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Original research paper

Development and characterization of mucoadhesive patches of salbutamol sulfate for unidirectional buccal drug delivery

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Buccal patches of salbutamol sulfate were prepared using five different water soluble polymers in various proportions and combinations using PEG-400/PG as plasticizers. A 3^2 full factorial design was used to design the experiments for each polymer combination. Patches were laminated on one side with a water impermeable backing layer for unidirectional drug release. The thickness of medicated patches ranged between 0.2 and 0.4 mm and showed an increase in mass whenever PEG-400 was used as plasticizer. The surface pH of all patches approached neutral. Eight formulations which had shown high folding endurance (> 300) were selected for evaluation. Patches prepared with PEG-400 showed a high swelling index. The residence time of the tested patches ranged between 105 and 130 min. Formulations A10, A32, B10 and B32 fitted the Higuchi model best, whereas formulations A19 and B19 showed super case II transport drug release. Stability studies indicated that there was no change in the chemical and physical characteristics during the test period of 6 months.

Keywords: salbutamol sulfate, mucoadhesive patches, buccal drug delivery, 3^2 full factorial design

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Adequate absorption and transport of drugs in the body is the ultimate aim of optimal drug delivery systems. Peroral administration of drugs, the preferred route of drug administration by both clinicians and patients, has several disadvantages, such as hepatic first pass metabolism, longer onset of action and enzymatic degradation of drugs within the GI tract. Mucoadhesive buccal drug delivery systems have currently become an interesting topic for drug delivery research owing to their potential to optimize localized drug delivery, by retaining dosage forms at the site of action or within the absorption site (1). Buccal mucosa is well supplied with both vascular and lymphatic circulation and drug administered through buccal mucosa can circumvent first-pass hepatic

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metabolism and pre-systemic elimination in the gastrointestinal tract (2). The large absolute surface area of the oral cavity contributes to rapid and extensive drug absorption. Also, buccal drug delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in lower inter-subject variability. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally (2).

Previously, studies have been carried out to formulate various mucoadhesive buccal drug delivery devices, including tablets (3), films (4), patches (5), disks (6), ointments (7) and gels (8). Among these formulations, buccal patches are preferred owing to their good flexibility compared to tablets and more accurate dosing of the drug in comparison with gels and ointments.

Asthma and chronic obstructive pulmonary disease (COPD) are among the most prevalent diseases on the earth (9). Salbutamol sulfate (SS) is a short-acting β_2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD. SS is readily absorbed from the GI tract and undergoes the first pass metabolism in the liver and possibly in the gut wall. The plasma half-life of this drug is 4 to 6 hours and thus it requires multiple dosing a day (10). Mucoadhesive buccal patches of SS which bypass the hepatic metabolism and release the drug at a desired rate may have distinct advantages over conventional dosage forms. The physicochemical and pharmacokinetic profiles of SS make it a suitable candidate for the preparation of a buccal adhesive drug delivery system. Therefore, the aim of the present study was to develop unidirectional mucoadhesive buccal patches of SS to ensure satisfactory drug release, and to prevent the first pass metabolism and improve bioavailability.

EXPERIMENTAL

Materials

Salbutamol sulfate was obtained as a gift sample from Dr. Reddy's Laboratories, India. The polymers hydroxypropyl methyle cellulose (HPMC), polyvinyl alcohol (PVA), Carbopol 934p (Cp), sodium carboxymethylcellulose (NaCMC), polyvinyl pyrolidine (PVP K30) were procured from Sigma Chemicals, USA. Agar, methanol, sodium saccharinate, sodium hydroxide, potassium dihydrogen phosphate, polyethylene glycol 400 (PEG-400) and proplylene glycol (PG) were purchased from Merck, India. Biaxially-oriented polypropylene (BOPP) film was supplied by Pidilite, India. Fresh pig buccal mucosa was obtained from a local slaughterhouse and was used within 2 hours of slaughter.

