IJMPR 2020, 4(1), 84-89

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

# STUDY OF PHYSICO MECHANICAL PROPERTIES OF BUCCAL PATCHES ALONG WITH THE PERMEATION OF LOADED ANTIHYPERTENSIVE DRUG

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**Received on: 06/01/2020**
**Revised on: 27/01/2020**
**Accepted on: 17//02/2020**

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## ABSTRACT

The buccal patches of Atenolol were designed in such a way that the mucoadhesive layers was incorporated along with the circumference of the circular patch. The major ingredients selected for the matrix layer were the drug and control release polymer (either HPMC K15M or HPMC K4M) while the Mucoadhesive layer was predominantly comprised of gum karaya. The designed patches were subjected to different evaluations like thickness uniformity, average weight, folding endurance, mucoadhesion strength, swelling behavior. The physico mechanical properties of the patches found to be satisfactory and they were subjected to permeation studies. In vitro permeation study was conducted for 8hrs in phosphate buffer pH 6.8 using dialysis membrane. The cumulative drug permeated from formulation was found to be 32 - 49 % and the permeation profiles for each batch was almost linear. The permeability coefficient was found in a range of 0.041 cm/h. to 0.053 cm/hr and flux was found in a range of 1.43- 1.85 mg $cm^{-2}$ $hr^{-1}$.

**KEY WORDS:** Buccal patch, mucoadhesion, Swelling, Permeation.

## INTRODUCTION

Buccal drug delivery system is an attractive drug delivery system as it has got some important merits over conventional dosage form. Drugs having high first pass effect, low aqueous solubility, low molecular weight, less biological half-life, instability to gastric pH can be used to deliver easily by this route.[1]

Various buccal formulations have already been developed like tablets, films, patches, gels, ointments, strips, disks. However, the patches have greater flexibility and they provide comfort to the patient. They can be easily administered and removed from the application site. So patient compliance is more than other dosage forms. Besides that, buccal region is highly vascular. So it has great accessibility. Drug can easily go to the systemic circulation by the jugular vein leading to high bioavailability.[2]

Rapid optimization in the field of molecular biology and gene technology resulted in generation of many macromolecular drugs including peptides, proteins and nucleic acids in great number possessing superior pharmacological effectiveness with site specificity and decrease the unwanted and toxic effects.[3]

The main obstruction for the oral delivery of these drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Hence those drugs are best suited via buccal route as oral mucous membrane being vascular and highly permeable and accessible, they allow the systemic uptake of drugs painlessly and at a steady state.[4]

HPMC and Gum Karaya are release retardant mucoadhesive polymer which have high swelling property. Hydroxy propyl methyl cellulose is a semi synthetic, inert, viscoelastic, hydrophilic polymer. It has the ability to form extensive hydrogen bonding with mucin which is present in the mucosal layer.

Natural polymers have advantages over synthetic or semi synthetic polymers. It is because these are nontoxic, cheap and easily available. Natural gums are natural polymers which are mainly plant exudates. Natural gums contain mostly carbohydrates and small amount of proteins and minerals. As these gums have high safety margin and easy availability they can use as thickeners in food industry and in cosmetic preparations. Gum karaya is gummy exudate which is obtained from the tree *Sterculia urens*. It belongs to the family Sterculiaceae. Swelling behavior of Gum karaya depends on the presence of acetyl group and deacetylation by alkali treatment makes the gum water soluble. Gum karaya can swell 60% in alcohol and almost 100% in water. Digestion and absorption of Gum karaya does not occur in the body. Apart from the medicinal industry Gum karaya is used in the food and cosmetic industry. Due to the high uronic acid content, Gum karaya resists hydrolysis in 10% hydrochloric acid solution at room temperature for at least 8 hours.

Here Atenolol has been selected to be included in buccal Patches. Atenolol is a BCS class III drug with pH dependent solubility. It has a moderate permeability of 50-84%. **Atenolol** is a beta blocker medication primarily used to treat high blood pressure and heart-associated chest pain. Other uses include the prevention of migraines and treatment of certain irregular heartbeats. It is taken by mouth or by injection into a vein. It can also be used with other blood pressure medications. Common side effects include feeling tired, heart failure, dizziness, depression, and shortness of breath. Other serious side effects include bronchospasm.[5]

## MATERIALS

Atenolol was gifted by Windlas Biotech LTD, Dehradun, India. Hydroxy Proply methyl Cellulose of different grades like i) HPMC K4M ii) HPMC K15M from Colorcon Pvt Ltd, India. Ethyl cellulose and Glycerine from Indian Drug House. Gum Karaya from Nutriroma, Hyderabad.

