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Original Article

Effect of permeation enhancers in the mucoadhesive buccal patches of salbutamol sulphate for unidirectional buccal drug delivery

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Abstract

The purpose of this work was to study the effect of various permeation enhancers on the permeation of salbutamol sulphate (SS) buccal patches through buccal mucosa in order to improve the bioavailability by avoiding the first pass metabolism in the liver and possibly in the gut wall and also achieve a better therapeutic effect. The influence of various permeation enhancers, such as dimethyl sulfoxide (DMSO), linoleic acid (LA), isopropyl myristate (IPM) and oleic acid (OA) on the buccal absorption of SS from buccal patches containing different polymeric combinations such as hydroxypropyl methyl cellulose (HPMC), carbopol, polyvinyl alcohol (PVA), polyvinyl pyrollidone (PVP), sodium carboxymethyl cellulose (NaCMC), acid and water soluble chitosan (CH_{AS} and CH_{WS}) and Eudragit-L100 (EU-L100) was investigated. OA was the most efficient permeation enhancer increasing the flux greater than 8-fold compared with patches without permeation enhancer in HPMC based buccal patches when PEG-400 was used as the plasticizer. LA also exhibited a better permeation enhancing effect of over 4-fold in PVA and HPMC based buccal patches. In PVA based patches, both OA and LA were almost equally effective in improving the SS permeation irrespective of the plasticizer used. DMSO was more effective as a permeation enhancer in HPMC based patches when PG was the plasticizer. IPM showed maximum permeation enhancement of greater than 2-fold when PG was the plasticizer in HPMC based buccal patches.

Keywords: Salbutamol sulphate; Permeation enhancer; Steady state flux; Permeability coefficient; Enhancement ratio

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are among the most common and prevalent diseases in the world (1). Salbutamol sulphate (SS) is a short-acting β_2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD and also indicated for acute asthma, symptomatic relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD), protection against exercise-induced asthma. After oral administration, SS is readily absorbed from the gastro intestinal tract and undergoes the first pass metabolism in the liver and probably in the gut wall. The plasma half-life of this drug is 4 to 6 h, the oral bioavailability of SS is approximately 40% and thus it requires multiple dosing a day (2). Therefore, this drug is now rarely delivered via the oral route.

Salbutamol sulphate is usually given by inhalation or slow intravenous injections (painful administration), in the management of severe asthmatic attacks. Actually, most (or all, in several countries) products containing this drug are administered by inhalation for direct effect on bronchial smooth muscle. This is usually achieved through metered dose inhalers (MDIs), nebulisers or other proprietary delivery devices (e.g. Rotahaler or Autohaler). All these drug delivery systems have reported to have many disadvantages like

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inaccuracy of dosing (require correct actuation and inhalation coordination to deliver accurate dose), patient compliance due to the presence of chlorofluorocarbon (CFC), cost of the preparation and frequency of administration (3).

In order to avoid above lacunas and achieve a better therapeutic effect, one promising method is to administer the drug via the buccal mucosa. The physicochemical and pharmacokinetic profiles of SS make it a suitable candidate for the preparation of a buccal adhesive drug delivery system. 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. However, the mucosa is a natural barrier, and only a few drugs can penetrate easily and in sufficient quantities to be effective. Therefore, in recent years, numerous studies have been conducted in the area of permeation enhancement (4,5). Permeation enhancers improve the ability of membrane to absorb drugs (6,7). In the present study, our aim was to investigate the effect of permeation enhancers in the release of SS from the SS buccal patches.

MATERIALS AND METHODS

Materials

Salbutamol sulphate was obtained as a gift sample from Dr. Reddy's Laboratories, India. The polymers; hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), carbopol 934p (Cp), sodium carboxymethyl cellulose (NaCMC), polyvinyl pyrolidone (PVP K30), chitosan water soluble (CH_{WS}), chitosan acid soluble (CH_{AS}) were procured from Sigma Chemicals, USA. Eudragit L100 (EU-L100, 95% dispersion) was obtained as a gift sample from Rohm Pharma, Germany. Oleic acid (OA), linoleic acid (LA), isopropyl myristate (IPM), and dimethyl sulphoxide (DMSO) were obtained from Loba Chemicals, Mumbai, India. Tween-80 was a gift sample from Sd Fine Chemicals, Bangalore, India. Agar, sodium hydroxide, potassium dihydrogen phosphate, polyethylene glycol 400 (PEG-400) and propylene 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 h of slaughter.

