

Development and Characterization of Mucoadhesive Buccal Patches of Salbutamol Sulphate

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Abstract: Mucoadhesive patch releasing the drug in the oral cavity at predetermined rate may present distinct advantages over traditional dosage forms such as tablets, gels and solutions. The present study was concerned with the preparation and evaluation of mucoadhesive buccal patches for the controlled systemic delivery of Salbutamol sulphate to avoid first pass hepatic metabolism. The developed patches were evaluated for the physicochemical, mechanical and drug release characteristics. The patches showed desired mechanical and physicochemical properties to withstand environment of oral cavity. The *in-vitro* release study showed that patches could deliver drug to the oral mucosa for a period of 7 h. the patches exhibited adequate stability when tested under accelerated conditions.

Keywords: Mucoadhesion, Buccal patch, Salbutamol sulphate, buccal delivery, release study.

INTRODUCTION

Buccal drug delivery has lately started representing an important route of drug administration. This route has recently been extensively reviewed [1]. Delivery of various therapeutic agents via the buccal route using conventional matrix tablets [2-5] disks [6,7], gel [8,9], films [8,10], patches [11-18], strips [19], ointment [20-22] laminated systems [23] and buccal cups [24] systems has been studied and reported by several research groups. The use of polymeric patches for buccal delivery has not yet been widely investigated, although they have been extensively employed in the modification of the drug release and their protection by way of coating and matrix formation in various solids like tablets, pellets, granules and powders.

An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated.

The buccal route has high acceptance due to avoidance of 1st pass metabolism and possibility of being accessible for controlled drug release [11, 25-26]. Various bioadhesive mucosal dosage forms have been developed which include adhesive tablets, gels, ointments, patches and more recently patches. Buccal patches are preferred over adhesive tablets in terms of flexibility and patients comforts.

Now day's bioadhesive polymers received considerable attention as platforms for buccal controlled delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability. Chitosan is composed of glu-

cosamine and N-acetylglucosamine, which are also constituent of mammalian tissue. It is non toxic, biocompatible and biodegradable polymer [27]. This polymer is known for its film as well as matrix forming abilities. In addition chitosan has enzyme inhibitor as well as permeation enhancer properties [14-16].

Not much work has been reported on salbutamol sulphate buccal delivery. The patches of Poly vinyl alcohol (PVA), Hydroxy propyl methyl cellulose (HPMC) and Chitosan in presence of Poly vinyl pyrrolidone (PVP) and Carbopol already reported earlier [28]. The salbutamol patches composed of different compositions of Eudragit RL 100, Ethyl cellulose (EC) and HPMC are reported [29]. Thus, the objective of this work was to design and characterize the buccal patches of salbutamol sulphate employing chitosan as buccal permeation enhancing polymer.

MATERIALS:

Salbutamol sulphate was procured from Cipla, India. Chitosan (degree of acetylation >80%, maximum granule size 0.2mm) was a gift sample from Central Marine Fisheries Research Institute, India. PVP K-30 (Kollidon 30) was gift sample obtained from Themis laboratory, India. Polyvinyl alcohol (PVA, Hot water soluble), Citric acid and Polyethylene glycol (PEG-400) were purchased from S.D fine chemicals, India.

PREPARATION OF THE PATCHES:

PVA (10% w/v), Chitosan (1% w/v) and PVP (5% w/v) solution in water were mixed together in a predetermined ratio and stirred continuously until a clear solution was obtained (Table 1). PEG-400 (2% w/w on dry basis as plasticizer) was mixed uniformly to get a clear viscous liquid. This was then poured in a petri dish (Anumbra) and allowed to dry in an oven maintained at 40 °C till a flexible film was formed. The dried patches were carefully removed from the Petri dish, checked for any imperfections or air bubbles and

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Table 1. Patch Formulae

Constituents	Identity	Plain Patches	Medicated Patches
Polymers	PVA	30.526 %	29 %
	PVP K30	61.05 %	58%
	Chitosan	6.316%	6%
Plasticizer	PEG 400	2.11%	2%
Drug	Salbutamol sulphate	-	5%

cut into pieces, of 2 dimensions viz. squares of 1cm x 1cm and circulars of diameter 1cm. The samples were packaged in aluminum foil and stored in a glass container maintained at room temperature and 58 % relative humidity. This condition maintained the integrity and elasticity of the patches. For the medicated patches, calculated amount of drug ($1.6 \pm 0.005 \text{ mg/cm}^2$ of the proposed film) was incorporated in polymeric solution before addition of plasticizer and casting was performed in the same way as mentioned above.