### Drug-Polymer Compatibility Study

### Fourier Transform Infrared Spectroscopy (FTIR) Study

Drug-Exicipients compatibility study was carried out using FTIR spectrophotometer (Perkin Elmer, spectrum GX FTIR). The IR spectrum of atenolol was recorded using FTIR spectrophotometer with diffuse reflectance principle sample preparation involved mixing the sample with Potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000-400 $cm^{-1}$. The Infrared absorption spectra of pure drug and physical mixture of polymer and drug was obtained.[6]

### Preparation of Buccal Patches

### Preparation of Backing Membrane

Backing membrane was prepared by PVA (Poly-vinyl Alcohol). 4 grams of PVA was weighed. Then, Double Distilled Water was heated upto 80ºC. The weighed PVA was added by continuous stirring until a proper viscous solution was prepared. Then the solution was poured into mould.

### Solvent Casting Method

The polymers were first dissolved in solvent and stirred. Then the drug was added and stirred till it turns into a viscous solution. After that, the plasticizer was added and continued stirring. Finally, humectants were added. Then it was poured to mould for solvent evaporation.

In the mould, the backing membrane was prepared which makes the patches drug release unidirectional. After preparation of the patch, a layer of Gum karaya was given for muco adhesion of the patch in the opposite side of backing membrane.[7]

### Inclusion of Mucoadhesive layer by Gum Karaya

2 gm Gum Karaya was dissolved in 20 ml of double distilled water while the temperature of water was upto 85ºC and the solution was continuously stirred by magnetic stirrer. After proper mixing, a layer of the gummy solution was poured through the circumference of the patch.

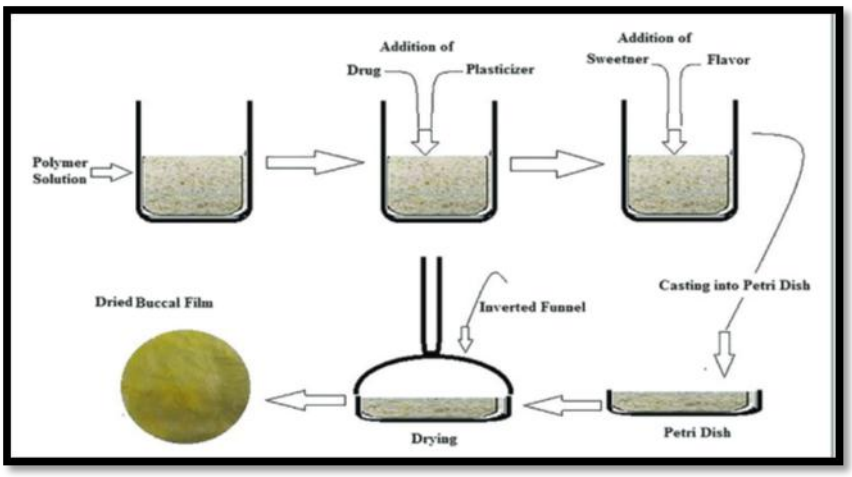


**Fig. 1: Preparation of Buccal Patches.**

**Table 1: Components of the formulations.**

| Formula | HPMC K4M:Ethyl Cellulose | HPMC K15M:Ethyl Cellulose | HPMC (K4M+K15M):Ethyl Cellulose |
|---|---|---|---|
| B1 | 1:1 | | |
| B2 | 3:1 | | |
| B3 | | 1:1 | |
| B4 | | 3:1 | |
| B5 | | | 0.5:0.5:1 |
| B6 | | | 1.5:1.5:1 |

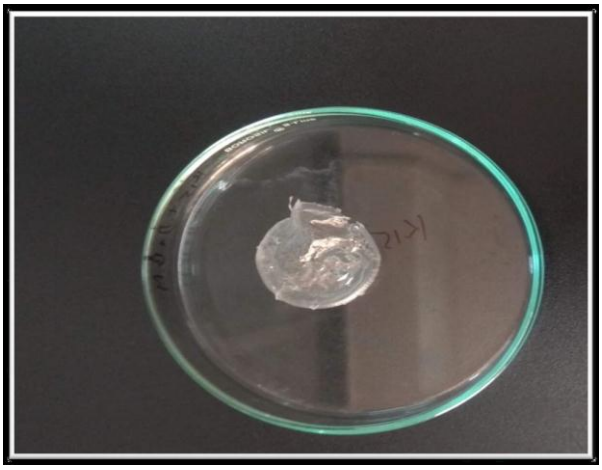

**Fig. 2: Buccal Patch.**

**Drug Content Study**

The drug contents in the buccal patches were determined by dissolving 5.72 $cm^2$ patch in 100 ml Methanol and shaken vigorously for 24 h at room temperature. These solutions were filtered through Whatman® filter paper. After proper dilution, optical density was measured spectrophotometrically using a UV–VIS spectrophotometer at 274 nm against a blank. The drug content was estimated from the calibration curve, which was constructed between 1 and 5 µg/ml concentration ranges. The method was validated for linearity, accuracy, and precision. The regression equation for the calibration curve was Y = 0.103X.

