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Formulation and evaluation of buccoadhesive tablet of Atenolol

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ABSTRACT

The present study was aimed to formulate the buccoadhesive tablet of atenolol by adopting Box-Behnken factorial design and using chotosan, carbopol 937P and CMC Na. The formulations were evaluated for drug content, hardness, thickness, friability, weight variation, invitro dissolution study and ex-vivo bioadhesive strength and time. The in vitro dissolution study showed higher and controlled drug release. The ex-vivo bioadhesion studies of formulations on sheep buccal mucosa showed better bioadhesion with high bioadhesion time.

Keywords: Buccoadhesive tablet, Chitosan, Carbopol 937P, CMC-Na.

INTRODUCTION

The oral cavity is being increasingly used for the administration of drugs which are mainly designed for the contained drugs through the oral mucosa into systemic circulation. Buccal mucosa consist of stratified squamous epithelium was investigated as a site for drug delivery several decades ago and the interest in this area for the transmucosal drug administration is still growing. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site. Buccal bioadhesive drug devices designed to remain in contact with buccal mucosa and release the drug over a long period of time in controlled manner. Such a delivery of drug through buccal mucosa overcomes premature drug degradation within the GI tract as well as active drug loss due to first pass metabolism. In addition there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period.

Atenolol, a β-blocker, prescribed widely in diverse cardiovascular diseases. e.g. hypertension, angina pectoris, arrhythmias and myocardial infraction. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels resulting in

manifestation of side effects or reduction in drug concentration at receptor site. Atenolol have poor membrane permeability in the gastrointestinal tract due to its hydrophilic nature, as it is sparingly soluble in water and having low partition coefficient. Hence, large fraction of the drug is excreted in an unchanged form and leads to incomplete absorption. Atenolol is selected as model drug because of its short half-life (6-8hrs.), low molecular weight and low dose (25-50 mg), which makes it a suitable candidate for administration by buccal route.

Formulation of buccoadhesive tablets of atenolol

Buccoadhesive tablets of atenolol were prepared by adopting Box-Behnken factorial design. Atenolol, carbopol 937P, chitosan, carboxymethylcellulose sodium (CMC-Na) and lactose were passed through 60 mesh sieve. Magnesium stearate was finally added as lubricant. The powder blend was compressed into 400 mg tablets of hardness 6-7 kg/sq.cm by using 12 mm flat faced punches on a single punch tablet machine.

Table:1 Formulation composition of buccoadhesive tablet of atenolol

Composition	Box-Behnken factorial batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Carbopol 937P	75.0	100	100	100	75.0	75.0	125	100	100
Chitosan	80.0	100	100	80.0	100	120	80.0	100	120
CMC-Na	80.0	80.0	80.0	100	100	80.0	80.0	80.0	100
Lactose	113	68.0	68.0	68.0	73.0	73.0	63.0	68.0	28.0
Mag. stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total weight	400	400	400	400	400	400	400	400	400

Table: 2 Formulation composition of buccoadhesive tablet of atenolol

Composition	Box-Behnken factorial batches							
	F10	F11	F12	F13	F14	F15	F16	F17
Atenolol	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Carbopol 937P	75.0	100	125	100	125	100	100	125
Chitosan	100	80.0	100	100	120	100	120	100
CMC-Na	60.0	60.0	100	80.0	80.0	80.0	60.0	60.0
Lactose	113	108	23.0	68.0	23.0	68.0	68.0	63.0
Mag. stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total weight	400	400	400	400	400	400	400	400

Evaluation of buccoadhesive tablets of atenolol

Formulated tablets of atenolol were evaluated for drug content, hardness, friability, thickness and weight variation, in vitro drug release study and ex-vivo bioadhesive strength and time.

The *in vitro* drug release study was performed by employing the USP XXVIII paddle method at 37 ± 0.5^0C and at 50 rpm and phosphate buffer (pH 6.8) as dissolution media. The samples were removed at predetermined interval maintaining sink condition. The removed samples were filtered through 0.45µ filter and were analyzed by UV spectrophotometer at 276 nm.

A modified balance method was used for determination of ex-vivo biodhesive strength. Ex-vivo studies were performed using sheep buccal mucosa as a model membrane, which was obtained

from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing the underlying fat and adipose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The fresh sheep buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8 and held on the left side of the balance. The glass vial with rubber stopper was placed and tightly fitted in the center of glass beaker containing phosphate buffer (pH 6.8, 37 ± 0.5^0C) just touching the mucosal surface. The tablet was stuck to the lower side of the rubber stopper of the glass vial with cyanoacrylate instant adhesive. The left and right pans were balanced by adding a 5gm weight on the right hand pan. When the 5gm weight was removed from the right pan, the left pan along with tablet was lowered over the mucosa. The balance was kept in this position for 5 min. Water was added slowly at 100 drops/min to the right pan until the tablet detached from the mucosal surface. The weight (gram force) required to detach the tablet from the mucosal surface gave the measure of bioadhesive strength.

