



### FORMULATION DEVELOPMENT AND EVALUATION OF TERBUTALINE SULPHATE MUCOADHESIVE BUCCAL TABLETS

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Article Received on: 19/01/13 Revised on: 01/02/13 Approved for publication: 10/03/13

DOI: 10.7897/2230-8407.04340

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#### ABSTRACT

The main objective of developing any new dosage form is reduce the side effects and increase the therapeutic effect of drug in existing dose of dosage form. Mucoadhesive drug delivery system is oral dosage form, where the tablet, gel or patch is attached to the buccal region for direct absorption of drug into blood circulation. This route can prevent the metabolism of drug in G.I tract or liver and side effects of metabolites avoided. In this study, the attempt was made to prepare mucoadhesive buccal tablets of Terbutaline sulphate with natural polymer sodium alginate with one side absorption by backing layer with ethyl cellulose. The buccal tablets of Terbutaline sulphate studied in detail. I R Spectroscopy did the compatible study between polymers and Terbutaline sulphate and No interaction was found between drug and polymers. Different formulations of oral Mucoadhesive buccal tablets of Terbutaline Sulphate (TS) were prepared using polymer sodium alginate, in different concentrations by direct compression. Post compressed evaluation studies, hardness, thickness, friability; weight variation and drug content, mucoadhesive strength of tablets were studied. The *in-vitro* release of TS was studied in buffer pH 6.8 at 37°C. All parameters of TS buccal tablets are passed the standard of mucoadhesive buccal tablets. It was found that mucoadhesive natural polymers exhibited better adhesiveness and mucoadhesiveness. The *in vitro* study of TS exhibited greater drug release profile with release of in the range of 79.25 to 99.85%.

**Keywords:** Buccal tablets, *in-vitro*, Sodium alginate, pH, COPD, TS.

#### INTRODUCTION

Mucoadhesive drug delivery system is bind to the gastric mucin or epithelial cell surface are useful in drug delivery for increasing the intimacy and duration of contact of drug with the absorbing membrane, this helps in sustained release of drug and prevent the metabolism of drug in gastric pH condition for the drug sensitive for acidic condition.

The mucoadhesive buccal drug delivery system offers several advantages over traditional methods of oral and systemic drug administration. The mucoadhesive buccal drug delivery system is a one of the significant dosage forms because it enhances the therapeutic effect of drugs by minimizing first pass metabolism in gastric acidic condition. With this drug delivery system, contraindications or side effects of drugs can be minimized, it gives sustained drug effect and dose of the drug can be reduced by developing in this dosage forms.

In recent days many people have been focused on placing a drug or a formulation in a particular region of the body for a specific period of time. This is because not only for targeting of drugs to a particular or effected part of the body but also to better control of systemic drug delivery to minimize side effects. Drugs that are absorbed through the mucosal region tissues will enter directly into the blood stream and thus they do not inactivate by enzymatic degradation in the gastrointestinal tract.

Several natural polymers have been used in various bioadhesive drug delivery systems. such as Xanthan gum, gaur gum, sodium alginate, acacia gum, etc.

The main aim of the present study was to develop suitable formulation for mucoadhesive buccal tablets Terbutaline sulphate (TS) using natural mucoadhesive polymer sodium alginate in different concentrations.

Terbutaline Sulphate (TS) is widely used as an effective bronco-dilator in the management of asthma. This is used as prophylactic drug as well as to prevent acute exacerbations of asthma. Because of first metabolism of Terbutaline sulphate

the patient may need to take more doses, if the drug is developed in mucoadhesive buccal tablet this problem will be solved.

#### MATERIALS AND METHODS

Terbutaline sulphate received as a gift sample from Astra genece Ltd, Bangalore, sodium alginate received from Himalaya laboratories Ltd, Bangalore. Other chemicals used are analytical grade, purchased from S.D Fine chemicals Mumbai.

#### Preparation of Mucoadhesive Bilayer Tablets<sup>7</sup>

Mucoadhesive buccal tablets of TS were prepared by direct compression techniques using sodium alginate polymer with varying concentration (Table 1).

The tablets were compressed using 8 mm flat circular punch on single station compression machine. For the application of the backing membrane, tablets were transferred to 10 mm die and a layer of ethyl cellulose was added in required amount & compressed on it.

#### Evaluation of Mucoadhesive Buccal Tablets

##### FTIR Studies

The Terbutaline sulphate (TS) and TS with sodium alginate polymer IR was recorded by a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets. (Figure 1 & Figure 2).

##### Ex- vivo bioadhesion strength<sup>1</sup>

The study of bioadhesive strength of TS buccal tablets is important to know the strength of the tablet to stay attached to the buccal. Here a tensile tester apparatus, similar to an Instron model 4301 tensile tester, was developed. The Porcine buccal mucosa obtained from slaughter's house was kept in Kerb's buffer of pH 7.4 at 37°C for 2 hours. The underlying mucus membrane was separated and cleaned

thoroughly for removal of unwanted contents from mucus membrane with pH 6.8 phosphate buffer. The skin (mucosa side) was fixed across the opening of a diffusion cell filled with phosphate buffer (pH 6.8). The test was carried out in triplicate and the results expressed as mean  $\pm$  standard deviation. The results are given in Table 2.

