Formulation and Evaluation of Bioerodible Bilayered Buccal Tablets Containing Atenolol

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ABSTRACT

The oral mucosa has confirmed principally valuable and provides more advantages than other dosage forms such as: bypass of the GIT, improving the bioavailability of drug that has high first-pass metabolism, controlled drug delivery, ease of application and immediate withdrawal of delivery by detaching the system. The aim of the study was to formulate and evaluate buccal atenolol bilayered tablet for systemic delivery. The buccal tablets were designed by direct compression using ethyl cellulose and mucoadhesive polymers namely, Sodium alginate, Hydroxyl propyl cellulose and Methyl cellulose. All the formulations were studied to physicochemical evaluation such as hardness, thickness, friability, surface pH, swelling index and weight variation. The mean surface pH and *ex-vivo* residence time of the tablets was found to 6-7.1 and 6.7 ± 0.99 to 7.00 ± 2.1, which is favorable for oral mucosa. *In-vitro* drug release studies demonstrated that atenolol release from the selected tablets followed diffusion kinetics with a good drug release and it is confirmed that the tablet has the ability to deliver the drug. The present study indicates great potential of erodible mucoadhesive bilayered atenolol buccal tablet for systemic delivery of circumventing the hepatic first pass metabolism.

KEY WORDS: Buccal delivery, atenolol, buccal tablet, *in vitro* drug release, swelling index.

1. INTRODUCTION

The buccal mucosa is well vascularized, more in blood supply and large contact surface area. Following buccal delivery, the agent attains direct release into the systemic absorption by bypassing the liver (Shojaei, 1998). Better patient compliance can be achieved in buccal route than the vaginal or rectal route. On top of that, buccal route administration could avoid first pass metabolism to result in drastic improvement of bioavailability of drug and it is applicable for both local and systemic delivery system as retentive dosage form, without compensating any patient compliance. In this research, a selective β_1 receptor antagonist atenolol selected as model drug (Shojaei, 1998; Sudhakar, 2006).

2. MATERIALS AND METHODS

Atenolol was gifted from Dr. Reddy's Laboratories Ltd., Hyderabad, Sodium alginate, hydroxyl propyl cellulose, methyl cellulose and ethyl cellulose were gifted from Shasun Pharmaceuticals Ltd., Puducherry. Other excipients such as mannitol, talc and magnesium stearate used and all other reagents used were of analytical grade.

Methods:

Construction of calibration curve of Atenolol: To prepare the stock solution, 10 mg of drug was weighed accurately and dissolved in phosphate buffer (pH 6.8). It was then transferred and topped up with phosphate buffer in 100 mL volumetric flask. Atenolol of concentrations 1 μg/mL, 2 μg/mL, 3 μg/mL, 5 μg/mL, 7 μg/mL and 10 μg/mL were prepared from stock solution and used to construction the calibration curve. The apparatus used was Shimadzu UV mini 1240 spectrophotometer. The λmax was determined at 241nm. The UV spectrum is shown in Fig.1.
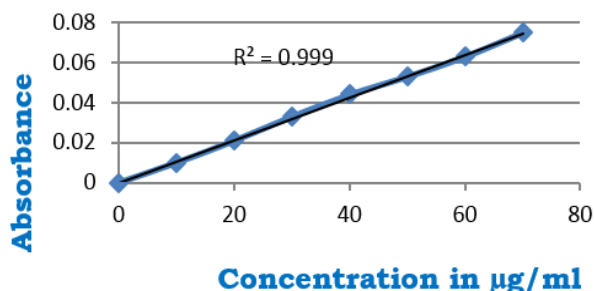

Fig.1. Calibration curve of Atenolol

Formulation of Atenolol bilayered buccal tablets: The tablets were formulated in two different steps by direct compression. Firstly, all the excipients including drug and mucoadhesive polymers exactly weighed and mixed

uniformly about 20 minutes in a glass mortar (Kulkarni, 1999). Then magnesium stearate (lubricant) and talc (glidant) were incorporated and mixed for 3 minutes. By using nine station rotary machine, 9 mm, flat punch, the 100 mg of powder blend was slightly compressed at single to form a one layer tablet. Secondly, final compression was made by adding ethyl cellulose 50 mg to get a final bilayer tablets weighing 150 mg (Wong, 1999). The composition of buccal tablet was given in table.1.