Formulation of salbutamol sulphate buccal patches without permeation enhancers

The buccal mucoadhesive patches of SS were prepared by the solvent casting technique. Different polymer combinations were tried out (HPMC / PVA / Cp, HPMC / PVA / NaCMC, PVA / NaCMC / Cp, PVA / NaCMC / PVP, CH_{WS} / PVP / HPMC, CH_{WS} / PVA / HPMC, CH_{AS} / PVP / HPMC, CH_{AS} / PVA / HPMC, EU-L100 / HPMCK4M / PVA, EUL100 / PVA / Cp-934P) (3,8,9). 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. EU-L100 (95%) was dissolved in ethanol, HPMC in ethanol: acetone mixture (3:1 v/v) and PVA in water. To 5 mL of EU-L100 dispersion (95%), 5 mL of ethanol and 0.05% of tween 80 were added and mixed well on a magnetic stirrer. Aqueous polymer solutions of different concentrations were mixed in different ratios as mentioned in Table 1.

Table 1. Composition of selected salbutamol sulphate buccal patches.

Composition	Formulation code					
	A_{10}	B_2	C_{18}	D_{36}	E_{12}	F_{12}
Salbutamol sulphate (mg)	10	10	10	10	10	10
Hydroxypropyl methyl cellulose K-4M (2%	15	13.8	13.3	13.3		
Poly vinyl alcohol (2% m/v) (mL)	10	9.2	10	10	7.5	7.5
Sodium carboxymethyl cellulose(1% m/v) (mL)	5					
Chitosan water soluble (2% m/v) (mL)			6.7			
Chitosan acid soluble (1% m/v) (mL)				6.7		
Eudragit-L100 (10 % m/v) (mL)					7.5	7.5
Carbopol-934P (1% m/v) (mL)		6.9			15	15
Propylene glycol (mL)		2		2		2
Polyethylene glycol (mL)	2		2		2	
Sodium saccharinate (mL)	1	1	1	1	1	1

Total volume of polymer solution added excluding plasticizer and drug solution was 30 mL.

Two ml of PG or PEG-400 were mixed with the above polymer solutions on a magnetic stirrer, for a period of 1 h, at low rpm, to get a homogeneous clear solution. To this solution, SS solution corresponding to 230.40 mg and sodium saccharinate was added, mixed thoroughly and was poured into a 9.6 cm diameter, specially fabricated Teflon® coated circular dish. Patches were then allowed to dry at room temperature for 2 h and were further dried for 36 h at 60 ^{o}C in a hot air oven. But in case of EU-L100 combination the patches dried only for 18 h at 40 ^{o}C. At last, the patches were vacuum dried for 4 h at room temperature in a vacuum desiccator. After careful assessment, the dried patches were detached from the circular dish, checked for any imperfections or air bubbles and cut into 2 cm diameter patches with 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 aluminum foil and stored in a glass container at room temperature.

Evaluation of patches

The prepared patches were evaluated for mass uniformity, thickness, folding endurance, drug content uniformity, surface pH, swelling behaviour, residence time (*ex vivo* mucoadhesion time), *in vitro* drug dissolution and *in vitro* drug permeation. The procedures were reported in our earlier publications (3,8,9). Briefly, mass uniformity, thickness and folding endurance were determined for the patches without the 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.

For drug content, the medicated patch (without backing membrane) was allowed to dissolve in 10 ml of simulated saliva solution (pH 6.2) for 2-3 h 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 patches were left to swell for 2 h 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 min. The experiment was repeated thrice and the average was taken.

For 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 min.

