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Development and evaluation of tamarind seed xyloglucan-based mucoadhesive buccal films of rizatriptan benzoate

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ABSTRACT

Mucoadhesive buccal films were developed using tamarind seed xyloglucan (TSX) as novel mucoadhesive polysaccharide polymer for systemic delivery of rizatriptan benzoate through buccal route. Formulations were prepared based on 3^2 factorial design with concentrations of TSX and carbopol 934P (CP) as independent variables. Three dependent variables considered were tensile strength, bioadhesion force and drug release. DSC analysis revealed no interaction between drug and polymers. Ex vivo diffusion studies were carried out using Franz diffusion cell, while bioadhesive properties were evaluated using texture analyzer with porcine buccal mucosa as model tissue. Results revealed that bilayer film containing 4% (w/v) TSX and 0.5% (w/v) CP in the drug layer and 1% (w/v) ethyl cellulose in backing layer demonstrated diffusion of 93.45% through the porcine buccal mucosa. Thus, this study suggests that tamarind seed polysaccharide can act as a potential mucoadhesive polymer for buccal delivery of a highly soluble drug like rizatriptan benzoate.

1. Introduction

Among the transmucosal routes, buccal route has prominent advantages such as faster uptake of drug into the systemic circulation and enhanced bioavailability of therapeutic agents (Kaur & Kaur, 2012), leading to rapid onset of action (Consuelo, Falson, Guy, & Jacques, 2007). In addition, buccal drug delivery system avoids first pass effect by directing absorption through the venous system that drains from the cheek (Morales & McConville, 2011). Buccal mucosa has several specific advantages like, faster and richer blood flow, lesser thickness of the buccal mucosa and versatility in designing unidirectional or multidirectional release system for local or systemic action (Vasantha, Puratchikody, Mathew, & Balaraman, 2011). For development of buccal drug delivery system, it should fit into the selection criteria as, size of 1–3 cm^2 and daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 2–6 h (Perioli & Ambrogi, 2004). Several buccal adhesive delivery devices have been developed such as tablet, wafers, gels and films. Overall, a mucoadhesive buccal film offers several benefits due to its small size, thickness and improved patient compliance compared to tablets and gels (Morales & McConville, 2011).

Natural polysaccharides have been widely used as bioadhesive polymers because of their biocompatibility and biodegradability properties. In this study Tamarind Seed Xyloglucan (TSX), a glucosaminoglycan polysaccharide extracted from the kernels of seeds of *Tamarindus indica* Linn., family Fabaceae was used for mucoadhesion and as film former in the dosage form. Chemically tamarind kernel powder is highly branched carbohydrate polymer, with average molecular weight 52,350 Da and is a monomer of glucose, galactose and xylose in a molar ratio of 3:2:1 (Khanna, 1987). It possesses properties like mucoadhesivity, high viscosity, and broad pH lenience. It is used as a stabilizer, thickener, binder and gelling agent. Furthermore, it is non-carcinogenic, biocompatible and has high drug holding capacity (Gupta, Puri, Gupta, Jain, & Rao, 2010).

Rizatriptan benzoate (RB) is a selective 5-HT (1B/1D) receptor agonist used in the treatment of migraine. Although, it is absorbed well after oral administration, it is extensively metabolized hepatically via oxidative deamination by MAO-A, resulting in oral bioavailability of ~45% (Vyas et al., 2000). The recommended dose of rizatriptan benzoate is 5–10 mg.

Though TSX has been reported to be used in buccal delivery of drugs, the effect of these drugs is mainly limited to the oral cavity (Burgalassi, Panichi, Saettone, Jacobsen, & Rassing, 2011). An attempt has been made in the present investigation to utilise TSX, which is abundantly available and a cheap source of polysaccharide xyloglucan in formation of a buccal film of RB.

Thus the aim of this work was to develop and characterize a mucoadhesive buccal film of rizatriptan benzoate using natural polysaccharide TSX and to evaluate TSX as film forming and mucoadhesive polymer for its buccal delivery.

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Table 1
Translation of coded levels in actual units.

Variable levels	Low (−1)	Medium (0)	High (+1)
% Mucoadhesive polymer TSX (X_1)	2	4	6
% Plasticizer glycerin (X_2)	4	8	12

2. Materials and methods

2.1. Materials

RB was obtained as a gift sample from Cipla Ltd. (Mumbai). Tamarind seed xyloglucan (TSX) was gifted by Arihant Industries, Barshi, India. Carbopol 934 (CP), sodium carboxy methylcellulose (SCMC) was purchased from Noveon Inc. All other chemicals and solvents were of analytical grade.

