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Formulation and Evaluation of Buccal Films Loaded with Antihypertensive Drug by Solvent Cast Technique

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Abstract: The current study aimed at designing, developing and characterising buccal films of Atenolol for the treatment of Hypertension. The films were prepared by using the solvent casting technique by utilizing HPMC K15M polymer. Various parameters were evaluated, including thickness, uniformity of weight, content uniformity, folding endurance, surface pH study, tensile strength, *in vitro* drug release, *ex vivo* drug permeation, Isotonicity and short-term stability. FTIR spectra analysis revealed no drug-excipient interactions. Among the formulations, FM-4 showed the most promising results in terms of tensile strength, *in vitro* drug release and *ex vivo* permeation studies. The study concludes that buccal films of Atenolol Complexed with β-cyclodextrin as a permeation enhancer can potentially enhance drug bioavailability and permeation.

Keywords: Atenolol, Hypertension, HPMC K15M, Atenolol, β-cyclodextrin complex, Buccal films

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Introduction

Extensive research work is done focusing on placing a drug in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. Buccal delivery of drugs provides an attractive alternate compared to other conventional methods of systemic drug administration, due to its relative permeability. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration.

Atenolol is a β_1-receptor selective antagonist and is mainly used in treating hypertension, angina, heart failure, and myocardial infarction;

chemically, it is 4-(2-hydroxyl-3-isopropyl amino-propoxy) phenylacetamide. The physic-chemical properties of atenolol, i.e., slight water solubility, low molecular weight (266.336), and its suitable elimination half-life ($t_{1/2}$ = 6–7 h) make it a suitable candidate for administration by buccal route.

The aim of the present investigation was to formulate and evaluate buccal patches comprising drug (atenolol)-containing mucoadhesive polymeric layer (HPMC K15M, PEG 400). The designed buccal films were evaluated for physico-mechanical properties, mucoadhesive characteristics, *in vitro* drug release, and *ex vivo* drug permeation. Such buccal patches of atenolol may provide sustained buccal delivery of atenolol for a long period and can be a good way to bypass the extensive hepatic first-pass metabolism in the management of hypertension.

Materials and Methods

Materials:

Atenolol was obtained as a gift sample from Zydus Life Sciences, Pvt. Ltd., Kundaim-Goa, HPMC, Crosspovidone and sodium starch glycolate from Kemphasol, Mumbai and Beta cyclodextrins used were procured from Hi-Media Laboratories Pvt Ltd, Nashik. All chemicals used were of analytical grade.

Preformulation Studies:

The first stage in the rational design of dosage forms for a drugs substance is preformulation testing of active and excipients. Preformulation testing's objective is to generate data that assists in the formulator develop stable, bioavailable dosage forms that can be mass manufactured.

Preformulation studies like description, melting point, solubility, IR spectra's, UV spectroscopic studies were performed on the procured drug samples and excipients to confirm its compatibilities.

Characterisation of Drug:

Solubility: 10 mg of drug was weighed and tested for solubility in water, organic solvents like ethanol, DMSO, and Dimethyl formamide.

Determination of Melting point: The Melting point of Atenolol was determined by open capillary method by using Thiele's tube.

IR Spectroscopy: FT-IR spectrum was obtained of drug by preparing pellets of Drug: Potassium bromide (1:20) and scanned in IR range of 400 – 4000 cm^{-1}. IR spectrum was then interpreted for characteristic functional group of drug and for checking compatibility of drug with other excipients.

UV-Spectroscopy:

Standard calibration curve of Atenolol in Phosphate buffer (pH 6.8):

Atenolol (100 mg) was accurately weighed into a 100 ml volumetric flask and volume made up with phosphate buffer to get a concentration of 1000 µg/ml. From this 10 ml was withdrawn and diluted to 100 ml in Phosphate buffer pH 6.8 to get a concentration of 100 µg/ml. Series of dilutions ranging from 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml and 3.5 ml were pipetted out into 10 ml volumetric flask. The volume was made up with Phosphate buffer pH 6.8 to get a final concentration of 5 µg/ml – 35 µg/ml. The aliquots were scanned using UV-visible spectrophotometer. The λ_{max} of Atenolol was found to be 223.4 nm. The data of calibration curve is given in Table 1 and Figure 1.