Methods

Formulation of mucoadhesive buccal patches. – The buccal mucoadhesive patches of SS were prepared by the solvent casting technique using water as solvent (11). Different polymer combinations were tried out (HPMC/PVA/Cp, HPMC/PVA/NaCMC, PVA/NaCMC/ Cp and PVA/NaCMC/PVP). A 3^2 full factorial design (Design Expert, Version 7, Stat-Ease Inc, Minneapolis, MN) was used to design the experiments for each polymer

combination. Aqueous polymer solutions of different concentrations were mixed in different ratios as mentioned in Table I. The above polymer solutions were mixed with 2 mL of PG or PEG on a magnetic stirrer, at low rpm, for a period of 1 hour to get a homogenous clear solution. To this mixture, a drug solution corresponding to 230.4 mg was added and mixed thoroughly. This solution was then poured into a specially fabricated Teflon® coated circular dish (9.6 cm diameter). Patches were then allowed to dry at room temperature for 2 hours and were further dried for 36 hrs at 60 °C in a hot air oven. Finally, the patches were vacuum dried for 4 hours at room temperature in a vacuum desiccator. After careful examination, the dried patches were removed, checked for any imperfections or air bubbles and cut into 2 cm diameter patches using a specially fabricated circular stainless steel cutter. The patches were laminated on one side with a water impermeable backing layer (Pidilite® BOPP film). The samples were packed in aluminium foil and stored in a glass container at room temperature.

Evaluation of patches. – Mass uniformity, thickness and folding endurance were determined for the patches without a backing membrane. Mass uniformity and thickness were tested in 3 different, randomly selected, individual patches from each batch using an electronic balance and a standard screw gauge, respectively. Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times without breaking (12).

For drug content evaluation, the medicated patch (without backing membrane) was allowed to dissolve in 10 mL of simulated saliva solution (pH 6.2) for 2–3 hours under occasional shaking. The resultant solution was filtered through 0.46-μm filter paper and after suitable dilution, the amount of SS present in the patch was determined spectrophotometrically at 278 nm (Shimadzu 1800, Japan)

Surface pH of the buccal patches (without backing membrane) was determined by a modified method reported by Bottenberg *et al*. (13). Buccal patches were left to swell for 2 hours on the surface of an agar plate, prepared by dissolving 2 % (*m*/*V*) agar in warmed isotonic phosphate buffer (pH 6.75) under stirring and then pouring the solution into a Petri dish till it gelled at room temperature. The surface pH was measured by bringing a combined glass electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The experiment was repeated thrice and the average was taken.

During the swelling studies, the diameter of the original patch (without backing membrane) was determined first (2 cm). Then the sample was allowed to swell on the surface of an agar plate (prepared as described in the measurement of surface pH section) kept in an incubator maintained at 37 °C. Measurement of the swollen patch diameter was carried out at predetermined time intervals for 90 minutes (11).

*Residence time (*ex vivo *mucoadhesion time)*

The *ex vivo* mucoadhesion (residence) time was determined using a locally modified USP 23 (Erweka ZT72) disintegration apparatus (14, 15). In the current study, pig mucosa was used as the mucosal membrane because pig buccal membrane closely resembles the human buccal membrane in structure and permeability. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with simulated saliva (pH 6.2) at 37 °C. Pig buccal

Table I. Composition of various patch formulations

Formulation[a,b]		HPMC K4M (2 %, *m*/*V*) (mL)	PVA (2 %, *m*/*V*) (mL)	CP 934P (1 %, *m*/*V*) (mL)	SCMC (1 %, *m*/*V*) (mL)	PVP K30 (2 %, *m*/*V*) (mL)	Salbutamol sulfate (mg)
A1	B1	15.0	10.0	5.0			
A2	B2	13.8	9.2	6.9			
A3	B3	12.8	8.6	8.6			
A4	B4	12.9	12.9	4.3			
A5	B5	12.0	12.0	6.0			
A6	B6	11.3	11.3	7.5			
A7	B7	11.3	15.0	3.8			
A8	B8	10.6	14.1	5.3			
A9	B9	10.0	13.3	6.7			
A10	B10	15.0	10.0		5.0		
A11	B11	12.9	8.6		8.6		
A12	B12	11.3	7.5		11.2		
A13	B13	12.9	12.9		4.3		
A14	B14	11.3	11.2		7.5		
A15	B15	10.0	10.0		10.0		
A16	B16	11.3	15.0		3.6		
A17	B17	9.9	13.3		6.7		
A18	B18	9.0	12.0		9.0		10.0
A19	B19		15.0	7.5	7.5		
A20	B20		12.0	6.0	12.0		
A21	B21		10.0	5.0	15.0		
A22	B22		13.3	10.1	6.7		
A23	B23		10.9	8.1	10.9		
A24	B24		9.2	6.9	13.9		
A25	B25		12.0	12.0	6.0		
A26	B26		10.0	10.0	10.0		
A27	B27		8.6	8.6	12.9		
A28	B28		10.0		10.0	10.0	
A29	B29		7.5		15.0	7.5	
A30	B30		6.0		18.0	6.0	
A31	B31		15.0		7.5	7.5	
A32	B32		12.0		12.0	6.0	
A33	B33		10.0		15.0	5.0	
A34	B34		18.0		6.0	6.0	
A35	B35		15.0		10.0	5.0	
A36	B36		12.9		12.9	4.3	

