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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								

Table 3
Factorial design with corresponding 9 formulations.

Batch no.	Variable levels in coded form		Tensile strength (kg/mm^2) Y_1	Bioadhesion force (N) Y_2	Drug release (%) Y_3
	X_1	X_2			
F1	−1	−1	11.2 ± 0.04	0.3687 ± 0.03	85.64 ± 0.5
F2	−1	0	13.01 ± 0.14	0.3645 ± 0.00	86.12 ± 0.8
F3	−1	+1	13.3 ± 014	0.3632 ± 0.01	85.14 ± 0.7
F4	0	−1	13.08 ± 0.08	0.7235 ± 0.00	94.36 ± 0.5
F5	0	0	15.70 ± 0.04	0.7270 ± 0.03	94.54 ± 0.9
F6	0	+1	16.30 ± 0.08	0.7123 ± 0.02	93.28 ± 0.4
F7	+1	−1	16.83 ± 0.04	0.9374 ± 0.01	90.48 ± 0.7
F8	+1	0	17.87 ± 0.03	0.9064 ± 0.01	89.07 ± 0.9
F9	+1	+1	19.31 ± 0.1	0.8815 ± 0.01	88.68 ± 0.7

tissue. After washing thoroughly with phosphate buffer (pH 6.8), mucosal membrane was fixed between two circular discs which were at lower perspex support. The upper circular disc had a cavity of 12.7 mm diameter through which the mucosal membrane was exposed to the probe. The discs were lowered into the jacketed glass container filled with phosphate buffer (pH 6.8) and maintained at 37 ± 1 °C. The membrane was allowed to equilibrate at this temperature for 30 min. The buccal film was tied tightly using thread on lower side of probe. The probe and circular cavity were aligned to ensure that film comes into direct contact with exposed surface of mucosal membrane. Before carrying out the investigation, exposed area of buccal film was moistened with phosphate buffer pH 6.8. The probe was lowered at a speed of 0.5 mm/s to contact the tissue with load, 90 g and with contact time 120 s. It was removed at the speed of 2 mm/s (Wong, Yuen, & Peh, 2011).

Data collection and calculations were performed using TexturePro CT V1.3 Build 14 software. The adhesive force and adhesiveness were used to evaluate the bioadhesive strength of film. Bioadhesion force (N) was calculated using formula:

$$\text{bioadhesion force}(N) = \frac{\text{bioadhesive strength(g)}}{1000} \times 9.81. \quad (3)$$

2.4.7. In vitro release of rizatriptan benzoate from buccal film

The release rate of film was determined using a design closely similar to USP dissolution apparatus 5 (paddle over disk). It was performed using a dissolution apparatus (TDT-08L, Electrolab). The dissolution medium comprised 500 ml of phosphate buffer pH 6.8 maintained at a temperature of 37 ± 0.5 °C and paddle rotation speed of 50 rpm was used. The film was fixed on the slide in such a way that the drug faced the medium, placed in a self-fabricated basket (50 mm diameter and 6 mm height) made from stainless steel with a sieve opening of approximately 850 μm (sieve No. 20, USP 23). The basket containing the sample was submerged into the dissolution medium at approximately 10 mm above the base of the dissolution vessel. Five ml of sample was collected at predetermined time interval for 2 h. The drug concentration was measured by a UV spectrophotometer (1800, Shimadzu, Japan) at 225 nm (Wong et al., 2011).

2.4.8. Ex vivo permeation studies

Ex vivo permeation study of film was carried out using porcine buccal mucosa on Franz diffusion cells of diffusional diameter 1.76 cm and volume of 7 ml which were placed on six station magnetic stirring unit (Whirlmatic, Spectralab, India). The diffusion media was continuously stirred with the help of a tiny teflon coated needle shaped magnetic stirrer moving at around 300 rpm. Phosphate buffer pH 6.8 was used as receptor solution. The temperature was maintained at 37 ± 5 °C with the help of circulating water. The diffusion was carried out for 2 h. At predetermined time intervals of 5, 10, 20, 40, 60, 80, 100, 120 min, 0.5 ml samples were withdrawn and replaced with fresh phosphate buffer pH 6.8. These aliquots after centrifugation were diluted appropriately and analyzed using UV spectrophotometer (1800, Shimadzu, Japan) at 225 nm (Semalty, Bhojwani, Bhatt, Gupta, & Shrivastav, 2005).

