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In Vitro Characterization of Buccoadhesive Atenolol Tablets

Nevin ÇELEBİ*°, Özlem SARACOĞLU (KIŞLAL)*, Füsun ACARTÜRK*

In Vitro Characterization of Buccoadhesive Atenolol Tablets

Summary : *A buccoadhesive tablet for the delivery of atenolol to the oral mucosa was prepared with hydroxypropylmethyl cellulose (HPMC), and polyacrylic acid (PAA) which served as the bioadhesive polymers.*

Buccoadhesive tablets were prepared by direct compression of atenolol with these polymers in different ratios. The in vitro release of atenolol from buccoadhesive tablets was carried out by USP XXIII paddle method in pH 6.8 phosphate buffer solution. The detachment force between buccoadhesive tablets and bovine buccal mucosa was measured by using Instron tensile tester apparatus.

The release behavior of buccoadhesive tablets containing PAA and HPMC was found to be non-Fickian.

The detachment force between buccoadhesive tablets and bovine buccal mucosa was decreased with decreasing PAA content

Key words: *Atenolol, buccoadhesive tablet, in vitro release, detachment force*

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Bukoadheziv Atenolol Tabletlerinin İn Vitro Karakterizasyonu

Özet : *Atenololün oral mukozadan verilişi için hidroksipropil metil selüloz (HPMC) ve poliakrilik asit (PAA) biyoadheziv polimerler kullanılarak bir bukoadheziv tablet hazırlanmıştır. Bukoadheziv tabletler, atenolol ve polimerin farklı oranlarında doğrudan basım yöntemine göre hazırlanmıştır. Atenolol'ün bukoadheziv tabletlerden in vitro salımı pH 6.8 fosfat tamponunda USP XXIII palet yöntemine göre yapılmıştır.*

Bukoadheziv tabletler ile sığır yanak mukozası arasındaki ayrılma kuvveti instron gerilme aleti kullanılarak ölçülmüştür. PAA ve HPMC içeren bukoadheziv tabletlerin salım davranışı non Fickian bulunmuştur.

Bukoadheziv tabletler ile sığır yanak mukozası arasındaki ayrılma kuvveti PAA içeriği azaldıkça azalmıştır.

Anahtar kelimeler: *Atenolol, bukoadheziv tablet, in vitro salım, ayrılma kuvveti*

INTRODUCTION

Recently the buccal mucosa has been studied as a potential site for delivery of drugs because of its accessibility and low enzymatic activitiy. The buccal route offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first - pass metabolism in the liver and presystemic metabolism in the GI tract are avoided[1]. Significant interest has been shown in the development of novel buccal bioadhesive controlled release systems for various drugs such as insulin, triamcinolon acetate, oxycodone hydrochloride, codeine phosphate, cetylprydinium chloride[2-6]. For this purpose bioadhesive polymers such as polyacrylic acid , hydroxypropylmethyl cellulose and sodium carboxymethylcellulose are suitable agents for use in buccoadhesive preparations because, when hydrated with water, they can adhere to the oral mucosa and swell for a significant period of time. In our previous study we attempted to achieve buccoadhesive tablet formulation for propranolol HCl[7].

* Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Etiler-06330- Ankara, Turkey.
° Correspondence

The main objective of the present study, which is the part of a series of studies, was to develop a buccoadhesive tablet formulation and investigate *in vitro* characteristics of another β - blocker agent (atenolol).

EXPERIMENTAL

Materials

Atenolol(ATN)(Doğu Pharm.Comp.Turkey), polyacrylic acid(PAA)(Carbopol 934-Biesterfeld, Hamburg, Germany), and hydroxypropylmethyl cellulose (HPMC) (visc.12000-21000 cps) (Dow Chemical, USA), were kindly supplied by the manufacturers. All other chemicals were either reagent or analytical grade and were used as received.

Methods

Preparation of Buccoadhesive Tablets

Atenolol (50 mg) was mixed manually with PAA and HPMC in various ratios and compressed into tablets of 8 mm diameter using flat-faced punches and a hydraulic press at 200 kg/cm^2. The formulations of buccoadhesive tablets are shown in Table 1.