The ex-vivo bioadhesion time was examined after application of the buccoadhesive tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and an identical side of each tablet was wetted with phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8.After 2 min a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the biodhesion time.

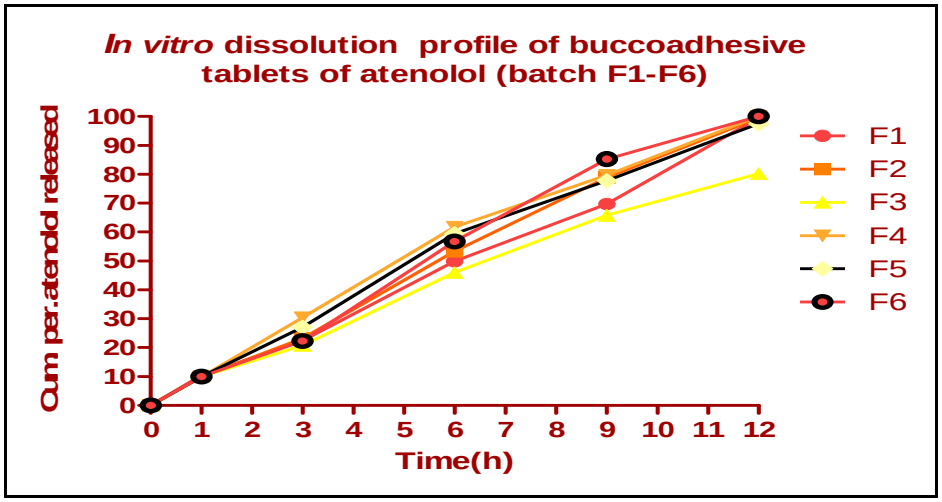
RESULTS AND DISCUSSION

The formulated buccoadhesive tablets of atenolol showed drug content between 95.19 and 100.03 % (Average drug content is 98.92 %), hardness between 6.9 and 7.4 kg/cm^2 (Average hardness 7.2 kg/cm^2), friability between 0.20 and 0.42 % (Average friability 0.36 %), thickness between 4.8 and 5.3 mm (Average thickness 5.1 mm) and weight variation. Thus all the parameters of factorial design batches of buccoadhesive tablets of atenolol were found to be practically within control.

In vitro drug release studies indicated that the drug release was higher and controlled when the polymer content (Carbopol 937P and chitosan) was 100 mg and per tablet. The release of atenolol was controlled by the diffusion from the matrix formed by the polymers. This composition correspond to the lactose content of 68 mg per tablet, which provides channels for water to penetrate so that to leach out soluble form of atenolol. The higher the uptake of water by the polymer, the greater the amount of drug diffused from the polymer matrix. Thus, this high amount of water uptake by carboxymethylcellulose sodium may lead to considerable swelling of the polymer matrix, allowing the drug to diffuse at a faster rate. The progressive decrease in the amount of drug released from batch F1 to F9 may be attributed to the increase in proportion of carboxymethylcellulose sodium, which is a water-swellable polymer; at higher concentrations, a decrease in the release rate was obtained, most likely because of high viscosity. All tablets remained intact during the 12-hour period.

The bioadhesive strength was determined in terms of weight required to detach the tablet form the sheep buccal mucosal membrane. The hydrogels (Carbopol 937P and Chitosan) are known to swell readily on contact with the hydrated mucus membrane. This glass-rubbery transition provides hydrogels plasticization, resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Increasing the polymer (Carbopol 937P and Chitosan) amount may provide more adhesive sites and polymer chains for interpenetration with mucin resulting in augmentation of bioadhesive strength (up to 26.75 gram force). The formulations showed bioadhesion time on sheep buccal mucosa from 11.20 h to 16 h. This indicate that the formulations have ability to remain localize on specific sites on mucosal membrane.

Fig.1: Dissolution profiles of buccoadhesive tablets of atenolol



CONCLUSION

Oral controlled release buccoadhesive tablets of atenolol were formulated as an approach to avoid fluctuations in plasma drug concentration and thereby to improve its bioavailability. The ex-*vivo* bioadhesion studies of formulations on sheep buccal mucosa showed better bioadhesion with high bioadhesion time.

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