Thickness uniformity of the patches:

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.[8]

**Folding endurance**

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on the patches.[9]

**Mucoadhesion Strength**

The mucoadhesive strength of patches was measured in a modified mucoadhesive test assembly. Patches were stuck to the lower side of a pan of the balance by glue. After little soaking of the patch by phosphate buffer pH-6.8,thepatch facing the side continuing gum karaya was allowed to get stuck to a glass slide. The weight needed to displace the patch from the glass slide was determined. That weight is the mucoadhesive strength of the patch in vitro.

Force of Adhesion (N) = (Muco-adhesion Strength/1000) ×9.81

Bond Strength ($N/m^2$) =Force of adhesion (N)/Surface area ($m^2$)

**Microscopic Image**

Microscopic imaging was done by Digital Microscope. Features HD Coloor CMOS Sensor, High Speed DSP, 24 bit DSP optimum Resolution 640×480, 5x, Digital Zoom, Contains Digital Measurement Software & Calibration Ruler, Compatible with USB 3.0 USB 2.0 USB 1.1.

**Weight Variation**

Each patch was weighed individually on an analytical balance (Shimadzu, Japan) and the average weights were calculated.

**Determination of Moisture Content and Moisture Absorption**

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed.

The moisture content (%) was determined by calculating moisture loss (%) using the formula:

**Moisture content (%) = [(Initial weight– Final weight)/Initial weight] ×100**

The buccal patches were weighed accurately and placed in the desiccators containing Sodium Hydroxide. After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula.

Moisture absorption (%)= [(Final weight –Initial weight)/Initial weight] ×100

**Surface pH**

Prepared patches were dipped into phosphate buffer 6.8 for 1 min then surface pH was measured by pH meter. The surface pH of all formulations was determined to check whether each film causes irritation to the buccal mucosa. pH probe was in contact with the surface of each film and was allowed to equilibrate for 1 min.[10]

**In vitro permeability**

The rate and extent of mucosal permeation of atenolol through was determined using a modified Franz diffusion

cell. Briefly, the receptor compartment (78 mL) was filled with PBS (pH 6.8) at $37^{O}$ ± 0.5 C and stirred at 50 rpm. The patch was sandwiched between the donor and receptor compartments of the diffusion cell on the dialysis membrane. Aliquots (5 mL) of the receptor medium were withdrawn at regular intervals and replaced immediately with equal volumes of PBS (pH 6.8). The amount of Atenolol released into the receptor medium was determined by measurement of absorption at 274 nm against a blank.

## RESULTS AND DISCUSSION

To check solubility of Atenolol in phosphate Buffer at pH 6.8, 1gm of drug was mixed in 25 ml buffer solution. The preparation was kept in B.O.D shaker for time intervals of 24 hrs, 48 hrs and 72 hrs (for three days continuously). At different time interval, 1 ml of sample was withdrawn and checked for absorbance at 274 nm. Solubility of Atenolol at pH 6.8 was found to be 15.37mg/ml.

Drug excipient interaction is a very important and prior to development of a new formulation. Among the various methodologies available to study drug-excipient interaction, Fourier Transform Infrared Spectroscopy spectrum has been adopted to get the information regarding the interaction between the molecules of the level of functional groups[6] (Figure 3), indicates that the IR spectra of drug, polymer and drug-polymer combinations and polymeric combinations respectively. Between (3400-3550) cm $^{-1}$ and (1630 – 1500) cm $^{-1}$, wave number, variations of transmission spectroscopy has been observed. Stretches are mainly responsible for functional groups for those regions.

It is suggested by the FTIR spectra, that there may be some physical interactions due to generation of weak bonds as no major shift of peaks has been observed.

