Research Article

# Atenolol-releasing buccal patches made of *Dillenia indica* L. fruit gum: preparation and ex vivo evaluations

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**Abstract**
The objective of present research deals with the utility of extracted dillenia fruit gum (DG) as pharmaceutical excipient in the formulation of buccal patches containing atenolol (for the use in the treatment of hypertension). The atenolol-releasing buccal patches having a mucoadhesive polymeric layer of extracted DG-hydroxypropyl methylcellulose (HPMC K4M) and a drug-free backing layer of ethyl cellulose (1%) were prepared through the solvent-casting process. Various physicochemical parameters such as drug content, average weight, thickness, folding endurance and moisture content of all these buccal patches were found satisfactory. Ex vivo buccoadhesion was also found satisfactory. Ex vivo drug permeation across the excised porcine buccal mucosal membrane demonstrated the atenolol permeation over 12 h, which obeyed the first-order model ($R^2 = 0.9858–0.9967$) with non-Fickian (anomalous) diffusion mechanism ($n = 0.72–0.75$). These buccal patches were also characterized by SEM and FTIR spectroscopy. These atenolol-releasing buccal patches can be used in the treatment of hypertension and angina pectoris bypassing the extensive hepatic first-pass metabolism.

**Keywords** Gum · Buccal patches · Buccoadhesion · Atenolol

**List of symbols**

| | |
|---|---|
| $(dQ/dt)_{ss}$ | The drug quantity permeated across buccal mucosal membrane per unit time function at the steady-state condition (µg/h) |
| $A$ | Area ($cm^2$) of buccal mucosal membrane exposed to Franz diffusion cell |
| $J_{ss}$ | Permeation flux (µg/$cm^2$/h) |
| $k_0$ | Zero-order rate constant |
| $k_1$ | First-order rate constant |
| $k_H$ | Higuchi rate constant |
| $k_{KP}$ | Korsmeyer–Peppas rate constant |
| $n$ | Diffusion exponent |
| $Q$ | Amount of atenolol permeation at time, t |
| $Q_0$ | Amount of atenolol permeation at time 0 |

**Abbreviations**

| | |
|---|---|
| DG | Dillenia fruit gum |
| DG-HPMC K4M | Dillenia fruit gum-hydroxypropyl methylcellulose |
| FTIR | Fourier-transform infrared |
| HPMC K4M | Hydroxypropyl methylcellulose |
| SEM | Scanning electron microscopy |

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## 1 Introduction

The delivery of different drugs by means of buccal mucosa to the systemic blood circulation is identified as buccal drug delivery [1, 2]. The buccal mucosa is recognized as one of the well-vascularised areas, and the drugs are believed to be speedily absorbed into the systemic blood circulation beneath the buccal mucosal surface [3, 4]. The buccal mucosa possesses a larger, smoother and relatively immobile surface facilitating a larger contact surface for the drug absorption by the buccal drug delivery systems, which confers to the rapid and wide-ranging absorptions of drugs [5]. Recent researches on the buccal drug delivery systems have already been proven as useful means of effective drug delivery through facilitating a number of benefits: circumventing of the gastro-intestinal tract as well as hepatic-portal systems, enhancement of the bioavailability for various drugs for oral administrations (eliminating the chances of hepatic first-pass metabolisms), facilitating drug administration to the unconscious patients, simplest way of drug administration (eliminating chances of invasive painful medications), improvement in the patient compliances, controlled and sustained drug releasing facilities, and easy termination of the drug delivery through detaching the dosage forms from the application site [6, 7].

Since the past few decades, a considerable amount of research endeavours towards the formulation and development of buccal patches have already been reported [8–10]. Buccal patches are the dosage forms in the form of films/membranes, where a thinner matrix is composed of matrix film/membrane forming polymers, mucoadhesive agents/polymers, other excipients and drugs. In the previously reported literature, several researches have already been carried out to prepare various buccal films/patches using plant-derived natural mucoadhesive polymers [10, 11]. Shiledar et al. [10] prepared and evaluated buccoadhesive bilayered patches of zolmitriptan employing xanthan gum. In another research, Avachat et al. [11] prepared and evaluated mucoadhesive films made of tamarind seed xyloglucan for buccoadhesive delivery of rizatriptan benzoate. However, no research is reported for the preparation of buccal films/patches using dillenia fruit gum (DG) as mucoadhesive polymer. DG is extracted from ripe dellinia (*Dillenia indica* L., family: Dilleniaceae) fruits [12]. It is water soluble and biocompatible [13]. It is reported as mucoadhesive gelling agents [12, 14]. In the recent years, DG is being exploited as pharmaceutical excipients in the formulation of various drug delivery dosage systems such as sustained drug releasing tablets, microbeads and mucoadhesive nasal gels [12–16]. Considering some useful properties of DG such as hydrophilicity, biocompatibility, biomucoadhesive potential, economic production and easy availability from the plant resources in the nature, in the current research, we made an endeavour to prepare and evaluate atenolol-containing buccal patches made of DG and hydroxypropyl methylcellulose (HPMC K4M) in the different amounts and combinations to make sure of the slower sustained releasing of atenolol over a longer period by means of reasonable biomucoadhesivity.