[a] A1-A36: plasticizer used is PEG 400 (2 mL); B1-B36: plasticizer used is PG (2 mL).
[b] Total volume of polymer solution added excluding plasticizer and drug solution was 30 mL.

mucosa, 3 cm long, was glued to the surface of a glass slide. One side of the patch was wetted with one drop of simulated saliva (pH 6.2) and pasted to the pig buccal mucosa by applying a light force with a fingertip for 20 seconds. The glass slide was vertically fixed to the disintegration apparatus and allowed to move up and down (25 times per min) so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The beaker was filled with 800 mL of simulated saliva (pH 6.2) and was kept at 37 ± 1 °C. The time required for the patch to detach from the buccal mucosa was recorded as the mucoadhesion time. The experiment was repeated thrice and the average was taken.

In vitro *drug dissolution*

The dissolution study was carried out using a USP 23 Type-2 rotating paddle dissolution test apparatus (Electrolab, EDT-08Lx) (14). The dissolution medium used was 100 mL of simulated saliva solution (pH 6.2) at 37 ± 5 °C, which was stirred at 50 rpm. The patch of 2-cm diameter was fixed onto the glass disk with the help of cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples (4 mL) were withdrawn at pre-determined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min) and replaced with an equal volume of dissolution medium. The samples were filtered through a 0.45-μm filter and appropriately diluted with simulated saliva solution (pH 6.2) and assayed spectrophotometrically at 278 nm. The mechanism of drug release from the buccal patches was determined by finding the best fit of the release data to Higuchi and Korsmeyer-Peppas plots (16, 17). The release rate constants k and n of each model were calculated by linear regression analysis. Coefficients of determination (R^2) were used to evaluate the accuracy of the fit.

In vitro *drug permeation*

The *in vitro* buccal permeation of SS was studied through the pig buccal mucosa using a Franz-diffusion cell. The tissue preparation was similar to that explained previously. Freshly obtained buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments were clamped together. The donor compartment was slightly wetted with 1 mL of simulated saliva. The receptor compartment was filled with isotonic phosphate buffer pH 7.4. The diffusion cell was thermostated at 37 ± 2 °C and the receptor compartment was stirred at a rate of 100 rpm (14, 18). One mL sample was withdrawn at pre-determined time intervals using a butterfly canula and syringe. The buffer was immediately replaced using blank pre-warmed buffer. After filtration through 0.45-μm filter and appropriate dilution, the samples were analyzed for the drug content at 278 nm.

Accelerated stability studies and stability in human saliva

Selected patches were subjected to accelerated stability testing by wrapping them in aluminium foil and packing in glass vials. These patches were kept in an incubator maintained at 37 ± 0.5 °C and 75 ± 5 % RH for 6 months. Changes in the appearance

(color, shape), residence time and drug content of the stored patches were investigated after 1, 2, 3, 5 and 6 months. The data presented were the mean of three determinations. Stability of the selected patches was assessed in natural human saliva collected from healthy human adult volunteers. Patches were placed in separate Petri dishes containing 5 mL of human saliva and kept in a temperature-controlled oven at 37 ± 0.2 °C.

RESULTS AND DISCUSSION

Formulation of mucoadhesive buccal patches

In the present study, buccal patches of SS were prepared by different polymer combinations of HPMC, PVA, Cp, NaCMC and PVP using the solvent casting method. A total of 72 formulations were prepared in triplicate using a 3^2 factorial design. Factorial design was used only to design the experiments. PG or PEG-400 were used as plasticizers.

Impermeable backing membrane is an essential part of a buccal mucoadhesive patch to obtain unidirectional drug flow. Backing membrane prevents loss of the drug at the required site and also minimizes the exposure of other tissues to the drug by preventing bidirectional flow. Many authors have used ethyl cellulose as a backing membrane but reports have shown some permeability. Also, laminating the patches with ethyl cellulose film was not completely successful (19). Therefore, in the current study, we have used the BOPP film as a backing membrane.

One of our major aims during the formulation step was to avoid use of organic solvents to prevent any unwanted residual solvent complications *in vivo*. Use of water as a solvent was the reason for the long duration of drying time during the formulation step (36 hours).

