
Formulation and Evaluation of Buccal Films of Salbutamol Sulphate

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Buccal films of salbutamol sulphate were prepared using three different polymers in various proportions and combinations. The physicochemical parameters like thickness, density, folding endurance, swelling index, mucoadhesive strength based on shear stress and tensile strength, water permeability, drug content and drug release characteristics were evaluated in order to study the effect of polymer and its concentration on the drug release. The properties of the drug free buccal films were compared with the films obtained after drug incorporation in order to study the effect of drug loading on the film characteristics. The thickness and density of all the films produced were in the range of 0.15 to 0.24 mm and 1.104 to 1.445 g/cm³, respectively. High folding endurance was observed for films containing ethyl cellulose and its combination with hydroxypropylmethyl cellulose. The swelling index was found to be high for formulation F₂ containing Eudragit RL100, 6% w/v and 3.2 g of glycerol 40% w/w. The results of the mucoadhesive strength measurement based on shear stress indicated that the buccal films of formulation F₄ containing each 3% of hydroxypropylmethyl cellulose and ethyl cellulose exhibited a high value, but the tensile strength measurement studies indicated high mucoadhesive strength for formulation F₂. Water permeability was found to be high for formulation F₁ containing 6% w/v of Eudragit RL 100 and 2.4 g of glycerol 40% w/w. Drug content uniformity was observed for all films. The drug release studies indicated the first order controlled release kinetics in all cases and the release was extended up to 8 h for formulation F₄. It was also observed that the lower the permeability coefficient the greater was the extended release characteristics for the buccal films. Finally it was concluded that the polymers and their combination influenced the film properties as well as release characteristics.

As the mucoadhesive buccal drug delivery systems affords several advantages¹ it is proposed to develop the buccal films of salbutamol sulphate (SS) using different polymers in order to achieve controlled release. Salbutamol sulphate is an adrenergic drug which is widely used in the treatment of asthma. SS was selected because of its shorter half-life of 4 h². Though there were a few reports on the formulation of SS buccal films³, the present study includes the measurement of mucoadhesive strength and comparison based on the values obtained from shear stress and tensile strength for the films. Further it is also aimed to study

the effect of the type of the polymer and its concentration on the film characteristics with main emphasis on drug release profiles.

MATERIALS AND METHODS

Salbutamol sulphate IP was supplied by Siris Laboratories Pvt. Ltd. Vijayawada. Hydroxypropylmethylcellulose-50 cps (HPMC 50 cps), ethyl cellulose and Eudragit # RL 100 were procured from S. D. Fine Chemicals, Mumbai. The other chemicals used were of AR grade.

Preparation of the films:

By following the solvent casting technique^{4,5} different buccal films of formulations F₁, F₂, F₃ and F₄ with and with-

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out drug were prepared. Glycerol 40% w/w and PEG-600 30% w/w were used separately as plasticizers. The polymer solutions containing 100 mg of SS were poured into a total area of 10 cm² in order to obtain the films.

Thickness, density and folding endurance:

Thickness was measured using a screw gauge at different places of the film and the average was calculated. The density was calculated by using the formula m/v where m and v were the weight and volume of films of size 2 cm², respectively. The volume of the film was calculated from its area multiplied by thickness. Folding endurance was measured manually for films of 2 cm² size⁶. The film was folded at the same place till it broke. The number of times a film could be folded at the same place without breaking gave the value of folding endurance.

Swelling index:

Buccal films of 2 cm² size were weighed accurately and immersed in 50 ml of water. The strips were taken out carefully at 5 and 10 min intervals, blotted with filter paper and weighed accurately. The swelling index was calculated by using the formula; Swelling index=(wet weight-dry weight/wet weight)×100.

Mucoadhesive strength based on shear stress:

A method developed and reported by Madhusudhan Rao *et al.*⁷ was used. In this *in vitro* study two smooth polished flexi glass blocks of size 10 cm² were selected. One block was fixed with adhesive gum on a glass plate, which was fixed on a leveled table. The level was adjusted horizontally. To the upper block a thread was tied and was passed through a pulley. A pan was attached at the end. The length of the thread from the pulley to the pan was fixed. A fixed amount of polymer solution i.e., 0.1 ml was kept on the center of the first block and then the second block was placed over it and pressed by applying 100 g of weight for uniform spreading of the polymer solution as film. After keeping the weight for fixed time intervals of 5 min and 10 min, the weight was removed and weights were added into the pan. The weight just sufficient to pull the upper block was expressed as adhesive strength, which is the shear stress.

Mucoadhesive strength based on tensile strength⁸:

It was measured using sheep's intestinal mucosa. In this method, two glass vials of equal size were taken and they were surrounded with intestine (mucous side exposed). Both the vials were clamped such that they were nearer to

each other. The prepared film of 1 cm×3 cm size was placed between the two vials with the help of a film holder (micro clip) and one end of a nylon thread was tied to the film holder, the thread was then passed over the pulley groove and a pan was tied to the other end. The vials were immersed in phosphate buffer solution of pH 7.4. Weights were added to the pan in an increasing order and the weight at which the film detaches from the mucous membrane was recorded as mucoadhesive bond strength.