Atenolol is a selective β-1 blocker candidate and mainly given in the management of hypertension as well as angina pectoris [17]. The chemical name of atenolol is (RS) 4-(2-hydroxy-3-isopropyl amino propoxy) phenyl acetamide. Its molecular formula is $C_{14}H_{22}N_2O_3$ with low molecular weight (i.e. 266.336) and low dosing (i.e. 25–50 mg) [18]. Atenolol has lower gastro-intestinal membrane permeability because of its hydrophilic properties as it is sparingly soluble in the aqueous medium, and also the partition coefficient value is low (i.e. 0.23). Moreover, atenolol is a drug candidate showing very extensive first-pass metabolism in the liver possessing poor bioavailability (i.e. 40%, approximately). The lower dose, low molecular weight, very extensive first-pass metabolism as well as short half-life make atenolol as an appropriate drug for the buccal administration [19, 20]. In the literature, a number of atenolol-releasing buccal drug delivery systems have been already reported by various research groups [19–26]. The goal of the current research was to prepare and assess the atenolol-releasing buccal patches having a mucoadhesive polymeric layer of isolated DG-HPMC K4 M and drug-free backing layer of ethyl cellulose (1%). These buccal patches were investigated for various physicochemical parameters (such as average weight, thickness, drug content, folding endurance and moisture contents) and ex vivo tests (such as ex vivo buccoadhesion and ex vivo drug permeation across excised porcine buccal mucosal membrane), which could be beneficial for providing sustained buccoadhesive delivery of atenolol over a prolonged period in the treatment of hypertension and angina pectoris bypassing the extensive hepatic first-pass metabolism.

## 2 Materials and methods

### 2.1 Materials

Atenolol (M/S. P.D.I.L, India), HPMC K4 M (Matrix Laboratories, India), ethyl cellulose (Matrix Laboratories, India), anhydrous calcium chloride (SD Fine Chemicals, India), glycerine (Loba Chemie Pvt. Ltd., India), sodium saccharin (Reidel India Chemicals, India) and acetone (Merck Ltd., India) were utilized. DG is extracted from ripe dellinia fruits

(*Dillenia indica* L., family: Dilleniaceae) fruits purchased from Baripada market (Dist: Mayurbhanj, Odisha) in the month of September 2015. All other reagents and chemicals were commercially available and of analytical grade.

## 2.2 Extraction of DG

DG was extracted from ripe dillenia fruits according to the previously reported method by Ketousetuo and Bandyopadhyay [12] with little modifications. Collected dillenia fruits were washed with demineralised water and reduced into small pieces with a knife. Small pieces of dillenia fruits (1 kg) were soaked in the demineralised water and then boiled at 45 ± 1 °C under occasional agitation using an electrical water bath until thick slurry was formed. The thick slurry was then cooled and kept in the refrigerator for 24 h to settle down the undissolved part. The clear solution at the upper part was transferred and then centrifuged for 20 min at a speed of 500 rpm. The supernatant of the prepared solution was separated. Afterwards, the separated solution was concentrated at 50 ± 2 °C using an electric water bath until the volume reduction to one-fourth of the original volume, and cooled down to the room temperature. The concentrated solution was then poured into one-third of the volume of acetone with constant stirring by using a magnetic stirrer (Remi Motors, India). The formed precipitate was washed repeatedly with acetone and subsequently with demineralised water. The washed precipitate was collected and then dried at 45 ± 1 °C in an oven for 12 h. The dried DG was crushed to fine powder, passed through the 80-mesh screen and stored in an airtight desiccator for further use.

## 2.3 Characterization of extracted DG

### 2.3.1 Determination of yield

A known quantity of crude material was weighed first. Yield was expressed as percentage of the mass of dried isolated material against the mass of the whole fresh crude material. The per cent yield of isolated material was determined by using the formula:

$$\% \text{ Yield} = \frac{\text{Mass of dried DG}}{\text{Mass of the whole fresh crude material}} \times 100 \quad (1)$$

### 2.3.2 Physicochemical characterization

Various physicochemical properties such as colour, odour, taste, solubility in water, pH (1% solution at 37 °C) and viscosity (1% solution at 37 °C) of the extracted gum were measured. pH of the 1% solution of extracting gum was measured using a digital pH meter (Systronics Instruments, India) by placing the glass electrode completely into the gel system. The viscosity of 1% solution of isolated gum was determined by using a Brookfield DV III ultra V6.0 RV cone and plate viscometer (Brookfield Engineering Laboratories, Middle-boro, MA) at 100 rpm spindle rotation using Rheocalc V2.6. Software.

### 2.3.3 $^1$H nuclear magnetic resonance ($^1$H NMR) spectroscopy analysis

$^1$H NMR (600 MHz, 25 °C) spectra of extracted gum sample in dimethyl sulfoxide (DMSO) were recorded on a BrukerAvance™ III 500 spectrometer (Bruker Biospin Gmbh, Germany) operating at 500.13 MHz using a 4-mm CP-MAS probe head.