Mass, thickness, folding endurance, drug content and surface pH

Physicochemical characteristics of the medicated patches are shown in Table II. The prepared patches were smooth, uniform in thickness, mass, drug content and showed no visible cracks or folds. The thickness of the medicated patches ranged between $0.2 \pm 0.00_2$ and $0.4 \pm 0.0_1$ mm, and the mass of the patches varied between 42.7 ± 2.8 and 85.19 ± 2.1 mg. It was noticed that the mass of the patches increased with PEG 400 as plasticizer. The surface pH of all the patches ranged from 6–7 and hence no mucosal irritation was expected. The patches showed favorable drug loading which varied between 8.3 ± 0.4 and 9.7 ± 0.4 mg per 2 cm^{-2} patches (*i.e.*, drug loading efficacy of 83 to 97 %). All patches showed satisfactory folding endurance of >150. Of these 72 formulations eight patches (A1, A10, A19, A32, B2, B10, B19 and B32) showed high folding endurance of over 300. Therefore these patches were selected for further evaluations.

Swelling studies

Swelling behavior of selected SS patches as a function of time is illustrated in Fig. 1. The swelling indices of the patches were high (up to 62 ± 4 for A10 at the end of 90 min) and varied between the formulations. Higher swelling indices may be due to the presen-

Table II. Physicochemical characteristics of SS patches

Formulation	Mass uniformity (mg)	Thickness (mm)[a]	Folding endurance (times)[b]	Drug content (mg)[a]	Surface pH[b]
A1	73.3 ± 5.8	0.4 ± 0.0$_0$	>300	9.0 ± 0.8	6.3
A2	70.4 ± 4.2	0.3 ± 0.0$_0$	175	9.1 ± 0.7	6.5
A3	76.8 ± 2.8	0.3 ± 0.0$_1$	180	8.5 ± 0.7	6.7
A4	72.6 ± 1.8	0.4 ± 0.0$_0$	150	8.8 ± 0.8	7.0
A5	75.3 ± 3.7	0.4 ± 0.0$_1$	198	9.0 ± 0.9	6.0
A6	76.5 ± 8.5	0.3 ± 0.0$_1$	220	8.6 ± 0.5	6.4
A7	74.1 ± 6.4	0.3 ± 0.0$_1$	194	8.5 ± 0.4	7.0
A8	72.2 ± 6.4	0.4 ± 0.0$_1$	188	9.1 ± 0.7	6.3
A9	75.4 ± 4.3	0.3 ± 0.0$_1$	178	9.1 ± 0.6	6.5
A10	83.3 ± 5.8	0.4 ± 0.0$_1$	>300	9.3 ± 0.6	6.1
A11	82.5 ± 2.4	0.4 ± 0.0$_1$	199	9.0 ± 0.5	6.5
A12	84.2 ± 2.7	0.3 ± 0.0$_1$	187	8.6 ± 0.4	6.6
A13	85.2 ± 2.1	0.4 ± 0.0$_1$	172	8.5 ± 0.4	7.0
A14	81.6 ± 5.8	0.4 ± 0.0$_1$	200	8.9 ± 0.7	6.4
A15	82.5 ± 3.3	0.2 ± 0.0$_1$	168	8.9 ± 0.6	6.4
A16	84.4 ± 4.3	0.3 ± 0.0$_1$	182	9.0 ± 0.6	6.8
A17	82.0 ± 3.4	0.2 ± 0.0$_1$	195	9.1 ± 0.8	6.7
A18	84.9 ± 7.2	0.4 ± 0.0$_1$	188	9.0 ± 0.6	6.5
A19	63.3 ± 8.3	0.4 ± 0.0$_1$	>300	9.5 ± 0.8	6.2
A20	64.9 ± 2.6	0.3 ± 0.0$_1$	197	9.0 ± 0.6	6.4
A21	65.6 ± 4.3	0.3 ± 0.0$_1$	176	8.8 ± 0.8	6.8
A22	62.5 ± 3.7	0.4 ± 0.0$_1$	165	8.7 ± 0.6	6.4
A23	65.8 ± 3.2	0.4 ± 0.0$_1$	186	8.3 ± 0.4	6.5
A24	63.5 ± 1.4	0.4 ± 0.0$_1$	197	8.5 ± 0.6	6.8
A25	63.8 ± 3.4	0.4 ± 0.0$_1$	172	8.6 ± 0.7	7.0
A26	62.0 ± 7.2	0.4 ± 0.0$_1$	168	9.0 ± 0.7	6.4
A27	64.5 ± 5.5	0.2 ± 0.0$_1$	241	8.8 ± 0.6	6.1
A28	75.0 ± 5.1	0.3 ± 0.0$_1$	186	8.6 ± 0.5	6.8
A29	74.1 ± 5.4	0.4 ± 0.0$_1$	200	8.9 ± 0.7	6.7
A30	76.2 ± 7.8	0.4 ± 0.0$_1$	195	9.0 ± 0.7	6.6
A31	74.2 ± 6.2	0.4 ± 0.0$_1$	165	9.0 ± 0.6	6.4
A32	79.9 ± 6.2	0.4 ± 0.0$_1$	>300	9.1 ± 0.5	6.4
A33	78.5 ± 5.1	0.3 ± 0.0$_1$	172	9.1 ± 0.6	6.3
A34	79.3 ± 4.3	0.3 ± 0.0$_1$	187	8.8 ± 0.5	6.8
A35	77.2 ± 6.7	0.4 ± 0.0$_1$	184	8.5 ± 0.7	6.6