EVALUATION

1. Patch thickness – Assessment of thickness was done on 5 patches using micrometer screw gauge.
2. Surface pH – Agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 7.4 under stirring and then pouring the solution in a petri dish and cooling till gelling at room temperature. Buccal patches were left to swell for 2 h on the surface of these plates. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch.
3. Folding endurance – The folding endurance of the patches was determined by repeatedly folding one patch at the same place up to maximum 300 times or till it broke.
4. Swelling – The sample was allowed to swell on the surface of the agar plate kept in an incubator (Meta lab, India) maintained at 37 °C. Measurement of the diameter of the swollen patch was done using microscope at hourly intervals for 5 h. Radial swelling was calculated from the following equation:

$$S_d (\%) = [(D_t - D_o) / D_o] \times 100$$

Where S_d (%) is the percent change in radial swelling of patches, D_t is the diameter of the swollen patch after time t , D_o is the original diameter i.e. at time zero.

5. Residence time –

In-vitro: The *in-vitro* residence time was determined employing a modified USP disintegration procedure. The disintegration medium was composed of 800 ml isotonic phosphate buffer of pH 7.4 (IPB) maintained at 37°C. A piece of porcine buccal tissue was used for this study. The tissue was attached to a rectangular glass piece using cyanoacrylate adhesive from non mucosal surface. The patch was tuck to the mucosal surface by applying small pressure. The glass piece with tissue and patch placed in

the basket of disintegration apparatus and set in motion. The time necessary for complete erosion or detachment of the patch from the mucosal surface was observed and recorded (mean of five determinations).

In-vivo: Five New Zealand rabbits were selected for the study. The rabbits were anesthetized with i.m. injections of ketamine (35 mg/Kg) and xylazine (3 mg/Kg). The experiment was carried out with plain as well as medicated patches. The mucoadhesive patch was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 s. Either complete erosion of the patch or failure of the adhesive bond would indicate the adhesion time. Repetition of application of the mucoadhesive patches using the same animal was allowed after a five-day rest period. The each animal was used twice for the *in-vivo* residence time study.

6. Mucoadhesion and Tensile strength– A manually controlled Microprocessor force gauge (Mecmesin, England) with a 2.5 kg / 5 lb / 25 N load cell, having accuracy of 0.001kg / 0.002 lb / 0.01 N was used for the mucoadhesion experiment. The pre-test speed, the test speed, and withdrawal speeds were set up at 2, 1 and 1 mm/s respectively.

For mucoadhesion measurement, a pair of stainless steel cylinders having diameter of $11 \pm 0.2 \text{ mm}$ was used in place of clamps. Sample of prepared polymeric patch circular in shape (1cm diameter) was used and preload of 0.5 N was applied for a period of 0.5, 2 and 15 mins. The maximum force of detachment (F_{max}) was recorded in Newton's

For tensile strength measurement same microprocessor force gauge was utilized and a square patch (1cm x 1cm) was mounted between the upper and lower clamps. The upper clamp was moved upward with speeds 1 or 2 mm/s until patch broke. The tensile strength of plain and drug loaded patches were directly recorded from the display of force gauge.

Content uniformity – The medicated patch was allowed to dissolve in 100 ml IPB, pH 7.4. The amount of salbutamol sulphate in the solution was measured spectrophotometrically at λ_{max} of 276 nm.

7. *In vitro* release study – This was carried out in a USP dissolution apparatus type 1 (six-station dissolution apparatus, Electro lab, India), with a modification in order to

take care of the small volume of dissolution medium. Only one station was used during each run. The dissolution medium, 50 ml IPB, pH 6.5, maintained at 37 ± 0.5 °C was kept in a glass beaker placed inside the dissolution flask. The patch was attached to end of the shaft (without basket), which was rotated at 50 rpm. Samples (2 ml) were collected at intervals of 1, 2, 3, 4, 5, 6 and 7 h and filtered using Whatman filter paper. The withdrawals were compensated using equal volumes of IPB kept at the same temperature. The concentration of drug released in the medium was assayed spectrophotometrically at 276 nm after suitable dilution with the dissolution medium whenever necessary. The experiment was carried out five times. Peppas kinetic treatment was given to the release data obtained.