Water permeability:

In this study each vial containing one 1 g of fused calcium chloride covered with a strip of the buccal film was used. These vials were placed on wire gauze over saturated solution of potassium chloride in the desiccator. Initially the weight of the vial at zero time was noted for each formulation. Then the weights were recorded at every 6 h and the test was continued up to 48 h. The difference in the weight of the vial at each time interval was noted. The experiment was performed in triplicate and the average values were calculated. The water permeability coefficient 'Q' was calculated by using the formula $Q=WL/S$ where W is the amount of water in g at 24 h, S is the surface area of the vial mouth and L is the thickness of the film. The permeability rate constant 'K' was calculated from the plot of time vs. percent unpermeated water.

Content uniformity:

SS content was estimated from the films by following the reported spectrophotometric method⁹. Films of 2 cm² sizes were dissolved in 5 ml of either acetone for F₁, F₂ or ethanol for F₃, F₄ and final volume was made up to 100 ml with distilled water. To 10 ml of each sample solution, 2 ml of 3% w/v of sodium nitrite, 2 ml of 1% w/v of copper acetate and 0.2 ml of 1 N hydrochloric acid were added and heated on a water bath for 30 min. The solution was cooled and the final volume was adjusted to 25 ml with distilled water. The optical density was measured at a λ max of 525 nm against a reagent blank. The drug contents were estimated from the calibration curve which was constructed between 50 to 400 μ g/ml concentration range.

In vitro drug release:

These studies were conducted by following the device developed by Ilango *et al.*⁹. According to the reported procedure the film of size 2 cm² containing 4 mg of the SS was clamped carefully to a microscopic slide. The slide was placed at an angle of 45° in a 250 ml beaker containing 100 ml of distilled water preheated to 37°. The temperature was

maintained at 37° by keeping the beaker in a water bath. A non-agitated system was selected to eliminate any effect of turbulence on the release rate so as to assure that no disruption of the strip occurred. Periodically 5 ml samples were withdrawn and the volume was replaced with fresh distilled water. The drug content and percent drug released was estimated by the analytical method mentioned earlier. The studies were conducted thrice and the average values were considered.

RESULTS AND DISCUSSION

The formulations for different films and their characteristics were shown in the Table 1. The *in vitro* drug release data was presented in the Table 2. From dissolution data $t_{50\%}$, $t_{90\%}$ and t_{max} of dissolution and dissolution rate constants were calculated and shown in Table 3.

films prepared with HPMC and EC were also found to be similar in properties except transparency. Thickness of the films was found to be between 0.15 mm and 0.24 mm. Density of the films was found to be in the range of 1.104 to 1.445 g/cm³. The density of F₃ with drug was high. Films of F₃ and F₄ did not show any cracks even after folding for more than 150 times hence it was taken as the end point. Except density, the thickness and folding endurance did not vary when comparison was made between plain films and drug-loaded films. The density was slightly increased for drug-loaded films. Eudragit films had possessed more swelling index than the films made with the combination of EC and HPMC. The films of formulation F₃ with and without drug eroded in water. The swelling index was slightly increased in case of drug-loaded films of all formulations. It was also observed that as the time of contact in water increases, the swelling index was also found to be increased.

TABLE 1: BUCCAL FILM CHARACTERISTICS

FC	Composition	TN cm	Dg/cc	FE	SI	ShS g	TS g	PM q (g/h)	PM k (h ⁻¹)	DC±SD (mg)
F ₁	EU-6% W/V +Glycerol- 2.4% W/W	0.15 (0.15)	1.12 (1.10)	34 (37)	11.56* (11.23) 33.0** (32.88) 15.37*	135* (143) 273** (290) 158*	29.6 (22.5)	0.033 7	0.0106	3.68 ±0.21
F ₂	EU-8% W/V +Glycerol- 3.2% W/W	0.24 (0.24)	1.25 (1.20)	45 (49)	(14.94) 43.89** (43.73)	(170) 343** (35)	37.5 (30)	0.027 9	0.0105	3.65 ±0.25
F ₃	HPMC-6% W/V +PEG- 600- (0.54% W/W)	0.17 (0.17)	1.44 (1.42)	>150 (>150)	Erosion* (Erosion) Erosion** (Erosion)	203* (215) 395** (407)	Erosion (Erosion)	0.023 4	0.0076	3.70 ±0.22
F ₄	HPMC 3% W/V +EC-3% W/V+ PEG - 600- (0.54% W/W)	0.16 (0.16)	1.34 (1.32)	>150 (>150)	10.75* (8.25) 18.25** (15.75)	206* (210) 395** (420)	30.7 (24.3)	0.021 4	0.0080	3.88 ±0.12

FC is film code. F₁, F₂, F₃ and F₄ are formulations. TN, D, FE, DC, SI, ShS, TS and PM are thickness, density, folding endurance, drug content, swelling index, shear stress, tensile strength and permeability, respectively. q and k are permeability coefficient and rate constants, respectively. Data in the parenthesis indicates film property without drug *Data after 5 min, **Data after 10 min and SD is the standard deviation.