The *ex-vivo* mucoadhesion (residence) time was determined using a locally modified USP 23 (Erweka ZT72) disintegration apparatus. In the current study pig mucosa was used as the mucosal membrane because their buccal membrane closely resembles the human buccal membrane in terms of structure and permeability. Fresh pig buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. 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 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 fingertip for 20 s. The glass slide was vertically fixed to the disintegration apparatus and allowed to move up and down (25 times /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 (3,8-10).

The dissolution study was carried out using USP 23 Type-2 rotating paddle dissolution test apparatus (Eight station dissolution test apparatus, EDT-08Lx, Electrolab, India). The dissolution medium used was 100 mL

simulated saliva solution (pH 6.2) at 37 ± 5 °C which was stirred at 50 rpm. The patch of 2 cm diameter was fixed on the glass disk with the help of a 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 equal volume of dissolution medium. The samples were filtered through 0.45μm 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 Zero order, First order, Higuchi and Korsmeyer-Peppas plots. The release rate constants k and n of each model were calculated by linear regression analysis using Microsoft Excel 2003 software. Coefficients of determination (R^2) were used to evaluate the accuracy of the fit.

In vitro salbutamol sulphate permeation studies

The *in vitro* buccal permeation of SS was studied as explained previously (3,8,9). Briefly, 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 clamped together. The donor compartment was slightly wetted with one mL of simulated saliva. The receptor compartment was filled with isotonic phosphate buffer (pH 7.4). The diffusion cell was thermostated at 37 ± 2 ^{o}C and the receptor compartment was stirred at a rate of 100 rpm. One mL sample was withdrawn at pre determined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min) using a butterfly cannula and syringe (3,8,9). 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.

Effect of various permeation enhancers on the permeation of salbutamol sulphate from the buccal patches

The SS buccal patches with different permeation enhancers were formulated to study the effect of permeation enhancers on the permeation of SS across buccal pig mucosa (11-14). The concentration of permeation enhancers in each patch was 5% w/w. The patches with their formulation codes are given in Table 2.

Table 2. Salbutamol sulphate patches with permeation enhancers.

Formulations with permeation enhancer	Permeation enhances
AD1	DMSO
AL2	LA
AI3	IPM
AO4	OA
BD1	DMSO
BL2	LA
BI3	IPM
BO4	OA
CD1	DMSO
CL2	LA
CI3	IPM
CO4	OA
DD1	DMSO
DL2	LA
DI3	IPM
DO4	OA
ED1	DMSO
EL2	LA
EI3	IPM
EO4	OA
FD1	DMSO
FL2	LA
FI4	IPM
FO3	OA

OA; oleic acid, LA; linoleic acid, IPM; isopropyl myristate, DMSO; dimethyl sulphoxide.

The effect of various permeation enhancers on the permeation of SS from the buccal patches was studied as explained previously under *in vitro* drug permeation without permeation enhancers (3,8,9). The flux and permeability coefficients were calculated using the following formula.

Flux at steady state = slope of the linear portion of the curve/area of exposed mucous surface and

Permeability coefficient = flux/initial drug load

RESULTS

Physicochemical characteristics of salbutamol sulphate buccal patches

The patches were evaluated for mass uniformity, thickness, folding endurance, drug content, surface pH, swelling behaviour, residence time (*ex vivo* mucoadhesion time), *in vitro* drug dissolution and *in vitro* drug permeation. Physicochemical characteristics like thickness, mass uniformity, folding endurance, surface pH and drug content of SS patches are shown in Table 3.

The thickness of the medicated patches ranged between 0.4 ± 0.006 and 0.59 ± 0.005 mm, and mass varied between 45.00 ± 4.2 and 95.02 ± 7.2 mg. The surface pH of all patches ranged from 6-7.1 and there were no mucosal irritation was expected due to the neutral surface pH of all the patches. All the patches showed favourable drug loading which varied between 9.1 ± 0.9 and 9.5 ± 0.3 mg (i.e. drug loading efficiency of 91 to 95%). All patches showed satisfactory folding endurance of >300. Therefore these patches were selected for further evaluation like swelling studies, residence time (*ex vivo* mucoadhesion time), *in vitro* drug dissolution and *in vitro* permeation.