8. Stability studies and ageing – Plain and drug loaded patches were packaged in aluminum foil and stored in glass bottles closed with screw caps. These bottles were subjected to accelerated stability testing using stability chambers (Newtronic, India) maintained at 37 ± 0.5 °C and 75 ± 5 % RH for 6 months. Fresh and 6 months aged medicated patches were evaluated.

RESULTS AND DISCUSSION

Physical characteristics of plain patches and patches containing drug are shown in Table 2.

The patches were 10 mm in diameter and 0.4 ± 0.02 mm in thickness. The mass ranged from 33.4 to 35.1 mg (1.25 ± 0.02 mg salbutamol sulphate per unit for medicated patch). The surface pH of all formulations was within the desirable 5.5 – 6.5 units which are near to neutral pH and hence no mucosal irritation would be expected [29]. The recorded folding endurance of the patches was > 300 times. This might be due to adequate content of PVA which provide it with high mechanical strength and good elasticity.

Assessment of the swelling behavior was done by measuring radial swelling. In the case of buccal patches, the contact area should be large enough to meet a requirement that must be balanced with patient compliance; excessive increase in patch diameter might cause discomfort and/or dislodgment of the swollen patch. The medicated patches showed higher radial swelling compared to plain patches. The swelling values after 5 h were 31 ± 2.4 % and 29.8 ± 2.2 % respectively (Fig. 1 and Table 2). Higher swelling values would result in excessively increased surface area which could result in unmanageable faster release of the drug. Also, higher swelling may cause patient discomfort due to occupying of larger space in the oral cavity and chances of dislodgement. The drug content in the patches was 99.21 % of the labeled value.

Observations related to the *in vitro* residence time including detachment as well as erosion for patches both plain and medicated, indicated adequate attachment to the mucosal surface without erosion.

Values of the *in vitro* residence time, as shown in Table 2, differed in plain and medicated patches. However, due to presence of PVP and PEG 400 in plain and medicated patches caused patch dislodgment after 4.3 and 4.1 h respectively, without erosion. The presence of Salbutamol sulphate, a water-soluble drug, slightly affected the residence time of the patch.

Comparing the *in-vivo* and *in-vitro* residence time of the tested patches, higher values were obtained *in vitro* (Table 2). Though the tongue movement would be minimal, excessive salivation was expected in the anesthetic animal. This could be postulated as the cause for the shorter residence time *in-vivo*. Not much work has been reported on the *in-vivo* residence studies in the rabbits. Thus, though a published method has been used for the *in-vitro* work, this calls for improvement on the same for its better correlation with *in-vivo* as well as new method to study residence time in rabbits.

Table 2. Characteristics of Plain and Medicated Mucoadhesive Buccal Patches

Characteristics	Plain Patches	Medicated Patches
Thickness (mm)	0.405 ± 0.004	0.417 ± 0.006
Mass (mg)	33.4 ± 0.3	35.1 ± 0.5
Surface pH	5.5 ± 0.66	5.5 ± 0.33
Drug content (%)	-	99.21 ± 0.8
Folding endurance (foldings)	More than 300	More than 300
Radial swelling (%)	29.8 ± 2.2	31 ± 2.4
Residence time: <i>In vitro</i> (h) <i>In vivo</i>	4.3 ± 0.33 3.9 ± 0.50	4.1 ± 0.66 3.5 ± 0.75
Mucoadhesion force (N)	3.33 ± 0.16	3.11 ± 0.21
Tensile strength (N)	6.91 ± 0.24	7.61 ± 0.11
Release kinetics n	-	0.7435
k	-	2.57
R	-	0.9888

A higher mucoadhesion was recorded for plain patches (3.33 ± 0.16 N), compared to medicated patches (3.11 ± 0.21 N) (Table 2). Explanation for this might be possibility of decreased mucoadhesion due to the higher of swelling (Fig. (1)).

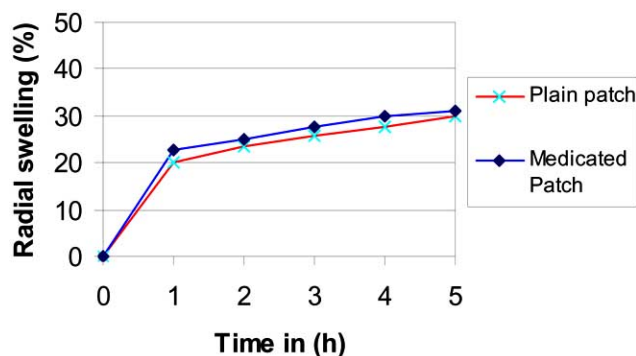


Fig. (1). Swelling profile of Mucoadhesive patches.