A36	76.5 ± 5.8	0.2 ± 0.0$_1$	169	8.9 ± 0.6	6.5
B1	42.8 ± 8.7	0.4 ± 0.0$_1$	196	9.0 ± 0.7	6.4
B2	45.0 ± 4.2	0.4 ± 0.0$_1$	>300	9.3 ± 0.8	6.3
B3	43.3 ± 3.4	0.4 ± 0.0$_1$	200	9.0 ± 0.6	6.3
B4	42.7 ± 2.8	0.3 ± 0.0$_1$	169	9.1 ± 0.7	6.8
B5	44.3 ± 1.8	0.2 ± 0.0$_1$	199	9.1 ± 0.7	6.2
B6	46.2 ± 6.4	0.4 ± 0.0$_1$	249	8.5 ± 0.6	6.4
B7	43.8 ± 3.5	0.4 ± 0.0$_1$	158	8.6 ± 0.7	6.3
B8	44.6 ± 1.9	0.4 ± 0.0$_1$	188	8.6 ± 0.6	6.3
B9	44.3 ± 1.6	0.4 ± 0.0$_1$	188	8.8 ± 0.6	6.4
B10	50.0 ± 8.1	0.3 ± 0.0$_1$	>300	9.6 ± 0.2	6.4
B11	49.5 ± 7.4	0.4 ± 0.0$_1$	186	9.1 ± 0.7	6.5
B12	48.3 ± 4.6	0.2 ± 0.0$_1$	198	9.1 ± 0.5	6.0
B13	49.8 ± 7.7	0.4 ± 0.0$_1$	194	8.9 ± 0.6	6.8
B14	47.8 ± 4.5	0.3 ± 0.0$_1$	187	9.0 ± 0.7	6.5
B15	47.6 ± 4.2	0.4 ± 0.0$_1$	197	8.9 ± 0.7	6.8
B16	46.0 ± 7.1	0.4 ± 0.0$_1$	186	9.1 ± 0.8	6.7
B17	46.8 ± 7.3	0.3 ± 0.0$_1$	192	9.0 ± 0.6	6.9
B18	42.9 ± 7.1	0.4 ± 0.0$_1$	191	9.0 ± 0.7	6.5
B19	50.0 ± 2.7	0.3 ± 0.0$_1$	>300	9.2 ± 0.6	6.4
B20	49.3 ± 2.7	0.2 ± 0.0$_1$	199	9.0 ± 0.8	6.3
B21	48.5 ± 6.1	0.4 ± 0.0$_1$	188	9.1 ± 0.8	6.6
B22	49.5 ± 4.6	0.4 ± 0.0$_1$	177	8.5 ± 0.6	6.8
B23	53.6 ± 3.2	0.4 ± 0.0$_1$	182	8.8 ± 0.8	6.8
B24	51.1 ± 2.8	0.4 ± 0.0$_1$	225	9.1 ± 0.7	6.4
B25	50.1 ± 3.0	0.4 ± 0.0$_1$	167	9.1 ± 0.6	6.6
B26	54.9 ± 2.6	0.4 ± 0.0$_1$	186	9.0 ± 0.6	6.4
B27	55.8 ± 3.4	0.4 ± 0.0$_1$	199	9.0 ± 0.6	6.7
B28	54.3 ± 1.8	0.3 ± 0.0$_1$	165	8.9 ± 0.4	6.8
B29	55.5 ± 4.8	0.2 ± 0.0$_1$	199	9.0 ± 0.8	6.8
B30	53.5 ± 2.2	0.3 ± 0.0$_1$	197	9.1 ± 0.4	6.3
B31	54.2 ± 5.4	0.4 ± 0.0$_1$	188	9.0 ± 0.6	6.5
B32	55.4 ± 3.5	0.4 ± 0.0$_1$	>300	9.7 ± 0.4	6.3
B33	53.2 ± 4.8	0.4 ± 0.0$_1$	197	9.0 ± 0.8	6.3
B34	52.1 ± 8.4	0.3 ± 0.0$_1$	197	8.9 ± 0.7	6.8
B35	53.4 ± 1.5	0.4 ± 0.0$_1$	233	8.5 ± 0.6	6.4
B36	54.3 ± 5.4	0.4 ± 0.0$_1$	200	9.0 ± 0.8	6.5