## 2.4 Preparation of atenolol-containing buccal patches

The solvent-casting process is one of the important processes for the preparation of biopolymeric films or patches, and this process has already been widely used for preparation of buccal patches [24, 25]. In brief, atenolol (50 mg) containing buccal patches composed of DG-HPMC K4 M and sodium saccharin (0.1%) were made via the solvent-casting process. The mixture solutions of DG, HPMC K4 M, sodium saccharin and atenolol were mixed well by means of a magnetic stirrer set (Remi Motors, India) at 400 rpm for 30 min and then homogenized using a homogenizer (Remi Motors, India) for 1 h at room temperature. Glycerine (15% of the dry weight of polymers used in the formulations) was added within the homogenized mixtures to act as a plasticizer. The mixtures were sonicated again for 20 min to eliminate air bubbles. The sonicated mixtures were then transferred in the Petri dishes of 54 cm$^2$ areas and also were dried for 24 h at 45 ± 1 °C in an oven. The drug-free backing layer was prepared onto the atenolol-containing mucoadhesive polymeric layers by using ethyl cellulose solution (1%) in ethyl alcohol by means of solvent-casting method, and the prepared bilayered patches were dried at 45 ± 1 °C overnight. Then, the dried patches were collected from the Petri dishes, cut into round, smaller pieces of 1 cm$^2$ and stored in a desiccator until use. Table 1 presents the composition formula of atenolol-containing buccal patches made by DG.

## 2.5 Measurement of average weight and thickness

Buccal patches of 56 cm$^2$ area size from all formulation batches were weighed separately by using a digital electronic weighing balance (Mettler Toledo) to calculate the average weights of buccal patches of each formulation

**Table 1** Composition formula of atenolol-containing buccal patches made of DG

| Formula | F-1 | F-2 | F-3 | F-4 |
|---|---|---|---|---|
| Atenolol (mg) | 50 | 50 | 50 | 50 |
| HPMC K4M (mg) | 500 | 400 | 300 | 200 |
| Extracted DG (mg) | 500 | 600 | 700 | 800 |
| Glycerine (% w/w) | 15 | 15 | 15 | 15 |
| Sodium saccharin (% w/v) | 0.1 | 0.1 | 0.1 | 0.1 |
| Distilled water (ml) | 40 | 40 | 40 | 40 |
| Ethyl cellulose (% w/v) (for backing membrane) | 1 | 1 | 1 | 1 |

batch. By using thickness gauze (Mitutoyo, Japan), the thickness of these prepared buccal patches was measured at different points. Three buccal patches were picked randomly for every formulation batch, and then measured [19].

## 2.6 Determination of drug content

Drug (here atenolol) contents within each prepared atenolol-containing buccal patch were measured via dissolving 1 $cm^2$ of buccal patches in the 100 ml of phosphate buffer (pH 6.8) using a magnetic stirrer set (Remi Motors, India) at a speed of 600 rpm for 24 h at the room temperature. The solutions obtained after dissolving prepared atenolol-containing buccal patches were filtered through the Whatman® filter paper (No. 42). Atenolol contents in the solutions were measured spectrophotometrically by UV–VIS spectrophotometer (Shimadzu, Japan) at 275 nm wavelength ($\lambda_{max}$) against the blank sample.

## 2.7 Measurement of folding endurance

The folding endurances of prepared atenolol-containing buccal patches were measured manually by the procedure of repetitively folding at the same position until the breakages of the tested patches. The number of folding times for tested buccal patches folded up the same position without breakages of the patches was taken as the measure of folding endurance [22].

## 2.8 Determination of moisture content

Buccal patches containing atenolol were weighed correctly and then kept inside a desiccator contained with calcium chloride (anhydrous). After completion of 3 days, buccal patches kept within the desiccator were removed and then weighed using an electronic balance (Mettler Toledo). The moisture content (%) of buccal patches was computed by the formula [24]:

$$\text{Moisture content}\,(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (2)$$

## 2.9 Ex vivo studies

### 2.9.1 Preparation of porcine buccal mucosal membrane

The porcine buccal mucosa was excised from the cheek pouch of pork, which was collected from the local slaughtering shop. The porcine cheek pouch was collected within 1 h after sacrificing the animal in slaughtering shop and then brought to the laboratory within the phosphate buffer (pH 6.8), instantly. The mucosal membrane was disconnected from the full thickness of the buccal mucosa layer and then immersed in the phosphate buffer (pH 6.8) for 1 min at 37 ± 0.5 °C. By using a scalpel, the fat layers present onto the buccal mucosal membrane were eliminated, and the buccal mucosal membrane was then separated. Finally, the collected excised buccal mucosal membrane was rinsed using phosphate buffer (pH 6.8) [22].