#### Drug Content<sup>7</sup>

The content uniformity of TS buccal tablet was determined. From each batch. The ten tablets weighted and finely powdered. An amount of powder equivalent to 4 mg of powder was accurately weighted and dissolved in 6.8 phosphate buffer. The resulting solution was suitably diluted with 6.8 Phosphate buffer and analyzed by Shimadzu UV spectrophotometer at 276 nm. The results are given in Table 2.

#### Hardness<sup>7</sup>

The hardness of tablets is directly proportional to friability loss and convenient in handling the tablets. Breaking under the condition of transportation, and handling before the uses depends on its hardness. Monsanto hardness tester was used to measure the hardness of tablets of each batch. The hardness expressed in terms of kg/cm<sup>2</sup>. The results are given in Table 3.

#### Friability<sup>12</sup>

A friability test was conducted on the TS buccal tablets using Friabilator. Approximately around twenty tablets were taken from each batch weighed for the initial weight ( $W^1$ ) and kept in friability machine at the speed of 100 rpm. After completion of 100 rpm the tablets were collected and removed any loose dust with the help of a soft brush before weighing. The tablets were weighed again as final weight ( $W^2$ ). The percentage of loss was calculated by following formula

$$F = [(W^1 - W^2) / W^1] \times 100$$

Percentage Friability of tablets less than 1% is considered acceptable. The results are given in Table 3.

#### Surface pH<sup>7</sup>

The objective of study of surface pH of buccal tablet was to know whether the TS buccal tablet causes any irritation to mucus membrane of buccal region. The Buccal tablets were allowed to swell at  $37 \pm 1^\circ \text{C}$  for 2 hrs in 50 ml phosphate buffer (pH 6.8). The surface pH of swollen buccal tablets was measured by using pH paper. The results are given in Table 2.

#### Swelling index study<sup>7,14</sup>

Swelling study of buccal tablets was done on 1% agar gel plates. Ten tablets of all the formulations are weighed (initial weight or dry tablet weight). The tablets were placed on the gel surface in Petri dishes, which were placed in an incubator at  $37^\circ \text{C}$ . The tablets were removed at time intervals of 1, 2, 3, 4, 5 up to 8 hrs excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed (weight of wet tablet). The swelling index was calculated by using following formula,

$$\% \text{ Swelling index (S.I)} = \frac{\text{Buccal tablet wet weight} - \text{Buccal tablet dry weight}}{\text{Buccal tablet wet weight}} \times 100$$

The results are given in Table 2.

#### In vitro residence time<sup>7,16</sup>

In-vitro residence time for tablets was determined using USP disintegration apparatus. The disintegration medium was composed of 800 ml of phosphate buffer of pH 6.8 maintained at  $37^\circ \text{C}$ . A segment of rabbit buccal mucosa 3 cm length was glued to glass slab. The tablet surface was moistened using 15 ml pH 6.8 buffers and then moist surface of tablet was brought into contact with the mucosal membrane. The glass slab was vertically fixed to tablets was completely immersed in the buffers solution at lowest and wash out at highest point the time necessary for complete erosion or detachment of tablets from mucosal surface was noted.

#### Ex vivo permeation studies.<sup>7,13</sup>

Various methods have been used to study the mucoadhesive permeation of buccal tablets.

Here we have used the modified K.Cell method that consists of two compartments one is receptor compartment and another is donor. From the local slaughter's house, the buccal mucosa was collected and immediately transported to the laboratory in cold normal saline solution. Then buccal epithelium was isolated from the underlying tissue. The buccal epithelium was used within 2 hrs upon removal. The receptor compartment was covered with water jacket to maintain temperature  $37^\circ \pm 1^\circ \text{C}$ . The separated buccal epithelium was mounted between two chambers and in receptor chamber phosphate buffer pH 6.8 was filled and buccal epithelium was allowed to stabilization. After stabilization of buccal epithelium, the tablet was kept on buccal epithelium and donor compartment filled with phosphate buffer pH 7.4. The samples were withdrawn with specific period and same volume of fresh buffer solution was replaced. The aliquots were analyzed spectrophotometrically at 276 nm.

#### In vitro release dissolution<sup>7,13</sup>:

The in vitro dissolution tests were performed using the basket method of USP 24. With the aid of a dissolution apparatus (TDT 08L Dissolution Tester Electro Lab) rotating at 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH 6.8) and the temperature maintained was at  $37^\circ \pm 1^\circ \text{C}$ . Samples of the dissolution solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was filtered to remove any undissolved solid particles. Then the concentration of TS in solution was measured with an Ultraviolet-Visible spectrophotometer, pharma spec1700 (Shimadzu) at a wavelength of 276 nm. The test was carried out in triplicate and the results expressed as mean  $\pm$  standard deviation (SD). Figure 3.