[a] Mean ± SD, n = 3.
[b] Mean, n = 3.

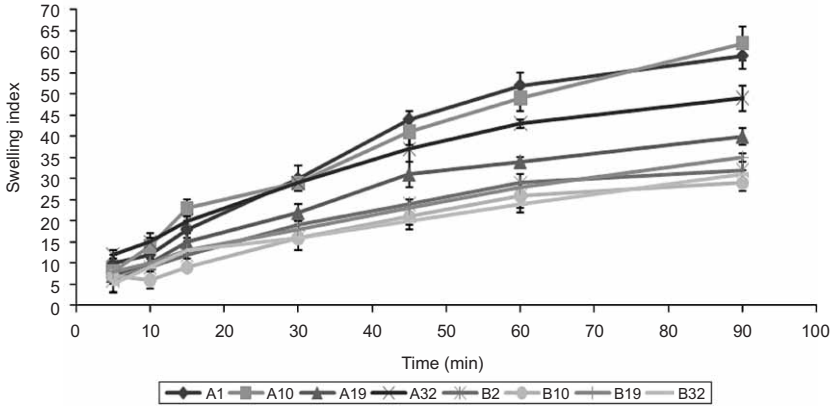

Fig. 1. Swelling behavior of selected SS patches. Mean ± SD, n = 3.

ce of water soluble polymers. The swelling behavior provides an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after absorption of moisture. Differences in swelling of the tested hydrophilic polymers could be explained by the difference in resistance of the matrix network structure (hydrogen bond) to the movement of water molecules. In addition, the presence of a water-soluble drug might have improved the surface wetting of the matrix. The swelling indices increased in the following order: B10<B32<B2<B19<A19<A32<A1< A10. It was seen that patches with PEG-400 showed more swelling compared to those with PG. This index even reached a maximum value of 62 for formulation A10 after 90 min. This could be due to higher water uptake of PEG-400 compared to PG. The presence of PEG-400 could have altered the water distribution within such systems and thereby modified the polymer matrix structure (20). Even though the swelling indices were high, the patches did not show any appreciable changes in shape and form and maintained their integrity during the study period.

*Residence time (*ex vivo *mucoadhesion time)*

The values of *ex vivo* mucoadhesion time are presented in Fig. 2. The residence time of the tested patches ranged between 105 and 130 min. Previous studies reported no relation between mucoadhesion strength and mucoadhesion time (18). However, none of the patches were detached from the mucosal membrane over the study period, which indicated that the bioadhesion of all patches was sufficient to retain the patch on the buccal mucosa.

In vitro *drug dissolution*

In vitro release of SS from different patches is shown in Fig. 3. The maximum *in vitro* release was evaluated to be 101.3 ± 1.8 % over a period of 60 min for formulation A10. This finding was also in agreement with the swelling studies where A10 showed the ma-

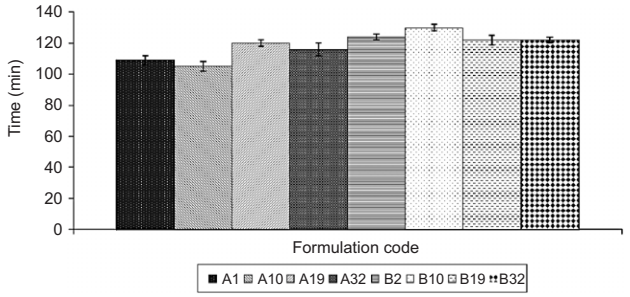

Fig. 2. *Ex vivo* mucoadhesion time. Mean ± SD, $n = 3$.

ximum swelling index. Formulations A1, B2, B10 and B32 showed maximum drug release after 45 min, A10, A32, B19 showed maximum drug release after 60 min and A19 showed maximum drug release after 90 min. Faster drug release can be correlated with the high swelling indices observed in this study. From the drug release profile we could not detect any relation between the drug release and polymer composition. From an initial examination, the drug release profile of all patches showed an erratic drug release, which was not appropiate for a controlled drug delivery system. The drug release mechanism from controlled release devices is very complex, and not yet completely understood. Although some processes may be classified as either purely diffusional or purely erosion controlled, many others can only be interpreted as being governed by both.

