



## Research Article

### DESIGN AND EVALUATION OF MUCOADHESIVE BILAYER TABLETS OF SALBUTAMOL SULPHATE

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#### ABSTRACT

The salbutamol mucoadhesive tablets were prepared with objective of avoiding first pass metabolism and prolonging duration of action. Salbutamol mucoadhesive bi layered tablets were prepared by a direct compression method using bio adhesive polymers such as Carbopol-934, PVP and PVA along with ethyl cellulose as backing layer. The interaction between the excipients and salbutamol was also studied through FTIR spectroscopy. Tablets were evaluated for their physical properties like hardness, friability and weight variation, uniformity of thickness, content uniformity and *in vitro* swelling study. *In-vitro* release studies of formulations were performed and data obtained from *in-vitro* release study were fitted to various kinetic models. The prepared formulations were passed the evaluation tests and the mechanism of drug release from tablets was found to be Quasi-Fickian Diffusion transport.

**Keywords:** Salbutamol, Mucoadhesive tablets, Buccal drug delivery, Bi layer tablets, Swelling index, *In-vitro* release study.

#### INTRODUCTION

A drug can be administered via a many different routes to produce a systemic pharmacological effect. Among the various routes of drug delivery the oral route is perhaps the most preferred. Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in drug effectiveness or increase incidence of side effects with subsequent undesirable toxicity and poor efficiency<sup>1</sup>. A drug taken orally must withstand large fluctuation in pH as it travels along the G. I. tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic route of administration for controlled systemic drug delivery. The buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery<sup>2</sup>. This is because the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems. The primary objective of Bilayer tablets is to ensure safety and improve efficacy of drug as well as patient compliance. Bi layered tablets drug release can be rendered almost unidirectional if the drug is incorporated in the upper non-adhesive layer and its delivery occurs into the whole oral cavity. These tablets are usually prepared by direct compression, but wet granulation techniques can also be used. The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the backing membrane must be inert and impermeable to drugs and penetration enhancers. Salbutamol is an anti-asthmatic drug, is a short acting beta<sub>2</sub> adrenergic receptor agonist used as a bronchodilator to manage asthma and other COPD. Salbutamol has low bio-availability of 40 % due to extensive metabolism via intestinal sulfonation and first pass

metabolism in the liver. It also undergoes degradation in the colon. In the present study, an attempt was made to design mucoadhesive bi layer tablets of Salbutamol to avoid first pass metabolism, to reduce dosing frequency and to improve patient compliance with improved bioavailability<sup>3</sup>.

#### MATERIALS AND METHODS

##### Materials

The following materials were used: Salbutamol Sulphate (Yarrow Chem Pvt Ltd., Mumbai, India), Carbopol-934 (Chemdyes corporation, Rajkot, India), Polyvinyl alcohol (Nice chemicals Pvt. Ltd), Poly vinyl pyrrolidone (Chemdyes corporation, Rajkot, India), Ethyl cellulose (Spectrum reagent and chemicals Pvt. Ltd), Magnesium Stearate (Nice chemicals Pvt. Ltd), Mannitol and  $\beta$  cyclodextrin (Chemdyes corporation, Rajkot, India).

##### Methods

##### Preparation of Mucoadhesive Buccal Devices

Mucoadhesive bi layered tablets were prepared by a direct compression procedure involving two consecutive steps. The mucoadhesive drug-polymer mixture was mixed homogeneously in a glass mortar for 15 minutes. The mixture was then compressed using a 10 mm, round-shaped flat punch in a single-stroke, multi station tablet machine. The upper punch was raised and the backing layer of ethyl cellulose (50 mg) was then added on the above compact and the second layers were compressed to form bi layered tablets. The bi layered tablets were prepared using compositions as given in Table 1.

##### Evaluation of buccal tablets

##### Hardness

For each formulation, the hardness of 3 tablets were determined using the Monsanto hardness tester and the average was calculated and recorded.<sup>4,5</sup>

**Friability**

For each formulation, the friability of 10 tablets was determined using the Roche friabilator respectively.

$$\% \text{ Friability} = (\text{Loss of weight} \times 100) / \text{Initial weight}$$

**Weight variation test**

Twenty tablets were selected randomly and weighed. Average weight of the tablet was then compared with the individual tablets for the determination of weight variation according to Indian pharmacopoeia.