Swelling behaviour

Swelling behaviour of selected SS patches as a function of time is illustrated in Fig. 1. The swelling indices of the patches were high (up to 65 ± 5 for C at the end of 90 min) and varied between the formulations. The swelling indices increased in the following order: F < B < E < D < A < C. It was observed that patches with PEG-400 showed more swelling compared to those with PG. This index even reached a maximum value of 65 for formulation C 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 (15). 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.

Table 3. Physicochemical characteristics of salbutamol sulphate patches.

Formulation code	Mass uniformity (mg±SD)*	Film thickness (mm±SD)*	Folding endurance (times)*	Drug content (mg±SD)*	Drug loading efficiency (%)*	Surface pH*
A	83.33 ± 5.8	0.4 ± 0.006	>300	9.3 ± 0.6	93 ± 0.3	6.1
B	45.00 ± 4.2	0.4 ± 0.006	>300	9.3 ± 0.8	93 ± 0.8	6.3
C	95.02 ± 7.2	0.5 ± 0.006	>200	9.5 ± 0.3	95 ± 0.5	6.0
D	82.12 ± 4.9	0.5 ± 0.005	>200	9.2 ± 0.3	92 ± 0.2	6.1
E	78.99 ± 6.9	0.48 ± 0.003	>300	9.4 ± 0.9	94 ±0.1	7.1
F	74.63 ± 3.9	0.59 ± 0.005	>300	9.1 ± 0.9	91 ± 0.7	6.8

*Mean ± SD, $n = 3$

Table 4. R^2, k and n values of salbutamol sulphate buccal patches.

Formul-ations	Zero Order		First Order		Higuchi		Korsmeyer–Peppas		Mechanism of drug release
	R^2	k ($min^{-1/2}$)	R^2	k($min^{-1/2}$)	R^2	k ($min^{-1/2}$)	R^2	n	
A	0.5609	0.4841	0.3659	0.0067	0.9985	1.6240	0.8013	1.2987	Diffusion/Fickian
B	0.5760	0.5363	0.4416	0.0071	0.9853	0.2356	0.9892	0.4012	Fickian
C	0.7298	0.5413	0.4417	0.0070	0.8640	0.8470	0.9200	1.4090	Super case-II transport
D	0.7328	0.5393	0.4397	0.0070	0.8610	0.8470	0.8210	0.7500	Predominatly Higuchi
E	0.8286	0.4992	0.3888	0.0058	0.9532	0.7335	0.9675	0.4341	Fickian
F	0.8412	0.5065	0.4109	0.0059	0.9547	0.7522	0.9613	0.4714	Fickian