### 2.9.2 Ex vivo mucoadhesion study

Various mucoadhesive parameters of all the prepared atenolol-containing buccal patches were determined by performing an ex vivo mucoadhesion evaluation using excised porcine buccal mucosal membrane by modified physical balance as described by Gupta et al. [27]. The excised porcine buccal mucosal membrane was fixed and then tied to the open mouth of a glass vial, which was filled up by the phosphate buffer (pH 6.8). Afterwards, the glass vial was compactly fixed at the centre of a glass beaker filled up by the phosphate buffer (pH 6.8) at the room temperature. The patches (i.e. buccal patches containing atenolol) were glued to the lower part of the rubber stopper. A preload initial pressure by fingertip for 5 min was applied to set the tested buccal patch and the excised porcine buccal mucosal membrane. The mass (in g) needed for detaching the tested patches from the buccal mucosal surface was the value of the mucoadhesive strength (i.e. shear stress). From the results of the mucoadhesive strengths of various buccal patches tested, force of adhesion and bonding strength of buccal patches was calculated [8]:

$$\text{Force of adhesion}(N) = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81 \quad (3)$$

$$\text{Bonding strength}\,\left(\text{N/m}^2\right) = \frac{\text{Force of adhesion}}{\text{Surface area of mucosal surface}} \quad (4)$$

#### 2.9.3 Ex vivo drug permeation study

Ex vivo drug (here atenolol) permeation study of these prepared atenolol-containing buccal patches across excised porcine buccal mucosal membrane was carried out by using the Franz diffusion cell. The effectual diffusion area of the Franz diffusion cell used was determined as 1.67 $cm^2$. The receptor compartment (50 ml) of Franz diffusion cell filled up by phosphate buffer (pH 6.8) and 37 ± 0.5 °C of temperature was controlled throughout the experiment. Applying a magnetic stirrer, 50 rpm speed of stirring was employed to simulate the buccal setting within the Franz diffusion cell. A prepared atenolol-containing buccal patch was fixed under the occlusion on excised porcine buccal mucosal membrane surface fitted between receptor and donor compartments of the Franz diffusion cell used in the experiment. At regular intervals, 5 ml of samples from receptor compartment was withdrawn. After each collection of samples from the Franz diffusion cell, 5 ml of fresh phosphate buffer (pH 6.8) was replaced immediately. Collected samples were filtered through the Whatman® filter paper (No. 42), and atenolol contents within the samples were measured spectrophotometrically using UV–VIS spectrophotometer (Shimadzu, Japan) at 274 nm wavelength ($\lambda_{max}$) against the blank sample.

#### 2.9.4 Ex vivo permeation data analysis

**2.9.4.1 Permeation flux** The atenolol amounts from various buccal patches permeated through the excised porcine buccal mucosal membrane were plotted against the time function. The intercept as well as the slope of the linear part of the plot was obtained via the regression analysis. Permeation fluxes of these atenolol-containing buccal patches from each formulation batch were determined by dividing the slope by the mucosal surface area [22]:

$$J_{ss} = (dQ/dt)_{ss} \cdot 1/A \quad (5)$$

where $J_{ss}$ is the permeation flux (μg/$cm^2$/h) at the steady-state condition, $A$ is the area ($cm^2$) of a buccal mucosal membrane exposed to Franz diffusion cell, and $(dQ/dt)_{ss}$ is the drug quantity permeated across a buccal mucosal membrane per unit time function at the steady-state condition (μg/h).

**2.9.4.2 Ex vivo permeation kinetics** The ex vivo permeation of atenolol from various buccal patches permeated across excised porcine buccal mucosal membrane was assessed kinetically by fitting with various important mathematical models such as zero-order, first-order, Higuchi and Korsmeyer–Peppas model equations [28–30]

$$\text{Zero-order model}: Q = k_0 t + Q_0 \quad (6)$$

$$\text{First-order model}: Q = Q_0 e^{k/t} \quad (7)$$

$$\text{Higuchi model}: Q = k_H t^{1/2} \quad (8)$$

$$\text{Korsmeyer–Peppas model}: Q = k_{kp} t^n \quad (9)$$

$Q$ and $Q_0$ symbolize the amount of atenolol permeation at time, $t$ and 0, respectively; $k_0$, $k_1$, $k_H$ and $k_{KP}$ designate atenolol permeation rate constants. In addition, n represents the diffusion exponent implying permeation mechanism. When $n$ is ≤ 0.5, Fickian diffusion (non-steady) phenomenon controls and when $n$ is≥1, the case-II transport (zero order) controls. When n is within 0.5–1, it refers to non-Fickian (anomalous) diffusion [31, 32].

### 2.10 Scanning electron microscopy (SEM)

The surface morphology of these atenolol-containing buccal patches was examined by SEM. The dried buccal patches were coated with the gold ion-sputter and then inspected under a scanning electron microscope (JEOL, Japan) functioning at the working distance of 6 mm and the accelerating voltage of 15 kV and × 5000 magnification.