Table.1. Formula of Atenolol buccal tablets

Component (mg)	T1	T2	T3	T4	T5	T6
Primary layer (core layer containing drug)						
Atenolol	50	50	50	50	50	50
Sodium alginate	30	15	7.5	-	-	-
Hydroxyl propyl Cellulose	-	-	-	30	15	7.5
Methyl cellulose	-	-	-	-	-	-
Mannitol	26	41	49	26	41	49
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	1.5	2	2	1.5
Secondary layer (Backing layer)						
Ethyl cellulose	40	40	40	40	40	40
Total weight	150	150	150	150	150	150

Physico-Chemical Evaluation of Atenolol Bilayered Buccal Tablets: The following physico chemical evaluations (Eouani, 2001; Isiklan, 2006) were performed.

Thickness: 10 tablets were chosen from all the batch and the thickness was calculated by using vernier calipers (Mitutoyo Corporation, Japan.) and the mean values were noted in table.2.

Weight variation: 10 tablets were chosen from all the batch individually weighed and the mean values were noted in table.2. It was measured by employing the formula.

$$\% \text{ Weight variation} = \frac{\text{Average weight - Individual weight}}{\text{Average weight}} X 100$$

Hardness: The tablets hardness was measured using Monsanto hardness tester (Singhala scientific industries, Ambala) to identify its ability to withstand the pressure. The 3 randomly chosen tablets from all batch were studied and the reports were noted in table.2.

Friability: The tablets friability was measured by the Roche friabilator (Campbell Electronics, Mumbai). In the apparatus twenty pre-weighed tablets were kept and operated for 25 rpm/4 minutes and the tablets were reweighed. It was studied by employing the formula and the reports were noted in table.2.

$$\% \text{ Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X 100$$

Uniformity of Drug content: From each batch 20 randomly chosen tablets were finely powdered and powder equivalent to 10mg of atenolol was weighed exactly and dissolved in 50 ml of methanol and contents were shaken thoroughly. The volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and then 0.1 ml was transferred to 10ml flask and the volume was made with phosphate buffer (pH 6.8). The absorbances were analysed on a UV/Vis spectrophotometer (Lab India) at 274 nm. Drug content was measured from a calibration curve and the reports were noted in table.2.

Surface pH: The test is performed by tablets were kept to swell in 1 ml of distilled water (pH 6.8) in beakers, and the pH was determined after 1 h by keeping the electrode contacts with the swollen tablets allowing it to equilibrate for 1 minute. The mean pH of five measurements was displayed in table.2.

Swelling Index (%S): This test is done by hot agar solution 5% w/v was transferred to petri plates and kept to solidify. Then from all batches 6 tablets were weighed and kept over the surface of the agar in the incubator at 37ºC for three hrs and the swelled tablet was reweighed. The % of moisture absorbed was measured by employing the formula:

% S = [(Final weight - Initial weight)/Initial weight] × 100.

The data's were displayed in table.2.

Ex-vivo **residence time:** The test was carried out (n = 3) after attachment of tablets on very freshly dissected porcine buccal mucosa. The beaker inner side, mucosa was placed about 2.5 cm from the bottom, using water proof adhesive tape. Mucoadhesive layer containing drug of individual tablet was moistened with one drop of phosphate buffer (pH 6.8) and attached to the mucosa by employing a little force. 200 ml of phosphate buffer (p^{H}6.8) was taken in a beaker and was kept at 37ºC ± 1ºC. After 2 minutes, a 50-rpm stirring rate was employed to create the buccal cavity atmosphere and adhesiveness of the tablet was observed for 8 hours (Kohda, 1997). The time needed for the tablet to detach from mucosa was noted as the mucoadhesion time and the results were reported in table.2 and fig.2.
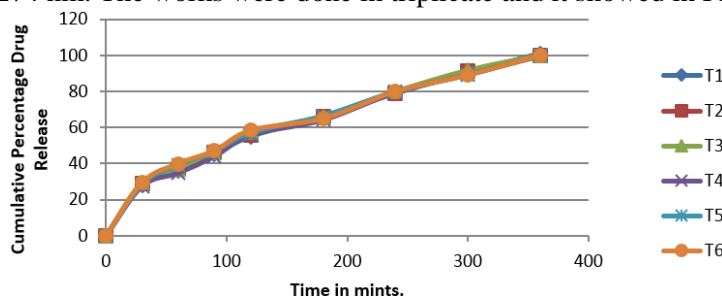
Table.2. Physiochemical parameters of atenolol buccal tablets

