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Bioadhesive okra polymer based buccal patches as platform for controlled drug delivery

Gurpreet Kaur*, Deepinder Singh, Vivekjot Brar

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, Punjab, India

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ABSTRACT

In the present investigation, polysaccharide from the Okra fruits (*Hibiscus esculentus*) was extracted, characterized and explored for its mucoadhesive potential. Mucoadhesive films of okra polymer (OP) were prepared by solvent casting method based on 3^2 factorial design. For these studies, OP (2.0%, 2.5%, 3.0%, w/v) and glycerol (plasticizer) (0.25%, 0.50%, 0.75%, v/v) were taken as independent variables while tensile strength, mucoadhesive strength, contact angle, swelling index and residence time as dependent variables. The developed films were evaluated for their physicochemical, mechanical and electrical properties. The formulated films were found to be smooth, flexible, and displayed adequate mucoadhesive and tensile strength. Their near neutral pH and negative hemolytic studies indicated their non-irritability and biocompatible nature with biological tissues. The formulation comprising of 3% OP and 0.5% glycerol (F8) was found to exhibit optimum mechanical properties. Further, optimized film was loaded with zolmitriptan (model drug) to determine its drug release profiles. *In vitro* and *ex vivo* drug release studies demonstrated a controlled release of zolmitriptan over a period of 8 h in simulated salivary fluid (SSF) pH 6.8, with the correlation coefficient values indicating its non-Fickian kinetics. Thus, OP can be used as a promising biomaterial for controlled drug delivery.

1. Introduction

Oral route, because of its administration ease, patient compliance and possible flexibility in formulation, has always been preferred over other prevailing administrative routes. Oral cavity, especially the buccal region (buccal mucosa) offers an attractive route for drug delivery for local action as well as systemic absorption. Anatomical and physiological features of buccal mucosa, like the presence of smooth muscles with high vascular perfusion, high accessibility, low enzymatic activity and avoidance of hepatic first pass metabolism make it an ideal route for drug delivery. However, the continuous salivary flush in oral cavity limits the transit time of the formulation at an application site within this route. This has further intensified the investigation for the use of bioadhesive polymers to prolong the residence time (RT) of formulation with biological tissues. Various dosage forms that have been developed for the drug delivery through the buccal mucosa includes tablets, lozenges, chewing gums, sprays, films, patches, hydrogels, pastes, ointments, solutions, microspheres, etc. but among these, the buccal films have been reported to be the most promising and successful approach for the effective delivery through the epithelium with higher patient compliance [1].

Bioadhesive buccal films are small, postage stamp sized, thin drug delivery system comprising of mucoadhesive and film forming polymers. The chief advantage of buccal films is that these can be applied even to comatose patient. Further, as the film remains confined to the buccal area over which it is applied, the absorption profile may have less inter and intra-individual variability [2].

Bioadhesive formulations generally employ polymers (natural or synthetic) as their adhesive components. Natural polysaccharides (biopolymers) being safe, biocompatible and biodegradable are preferred over synthetic polymers [3]. Although the characteristic reproducibility of polymers derived from natural sources is a critical issue, yet advances in purification and characterization techniques has led to optimization and standardization of natural products surmounting the above shortcomings [4]. Further, these biopolymers can form non-covalent bonds with the mucin molecules because of the presence of number of carboxyl, hydroxyl and amino groups. As a result, large numbers of medical and pharmaceutical companies are looking upon these biopolymers as potential alternatives to the synthetic analogues. Thus, considering the advantages of the biopolymers, a natural polymer was extracted from okra fruits and investigated for its mucoadhesive potential in this study. The okra polymer (OP) is an acidic

* Corresponding author. Tel.: +91 9814724622.
E-mail address: kaurgpt@gmail.com (G. Kaur).

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polysaccharide, present in fruits of *Hibiscus esculentus* (Malvaceae family) and consists mainly of galactose, rhamnose and galacturonic/glucoronic acid [3,5].

OP has been used earlier in the preparation of controlled drug delivery systems [6], however, no reports have been published regarding its use in formulating buccal films. The presence of hydroxyl and carboxylic acid groups in OP suggest its possible interaction with the glycoprotein chains of mucus indicating its potential as a bioadhesive polymer. Thus, this study was designed to formulate and evaluate OP based mucoadhesive films employing zolmitriptan as a model drug.