### 2.11 Fourier-transform infrared (FTIR) spectroscopy

Drug–polymer compatibility of the prepared atenolol-containing buccal patches was examined by FTIR spectroscopy by potassium bromide pellet method. Pure atenolol and atenolol-containing buccal patches were scanned by a FTIR spectrophotometer (BRUKER, UK) within the frequency range of 3600–600 $cm^{-1}$ of the transmission mode.

### 2.12 Statistical analysis

Data were examined by the simple statistical analyses. Simple statistical analysis was performed by MedCalc software version 11.6.1.0.

## 3 Results and discussion

### 3.1 Extraction, identification and characterization of extracted DG

DG was extracted from ripe *Dellinia indica* L. fruits using the previously reported method by Ketousetuo and

**Table 2** Physicochemical properties of extracted DG

| Physicochemical properties | Results |
|---|---|
| Colour | White |
| Odour | Odourless |
| Taste | Tasteless |
| Solubility in water | Soluble in water at room temperature; also soluble in cold and hot water |
| pH (1% solution at 37 °C) | 6.18 ± 0.17 (mean ± S.D.; *n* = 6) |
| Viscosity (1% solution at 37 °C) | 14.27 ± 1.22 cps (mean ± S.D.; *n* = 6) |

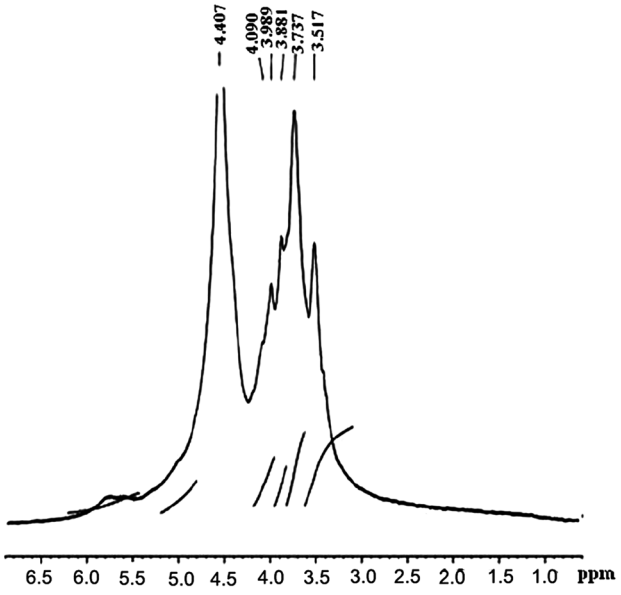


**Fig. 1** $^{1}$H NMR spectrum of extracted DG

Bandyopadhyay [12] with little modifications. The yield (%) of extracted DG was found to be 14.73%.

## 3.2 Physical characteristics of extracted DG

Physical characterization of extracted DG is presented in Table 2. Extracted DG was of white powder. It was odourless and tasteless. It was found soluble in water at room temperature, in cold water (less) and hot water (more). The pH of 1% extracted DG solution at 37 °C was measured to be 6.18 ± 0.17, whereas the viscosity of the same solution at 37 °C and 100 rpm spindle rotation was measured to be 14.27 ± 1.22 cps.

## 3.3 $^{1}$H NMR spectroscopy of extracted DG

$^{1}$H NMR spectrum of extracted DG is presented in Fig. 1. The $^{1}$H NMR spectrum showed typical characteristic signals of polysaccharides that crowded in a narrow region in-between 3 and 5 ppm, indicating the presence of sugar residues [33].

## 3.4 Preparation of atenolol-containing buccal patches

During the past few years, various buccal drug releasing dosage forms were developed using plant-derived natural mucoadhesive polymers [10, 11]. However, development of buccal drug releasing dosage forms using DG as mucoadhesive composition material is not reported till date. In the current research, novel buccal patches containing atenolol (an anti-hypertensive drug) comprising a drug containing mucoadhesive polymeric layer of isolated DG-HPMC K4M and drug-free backing membrane of ethyl cellulose (1%) were formulated by the solvent-casting process (Table 1). Backing layer was formed to avoid backside releasing occurrence of the drug from the buccal patches after application.

## 3.5 Average weight and thickness

The average weights of these newly prepared atenolol-containing buccal patches (56 $cm^2$ in size) were calculated within the range of 2.15 ± 0.07–2.22 ± 0.11 g. The thicknesses of these buccal patches were measured as 0.60 ± 0.07–0.65 ± 0.09 mm. The overall results of average weight and thickness are presented in Table 3.