Table 5. The permeation data of salbutamol sulphate through pig buccal mucosa

Formulation code	Steady state flux ($mg.cm^2. min^{-1}$)	Permeability coefficient (cm/ min)	Enhancement ratio
A (without permeation enhancers)	0.08260 ± 0.22	0.008260 ± 0.04	1.0
AD1 (DMSO)	0.08945 ± 0.14	0.008945 ± 0.12	1.08
AL2 (LA)	0.35795 ± 1.32	0.035795 ± 0.18	4.33
AI3 (IPM)	0.17995 ± 0.21	0.017995 ± 0.06	2.17
AO4(OA)	0.35810 ± 2.12	0.035810 ± 0.12	4.33
B (without permeation enhancers)	0.12170 ± 1.52	0.012170 ± 0.18	1.00
BD1(DMSO)	0.17015 ± 1.11	0.017015 ± 0.19	1.39
BL2(LA)	0.34210 ± 2.24	0.034210 ± 0.08	2.81
BI3(IPM)	0.18125 ± 0.08	0.018125 ± 0.12	1.48
BO4(OA)	0.34215 ± 0.32	0.034215 ± 0.04	2.81
C (without permeation enhancers)	0.04240 ± 0.71	0.004240 ± 0.09	1.00
CD1(DMSO)	0.05745 ± 1.26	0.005745 ± 0.12	1.35
CL2(LA)	0.17100 ± 0.43	0.017100 ± 0.16	4.03
CI3(IPM)	0.07705 ± 2.65	0.007705 ± 0.07	1.81
CO4(OA)	0.35345 ± 0.76	0.035345 ± 0.05	8.33
D (without permeation enhancers)	0.03345 ± 1.20	0.003345 ± 0.18	1.00
DD1(DMSO)	0.05775 ± 0.54	0.005775 ± 0.11	1.72
DL2(LA)	0.10335 ± 0.62	0.010335 ± 0.07	3.08
DI3(IPM)	0.07585 ± 1.81	0.007585 ± 0.11	2.26
DO4(OA)	0.16415 ± 0.98	0.016415 ± 0.05	4.90
E (without permeation enhancers)	0.03620 ± 0.76	0.003620 ± 0.03	1.00
ED1(DMSO)	0.03565 ± 0.45	0.003565 ± 0.02	0.98
EL2(LA)	0.09240 ± 1.43	0.009240 ± 0.18	2.55
EI3(IPM)	0.06945 ± 2.76	0.006945 ± 0.09	1.91
EO4(OA)	0.14905 ± 0.65	0.014905 ± 0.12	4.11
F (without permeation enhancers)	0.02520 ± 1.08	0.002520 ± 0.14	1.00
FD1(DMSO)	0.02685 ± 0.43	0.002685 ± 0.06	1.06
FL2(LA)	0.04715 ± 1.92	0.004715 ± 0.02	1.87
FI3(IPM)	0.03200 ± 0.61	0.003200 ± 0.12	1.26
FO4(OA)	0.14120 ± 2.12	0.014120 ± 0.16	5.60

*Mean ± SD, $n = 3$, DMSO; dimethyl sulfoxide, LA; linoleic acid, IPM; isopropyl myristate and OA; oleic acid.

Residence time (ex vivo mucoadhesion time)

The residence time of the tested patches ranged between 105 ± 3 min and 124 ± 2 min. However, none of the patches were detached from the mucosal membrane over the study period, which indicated that the bioadhesion of all patches were satisfactory to retain the patch on the buccal mucosa. In the current study we have used pig mucosa as the mucosal membrane because their buccal membrane closely resembles the human buccal membrane in terms of structure and permeability.

In vitro drug dissolution

In vitro release of SS from SS buccal patches are shown in Fig. 2. The maximum *in vitro* release was evaluated to be 101.4% over a period of 120 min for formulation C. This finding was also in agreement with the swelling studies where C showed the maximum swelling index. Formulations D, E and F showed maximum drug release after 120 min, B showed maximum drug release after 45 min and formulation A, showed maximum drug release after 60 min. The R^2, '*k*' and '*n*' values of Zero order, First order, Higuchi and Korsmeyer–Peppas models are given in Table 4.

Formulations A and D was good fit to the Higuchi model. The remaining formulations showed the best fit to the Korsmeyer-Peppas model. Formulations B, E and F showed Fickian release and formulation C exhibited super case-II transport mechanism of drug release.

In vitro drug permeation without permeation enhancers

The drug permeation was fast and showed a similar profile to that of the *in vitro* drug release. From formulation C, 101.4 % of SS was permeated over a period of 120 min. This finding was also in agreement with the

swelling studies where C showed the maximum swelling index. Formulation A showed maximum drug permeation after 60 min, B after 45 min, D after 150 min, E after 120 min and F showed after 180 min. There was a good correlation between the *in vitro* drug release and *in vitro* drug permeation results.

Effect of various permeation enhancers on the permeation of salbutamol sulphate from the buccal patches

The permeation data of SS from the SS buccal patches (with and without permeation enhancers) through pig buccal mucosa is provided in Figs 3-5. Comparison of the permeation profiles of the formulations (with and without permeation enhancers) showed that these formulations produced better permeation of drug through buccal pig mucosa in the presence of permeation enhancers. The permeation data of SS through pig buccal mucosa is presented in Table 5.