Table 1. Composition of buccoadhesive tablet formulations

Code	ATN (wt%)	PAA (wt%)	HPMC (wt%)
ATN1	50	50	–
ATN2	50	45	5
ATN3	50	35	15
ATN4	50	25	25
ATN5	50	15	35
ATN6	50	5	45

In vitro Release of Atenolol from Buccooadhesive Tablets

The *in vitro* release of atenolol from buccoadhesive tablets was carried out by USPXXIII paddle method in pH 6.8 phosphate buffer solution at 37 ± 0.5°C. The paddle was rotated at 50 rpm. Samples were collected at appropriate time intervals. The solubility of atenolol was 49.3 mg / ml in pH 6.8 phosphate buffer solution. Concentration of atenolol was assayed spectrophotometrically (Perkin Elmer-Hitachi 200 - Spectrophometer) at 274 nm. The experiments were carried out in triplicate. The release data were evaluated kinetically with a computer program (DISSOL) written for this purpose[8].

Bioadhesion Studies

For the bioadhesion studies of tablets, the tensile experiment[9] was adapted using the Instron (Model 4301, Instron Ltd.) apparatus. Bovine buccal mucosa (50.24) was collected immediately after sacrificing the animal and frozen at -20°C until use, when it was thawed to 4°C in isotonic phosphate buffer solution pH 7.2 and 2 mm thick mucosa was cut carefully and placed on the lower support of the Instron apparatus. Cyanoacrylate adhesive was used to fix the tablet and the bovine buccal mucosa to the upper and lower metallic supports, respectively. 10 ml of phosphate buffer solution pH 6.8 was placed on the tablet surface .The tablet and buccal mucosa were allowed to remain in contact with a force of 0.5 N and kept in this condition for 10 min. The tablet - mucosa system was stretched at an extension rate of 5 mm/min and the force required to detach the tablet from the mucosa. The force needed to break the adhesive bond was recorded. All tests were made at room temperature at 60 % relative humidity.

The tensile experiment was repeated with fresh tablets and fresh mucosa in an identical manner (n=5).

RESULTS AND DISCUSSION

In vitro Release Studies

In vitro release profiles of atenolol from buccoadhesive tablets containing PAA and HPMC are shown in Fig.1. After a 3-hr period, 45 % atenolol was released from all the formulations. It was seen from Fig 1 that released atenolol was 102±2.31% and 97.9±2.28 % for ATN1 and ATN2, respectively for 6 hrs. However, approximately 75 % of the drug was released from the other formulation. The cumulative amount of atenolol released from tablets increased with increasing amounts of PAA. This may be explained by the swelling behavior of the PAA. The

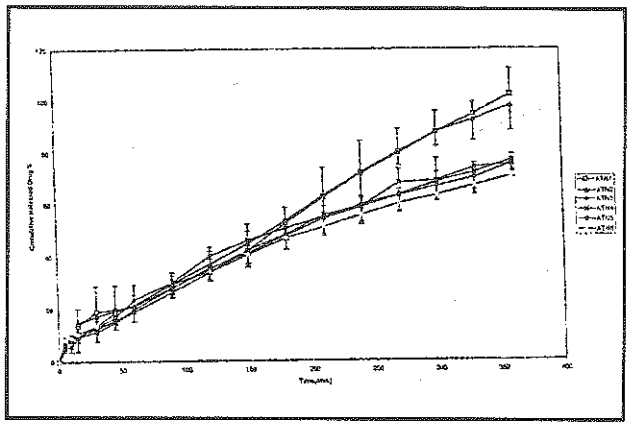

Figure 1. The *in vitro* release profiles of atenolol from buccoadhesive tablets containing different ratios of PAA ve HPMC in pH 6.8 phosphate buffer solution at 37°C.

higher amount of PAA led to fast swelling of the tablets. This result was in accordance with our previous study[7].