**Table 3** Average weight, thickness, drug content, folding endurance and moisture content of atenolol-containing buccal patches

| Formulations | F-1 | F-2 | F-3 | F-4 |
|---|---|---|---|---|
| Average weight (g)[a] | 2.15 ± 0.07 | 2.22 ± 0.11 | 2.18 ± 0.09 | 2.16 ± 0.10 |
| Thickness (mm)[a] | 0.60 ± 0.07 | 0.62 ± 0.08 | 0.63 ± 0.08 | 0.65 ± 0.09 |
| Drug content (%)[b] | 98.18 ± 2.63 | 98.94 ± 2.88 | 99.05 ± 2.57 | 99.12 ± 2.05 |
| Folding endurance | 28 | 24 | 22 | 20 |
| Moisture content (%)[b] | 1.18 ± 0.07 | 1.29 ± 0.12 | 1.43 ± 0.14 | 1.73 ± 0.27 |

[a]Mean ± standard deviation, *n* = 6

[b]Mean ± standard deviation, *n* = 3

### 3.6 Drug content

The drug contents present in each 1 $cm^2$ buccal patch were measured separately. The drug contents in all these newly prepared atenolol-containing buccal patches were in-between the range of 98.18 ± 2.63–99.12 ± 2.05% (Table 3). This result designates that the drug (here atenolol) was consistently dispersed throughout the drug containing a polymeric layer of the buccal patches.

### 3.7 Folding endurance

The folding endurances of these newly prepared atenolol-containing buccal patches were manually assessed. The highest folding endurance value was noticed for the buccal patch F 1 (28), whereas the lowest endurance value was measured for the buccal patch F 4 (20) (Table 3). From the overall results of the folding endurance, it was noticed that the folding endurances of the prepared buccal patches were lessened with the decreasing incorporation of isolated DG in the buccal patch formula. The results of the folding endurance study ensured the flexibility of these newly prepared atenolol-containing buccal patches.

### 3.8 Moisture content

The moisture content (%) of all these newly prepared atenolol-containing buccal patches was calculated, and this ranged in between 1.18 ± 0.07 and 1.73 ± 0.27 (Table 3). The lower moisture content within the buccal patches is well appreciable to avoid the chances of microbial contaminations. In addition, it can help to preserve the stability enough from being dried and brittle [22].

### 3.9 Ex vivo mucoadhesion

Mucoadhesion of buccal patches can be described as the adhesion in between the mucoadhesive patches and buccal mucosal surface. The mucoadhesive nature of patches can be influenced by a variety of factors such as biological membrane, molecular mass as well as the swelling rate of polymers in the patch formula [34]. In this work, freshly excised porcine buccal mucosal membrane was exercised as mucosal membrane. Various mucoadhesive parameters such as mucoadhesive strength (g), force of adhesion (N) and bonding strength ($N/m^2$) were calculated by employing modified physical balance as described by Gupta et al. [27] utilizing excised porcine buccal mucosal membrane. The calculated results of the ex vivo mucoadhesion of atenolol-containing buccal patches using excised porcine buccal mucosal membrane are shown in Table 4. The measured mucoadhesive strengths of all these buccal patches ranged between 22.27 ± 1.44 and 32.70 ± 2.37 g. The force of adhesion values of buccal patches was calculated within the range $21.85 \times 10^{-2}$–$32.08 \times 10^{-2}$ N, whereas bonding strength ranged between 1308.20 and 1920.90 $N/m^2$. Amongst all these newly prepared atenolol-containing buccal patches, buccal patch F-4 exhibited the highest mucoadhesive strength, force of adhesion and bonding strength. From the results of ex vivo mucoadhesion study, it was observed that mucoadhesion of the prepared buccal patches was enhanced with the increment of isolated DG incorporation as mucoadhesive polymer in the buccal patch formula. Various ex vivo mucoadhesive parameters of these newly formulated buccal patches were found satisfactory.

### 3.10 Ex vivo drug permeation

Ex vivo drug (here atenolol) permeation results of various buccal patches across excised porcine buccal mucosal membrane demonstrated ex vivo atenolol permeation over 12 h (Fig. 2). The maximum atenolol permeation (55.96 ± 2.58%) over 12 h was observed for buccal patch F-4, while the minimum atenolol permeation was found for buccal patch F-1 (43.75 ± 1.77%) over 12 h of ex vivo permeation (Table 5). Ex vivo permeation flux results exhibited the highest permeation flux (32.27 $\mu g/cm^2/h$) for buccal patch F-4 than that of others. Probably, higher buccoadhesivity and higher moisture content of the buccal patch F-4 could help to facilitate higher permeation flux than others.

The ex vivo atenolol permeation from these newly prepared buccal patches results across the excised porcine buccal mucosal membrane was evaluated for the curve fitting in some important mathematical models, and the curve-fitting results are presented in Table 6. When the relevant correlation coefficients for the tested mathematical models were compared, ex vivo atenolol permeation from these newly prepared buccal patches

**Table 4** *Ex vivo* mucoadhesive parameters (mucoadhesive strength, force of adhesion and bonding strength) of atenolol-containing buccal patches

| Formulations | F-1 | F-2 | F-3 | F-4 |
|---|---|---|---|---|
| Mucoadhesive strength (g)[a] | 22.27 ± 1.44 | 25.38 ± 1.38 | 28.44 ± 1.63 | 32.70 ± 2.37 |
| Force of adhesion (N)[a] | $21.85 \times 10^{-2}$ | $24.89 \times 10^{-2}$ | $27.90 \times 10^{-2}$ | $32.08 \times 10^{-2}$ |
| Bonding strength ($N/m^2$)[a] | 1308.20 | 1490.90 | 1670.66 | 1920.90 |