2. Materials and methods

2.1. Materials

The fruits of *H. esculentus* (commonly known as bhindi) were purchased from local market. Zolmitriptan was purchased from Molekula Life Sciences Limited (Hyderabad, India). Barium hydroxide, zinc sulfate and glycerin were purchased from S.D. fine chemicals, India. All the chemicals used in the study were of analytical grade.

2.2. Isolation of okra polymer (OP)

OP was isolated by first allowing the okra fruit to swell in water for 8–12 h. This was followed by filtration through muslin cloth, deproteinization with barium hydroxide $(BaOH)_2$ and zinc sulfate $(ZnSO_4)$ and precipitation with acetone. Procedure for extraction of OP from the fruits of *H. esculentus* is diagrammatically represented in Fig. 1 [7].

2.3. Physicochemical characterization of OP

2.3.1. ATR spectroscopy

The powdered OP sample was characterized using ATR spectroscopy employing ALPHA-E, ATR/FTIR spectrometer (Bruker IR, Germany). The scans were taken from 4000 to 500 cm^{-1} wavenumber.

2.3.2. DSC studies

The thermal properties of the powdered OP were evaluated using differential scanning calorimeter (EVO 131, SETARAM Instrumentations France). The sample was heated in the range of 30–400 °C at a heating rate of 10 °C min^{-1}.

2.3.3. X-ray diffraction (XRD)

The detailed information about phase identification and crystal structure of OP was determined using X'Pert Pro XRD with vertical theta–theta goniometer having range of 0–160° 2θ.

2.4. Phytochemical examination

The presence of polysaccharide in OP were confirmed by performing preliminary tests like Ruthenium Red, Molisch, and Iodine test [7,8].

2.5. Micrometric properties

The flow properties and densities of OP [9,10], were determined employing the following tests:

2.5.1. Bulk and tap density

A known amount of the powdered sample was placed in a graduated measuring cylinder and the volume (V_0) occupied by the sample (without tapping) was noted. The cylinder was then tapped and the volume occupied after 100 taps (V_{100}) was read. The bulk and tap densities were calculated using the equation:

$$\text{bulk density}\,(b) = \frac{M}{V_0} \tag{1}$$

$$\text{tap density}\,(t) = \frac{M}{V_{100}} \tag{2}$$

where M is the mass of powdered OP sample taken.

2.5.2. Hausner's index (HI)

HI was calculated as the ratio of tap density to bulk density of the sample.

$$\text{HI} = \frac{t}{b} \tag{3}$$

2.5.3. Compressibility index (C %)

C % was calculated using the following equation:

$$C\% = \frac{(t-b)}{t} \times 100 \tag{4}$$

2.5.4. Angle of repose (θ)

Angle of repose was determined according to the fixed funnel and free standing cone method. Powdered gum sample (100-mesh sieved) was poured via the funnel clamped with its tip above a graph paper. The angle of repose was calculated from values of mean diameter (D) of the base and the height of cone formed by applying following equation:

$$\tan\theta = \frac{2h}{D} \tag{5}$$

2.5.5. Effective pore radius (E_{PR})

A transparent micropipette tip was filled completely with the powdered OP and weighed (W_i). This was followed by drop-wise addition of n-hexane [surface tension (γ) 18.4 mN m^{-1}] on bed top till the entire powder got wet by the solvent and the tip was re-weighed (W_f). The experiment was repeated in triplicate [11]. E_{PR} was determined as follows:

$$E_{PR} = \frac{W_f - W_i}{2\pi\gamma} \times 100 \tag{6}$$

2.6. Physiological properties of OP

2.6.1. Loss on drying (LOD%).

Powdered OP sample (1 g) was placed in a tarred Petri-dish and dried in oven at 105 °C, till constant weight was obtained [7,9]. The sample was then removed, weighed, and moisture content was determined using the equation:

$$\text{LOD\%} = \frac{W_i - W_f}{W_i} \times 100 \tag{7}$$

where W_i is the initial weight of sample and W_f is the final weight after drying.

2.6.2. Solubility

Powdered OP (1 g) was added to 100 ml of distilled water and left undisturbed (6–8 h), allowing it to swell completely. It was then stirred on magnetic stirrer at room (25 ± 1 °C) and elevated temperature (60–70 °C) for approx. 60 min. The solution so formed was cooled and centrifuged at 4000 × g for 20–30 min to remove the insoluble material. The settled portion was then transferred to Petri dish and dried at 105 °C in an oven till constant weight was obtained [10]. Solubility was determined employing the following equation:

$$\text{solubility}\,(\%) = \frac{C_2 - C_1}{C_2} \times 100 \tag{8}$$