The R^2, k and n values are given in Table III. Formulations A10, A32, B10 and B32 provided good fit to the Higuchi model. According to this model, the drug release from these patches may be controlled by diffusion through the micropores. The remaining formulations showed the best fit to the Korsmeyer-Peppas model. Formulations A1, A10, B2, A32, B10 and B32 showed Fickian release, which is characterized by a linear dependence of the released drug on the square root of time, which is concentration dependent. Formulations A19 and B19 showed super case II transport drug release. This mechanism could result from increased plasticization at the relaxing boundary. When swelling is predominant, drug diffusion probably occurs through the solvent-filled pathways of the

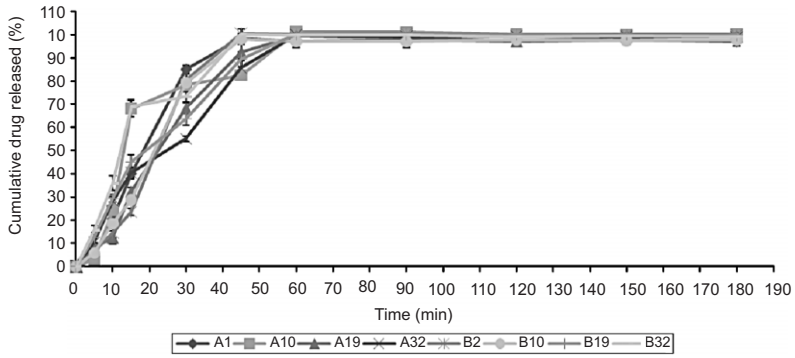

Fig. 3. *In vitro* release of SS from different patch formulations. Mean ± SD, $n = 3$.

Table III. R^2, k *and* n *for selected formulations*

Formulation	Higuchi		Korsmeyer-Peppas		Mechanism of drug release
	R^2	k ($min^{-1/2}$)	R^2	n	
A1	0.9811	0.2266	0.9833	0.3866	Fickian
A10	0.9985	1.6240	0.8013	1.2987	Diffusion/Fickian
A19	0.9754	2.2032	0.9974	1.3154	Super case II transport
A32	0.9981	1.6129	0.9846	0.8332	Diffusion/Fickian
B2	0.9853	0.2356	0.9892	0.4012	Fickian
B10	0.9918	1.5901	0.7701	1.3735	Diffusion/Fickian
B19	0.9773	2.2113	0.9834	1.3064	Super case II transport
B32	0.9058	1.7526	0.8982	0.8028	Diffusion/Fickian

swollen patch. Erosion of the matrix can also influence drug release from this polymer matrix. A relative contribution of erosion and diffusion to the overall release mechanism is suggested. Since all the polymers studied in these formulations were hydrophilic in nature, we could not correlate the difference in the mechanism of drug release with the polymer properties.

In vitro *drug permeation*

The drug permeation was fast and showed a similar profile to that of the *in vitro* drug release. From formulation A10, 100 % of SS was permeated over a period of 60 min. This finding was also in agreement with the swelling studies where A10 showed the maximum swelling index. Formulations A1, B2, B10 and B32 showed maximum drug permeation after 45 min, A10, A32 and A19 showed maximum drug permeation after 60 min, and A19 showed maximum drug permeation after 90 min. SS was released from the formulations and permeated through the porcine buccal membrane and hence could possibly permeate through the human buccal membrane as well. There was a good correlation between the *in vitro* drug release and *in vitro* drug permeation results. The coefficient of determination, R^2 was > 0.994 for A1, A10, A19, A32, B2, B10, B19 and B32.

Accelerated stability studies and stability in human saliva

Accelerated stability study data of the medicated patches is shown in Table IV. During and at the end of the accelerated stability study, the tested patches showed non-significantly different drug content from that observed at the beginning of the study. They also showed satisfactory flexibility and elastic properties during and at the end of the accelerated study period. We have conducted stability studies in normal human saliva to appropriately mimic the drug and device stability in the oral cavity *in vivo*. No color changes or unexpected changes in the texture were observed. The drug content of the tested patches was in the range of 8.7 ± 0.5 and 9.6 ± 0.3 mg per 2 cm^2 patch. The results of stability studies indicated that there was no influence on the chemical and physical stability of the formulations during the test period.