**Uniformity of Thickness**

Uniform compression force and volume of die fill leads to uniform thickness. From each batch, 3 buccal tablets were taken and checked with a thickness screw gauge and standard deviation was calculated.

**IR spectral analysis**

In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Therefore FT-IR spectroscopy was employed to ascertain the compatibility between Salbutamol Sulphate and the selected polymers. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Salbutamol Sulphate was compared with FT-IR spectra of formulations.

**Drug content uniformity**

Tablets of each formulation were ground in a mortar to make powder. An accurately weighted amount of the powder, equivalent to 4 mg of the drug was dissolved in 6.8 phosphate buffer using a magnetic stirrer. After filtration the solution was assayed using UV spectrophotometer at 277 nm.

**Surface pH study**

pH of the surface of the tablet was measured by using a pH paper. The tablets were allowed to swell for two hour in 50 ml phosphate buffer (pH 6.8). The surface pH of the tablet was measured in order to investigate the possibility of toxicity of tablets in buccal cavity.

**In vitro swelling study**

The swelling index of the buccal tablet was evaluated by using pH 6.8 phosphate buffer. The initial weight of the tablet is determined ( $w_1$ ). The tablet was placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at  $37^\circ \pm 0.5^\circ\text{C}$  and tablet was removed at different time intervals (1.0 to 6.0 h) and reweighed ( $w_2$ ). The swelling index was calculated using the formula:

$$\text{Swelling index} = 100 (w_2 - w_1) / w_1$$

**In vitro drug release studies**

The study was carried out in the USP XXXIV Type I apparatus using 900 ml phosphate buffer (pH 6.8) solution and rotated at constant speed (100 rpm) and the temperature of the medium was maintained at  $37^\circ \pm 0.5^\circ\text{C}$  for 6 hours. An aliquot of the sample was periodically withdrawn at the regular time intervals and an equal volume was replaced with fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with respective medium.

Absorbance of these solutions was measured at 277 nm using UV-Visible spectrophotometer. The percentage drug released at different time intervals were calculated.

**Kinetics of in-vitro drug release**

To study the release kinetics of *in-vitro* drug release, data obtained from *in-vitro* release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs  $\sqrt{\text{time}}$ , Korsmeyer- Peppas as log % drug released Vs log time and Hixson-Crowell as (% drug retained)<sup>1/3</sup> Vs time. By comparing the r-values obtained, the best-fit model was selected.

**Stability studies**

To study the effect of temperature and humidity on the tablets, they were stored at  $40^\circ\text{C}$  and 75 % RH in Stability chamber (Lab Top Instruments Pvt. Ltd.). After three months hardness, friability, Weight variation test, drug content, FTIR spectrum and *in vitro* drug release were recorded to observe any effect on the tablets by the exposure to humidity and temperature.

**RESULTS AND DISCUSSION****Evaluation of buccal tablets**

The hardness values ranged from 3.4 to 3.8 kg/cm<sup>2</sup> for all formulations (Table 2). The entire tablets passes weight variation test as the average % weight variation was the pharmacopoeial limit of 5% (Table 2). The friability values were found to be within the limit (Table 3). The drug content of Salbutamol Sulphate determined at 277 nm ranges from 97.68 mg to 99.7 mg and complies with IP standard. The surface pH of tablets of batches was found in the range of 6.71 to 7.01 (Table 3). In the study, the *in vitro* swelling study ranges 101.69 % to 197.24 % (Table 3). FRIR spectroscopy was performed to assess the compatibility of Salbutamol Sulphate with excipients. Analysis of Salbutamol Sulphate structure reveals that few intense peaks which are characteristic of the drug, the similar peaks were observed in all formulations. The results clearly indicate no shifting of peaks was significantly found, indicating the stability of the drug during tablet formulation. Thus the IR study indicates stable nature of Salbutamol Sulphate in the tablet formulations. This also confirmed that the drug and polymer does not interact. The faster release of the drug in the formulation F2 may due to low concentration of Carbopol (Figure 1). The increased concentration of the polymers resulted in the prolonged release of the drug from the tablets. Criteria for selecting the most appropriate model were based on the best goodness of fit indicated by the value of regression coefficient (r). The *in vitro* release profiles of drug from all the formulations could be best expressed by zero order equation. The n value obtained from Korsmeyer-Peppas model reveals that all formulation follows Quasi-Fickian Diffusion transport. The results of accelerated stability studied indicated that there was no significant change in the tablets. The drug content was found to be within  $100 \pm 5$  % for all the formulations at the end of 90 days. FTIR analysis suggested that there was no significant degradation or changes taking place in the tablets during the study period.