F. Code	Uniformity of Weight ± SD	Surface P^H ± SD	Assay ± SD	Thickness ± SD	Hardness ± SD	Friability ± SD	Swelling Index ± SD	*Ex-vivo* residence time in hrs
T1	148.6±1.12	7.02±0.10	99.09±1.3	2.04±0.02	4.2±0.02	0.40±0.02	41.28±1.21	7.00±0.12
T2	149.2±1.03	7.01±1.20	100.1±1.12	2.13±0.12	4.1±0.03	0.41±0.09	40.11±2.31	6.87±1.33
T3	148.7±1.23	6.92±0.61	101.02±1.1	2.04±0.11	3.9±0.35	0.40±0.01	39.01±1.31	6.72±0.33
T4	148.7±1.01	7.1± 1.11	99.3±1.06	2.12±0.04	4.3±0.01	0.40±0.03	41.30±1.21	7.0±2.1
T5	150.2±1.31	6.95±1.30	99.9±1.00	2.21±0.5	4.1±0.41	0.41±0.12	40.10±1.11	6.8±1.01
T6	149.1±1.60	6.8±0.11	100.1±1.21	2.17±0.06	4.0±0.82	0.42±0.09	40.01±1.11	6.7±0.99

Results are expressed as mean ±standard deviation (mean±SD) n=3
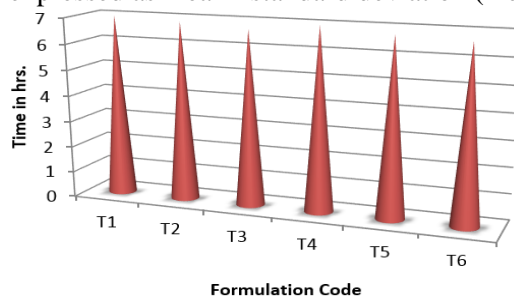
Fig.2. *Ex-vivo* residence time of atenolol buccal tablets

***In Vitro* Drug Release Dissolution Studies:** It was performed by USP 28, type II dissolution test apparatus. The phosphate buffer (P^H 6.8), 500 ml of was employed as the dissolution medium, at 37.0 ± 0.5ºC, and 50 rpm was used. Backing side of the tablet was fasten to the paddle using adhesive tape. Samples (5 ml) were taken at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 hrs periods and reinstated with same amount of fresh buffer. The solutions were filtered through 0.45μm Whatman filter paper and measured (Artusi, 2003). The drug concentrations were analysed spectrophotometrically at 274 nm. The works were done in triplicate and it showed in Fig.3.

Fig.3. *In vitro* drug release of atenolol mucoadhesive buccal tablets

3. RESULTS AND DISCUSSION

All the physiochemical parameters results were displayed in table.2. All the tablets prepared had complied with the weight variation acceptance criteria. All tablets thickness are very uniform at approximately 2.10±0.02 mm. Hardness obtained ranged from 3.9-4.3 kg/cm^2 and content uniformity ranged from 99.09-101.02. The percentage weight loss in friability test ranged from 0.39– 0.42%. All the test results had shown that the tablets had fulfilled the standard official requirements.

The surface pH obtained ranged from 6.80 – 7.10, which is within the buccal environment pH range of 6.2 – 7.4, indicating that the tablets formulated could not induce any buccal irritation as all formulation have very similar pH nature with the buccal environment.

The swelling index ranged from 39.01 – 41.30, indicating that the hydrated gel forming polymers are able to give a good matrix upon exposure to wet surface.

***In Vitro* Drug Release Dissolution Studies:** The backing ethyl cellulose layer of tablet remained intact with the swollen polymer matrix until the release of minimal 85% drug concentration. For T1 batch, the release had achieved 90.2% by the 5th hour and the average T50 was 2.5 hours. The T2 and T3 batches only achieved 91.2% and 91.6% drug release by the 5th hour. For all batches (T1-T6), the release had achieved more than 85% by the end of 6th hour. The dissolution profiles of all formulations are displayed in fig.2. All the formulations were showing good and satisfactory results. The release kinetics of tablets were best fitting in zero order release with non-fickian diffusion mechanism.

***Ex-vivo* residence time:** *Ex-vivo* residence time were shows the values between 6.7±0.99 to 7.00±2.1. Among the other mucoadhesive systems, buccal tablets are best due to wider residence stay and less discomfort.

4. CONCLUSION

The goal of the current investigation was to formulate and evaluate novel buccal delivery system of beta blockers of atenolol. All the formulated buccal tablets passed the weight variation test. The friability test results were less than 1%. The surface pH results were all within the buccal environment pH range indicating that the formulation would not result in any pH related irritation and tablets gives better drug release. Further studies of different polymers at various concentrations can be used to optimize and optimize the sustained release buccal tablets. Also, *in vivo* experiments using animals or human can be carried out for further analysis.

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