FORMULATION OF BUCCAL FILMS

Pre-soaking of the Polymer:

Required weighed quantity of HPMC K15M was added to beaker containing 10 ml of distilled water and soaked overnight.

Preparation of Drug- β-Cyclodextrin complex:

Complex of atenolol and β-cyclodextrinwas was prepared on the basis of the drug's molecular weight by the solvent cast method. The resultant dry powder of Drug: β-Cyclodextrin complex was weighed.

Preparation of Aqueous solution:

Table 1: Calibration Curve Data of Atenolol in phosphate buffer pH 6.8

S. No.	Atenolol (223.4 nm)	
	Concentration (µg/ml)	Absorbance
1	5	0.194 ± 0.001528
2	10	0.323 ± 0.002517
3	15	0.437 ± 0.006083
4	20	0.576 ± 0.009504
5	25	0.728 ± 0.006506
6	30	0.855 ± 0.009539
7	35	1.029 ± 0.004583

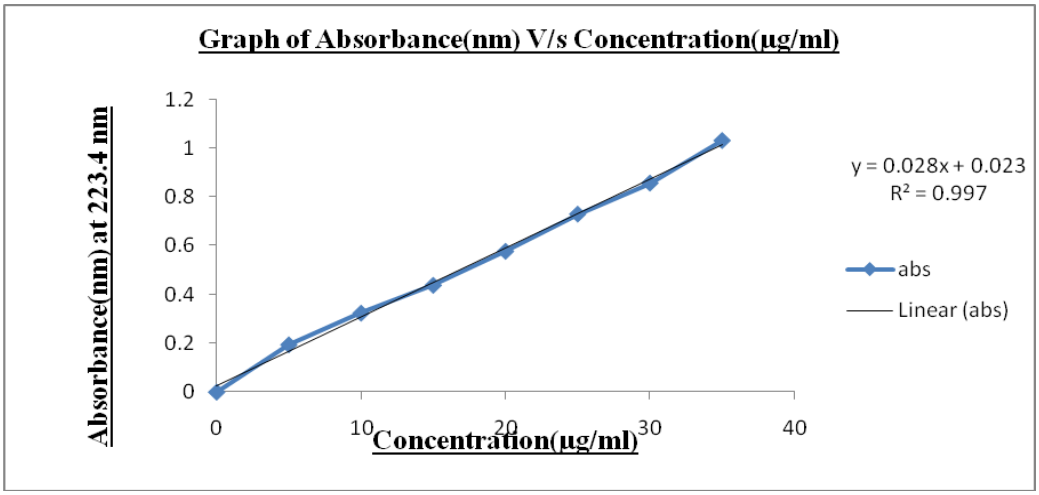


Fig. 1: Standard Calibration curve of Atenolol in 6.8 pH phosphate buffer.

In 5 ml of distilled water added required quantity of sucrose EP, sodium starch glycolate, crossprovidone, and citric acid and stirred to ensure complete dissolution.

Preparation Polymer dispersion:

Required weighed quantity of Drug: β-Cyclodextrin complex was added to the polymer solution along with aqueous solution of excipients and kept for stirring on Magnetic stirrer at 500 RPM for 3 h for ensuring uniform dispersion of the polymer, complex and excipients.

On mixing the polymer dispersion was poured in petri dish of specified diameter. Allowed to dry at 40°C for 4 h. On drying the films were then cut into 2 X 2 cm^2 size and wrapped in aluminium foil and stored in desiccators. Similarly blank films were also prepared without addition of drug. The composition of various films prepared is shown in Table 2 and Figure 2.

Results and Discussion

Thickness: The thickness of films was measured by screw gauge micrometre with least count 0.01 mm. The sizes uniformity was measured at six different sites and average of six readings was taken with standard deviation. Thickness is illustrated in Table 3.