During the first 2 hrs atenolol was released at a slow rate followed by an increased release rate, in later stages for ATN1-ATN2 formulations at the end of the same period. This phenomen may be attributed to the formation of a strong matrix between PAA and HPMC. This matrix is a three dimensional network structure formed by a complex formation following the penetration of dissolution medium into the tablet. Although the pH value of the dissolution medium (phosphate buffer solution pH 6.8) was higher than the critical pH for complexation, the pH value in the polymer matrix could be low enough for the complexation owing to the acidity of PAA. As a result, it could be inferred that the drug was tightly held in the matrix initially and, with the continous penetration of the dissolution medium, the pH value in the matrix increased gradually. When it reached the critical pH value for decomplexation, the network structure disappeared and the drug was released rapidly.

To examine the release mechanism of atenolol from buccoadhesive tablets, the release data which covers 60 % of the release profiles were analyzed according to the following equation[10]

$$Mt / M^{\infty} = kt^{n}$$

where Mt / M^{∞} is the fraction of atenolol released at time t, n is a diffusional exponent related to the mechanism of the release and k is the apparent release rate constant. n value falls between 0.5 and 1.0, which indicate non- Fickian release [(n value lower than 0.5 for Fickian (Case I)] and n =1.0 for zero order release (Case II transport).

Table 2 shows n values for PAA/ HPMC buccoadhesive systems. The value of n was greater than 0.5 for buccoadhesive tablets containing PAA and HPMC. These systems (ATN1-ATN6) exhibit non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism as suggested by Ponchel et al[9].

Table 2. Kinetic constants (k), diffusional exponents (n) and determination coefficient (r^2) by linear regression of ln (Mt/M^{∞}) vs ln(t).

Code	n±SD	k±SD	r^2
ATN1	0.558±0.057	$2.63x10^{-2}$±0.11	0.931
ATN2	0.569±0.056	$2.55x10^{-2}$±0.15	0.928
ATN3	0.599±0.029	$2.13x10^{-2}$±0.13	0.975
ATN4	0.587±0.037	$2.10x10^{-2}$±0.16	0.962
ATN5	0.668±0.027	$1.43x10^{-2}$±0.12	0.982
ATN6	0.537±0.029	$2.72x10^{-2}$±0.13	0.970

The kinetic assessment of release data which was evaluated with a computer program is shown in Table 3. Upon checking the results according to the values of the determination coefficient (r^2) and the sum of the weighted squared deviations (SWSD), formulations showed almost Q√t kinetics (Table 3). The k values of ATN1 and ATN2 formulations were higher than those of ATN3-ATN6 formulations.

Table 3. The kinetic assessment of release data[a]

Kinetics	Parameters	ATN1	ATN2	ATN3	ATN4	ATN5	ATN6
zero[b]	k_0	8.10	7.80	5.84	6.34	6.19	5.55
Order	r^2	0.994	0.995	0.971	0.984	0.987	0.983
	SWSD	$0.142x10^{1}$	0.334	0.160	$0.687x10^{1}$	$0.857x10^{1}$	$0.817x10^{1}$
First[c]	k_1	1.42	0.486	0.215	0.228	0.230	0.817
Order	r^2	0.363	0.871	0.995	0.992	0.995	0.999
	SWSD	0.143	1.50	$0.279x10^{1}$	$0.212x10^{1}$	$0.755x10^{2}$	$0.779x10^{2}$
Hixson[d]	K	0.242	0.214	0.146	0.142	0.147	0.127
Crowell	r^2	0.830	0.950	0.993	0.994	0.999	0.998
	SWSD	0.568	0.198	$0.383x10^{1}$	$0.908x10^{2}$	$0.773x10^{2}$	$0.135x10^{2}$
	k	4.79	4.77	3.47	3.17	3.39	0.280
Q→√t[e]	r^2	0.949	0.960	0.990	0.977	0.987	0.999
	SWSD	0.545	0.431	$0.411x10^{1}$	0.136	$0.852x10^{1}$	$0.536x10^{1}$

[a] Summary of output obtained from the program DISSOL; [b]k_0 zero order release constant ($mg.h^{-1}$); [c]k_1 first order release rate constant (h^{-1}); [d]K is the dissolution rate calculated from the Hixson-Crowell plot ($mg.h^{-1}.cm^{-2}$); [e]k is the rate constant obtained from the slope of the linear regression of cumulative amount released per unit area versus square root of time ($mg.cm^{-2}.h^{-1/2}$); r^2 is the coefficient of determination; SWSD is the sum of weighted squared deviations.