The films prepared with Eudragit RL 100 were found to be transparent, dry, flexible, non sticky and smooth but the

Shear stress measurements from Table 1 for unloaded films were observed as F₄>F₃>F₂>F₁ and the greater value was obtained for films containing HPMC and EC because of

TABLE 2: *IN VITRO* DRUG RELEASE OF THE BUCCAL FILMS*

Time (min)	% Drug release \pm SD		
	F ₁	F ₂	F ₄
5	8.7 \pm 0.3	3.2 \pm 0.3	4.5 \pm 1.0
10	16.8 \pm 0.2	10.9 \pm 0.5	8.1 \pm 0.5
30	41.1 \pm 0.9	25.9 \pm 0.1	22.4 \pm 0.6
60	64.5 \pm 0.02	47.6 \pm 0.4	38.3 \pm 0.4
120	87.4 \pm 0.1	72.5 \pm 0.6	62.8 \pm 0.2
240	98.4 \pm 0.5	92.1 \pm 0.3	85.5 \pm 0.6
360	-	97.8 \pm 1.2	95.5 \pm 1.5
480	-	-	98.3 \pm 1.6

F₃ was eroded and hence the release studies were not conducted *Average of three trails. SD stands for standard deviation

polymer characteristics. It was also observed that as the time of contact increases in the study the shear stress values were found to be increasing. A difference in shear stress was observed between drug-loaded and unloaded films.

TABLE 3: DISSOLUTION DATA FOR FILMS

Parameter	F ₁	F ₂	F ₄
Dissolution rate constant (k), h ⁻¹	0.01704	0.01068	0.0083
t _{50%} (min)	43.7	64.9	93.5
t _{90%} (min)	126	220	263
t _{max} (min)	240	360	483

Drug-loaded films comparatively exhibited less mucoadhesive strength.

Tensile strength measurements from Table 1 for unloaded films were observed as F₂>F₄>F₁. The type of polymer and its concentration in the formulation F₂ might have contributed high shear stress to the film. It was also observed that the drug-loaded films have exhibited greater bioadhesive strength than unloaded films which might again be due to the net effect of drug and polymer. The drug by its presence in the polymer due to its physicochemical properties might have contributed some additional mucoadhesive property at molecular level. The permeability characteristics, swelling index, hydration, electrostatic bond formation and physical and chemical bonding between buccal films and the tissue carries a lot of influence on the final mucoadhesive characteristics of the film. Between shear

stress and tensile strength measurements the results of tensile strength measurements shall represent the true values of mucoadhesion since these studies were conducted directly by the utilization of sheep's intestinal mucosal membrane. The water permeability coefficients were in the order of F₁>F₂>F₃>F₄. The water permeability coefficient for all the films was found to be zero order kinetics. The permeability rate constants for F₃ and F₄ were considerably different from those of F₁ and F₂, which in turn had influenced their respective release profiles. The *in vitro* release studies have indicated that in F₁ the drug release was extended up to 4 h. Hence F₂ was proposed by increasing the Eudragit concentration up to 2% in order to study its effect on drug release. It was noticed from Table 3 that the drug release was extended for further 2 h i.e., a total 6 h upon consideration of t_{max} values which suggests that the polymer concentration influences drug release.

Films of F₃ lost their texture in water during the studies of swellability. They were eroded in water owing to the type and quantity of polymers present i.e., HPMC and PEG 600 are water swellable and soluble respectively, as a result the texture of the film was not retained during the studies and hence they were found unsuitable for further studies. It was reported that PEGs presence causes erosion in buccal tablets^{10,11}. Hence F₄ was developed by incorporating EC. The drug release from F₄ films was found to be extended up to 8 h (Table 2). The drug release profiles were related to water permeability characteristics of the films i.e., the lower the permeability co-efficient the greater the extended drug release characteristics observed. The swelling index values were also found to be related with drug release pro-

files, i.e., as the swelling index values increases faster release profiles were noticed, in case of F_1 and F_4 , however F_2 was deviated from this generalization because of the type of the polymers present in the film. Hence though there was some sign of swelling to the films it may not influence the drug release at all times.

The drug release profiles followed first order kinetics. Hence the type of the polymer and its concentration and the combination of the polymers greatly influences film characteristics and the drug release. Finally it is concluded that the desired release characteristics can be obtained by appropriate and rational selection of polymers and their combination in the buccal films formulations.

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