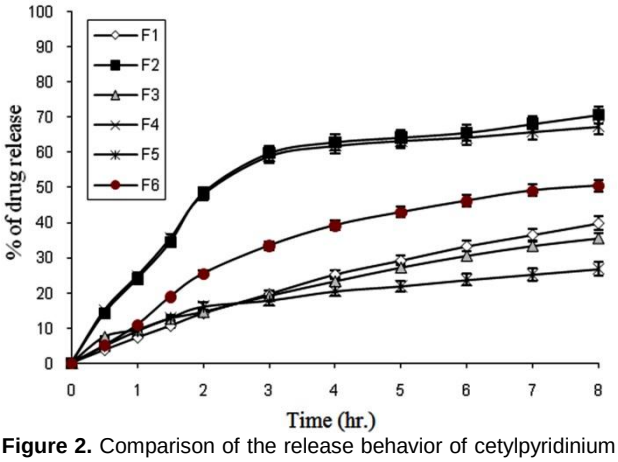

Figure 2. Comparison of the release behavior of cetylpyridinium chloride from buccoadhesive tablets containing carbopol 974P, polycarbophyl, and HPMC K100M (n=3).

It was observed that the type of polymer influences the drug release pattern. Amount of polymer affects the drug release. Drug release from HPMC K100M was lesser owing to its high viscosity and also due to less permeability of water to HPMC K100M. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used.

Figure 2 shows the effect of replacement of HPMC, Polycarbophil and Carbopol 974P by lactose on the release profile of drug. The figure shows that replacement of polymer by lactose increases the release rate of drug from buccoadhesive tablets. Changing the polymer /filler ratio increases the release rate by altering the diffusivity of drug in gel layer. Water diffusivity depends only on the total concentration of viscosity inducing agents in the system irrespective of their nature or polymerization degree. Replacement of polymer by lactose decreases the concentration of polymer in gel layer and therefore diffusion of water into the tablet is facilitated. Lactose also decreases the tourtosity of the path of diffusion. The results confirmed the finding of Lapidus and Lordi that replacement polymer by either a soluble or an insoluble diluents increased dissolution rate.[21] Also Diasa et al. formulated the mucoadhesive Acyclovir tablet with using the HPMC K100M. Their results showed high HPMC K100M content results in a greater amount of gel being formed. This gel layer increases the diffusion path length of the drug, hence controlling drug release via diffusion through the gel and erosion of the gel barrier. Its viscous nature also affects the diffusion coefficient of the drug. As a result, drug release was found to be decreased as the amount of HPMC K100M was increased.[23]

Kinetic evaluation

Dissolution rate data were analyzed based on Eqs. (1-4) and their results are listed in Table 2. The results showed that altering the type of polymer and the ratio of two polymer, had effect on the release kinetic of CPC from buccoadhesive tablets and the highest correlation coefficient were achieved with the various models.

Table 2. The kinetics of Cetylpyridinium Chloride release from mucoadhesive tablets with different kind and amount of polymer

Formulation code	Zero-order model			First-order model			Higuchi model			Peppas model			
	K_0 (%.min)	r^2	*ss*	K_1 (min^{-1})	r^2	*ss*	K_H (%.$min^{-1/2}$)	r^2	*ss*	K_p (%.min^{-n})	*n*	r^2	*ss*
F1	0.0009	0.948	25711	-0.0013	0.978	13961	0.0249	0. 994	1786	0.0155	0. 574	0.991	212
F2	0.0011	0.779	33779	-0.023	0.860	13780	0.033	0. 888	2680	0.0109	0.764	0.960	404
F3	0.0006	0.988	19014	-0.0008	0.995	12146	0.018	0.993	7312	0.0090	0.595	0.992	209
F4	0.0010	0.756	36943	-0.002	0.827	17468	0.0315	0.873	2777	0.0175	0.657	0.967	763
F5	0.0004	0.905	29330	-0.0005	0.926	23470	0.0126	0.972	2326	0.0085	0.554	0.971	1310
F6	0.0010	0.905	15027	-0.0015	0.946	5414	0.0287	0.974	30616	0.0090	0.595	0.951	2718

k_0: zero order release rate constant, k_1: first order release rate constant, k_H: Higuchi model release rate constant, k_p: Peppas model release rate constant, *n:* release exponent in Peppas model, r^2: definition coefficient, *ss*: sum of squares of errors

There are the following possible mechanisms by which drug release from a polymeric matrix may occur: (a) the first and the most often encountered mechanism is drug diffusion through the outside layers of the matrix, also known as ‘‘Fickian’’ release or ‘‘Case I’’ mechanism (b) non-Fickian or anomalous (c) ‘‘zero-order’’ release or ‘‘Case II’’ mechanism Another mechanism of release involves devices made from water-soluble or swellable polymers, where matrix swelling and drug diffusion occur concurrently. This mechanism has been described as non-Fickian or anomalous transport and the release is controlled by swelling and diffusion. However, in

practice, polymeric matrices release the drug via a combination of mechanisms. The exponent, *n*, depends on the polymer swelling characteristics and the relaxation rate at the swelling front.[24]

The CPC release from matrix tablets containing different types of polymers showed a good fit into the Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. As shown in Table 2, release data fit well with this model as a correlation coefficient (r^2) greater than 0.951 was obtained in all cases.

According to the criteria for release kinetics from swellable systems, a value of release exponent, $n = 0.45$, $0.45<n< 0.89$, and $0.89<n<1.0$ indicates Fickian (Case I) diffusion, non-Fickian (anomalous) diffusion and zero-order (Case II) transport, respectively.[25]

The value of diffusional coefficient, *n*, for mucoadhesive matrices was 0.574-0.764 which indicates non-Fickian (anomalous) behaviour and that the drug partially diffuses through the swollen polymer matrix and also partly through the gradually expanding hydrated matrix with increasing diffusional path length.