Uniformity of weight: The films of area 2 x 2 cm were cut from different parts of the film & weight was recorded using digital balance. Uniformity of weight is depicted in Table 3.

Content uniformity: The film of area 2 x 2 cm was dissolved in 10 ml of Phosphate buffer pH 6.8 with help of ultrasonic bath sonicator. Sufficient dilutions were made and absorbance was measured at 223.4 nm using UV-visible spectrophotometer and drug content was calculated. Content uniformity is illustrated in Table 3.

Table 2: Composition of films Containing Atenolol: β-cyclodextrin complex

Formulation				
Ingredients	FM-1	FM-2	FM-3	FM-4
Drug	25 mg	25 mg	25 mg	25 mg
β-Cyclodextrin (molecular Ratio of the drug)	-	1: 0.25	1: 0.5	1:1
HPMC K15M (mg)	150	150	150	150
Glycerin (mg)	1.5	1.5	1.5	1.5
PEG 400 (mg)	1.5	1.5	1.5	1.5
Tween 20 (ml)	1.25	1.25	1.25	1.25
Sucrose EP (mg)	20	20	20	20
Sodium starch glycolate (mg)	6	6	6	6
Crossprovidone (mg)	4	4	4	4
Citric acid (mg)	1	1	1	1

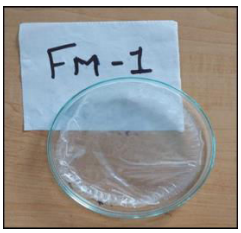
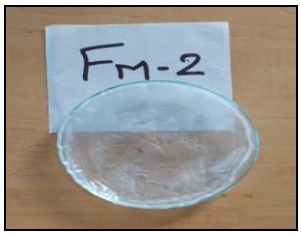
Buccal film containing Atenolol	Buccal film containing Atenolol : β-cyclodextrin complex (1:0.25)	Buccal film containing Atenolol : β-cyclodextrin complex (1:0.5)	Buccal film containing Atenolol : β-cyclodextrin complex (1:1)
			

Fig. 2: Buccal films loaded with drug and complexing agent.

Table 3: Evaluation parameters of Atenolol: β-Cyclodextrin complex loaded film (n =3)

Formulation Batch	FM -1	FM – 2	FM – 3	FM – 4
Surface Texture	Smooth	Smooth	Smooth	Smooth
Tensile Strength (g/cm^2)	128 ± 0.04	112 ± 0.08	95 ± 0.05	83 ± 0.02
Surface pH	6.552±0.125	6.632±0.113	6.654±0.109	6.789±0.10
Thickness (mm)	0.48±0.0135	0.50±0.0123	0.49±0.0118	0.52±0.0115
Content uniformity %	67.57±0.575	74.98±0.831	87.57±0.268	97.3±0.787

Table 4: % Cumulative Drug release

Time (min)	Cumulative Drug release in % Formulation (n=3) Mean ± SD			
	FM-1	FM-2	FM-3	FM-4
30	42.701 ± 0.720	17.247 ± 0.662	30.302 ± 0.773	23.614 ± 0.552
60	47.578 ± 0.526	39.935 ± 0.367	58.288 ± 0.294	42.535 ± 0.556
90	55.204 ± 0.088	50.741 ± 0.569	73.77 ± 0.872	49.654 ± 0.437
120	58.658 ± 0.540	62.447 ± 0.519	80.315 ± 0.460	58.671 ± 0.825
150	57.849 ± 0.512	68.972 ± 0.323	83.938 ± 0.347	68.492 ± 0.531
180	58.828 ± 0.951	74.459 ± 0.474	90.636 ± 0.733	77.614 ± 0.707
210	61.302 ± 0.546	75.642 ± 0.565	85.527 ± 0.864	88.335 ± 0.532
240	63.783 ± 0.458	77.03 ± 0.545	88.175 ± 0.331	96.018 ± 0.297

Folding Endurance: The folding endurance was measured manually by repeatedly folding the film , same place until it breaks or folded up to 450 times. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance (Table 3).