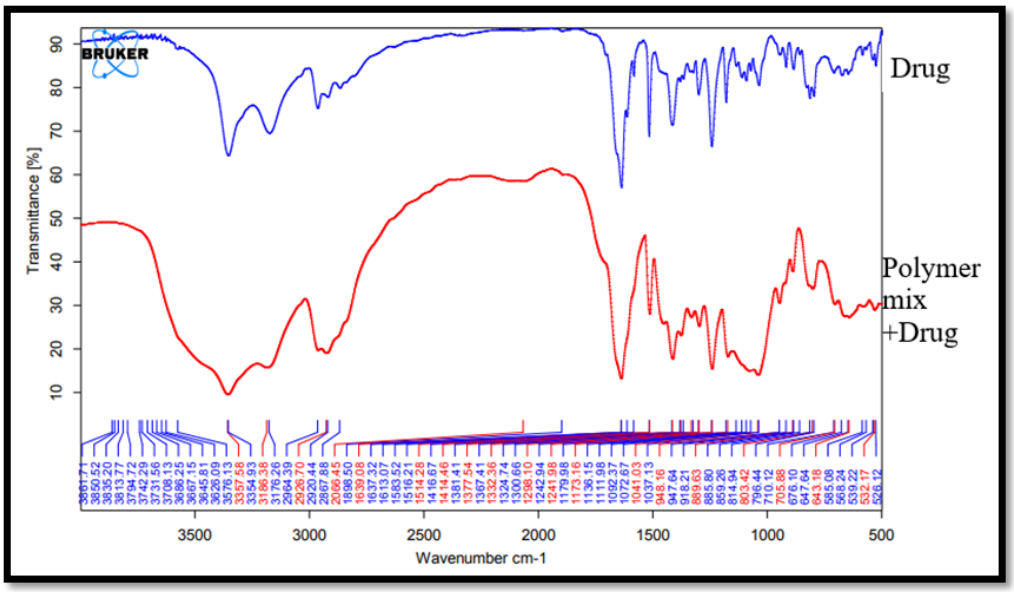


**Fig. 3: Overlaid FTIR Spectra of Polymer mix with Drug and Drug individually.**

**Table 2: Physico mechanical parameters.**

| PARAMETERS | B1 | B2 | B3 | B4 | B5 | B6 |
|---|---|---|---|---|---|---|
| **Drug Content** | 99.51 | 99.51 | 96.85 | 96.85 | 97.75 | 97.75 |
| **Thickness Uniformity (mm)** | 0.12 ± 0.00707 | 0.13 ± 0.00608 | 0.11 ± 0.11402 | 0.12 ± 0.10502 | 0.9 ± 0.11402 | 0.10 ± 0.1245 |
| **Folding Endurance** | >300 | >300 | >300 | >300 | >300 | >300 |
| **Mucoadhesion Strength (gm)** | 15.2 ± 1 | 17.2± 1 | 19.30 ± 1 | 21.23 ± 1 | 16.50 ± 1 | 18.1 ± 1 |
| **Weight Variation (%)** | 125.10 | 126.15 | 127.17 | 128.18 | 127.16 | 125.25 |
| **Moisture Uptake (% w/w)** | 7.2 | 6.9 | 3.45 | 3.13 | 5.7 | 4.9 |
| **Moisture Content (% w/w)** | 5.26 | 5.50 | 4.90 | 4.98 | 5.10 | 5.12 |
| **Surface pH** | 6.80 | 6.85 | 6.85 | 6.85 | 6.80 | 6.80 |

### Measurement of Mucoadhesion Strength

These evaluation tests were conducted for all the formulations and there was a change in mucoadhesion strength from formulation to formulation depending on the ratio of HPMC to ethyl cellulose. The maximum mucoadhesion strength (21.23 g) minimum (15.2 g) were found in the formulation B4 and B1 respectively. (Table 2).

In general, mucoadhesion/bioadhesion may be defined as the adhesion between a bioadhesive polymer and mucus. Mucoadhesion is considered to occur in four major stages: wetting, interpenetration, adsorption, and formation of secondary chemical bonds between mucus membrane and polymer. The strength of mucoadhesion is affected by different factors like molecular weight of the polymer, contact time with membrane, degree of swelling of the polymer. The adhesion will increase with the degree of hydration. The degree of swelling was increased with increase in HPMC along with gum karaya.

The surface pH of the buccal patches was determined in order to investigate the possibility of any irritation effects, as acidic or alkaline pH may cause irritation to the buccal mucosa. Surface pH of all the formulation was found to be 6.80- 6.85 (near to neutral pH). It was inferred that neutral pH of the formulation does not cause any irritation to the buccal mucosa.