3. Results and discussion

Experimental trials were performed for all 9 possible combinations by 3^2 randomized full factorial design. Various models, such as Linear, 2FI, Quadratic and Cubic, were fitted to the data for two responses simultaneously using Design Expert software 8.0.6 and adequacy and good fit of the models were tested using analysis of variance (ANOVA). Mathematical relationships generated for the studied response variables are expressed as Eqs. (4)–(6). Data were analyzed using Design expert 8.0.6 software. The formulation layout for the factorial design batches F1–F9 is shown in Table 3.

3.1. Characterization of buccal films

Physcio-chemical characteristics of the bilayer films are shown in Tables 3 and 4.

3.1.1. Thickness and weight

The average thickness of all prepared buccal films ranged from 0.28 to 0.31 mm. Weight variation values (mg) of film (1 cm^2) for formulations F1 to F9 were found to be between 48 and 55 mg. Thus the proportional gain in weight of films was observed as the thickness of films increased. The values were uniform for the films within the respective group of formulation type. This depicts that the film cast was uniform.

3.1.2. Swelling studies

Swelling behavior of films as a function of time is illustrated in Table 4. TSX concentration in formulations F1–F3 (2%, w/v) were found to be lesser swelling than other formulations (4%, w/v and 6%, w/v). So, swelling index of films was found to increase with increase in polymer concentration. This property of film has direct influence on release of drug.

3.1.3. Measurement surface pH

Surface pH for formulation F1–F9 was found to range from 6.58 to 7.41. Since range of the pH of film is near to the salivary pH (6.5–7.2), no mucosal irritation was expected.

3.1.4. Folding endurance

The folding endurance of films was found to increase with increase in glycerin concentration. Formulations F5, F6, F8 and F9 showed folding endurance values more than 300. Folding endurance values for films more than 300 indicates high mechanical strength of these films. This is highly desirable because it would

Table 4
Result for physcio-chemical characteristics of the bilayer films.

Code	Thickness uniformity (mm) ±S.D.	Weight uniformity (mg) ±S.D.	Swelling index ±S.D.	Surface pH ±S.D.	Folding endurance ±S.D.	Permeation studies (%) ±S.D.
F1	0.28 ± 0.005	48 ± 0.005	33.4 ± 0.1	6.58 ± 0.02	249 ± 1.52	84.16 ± 0.5
F2	0.28 ± 0.005	49 ± 0.005	32.2 ± 0.2	6.67 ± 0.02	285 ± 1.52	85.46 ± 0.7
F3	0.29 ± 0.005	50 ± 0.005	31.4 ± 0.1	6.84 ± 0.03	294 ± 1.00	84.67 ± 0.5
F4	0.28 ± 0.01	49 ± 0.005	41.27 ± 0.1	7.21 ± 0.01	296 ± 2.08	94.14 ± 0.9
F5	0.30 ± 0.005	54 ± 0.005	42.53 ± 0.1	7.28 ± 0.01	348 ± 1.52	94.45 ± 0.7
F6	0.30 ± 0.01	53 ± 0.005	39.1 ± 0.2	7.31 ± 0.02	378 ± 3.12	91.64 ± 0.5
F7	0.29 ± 0.005	52 ± 0.005	44.78 ± 0.3	7.41 ± 0.01	289 ± 3.16	89.36 ± 0.7
F8	0.31 ± 0.005	55 ± 0.005	44.37 ± 0.1	7.56 ± 0.01	324 ± 2.30	87.49 ± 0.1
F9	0.30 ± 0.005	54 ± 0.005	44.07 ± 0.2	7.43 ± 0.04	356 ± 2.08	89.06 ± 0.5

not allow easy dislocation of the films from the site of application or breaking of film during administration.