Among these permeation enhancers, OA, LA, and IPM produced noticeable increase in SS flux compared with patches without permeation enhancer, while DMSO only increased the flux slightly and in most cases the increase was negligible. OA was the most efficient permeation enhancer increasing the flux >8-fold compared with patches without permeation enhancer in formula C and D based buccal patches when PEG-400 was used as the plasticizer. LA also exhibited a better permeation enhancing effect of >4-fold in formula A, B, C and D based buccal patches. In formula A and B based patches, both OA and LA were almost equally effective in improving the SS permeation irrespective of the plasticizer used. DMSO was more effective as the permeation enhancer in formula C and D based patches when PG was the plasticizer. IPM showed maximum permeation enhancement of >2-fold when PG was the plasticizer in formula C and D based buccal patches.

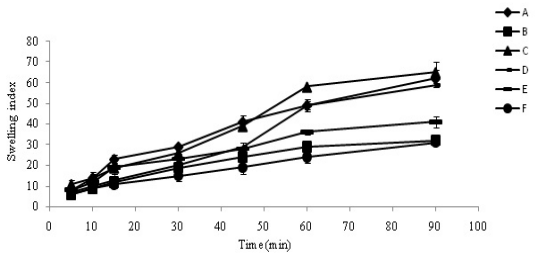

Fig. 1. Swelling behaviour of salbutamol sulphate buccal patches.

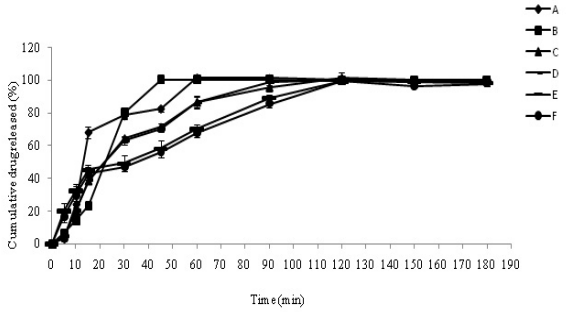

Fig. 2. *In vitro* release of salbutamol sulphate buccal patches.

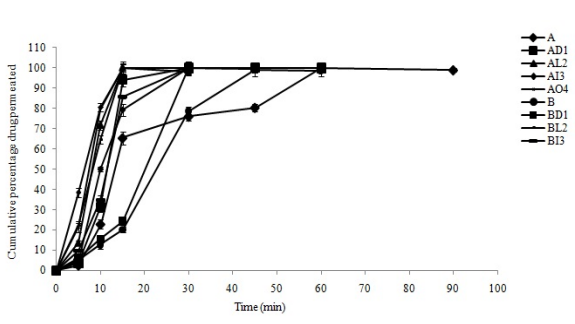

Fig. 3. Percentage of drug permeated from salbutamol sulphate patches across pig buccal mucosa based on formula A and B (with and without permeation enhancers).

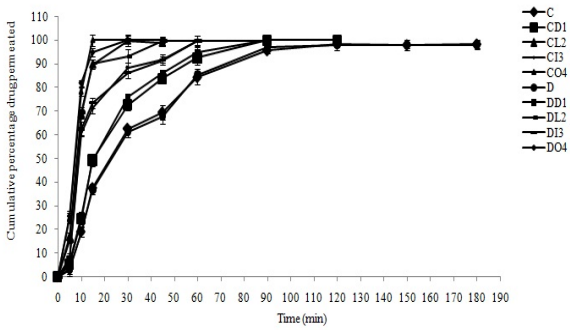

Fig. 4. Percentage of drug permeated from salbutamol sulphate patches across pig buccal mucosa based on formula C and D (with and without permeation enhancers).

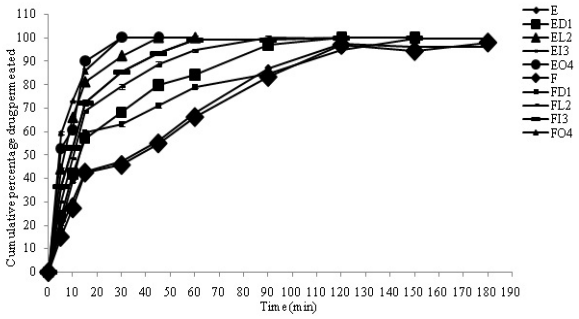

Fig. 5. Percentage of drug permeated from salbutamol sulphate patches across pig buccal mucosa based on formula E and F (with and without permeation enhancers).