To investigate the drug permeation kinetics pieces of dialysis membrane was fixed on the Franz diffusion cell. A buccal patch was fixed over the dialysis membrane keeping the drug release site downward. The receiver compartment was filled with phosphate buffer pH-6.8 Samples were taken after 5, 15, 30, 45, and 60 min and then every h up to 8 h, replaced by fresh buffer. The formulations were subjected to permeation study. The cumulative drug permeated from formulation B1 was found to be 49 % and lowest was from B4 (32 %).

The drug permeation might be described by zero order kinetics during the time of study **(Fig:3)**. The permeability coefficient was calculated using P = J/S Cd where J is the slope of the line, Cd is the drug concentration within the receiver chamber, S is the surface area of the dialysis membrane, and P is the permeability coefficient. The permeation profiles for each batch was almost linear. The permeability coefficient was found in a range of 0.041-.052 cm/h. and flux was found in a range of 1.43- 1.83 mg $cm^{-2}$ $hr^{-1}$.

**Table 3: Drug Permeation.**

| TIME(h) | CUMULATIVE PERCENTAGE OF DRUG PERMEATION | | | | | |
|---|---|---|---|---|---|---|
| | **B1** | **B2** | **B3** | **B4** | **B5** | **B6** |
| 1 | 27.29 | 21.64 | 19.54 | 14.62 | 26.48 | 22.52 |
| 2 | 30.60 | 26.42 | 22.19 | 17.14 | 29.19 | 30.51 |
| 3 | 33.47 | 30.09 | 22.75 | 19.46 | 30.66 | 32.10 |
| 4 | 35.48 | 33.35 | 23.95 | 21.94 | 31.29 | 34.52 |
| 5 | 38.41 | 35.42 | 25.54 | 23.67 | 32.18 | 35.19 |
| 6 | 42.53 | 39.16 | 32.78 | 24.94 | 34.89 | 36.63 |
| 7 | 46.48 | 43.08 | 33.59 | 28.41 | 36.74 | 41.69 |
| 8 | 49.84 | 46.30 | 35.36 | 32.37 | 40.35 | 44.64 |

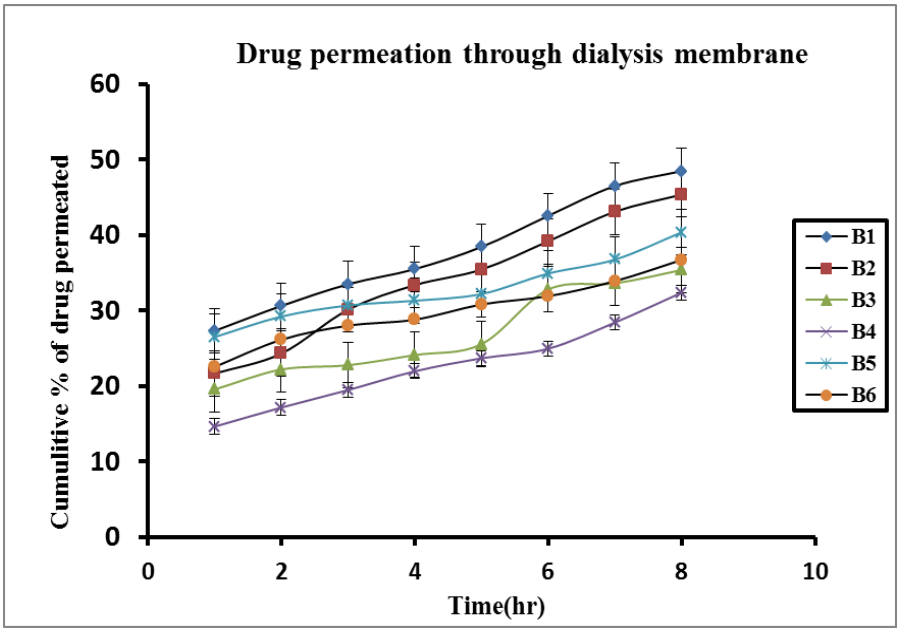


**Fig. 3: Drug Permeation from Formulation B1, B2, B3, B4, B5, B6.**

**Table 4: Flux, Permeation coefficients of the formulations.**

| Formulation | Slope | Flux (mg $cm^{-2}$ $h^{-1}$) | Permeation Coefficient (cm /h) |
|---|---|---|---|
| **B1** | 3.067 | 1.79 | 0.042 |
| **B2** | 3.442 | 1.61 | 0.041 |
| **B3** | 2.3723 | 1.43 | 0.045 |
| **B4** | 2.663 | 1.85 | 0.051 |
| **B5** | 1.7669 | 1.65 | 0.052 |
| **B6** | 1.8075 | 1.53 | 0.049 |

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