3.1.5. Effect of formulation variables on tensile strength

The observation of the data for all formulations for tensile strength (Table 3) depicts that films have sufficient strength to withstand wear and tear occurring during administration and transportation. Tensile strength values for films of more than 7 kg/mm^2 indicate good mechanical strength.

The constant and regression coefficient for Y_1 (tensile strength) are as follows:

$$Y_1 = 15.31 + 2.75X_1 + 1.30X_2. \quad (4)$$

The quadratic model was found to be significant with F value 78.57 ($p < 0.0001$) that implies that the model is significant. Fig. 1 represents the contour plot showing the effect of different proportions of independent variables on the response Y_1. Tensile strength of buccal films increases with increase in glycerin concentration at same concentration of TSX. The combined effect of factor X_1 (TSX) and X_2 (Glycerin) can be further elucidated with the help of response surface plot (Fig. 1). High level of factor X_2 gave high value of tensile strength at all the levels of factor X_1 which indicates that the factor X_2 has significant positive effect on tensile strength. The increase in tensile strength was observed due to increase in concentrations of glycerin and TSX.

3.1.6. Effect of formulation variables on in vitro bioadhesion force

This is an important property as it ensures delivery of drug at the site of administration. This property is directly related to the swelling index. The polymer having greater swelling index has greater bioadhesion force. Formulation F7–F9 show good bioadhesion due to its good swelling index. The bioadhesion force was found to increase with increase in concentration of polymer. This ensures bioadhesion of the film at the site.

The constant and regression coefficient for Y_2 (Bioadhesion force) are as follows:

$$Y_2 = 0.72 + 0.27X_1 - 0.012X_2 - 0.013X_1X_2 - 0.084X_1^2 - 1.862X_2^2. \quad (5)$$

The quadratic model was found to be significant with F value 45.37 ($p < 0.0001$) that implies that the model is significant. Fig. 2 represents the contour plot showing the effect of different proportions of independent variables on the response Y_2. Bioadhesion force of buccal films increases with increase in TSX concentration. The combined effect of factor X_1 (TSX) and X_2 (glycerin) can be further elucidated with the help of response surface plot (Fig. 2). High level of factor X_1 gave high value of bioadhesion force at all the levels of factor X_2 which indicates that the factor X_1 has significant positive effect on bioadhesion force.

3.1.7. Effect of formulation variables on in vitro release of rizatriptan benzoate from buccal film

All the formulations showed negligible release of the drug till complete swelling was achieved i.e., for 40 min. TSX at 4% and 6% shows good swelling index values, greater hydration rates, which would permit faster and ready disentanglement of individual chains, thus increasing the porosity of the film and gives good release. Formulation F5 showed highest drug release (94.54%) in 2 h. This optimized formulation (F5) was subjected to various mathematical models to understand the release pattern. The value of the coefficient of regression (R^2) suggests the best fit kinetic model. It was found to be 0.9813 for Korsmeyers–Peppas and release exponent (n) was 0.6110 indicating that drug transport mechanism is mainly anomalous transport i.e., drug release is being governed by both diffusion as well as erosion.