Conclusion

In this study, the effect of type and amount of polymer on the bioadhesive strength and release rate of Cetylpyridinium Chloride were evaluated. Different mucoadhesive tablets were formulated to adhere to the buccal mucosa for a local CPC release. The dissolution rate, release kinetic and bioadhesion force of tablets were evaluated. The results showed that as the concentration of polymer increased, the release rate decreased. The lowest release rate observed with HPMC K100M. The bioadhesion strength of mucoadhesive tablets were evaluated by method that described by Akbari et al. the results showed that the highest bioadhesion force also was observed with HPMC K100M.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Ahn JS, Choi HK, Chun MK, Ryu JM, Jung JH, Kim YU, et al. Release of triamcinolone acetonide from mucoadhesive polymer composed of chitosan and poly (acrylic acid) *in vitro*. *Biomaterials* 2002;23(6):1411-6.
2. Bernkop-Schnürch A. Mucoadhesive systems in oral drug delivery. *Drug Discov Today Technol* 2005;2(1):83-7.
3. Rathbone MJ, Drummond BK, Tucker IG. The oral cavity as a site for systemic drug delivery. *Adv Drug Del Rev* 1994;13(1-2):1-22.
4. Ameye D, Mus D, Foreman P, Remon JP. Spray-dried Amioca® starch/Carbopol® 974P mixtures as buccal bioadhesive carriers. *Int J Pharm* 2005;301(1–2):170-80.
5. Chun MK, Cho CS, Choi HK. Mucoadhesive drug carrier based on interpolymer complex of poly (vinyl pyrrolidone) and poly (acrylic acid) prepared by template polymerization. *J Control Release* 2002;81(3):327-34.
6. Ameye D, Voorspoels J, Foreman P, Tsai J, Richardson P, Geresh S, et al. *Ex vivo* bioadhesion and in vivo testosterone bioavailability study of different bioadhesive formulations based on starch-g-poly(acrylic acid) copolymers and starch/poly(acrylic acid) mixtures. *J Control Release* 2002;79(1-3):173-82.
7. Kast CE, Bernkop-Schnürch A. Polymer–cysteamine conjugates: new mucoadhesive excipients for drug delivery? *Int J Pharm* 2002;234(1-2):91-9.
8. Wu CD, Savitt ED. Evaluation of the safety and efficacy of over-the-counter oral hygiene products for the reduction and control of plaque and gingivitis. *Periodontol 2000* 2002;28(1):91-105.
9. Pitten FA, Kramer A. Efficacy of cetylpyridinium chloride used as oropharyngeal antiseptic. *Arzneimittelforschung* 2001;51(7):588-95.
10. Quisno R, Foter MJ. Cetyl pyridinium chloride: I. Germicidal properties. *J Bacteriol* 1946;52(1):111.
11. Bereswill S, Vey T, Kist M. Susceptibility in vitro of Helicobacter pylori to cetylpyridinium chloride. *FEMS Immunol Med Microbiol* 1999;24(2):189-92.
12. Bonesvoll P, Gjermo P. A comparison between chlorhexidine and some quaternary ammonium compounds with regard to retention, salivary concentration and plaque-inhibiting effect in the human mouth after mouth rinses. *Arch Oral Biol* 1978;23(4):289-94.
13. Friedman M, Harrari D, Rimer A, Stabholz A. Inhibition of plaque formation by a sustained release delivery system for cetylpyridinium chloride. *Int J Pharm* 1988;44(1-3):243-7.
14. Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. *Acta pharm* 2003;53(3):199-212.
15. Saeedi M, Morteza-Semnani K, Ansoroudi F, Fallah S, Amin G. Evaluation of binding properties of Plantago psyllium seed mucilage. *Acta Pharm* 2010;60(3):339-48.
16. Akbari J, Saeedi M, Enayatifard R, Sagheb-Doost M. Development and evaluation of mucoadhesive chlorhexidine tablet formulations. *Trop J Pharm Res* 2010;9(4):321-7.
17. Choi HG, Kim CK. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. *J Control Release* 2000;68(3):397-404.
18. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. *Adv Drug Deliv Rev* 2005;57(11):1666-91.
19. Majithiya RJ, Raval AJ, Umrethia ML, Ghosh PK, Murthy RSR. Enhancement of Mucoadhesion by Blending Anionic, Cationic and Nonionic Polymers. *Drug Deliv Tech* 2008;8:40-5.
20. Chandira RM, Palanisamy P, Jayakar B, Chatakonda R. Design and Development of Controlled Release

Mucoadhesive Oral tablet of Clarithromycin. *Int J Pharma Recent Res* 2009;1(1):59-66.
21. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, Saeedi M. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: effect of fillers. *Farmaco* 2004;59(2):155-61.
22. Maniyar AH, Patil RM, Kale MT, Jain DK, Baviskar DT. Mucoadhesion: A new polymeric controlled drug delivery. *Int J Pharm Sci Rev Res* 2011;8(1):54-60.
23. Jacky Dias R, Shamling Sakhare S, Krishnat Mali K. Design and development of mucoadhesive acyclovir tablet. *Iran J Pharm Res* 2010;8(2):231-9.
24. Sinha Roy D, Rohera BD. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. *Eur J Pharm Sci* 2002;16(3):193-9.
25. Ritger PL, Peppas NA. A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Release* 1987;5(1):23-36.