[a]Mean ± standard deviation, $n = 3$

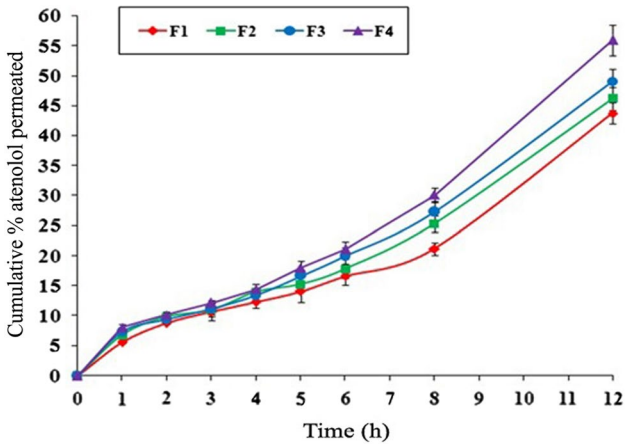


**Fig. 2** *Ex vivo* atenolol permeation from various atenolol-containing buccal patches (mean ± standard deviation, n = 3)

**Table 5** Permeation flux (*J*, μg/cm$^2$/h) results for various atenolol-containing buccal patches

| Formulations | Permeation flux (*J*, μg/cm$^2$/h) |
|---|---|
| F-1 | 25.73 |
| F-2 | 28.03 |
| F-3 | 28.93 |
| F-4 | 32.27 |

across the excised porcine buccal mucosal membrane was observed to follow the first-order kinetic model (here $R^2 = 0.9858$ to 0.9943) over 12 h of permeation study. The calculated values of the diffusion exponent (*n*) of these newly formulated atenolol-containing buccal patches ranged between 0.72 and 0.75 (Table 6) demonstrating non-Fickian (anomalous) diffusion mechanisms. The anomalous diffusion mechanism reveals mutually diffusion-controlled as well as swelling-controlled permeations of drugs from the tested buccal patches [35].

### 3.11 SEM analysis

The surface morphology of buccal patch F-4 was examined by SEM, and the SEM photograph of buccal patch F-4 demonstrated a nearly smooth surface in the presence of some polymeric derbies and drug particles (Fig. 3), which suggested a fine lamination of the excipient polymers within the prepared buccal patch tested (F-4), where the drug particles were homogeneously dispersed throughout the patch matrix. The occurrence of the drug (atenolol) particles on the patch matrix surface could be because of the migrations of drug particles along with water to patch surface during the drying process.

### 3.12 FTIR spectroscopy analyses

The drug–polymer compatibility of the atenolol-containing buccal patches was analysed by FTIR spectroscopy. The FTIR spectra of pure atenolol and atenolol-containing buccal patch F-4 are shown in Fig. 4. The FTIR spectrum of pure atenolol exhibited different typical peaks at 3316 and 1420 cm$^1$ due to –O–H, at 1337 cm$^1$ due to –$CH_3$, at 1036 and 1242 cm$^1$ due to –N–C, as expected [36]. All these typical peaks of pure atenolol emerged in the spectra of atenolol-containing buccal patch F-4 without or with very minute shifting, demonstrating that there was nonexistence of any chemical interaction(s) in between atenolol and biopolymers utilized in the patch formula. Intensities of the peaks of pure atenolol were found to be diminished because of the molecular dispersion of atenolol in the polymer matrix formed within the buccal patch. Therefore, the results of FTIR analyses suggested no chemical interaction had taken place between atenolol and biopolymer excipients utilized in the buccal patch formula.

## 4 Conclusion

Atenolol-releasing buccal patches containing mucoadhesive polymeric layer of isolated DG-HPMC K4 M and drug-free backing layer of ethyl cellulose (1%) were

**Table 6** Results of curve fitting of the ex vivo permeation of different atenolol-containing buccal patches

| Models | Formulation codes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F-1 | | F-2 | | F-3 | | F-4 | |
| | $R^2$ | $k_0$ | $R^2$ | $k_1$ | $R^2$ | $k_H$ | $R^2$ | $k_{KP}$ |
| Zero-order model | 0.9290 | 0.6623 | 0.9481 | 0.6461 | 0.9594 | 0.6167 | 0.9464 | 0.6567 |
| First-order model | 0.9895 | 1.7617 | 0.9858 | 1.8921 | 0.9926 | 1.9013 | 0.9967 | 1.9718 |
| Higuchi model | 0.5993 | 6.9366 | 0.6352 | 7.7447 | 0.6228 | 8.0473 | 0.5882 | 8.7419 |
| Korsmeyer–Peppas model | 0.9275 | 4.9170 | 0.9174 | 5.6937 | 0.9129 | 5.7473 | 0.8968 | 6.2202 |
| *n* (diffusion exponent) | 0.75 | | 0.72 | | 0.74 | | 0.75 | |