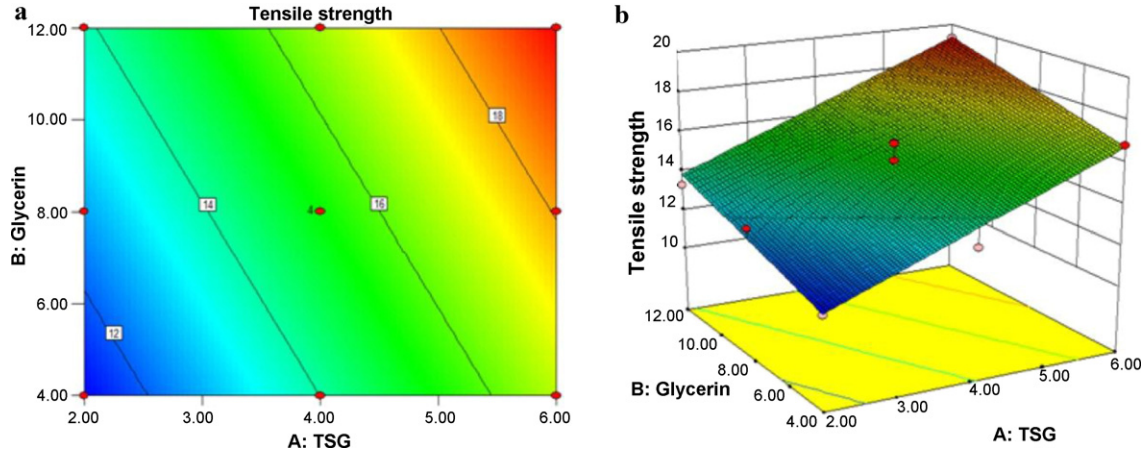

Fig. 1. Two dimensional contour plot (a), three dimensional response surface plots for tensile strength (b).

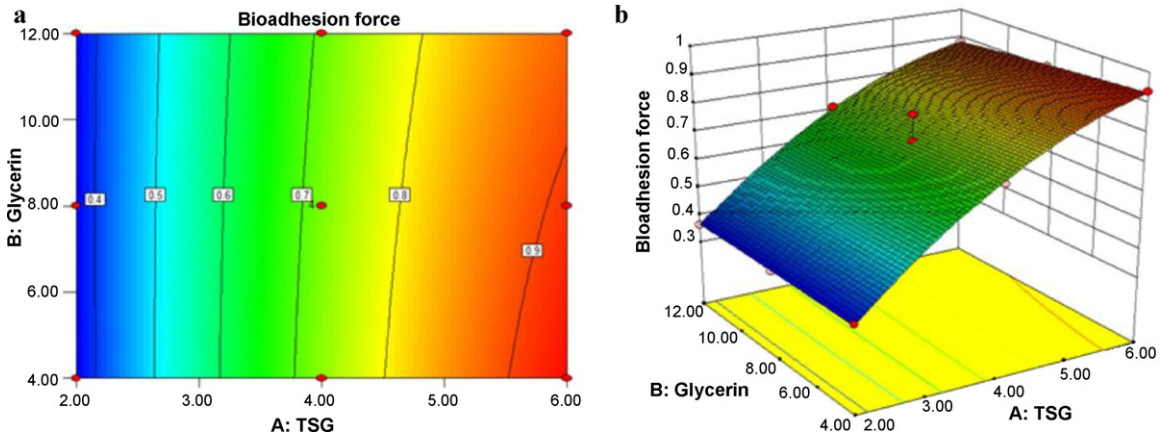

Fig. 2. Two-dimensional contour plot (a), three dimensional response surface plots for bioadhesion force (b).

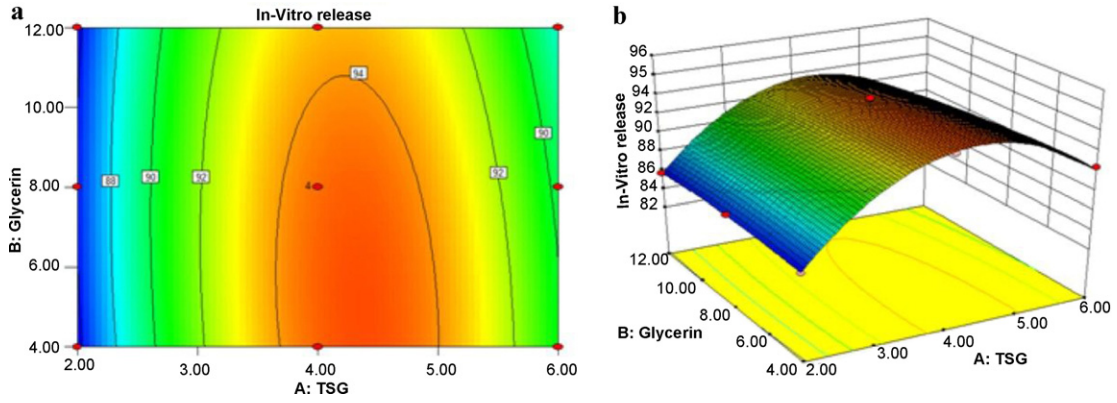

Fig. 3. Two-dimensional contour plot (a), three dimensional response surface plots for % drug release (b).