The higher tensile strength showed by medicated patches (7.61 ± 0.11 N) in comparison to plain patches (6.91 ± 0.24 N) might be due to internal bonding and other forces responsible for increased cohesive strength in the latter.

The inefficient permeability properties of drugs contribute to their low systemic bioavailability [30]. The presence of the hydrophilic additives, PVP and PEG 400 in patches seemed to increase the surface wettability and swelling of the patches. The achievement of plateau seen in the swelling profiles might be due to either the solvent front on each surface meeting in the center of the patch (thus there was no further unhydrated polymer to hydrate and expand) or to the protective gel coat only allowing a small quantity of water to diffuse into the inner core [31].

Comparing the radial swelling of plain patches and those containing salbutamol sulphate (Fig. 1), an increase in patch swelling due to the presence of the drug was noted. Undoubtedly, the drug would modify the way water is taken up by or bound to the polymer. Alteration in water distribution within such systems would thus modify the matrix structure. In addition, the presence of a water-soluble drug could improve the surface wetting of the matrix [32].

The extent of the drug release within 1 h from the patch was 46.1% (Fig. 2). The coefficient of liner regression was found to be 0.9888. Drug release kinetic parameters were calculated according to Peppas equation [33]

$$M_t/M_\infty = K t^n$$

Where M_t/M_∞ is the fractional release of the drug, t denotes the release time, K is a constant incorporating structural and geometric characteristic of the controlled release device and n is the release exponent, indicative of the drug release mechanism. In particular, the exponent n is indicative of the release kinetics. A value of 0.5 corresponds to conventional Fickian kinetics, while $n = 1$ is indicative of zero order kinetics. A value of n between 0.5 and 1 indicates anomalous drug release kinetics. The value of K in terms of aspect ratio was well described by the Peppas for the Fickian diffusion [33]. Salbutamol containing patches showed n value of

0.7435. In this case, the rates at which the swelling and eroding fronts moved relative to each other might have been synchronized and a constant diffusional path-length (concentration gradient) might be the possibility. Thus, a relative contribution of erosion and diffusion to the overall release mechanism is suggested.

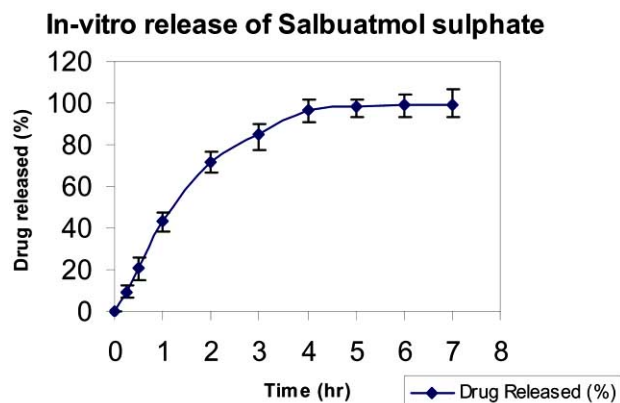


Fig. (2). *In-vitro* profile of salbutamol from Mucoadhesive patches.

The amount of the drug released after stability testing period of 6 months was 98.7 % and the *in-vitro* mucoadhesion time recorded was 4.05 ± 0.25 h. The stability study data revealed that the buccal patches retained their drug release and mucoadhesion properties during the study period.

PVP is a water soluble polymer, not known as sustain release matrix former. This polymer might act as release retardant due to possibility of complex formation with cationic drugs and/or cationic polymers. Earlier workers have reported such PVP complexation with various drugs and polymers [34]. In the present situation Chitosan, a cationic polymer might have formed complex with PVP, a nonionic polymer leading to a favorable extension of the drug release. The phenomena of inter polymer complex formation between Chitosan and other polymers have been extensively reported [35-37]. Thus, in this work combination of Chitosan and PVP could act as rate controlling polymer when incorporated in the PVA patches. Recently, PVP and chitosan patches were reported for the delivery of hydrophilic drug [38]. In addition, presence of chitosan may also improve mucosal permeation of the drug [39-42].

CONCLUSION

It may be concluded that mucoadhesive patches for oral cavity are a promising drug delivery system for Salbutamol sulphate. The combination of polymers PVA, Chitosan and PVP showed good mucoadhesive and swelling characteristics. Medicated patches maintained a satisfactory residence in the buccal cavity and demonstrated non-Fickian release of the drug over a relatively long period (5 h).

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