DISCUSSION

In the present investigation, buccal patches of SS were prepared by different polymer combinations of HPMC, PVA, Cp, NaCMC, PVP, CH_{AS}, CH_{WS} and EU- L100 using solvent casting method in triplicate using a 3^2 factorial design. Factorial design was used only to design the experiments. PG or PEG-400 was used as the plasticizer.

Impermeable backing membrane is an essential part of buccal mucoadhesive patch to obtain unidirectional drug flow. Backing membrane prevents the loss of 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 backing membrane but reports show that it has some permeability. Also laminating the patches with ethyl cellulose film was not completely successful. Therefore, in the current study, we have used BOPP film as 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 long duration of drying time during the formulation step.

From physico-chemical characteristics of the medicated patches, it was noticed that the prepared patches were smooth, uniform in thickness, mass, drug content and showed no visible cracks or folds. It was noticed that, the patches prepared with PEG-400 as a plasticizer showed increased mass uniformity. This may be due to the high molecular mass of PEG-400 when compared to PG.

Higher swelling indices may be due to the presence of water soluble polymers. The swelling behaviour provides an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after absorption of moisture. The presence of a water-soluble drug might have improved the surface wetting of the matrix. The swelling indices of the prepared patches were found to be moderate and varied between the formulations, which could be due to the presence of the water insoluble polymer EU-L100. It was difficult to interpret the relation between hydrophilicity of polymers and swelling index from these results, since the patch was composed of both hydrophilic and hydrophobic polymers. At the same time, when we consider the fact that all tested patches contained one part of EU-L100 polymer and there by assuming that the effect of EU-L100 in swelling of the patches are common and can be neglected. Then the 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 (16).

The time required for the patch to detach from the buccal mucosa is defined as the mucoadhesion time. Mucoadhesion is considered to occur in three major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion and the mucoadhesion time are usually affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer and the biological membrane used in the study (17).

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 appropriate 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 (18,19).

According to Higuchi model, the drug release from these patches may be controlled by diffusion through the micropores. The Fickian release, which is characterized by a linear dependence of the released drug on the square root of time is concentration dependent. Formulation C exhibited super case-II transport and could result from increased plasticization at the relaxing boundary. When swelling is predominant, drug diffusion probably occurs through the solvent-filled pathways of the 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. 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.

The mechanism by which these permeation enhancers (fatty acids) enhance the permeation of drugs through the buccal mucosa is not clearly understood. However, the mechanisms are supposed to be the same as that proposed for skin permeation enhancement. OA and LA may interact with lipids and disrupt their structures, which leads to increased fluidity and, thereby improved flux (20). Among unsaturated fatty acids, the highest enhancement factor was achieved by OA, which contains one double bond. The presence of additional double bonds decreases the enhancement ratio. The permeation enhancement capacity of IPM could be attributed to its interaction with lipid components of the buccal mucosa. It can also be manifested by virtue of its intermediate polar nature, and can be partitioned into both the lipid and polar phase of the skin (21).

CONCLUSION

Novel mucoadhesive buccal patches of SS with unidirectional drug delivery were developed to overcome the first-pass metabolism and subsequent low bioavailability of the SS. From this study, it is concluded that, the buccal patches of SS can be formulated using PVA, HPMC and EU-L 100 as the mucoadhesive polymers to obtain satisfactory unidirectional drug release with adequate mucoadhesion. The *in vitro* studies have shown that this is a potential drug delivery system for SS with a considerably good stability and release profile. All the analyzed formulations were equally good in their physicochemical characteristics. The permeation is further customised by using different permeation enhancers. All permeation enhancers produced noticeable increase in SS flux compared with patches without permeation enhancer. Among these permeation enhancers (OA, LA, IPM and DMSO), OA was the most efficient permeation enhancer. The present study indicated that, SS buccal patches can be formulated with permeation enhancers to improve the release of the drug from the patches. Future studies using the formulations with these promising permeation enhancers are warranted to confirm these results *in vivo*.

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