2.2. Experimental design

A 3^2 randomized full factorial design was used for optimization of buccal films. In this model two factors were evaluated, each at three levels. Higher and lower levels of each factor were coded as +1 and −1, respectively, and the mean value as 0. The concentrations of mucoadhesive polymer TSX (X_1), and glycerin (X_2) as a plasticizer were selected as independent variables. The response variables tested include tensile strength (Y_1), bioadhesion force (Y_2) and % drug release at 2 h (Y_3). The selected factor levels are summarized in Table 1.

2.3. Preparation of mucoadhesive buccal films

Mucoadhesive buccal films were prepared by solvent casting method. RB and sodium saccharine (0.1%, w/v) were dissolved in 0.5% (w/v) aqueous solution of sodium bicarbonate. TSX and CP were dissolved in distilled water separately. RB solution was then added to this solution with stirring for 15 min by mechanical stirrer. Glycerin was added as a plasticizer. This solution was then sonicated for 30 min to remove air bubbles. The solution was poured in Petri plate of size 7.7 cm in diameter and was dried in vacuum oven at 50 °C for 24 h. The backing layer was prepared by mixing ethanolic solution of ethyl cellulose (1%, w/v) in a 100 ml volumetric flask. This homogenous solution was poured on the dried medicated film. It was dried in vacuum oven at 50 °C for 5 h. The dried bilayer films were cut into square pieces of sides 1 cm containing 10 mg of drug per patch. Table 2 shows the composition of formulated buccal films.

2.4. Characterization of buccal films

2.4.1. Thickness and weight

The thickness of films was measured using a micrometer screw gage. For each formulation, three randomly selected films with surface area 1 cm^2 were used. Each film was weighed individually on an analytical balance (Shimadzu, Japan) and average weight calculated.

2.4.2. Swelling studies

Swelling index study was performed to study and compare the hydration characteristics of film polymers. Films were weighed individually (designated as w_1) and placed separately in petriplate containing phosphate buffer 6.8 pH. At regular intervals (5, 10, 15, 20, 25, 30, 35, 40, 60 min), samples were removed from the petriplate and excess water was removed carefully by using filter paper. The swollen films were reweighed (w_2). The swelling index of each system was calculated using the following formula (Vasantha et al., 2011):

$$\text{swelling index} = \frac{w_2 - w_1}{w_1 \times 100}. \quad (1)$$

2.4.3. Measurement of surface pH

Surface pH of film was determined to check whether the film causes irritation to the mucosa. The surface pH study was carried out by selecting 3 films randomly. pH measurement was done using pH meter (Equip-Tronics, EQ-614, India). In this method pH probe was placed in close contact with the wetted film surface and pH was recorded for each film (Vasantha et al., 2011).

2.4.4. Folding endurance

Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. This was determined by repeatedly folding the films at the same place until they broke or were folded for 300 times which ever is less (Goud, Desai, & Kumar, 2004).

2.4.5. Tensile strength

Tensile strength of the formulation was checked by Texture Analyzer (CT-3/10,000, Brookfield, USA) equipped with a 10 kg load cell. The film of 200 mm^2 was randomly selected and was fixed between the two clamps of probe TA-DGA and for a hold time of 60 s. The lower clamp was held stationary and the film was pulled apart by the upper clamp. It was pulled at a speed of 2.0 mm/s to a distance of 6 mm with trigger load 0.05 N. The force of the film at the point when the film broke was recorded (Navneet & Pronobesh, 2011).

Data collection and calculations were performed using Texture-Pro CT V1.3 Build 14 software. The tensile strength at break value was calculated using formula:

$$\text{tensile strength}\left(\frac{\text{kg}}{\text{mm}^2}\right) = \frac{\text{force at break}}{\text{initial cross sectional area}}. \quad (2)$$

2.4.6. In vitro bioadhesion force

The bioadhesion force of buccal patches was determined using Texture Analyzer (CT-3/100, Brookfield, USA) equipped with a 100 g load cell. The measurement of bioadhesive force was done on porcine buccal mucosa as the model membrane. The mucosal membrane was excised by removing the underlying connective

Table 2
Composition of various buccal film formulations.

Ingredients (%, w/v)	Formulations and quantity								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rizatriptan benzoate (mg)	10	10	10	10	10	10	10	10	10
Carbopol 934	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
TSX	2	2	2	4	4	4	6	6	6
Glycerin	4	8	12	4	8	12	4	8	12
Na saccharine	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Na bicarbonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose (1%, w/v)	Backing layer on F1–F9 formulations								