**Table 1: Composition of Bi layered Buccal Tablets of Salbutamol Sulphate**

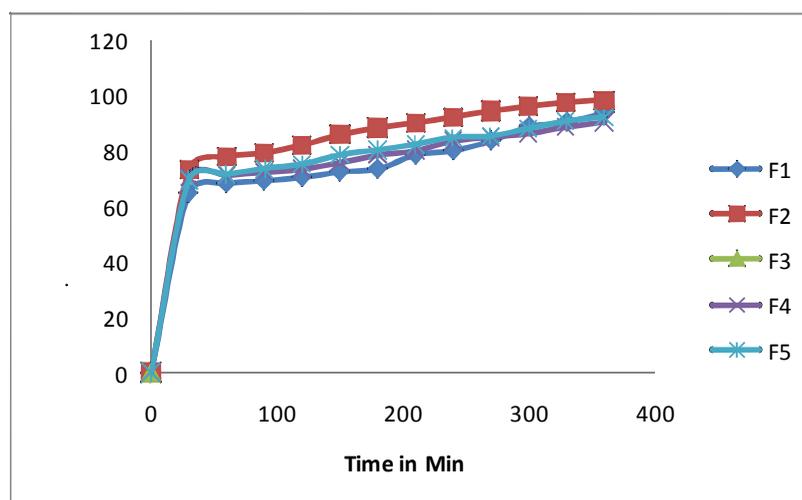
Formulation ingredients	F <sub>1</sub> (mg)	F <sub>2</sub> (mg)	F <sub>3</sub> (mg)	F <sub>4</sub> (mg)	F <sub>5</sub> (mg)
Salbutamol Sulphate	4	4	4	4	4
Carbopol-934	120	100	120	120	100
PVP (Polyvinyl pyrrolidone)	80	60	60	40	50
PVA (Polyvinyl alcohol)	0	40	20	40	50
Magnesium Stearate	4	4	4	4	4
Mannitol	40	40	40	40	40
β cyclodextrin	2	2	2	2	2
<b>Backing Layer</b>					
Ethyl cellulose	50	50	50	50	50

**Table 2: Evaluation of buccal tablets**

Formulation	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Average Weight Variation (%)	Thickness (mm)
F1	3.8 ± 0.16	0.625	1.245 ± 0.08	3.5
F2	3.6 ± 0.22	0.513	1.261 ± 0.10	3.8
F3	3.7 ± 0.12	0.465	1.248 ± 0.12	3.9
F4	3.4 ± 0.10	0.383	1.31 ± 0.20	4.1
F5	3.5 ± 0.06	0.391	1.33 ± 0.16	4.2

**Table 3: Evaluation of buccal tablets**

Formulation	Drug content uniformity (%)	Surface pH	<i>In vitro</i> swelling study (%)
F1	98.92	6.71	193.86
F2	97.68	6.9	101.69
F3	98.62	6.78	197.24
F4	99.7	6.79	163.69
F5	98.7	7.01	158.62

**Figure 1: *In vitro* release profile of buccal tablets F1-F5**

## CONCLUSION

The results of the present study indicate that mucoadhesive bi layer tablets of salbutamol with controlled drug release. It can be successfully prepared by direct compression method using PVP and PVA along with Carbopol-934 as mucoadhesive polymers because of high wettability of the mucous membrane and ethyl cellulose as backing layer. The mucoadhesive buccal tablets of salbutamol may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of salbutamol through buccal mucosa.

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