Surface pH: The buccal patch was allowed to swell by keeping it in contact with 1ml of distilled water for 1 hr at room temperature. The pH was measured by bringing the electrode in contact with surface of the patch and allowing it to equilibrate for 1 min. The Surface pH is given in Table 3.

In vitro release studies: A patch of 2 x 2 cm^2 size was placed on an egg shell membrane (barrier) and it was firmly secured using adhesive and rubber band which acts as a donor compartment. This study was carried out in a 50 ml beaker which acts as a receptor compartment. The receptor compartment was filled with 20 ml of phosphate buffer pH 6.8 and temperature was maintained at 37±0.5°C. The whole assembly was kept on a magnetic stirrer with optimal speed 100 rpm. 1 ml sample were withdrawn periodically from receptor compartment using a graduated pipette and the same amount was replaced every time with fresh phosphate buffer pH 6.8 so as to maintain the sink condition. The release studies were conducted for three times and average was determined. The aliquots were analysed spectrophotometrically as shown in Table 4 and Figure 3.

Ex vivo permeation studies:

The *ex vivo* drug permeation studies of optimised buccal film was performed by using inverted glass cylinder apparatus. The buccal mucosa was collected from the local slaughterhouse and immediately transferred to the laboratory in cold normal saline solution with continuous aeration. The buccal epithelium was isolated from the underlying tissue. Defatting was done using n-hexane and distilled water. The buccal epithelium was used within 2 h upon removal. The diffusion apparatus was used to study permeation studies, consisting of two compartments. After stabilization of buccal epithelium, donor compartment filled with 20 ml of Phosphate buffer solution pH 6.8. Periodically 1 ml samples were withdrawn at a predetermined time intervals and

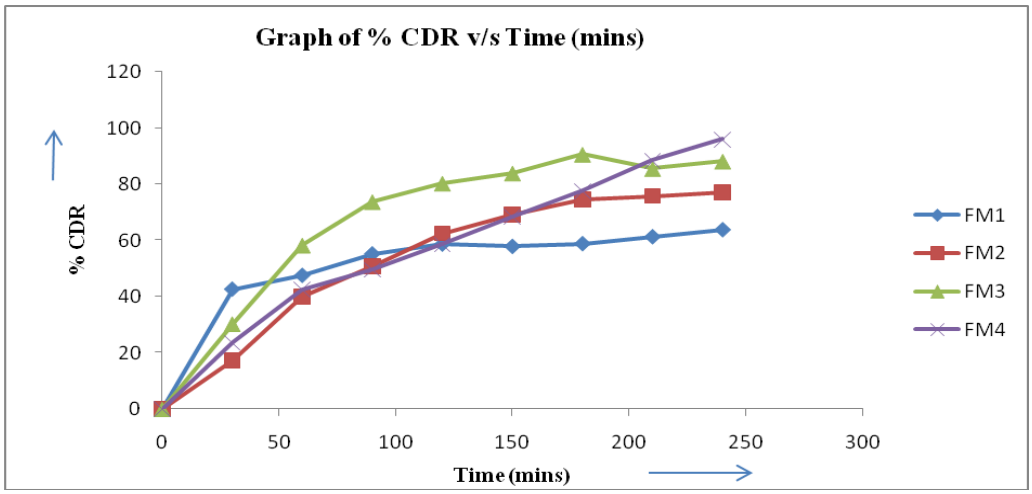
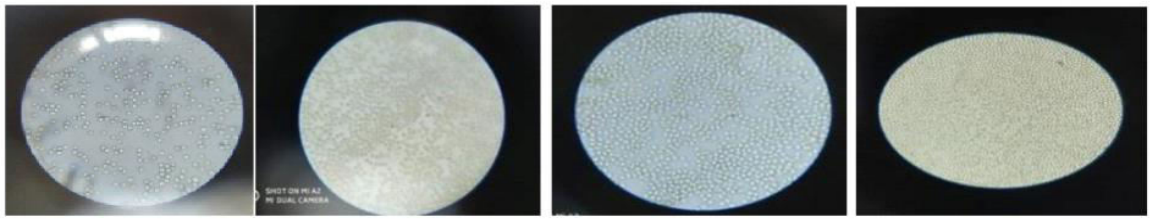


Fig. 3: Graph of% CDR v/s Time.