Bioadhesion Characteristics of PAA/HPMC Tablets

Table 4 shows the detachment force of buccoadhesive tablets consisting of PAA and HPMC at various mixing ratio to the bovine buccal mucosa. PAA has better buccoadhesive characteristics than that of HPMC[11]. The results of this study also indicate that as the PAA content decreased the detachment force decreased. These results were in agreement with several reports given in the literature[9,12]. The interpenetration and entanglement of the bioadhesive polymer have been proposed as playing an important role in the bioadhesion.

Table 4. Detachment force between tablet and bovine buccal mucosa (n=5)

Code	Mean±SD (N)
ATN1	3.89 ± 0.45
ATN2	3.62 ± 0.60
ATN3	3.51 ± 0.95
ATN4	3.29 ± 0.70
ATN5	2.50 ± 0.28
ATN6	1.98 ± 0.99

In conclusion, a buccoadhesive tablet for the release of atenolol was developed using PAA/HPMC in various amounts. The results indicate that non-Fickian release behavior was obtained for PAA/HPMC buccoadhesive tablets. This result suggests that the release of atenolol is controlled by a combination of diffusion of matrix and swelling of the matrix followed by water penetration into the tablet. It was observed that the detachment force between buccoadhesive tablets and bovine buccal mucosa increased with increasing PAA content.

REFERENCES

1) Cassididy JP, Landzert NM, Quadros E, Controlled Buccal Delivery of Buprenorphine, *J.Control.Rel.*, 25, 21-29,1993.
2) Ishida M, Machida Y, Nambu N, Nagai T, New Mucosal Dosage Form of Insulin, *Chem.Pharm.Bull.*, 29, 810-816,1981.
3) Nagai T, Buccal / Gingival Drug Delivery Systems, *J.Contr.Rel.*, 6, 353-360, 1987.
4) Parodi B, Russo E, Caviglioli G, Cafaggi S, Bignardi G, Development and Characterization of Buccoadhesive Dosage Form of Oxycodone Hydrochloride *Drug.Dev.Ind.Pharm* 22, 445-450,1996
5) Rao RKV, Ben-Amor A, Buri P, Studies on Buccoadhesive Tablet Formulation of Codein Phosphate, *STP Pharma*, 5, 899-903, 1989.
6) Collins AE, Deasy PB, Bioadhesive Lozange for The Improved Delivery of Cetylpridinium Chloride, *J. Pharm. Sci.*, 79, 116-119, 1990.
7) Çelebi N, Kışlal O, Development and Evaluation of A Buccoadhesive Propranolol Tablet Formulation, *Pharmazie*, 50, 470-472, 1995.
8) Ağabeyoğlu TI, Un Programme Dans La Langue Basique de Microcomputer Pour la Determination des Données de Dissolution, *XVIII^eme Semaine Medicale Balkanique*, Istanbul, 30 Aout-4 Sept., Resumes, p.327,1984.
9) Ponchel G, Touchard F, Wouessidjewe D, Duchene D, Peppas NA, Bioadhesive Analysis of Controlled-Release Systems. III.Bioadhesive and Release Behaviour of Metronidazole-Containing Poly(acrylic acid)-hydroxypropylmethyl cellulose Systems, *Int.J.Pharm.*, 38, 65-70, 1987.
10) Peppas NA, Analysis of Fickian and Non-Fickian Drug Release from Polymers, *Pharm.Acta.Helv.*, 60, 110, 1985.
11) Smart JD, Kellaway ID, Worthington HEC, An In-Vitro Investigation of Mucosa-Adhesive Materials for Use in Controlled Drug Delivery, *J. Pharm. Pharmacol.*, 36, 295-299, 1984.
12) Smart JD, An In Vitro Assessment of Some Mucosal-Adhesive Dosage Forms, *Int.J.Pharm.*, 73, 69-74, 1991.