Table IV. Physical stability of selected SS patches

Evaluation parameter	Formulation code	1st month	2nd month	3rd month	5th month	6th month
Drug (mg)[a]	A1	8.9 ± 0.7	8.9 ± 0.6	8.8 ± 0.5	8.8 ± 0.6	8.7 ± 0.5
	A10	9.2 ± 0.5	9.1 ± 0.4	9.0 ± 0.5	9.0 ± 0.3	8.9 ± 0.2
	A19	9.4 ± 0.6	9.3 ± 0.7	9.2 ± 0.5	9.1 ± 0.4	9.0 ± 0.5
	A32	9.0 ± 0.3	8.9 ± 0.4	8.9 ± 0.2	8.8 ± 0.4	8.8 ± 0.2
	B2	9.2 ± 0.6	9.2 ± 0.7	9.1 ± 0.5	9.0 ± 0.4	9.0 ± 0.5
	B10	9.5 ± 0.2	9.5 ± 0.1	9.4 ± 0.2	9.3 ± 0.2	9.2 ± 0.1
	B19	9.1 ± 0.5	9.1 ± 0.4	9.0 ± 0.3	9.0 ± 0.2	8.9 ± 0.4
	B32	9.6 ± 0.3	9.5 ± 0.2	9.5 ± 0.4	9.4 ± 0.3	9.3 ± 0.2
Residence time[a]	A1	108 ± 3	107 ± 4	106 ± 2	105 ± 4	103 ± 3
	A10	104 ± 3	102 ± 3	102 ± 2	100 ± 4	100 ± 3
	A19	118 ± 2	114 ± 2	113 ± 4	112 ± 3	111 ± 4
	A32	115 ± 4	113 ± 2	112 ± 2	110 ± 2	109 ± 2
	B2	123 ± 2	121 ± 3	120 ± 3	119 ± 2	119 ± 2
	B10	129 ± 2	127 ± 4	126 ± 3	124 ± 2	122 ± 2
	B19	121 ± 3	120 ± 4	120 ± 2	119 ± 4	118 ± 4
	B32	120 ± 2	119 ± 2	118 ± 4	117 ± 4	117 ± 3
Appearance	A1	No change	No change	No change	No change	No change
	A10					
	A19					
	A32					
	B2					
	B10					
	B19					
	B32					

[a] Mean ± SD, $n = 3$.

CONCLUSIONS

Novel mucoadhesive buccal patches of SS with unidirectional drug delivery were developed to overcome the first-pass metabolism and subsequent low bioavailability of the salbutamol sulfate. The *in vitro* studies have shown that this is a potential drug delivery system for SS with a considerably good stability and release profile. Future studies are warranted to confirm these results *in vivo*.

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S A Ž E T A K

Razvoj i karakterizacija mukoadhezivnih flastera salbutamol sulfata za jednosmjernu bukalnu isporuku

AYRIVAN PURATCHIKODY, VISWANADHAN VASANTHA PRASANTH, SAM THOMAS MATHEW i BALARAMAN ASHOK KUMAR

U radu je opisana priprava flastera za bukalnu primjenu upotrebom različitih omjera pet vodotopljivih polimera i PEG-400/PG kao plastifikatora. Potpuni 3^2 faktorijalni dizajn upotrebljen je za dizajniranje eksperimenata za svaku kombinaciju polimera. Flasteri su postavljeni na jednu stranu usta s vodonepropusnom podlogom, koja omogućava jednosmjerno oslobađanje lijeka. Debljina flastera varirala je između 0,2 i 0,4 nm. Flasteri s PEG-400 bili su malo veće mase. pH na površini svih flastera bio je blizu neutralnog. Osam pripravaka vrlo otpornih na presavijanje (> 300) izabrano je za daljnju evaluaciju. Flasteri pripravljeni s PEG 400 imali su veliku sposobnost bubrenja. Flasteri su se zadržali na mjestu primjene između 105 i 130 min. Pripravci A10, A32, B10 i B32 najbolje su slijedili Higuchijev model, dok su pripravci A19 i B19 pokazivali anomalno oslobađanje koje ne slijedi Fickov zakon. Ispitivanje stabilnosti pokazalo je da ne postoje promjene u kemijskim i fizikalnim svojstvima pripravaka tijekom 6 mjeseci.

Ključne riječi: salbutamol sulfat, mukoadhezivni flasteri, bukalna isporuka, 3^2 potpuni faktorijalni dizajn

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