(a) (b) (c) (d)

Fig. 4: (a) Isotonic standard, (b) Isotonic film, (c) Hypertonic standard and (d) Hypotonic standard.

Table 5: *Ex vivo* drug permeation studies (n=3), Mean ± SD

Time (min)	30	60	90	120	150	180	210	240
Drug Release in %	25.357± 0.553	43.256± 0.887	51.011± 0.856	58.432± 0.896	66.283± 0.757	75.424± 0.597	86.105± 0.615	95.718± 0.493

same volume of fresh medium was replaced. The samples were analysed spectrophotometrically and result is depicted in Table 5.

Evaluation of Isotonicity:

The isotonicity of the film is an important criteria as tissue damages occur if the tonicity of the film is not maintained. Three different concentrations of sodium chloride solutions, including hypertonic (HT - 3% w/v), hypotonic (HP - 0.2% w/v), and isotonic (IS - 0.9% w/v), were prepared. The terms HT (hypertonic), HP (hypotonic), IS (isotonic), and Test were written on four clean slides. To avoid coagulation, a drop of blood containing heparin (1% w/v) was collected and then applied to each slide. All four slides were covered with cover slips and checked under a microscope at a magnification of 45x after the optimised film drop was placed on the test slide. RBC morphology was examined and depicted in Figure 4.

Buccal films of Atenolol were successfully prepared using HPMC K15M as a film former and drug reservoir, with PEG 400 and Glycerin as plasticizers through the solvent casting method. Solubility was considerably enhanced by employing β-Cyclodextrin as a complexing agent in different ratios (1:0.25, 1:0.5, and 1:1) in

conjunction with the drug's molecular weight. The IR spectroscopy study indicated that there were no interactions between the drug and excipients used in the formulation. The formulated buccal films exhibited satisfactory characteristics, including physical appearance, surface texture, weight uniformity, thickness uniformity, % drug release, and *ex vivo* drug permeation and isotonicity testing. The tensile strength and folding endurance of these films were sufficient, and it was observed that both overall tensile strength and folding endurance of all formulations increased with higher polymer concentration. Among the formulations, FM-4 emerged as a promising buccal drug delivery system, displaying considerable tensile strength. In the *in vitro* release study, almost 50% of the drug was released within one and a half hours, and over 95% of the drug was released at the end of 4 h. *Ex vivo* release studies of formulation FM-4 demonstrated that 95.718% of the drug was released at the end of 4 h. Isotoncity testing for the film was conducted at different concentrations of solution, and no significant changes were observed.

Based on the findings of this investigation, it can be concluded that buccal films of Atenolol can be formulated to increase drug bioavailability and enhance permeation using β-cyclodextrin as a permeation enhancer.

Conclusion

The primary objective of the research was to develop buccal films of Atenolol with HPMC K 15M, as a film former and drug reservoir, with PEG 400 and Glycerin as plasticizers through the solvent casting method for the management of hypertension. Solubility of active was enhanced using beta-Cyclodextrin as a complexing agent in different ratios such as (1:0.25, 1:0.5, and 1:1) in conjunction with the drug's molecular weight so the drug could easily disperse in the buccal film. The ultimate goal of this study was to easily incorporate the drug in elderly patients over conventional tablet form.

Preformulation studies on active drug was conducted to finalize the master formula and formulate as the buccal films. The films were prepared by solvent cast method and evaluated for different evaluation tests which included drug content, diffusion studies and other physics chemical tests. The formulated films are a promising drug delivery system especially for elderly people having better patient compliance.

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