The constant and regression coefficient for Y_3 (tensile strength) are as follows:

$$Y_3 = 94.41 + 1.78X_1 - 0.46X_2 - 0.47X_1X_2 - 6.55X_1^2 - 0.35X_2^2. \quad (6)$$

The quadratic model was found to be significant with F value 78.57 ($p < 0.0001$) which implies that the model is significant. Fig. 3 represents the contour plot showing the effect of different proportions of independent variables on the response Y_3. The cumulative percentage release increased with increase in concentration of TSX up to certain concentration and then declined. The combined effect of factor X_1 (TSX) and X_2 (glycerin) can be further elucidated with the help of response surface plot (Fig. 3). Medium level of factor X_2 gave high value of drug release which indicates that the factor X_1 has significant positive effect on drug release.

3.1.8. Ex vivo permeation studies

The permeation profiles of RB across porcine buccal mucosa are shown in Fig. 4. Films containing TSX 4%, w/v (F4–F6) provided greater amount of permeated drug than other formulations. Formulations F4 and F5 showed highest diffusion of around 94% at the end of 2 h however the tensile strength of F5 was better than F4. Drug permeation from formulations F1–F3 was less than other formulations. It may be because of poor swelling values and slow hydration rates, which permitted slower release. This behaviour can be correlated with in vitro drug release profiles, which influences drug availability at the absorption site.

3.1.9. Optimization

The computer optimization technique by the desirability approach was used to produce the optimum formulation. The process was optimized for the response variables Y_1–Y_3. The optimized formula was arrived by setting maximum percentage drug release at 2 h with a bioadhesion force being targeted in the range of 0.7–0.9 N and tensile strength greater than 15 kg/mm^2. Formulation F5 was found to be optimized formulation which contained 4% TSX, 0.5% of carbopol and 8% glycerin as plasticizer.

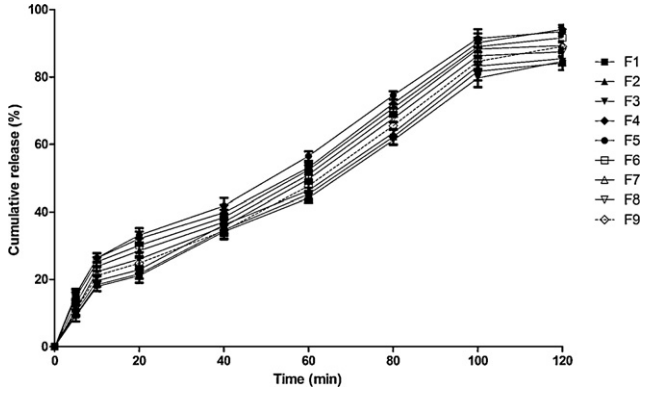

Fig. 4. Ex vivo permeation studies.

4. Conclusion

In the present study mucoadhesive buccal film based on tamarind seed xyloglucan and carbopol was developed, which released the drug over the required period of time (2 h) which would prevent first-pass metabolism to a large possible extent.

Bilayer films were prepared by 3^2 level factorial design and effect of formulation variables on drug release, bioadhesion force and tensile strength were analyzed by applying the computer optimization technique. Based on the results for dependent variables, formulation F5 was found to be optimal formulation with design quadratic model.

Thus, an attempt of formulating a stable mucoadhesive buccal film of RB for treatment of migraine using novel polysaccharide polymer TSX was made by optimization technique. TSX showed good film forming property as well as satisfactory bioadhesion with carbopol 934 than carbopol 934 alone. Thus, cheap and abundantly available natural polysaccharide TSX could be a promising vehicle for systemic delivery of a soluble drug like RB through buccal route. The in vitro studies have shown that this is a potential drug delivery system for RB with considerable good stability and release profile. But, in vivo studies in future would be needed to confirm these results.

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