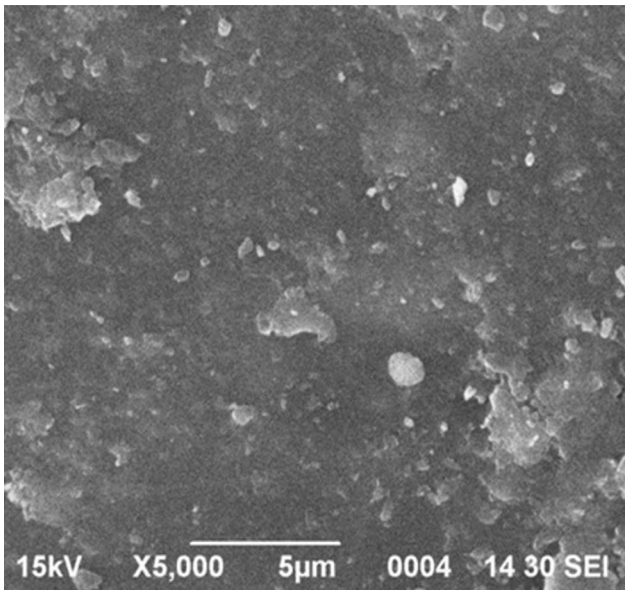


**Fig. 3** SEM microphotograph of atenolol-containing buccal patch F-4

prepared through the solvent-casting process. Drug content, average weight, thickness, folding endurance and moisture content of all these buccal patches were found satisfactory. Ex vivo mucoadhesive properties were found satisfactory for the buccoadhesion with buccal mucosal membrane. Amongst all, buccal patch F-4 exhibited the highest mucoadhesive strength ($32.70 \pm 2.37$ g), force of adhesion ($32.08 \times 10^{-2}$ N) and bonding strength (1920.90 N/m$^2$). The ex vivo drug permeation results of various buccal patches across the excised porcine buccal mucosal membrane demonstrated ex vivo atenolol permeation over 12 h. The highest permeation flux (32.27 μg/cm$^2$/h) was measured for the buccal patch F-4. The ex vivo atenolol permeations from these buccal patches followed the first-order model ($R^2 = 0.9858–0.9967$) and non-Fickian (anomalous) diffusion mechanism ($n = 0.72–0.75$) over 12 h across the excised porcine buccal mucosal membrane. The SEM observation suggested a fine lamination of the excipient polymers within the prepared buccal patch tested (F-4), where the drug particles were homogeneously dispersed throughout the patch matrix. The FTIR analyses suggested no chemical interaction had taken place between atenolol and biopolymer excipients utilized in the buccal patch formula. These atenolol-releasing buccal patches were found suitable for providing sustained buccoadhesive delivery of atenolol over a prolonged period in the treatment of hypertension and angina pectoris bypassing the extensive hepatic first-pass metabolism.

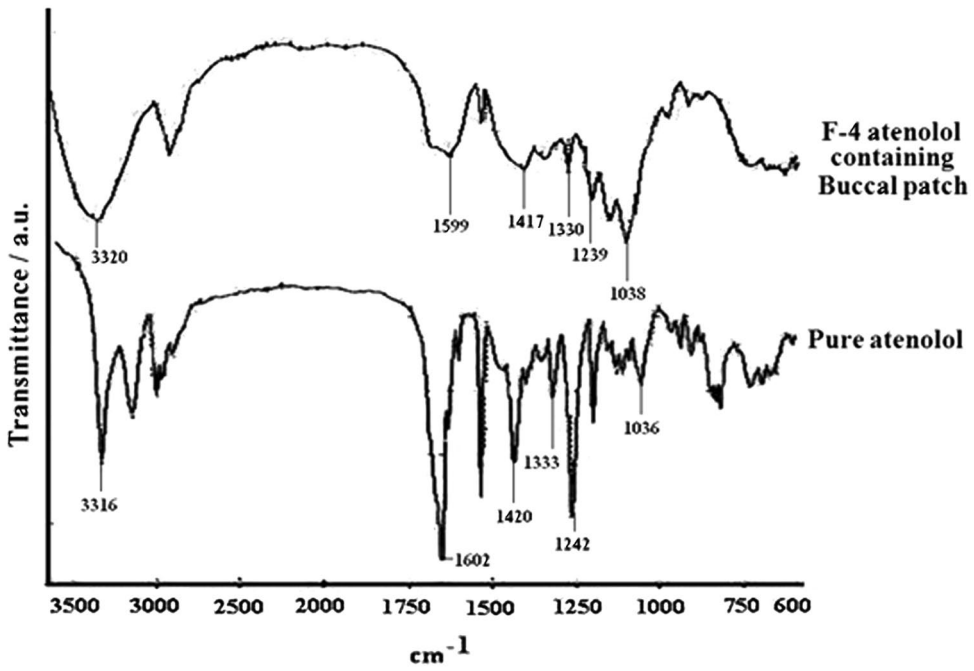


**Fig. 4** FTIR spectra of pure atenolol, atenolol-containing buccal patch F-4

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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