#### Kinetic study<sup>1,2,4,9</sup>

To study the mechanism of drug release from the Terbutaline sulphate buccal tablets, the *in vitro* dissolution data were fitted to zero order ( $K=kt$ ), first order, Korsmeyer and Peppas model ( $F=ktn$ ), Higuchi ( $F=k\sqrt{t}$ ) release models. Where  $F$  is the fraction of drug release,  $k$  is the release constant and  $t$  is time. The details are given in Table 4

#### Stability study<sup>7,3</sup>

The stability study of TS tablets was carried out according to ICH guidelines at  $40^\circ \text{C}$  and relative humidity at 75 %, to know the how much drug may loss from the formulation after storage for specific period. For stability study, the tablets

were sealed in aluminum packing coated with polyethylene inside. These sample containers were placed in desiccators maintained at 75% RH. The product was evaluated for drug

content, bioadhesive strength swelling index study and in-vitro release study.

**Table 1: Formulation of mucoadhesive buccal tablets of TS**

| Ingredients (MG)     | TSSA1 | TSSA 2 | TSSA 3 | TSSA 4 | TSSA 5 |
|----------------------|-------|--------|--------|--------|--------|
| Terbutaline Sulphate | 4     | 4      | 4      | 4      | 4      |
| Sodium alginate      | 50.0  | 40.0   | 30.00  | 25.00  | 15.00  |
| Mg Stearate          | 1     | 1      | 1      | 1      | 1      |
| Talc                 | 1     | 1      | 1      | 1      | 1      |
| Lactose              | 44.00 | 54     | 64     | 69     | 79     |
| Ethyl Cellulose      | 25    | 25     | 25     | 25     | 25     |

**Table 2: Physical parameters of mucoadhesive buccal tablets of TS**

| FC    | Drug content (%) | Surface pH | Mucoadhesive Strength | Swelling Index (%) |
|-------|------------------|------------|-----------------------|--------------------|
| TSSA1 | 98.83 ±1.25      | 6.855±0.32 | 8.65±0.36             | 59.61±0.67         |
| TSSA2 | 87.5 ±5.62       | 6.78±0.42  | 8.12±0.15             | 54.80±0.66         |
| TSSA3 | 95.75±1.29       | 6.80±0.30  | 7.95±0.40             | 50.62±0.49         |
| TSSA4 | 97.00±0.04       | 7.03±0.16  | 6.41±0.37             | 43.7±0.63          |
| TSSA5 | 98.50±1.14       | 7.15±0.02  | 6.15±0.30             | 37.81±1.12         |

**Table 3: Physical parameters of mucoadhesive buccal tablets of TS**

| FC    | Friability (%) | Weight variation | Thickness | Hardness   |
|-------|----------------|------------------|-----------|------------|
| TSSA1 | 0.53 ±0.02     | 125.88±1.48      | 3.41±0.01 | 4.09±0.096 |
| TSSA2 | 0.59 ±0.06     | 124.51±1.46      | 3.46±0.04 | 4.06±0.075 |
| TSSA3 | 0.65±0.030     | 125.55±0.60      | 3.46±0.05 | 4.02±0.15  |
| TSSA4 | 0.72±0.015     | 126.00±0.25      | 3.45±0.01 | 3.97±0.12  |
| TSSA5 | 0.70±0.002     | 125.5±0.60       | 3.47±0.06 | 3.82±0.064 |

**Table 4: Kinetics study of mucoadhesive buccal tablets of TS**

| FC    | Zero order<br>R <sup>2</sup> | First order<br>R <sup>2</sup> | Higuchi's<br>R <sup>2</sup> | Korsmeyer<br>R <sup>2</sup> |
|-------|------------------------------|-------------------------------|-----------------------------|-----------------------------|
| TSSA1 | 0.974                        | 0.885                         | 0.974                       | 0.898                       |
| TSSA2 | 0.968                        | 0.852                         | 0.968                       | 0.893                       |
| TSSA3 | 0.973                        | 0.831                         | 0.973                       | 0.892                       |
| TSSA4 | 0.963                        | 0.569                         | 0.963                       | 0.876                       |
| TSSA5 | 0.987                        | 0.759                         | 0.987                       | 0.795                       |

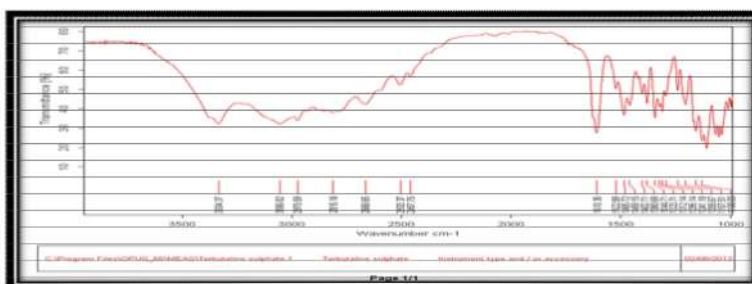


**Figure 1: FTIR of Terbutaline Sulphate**

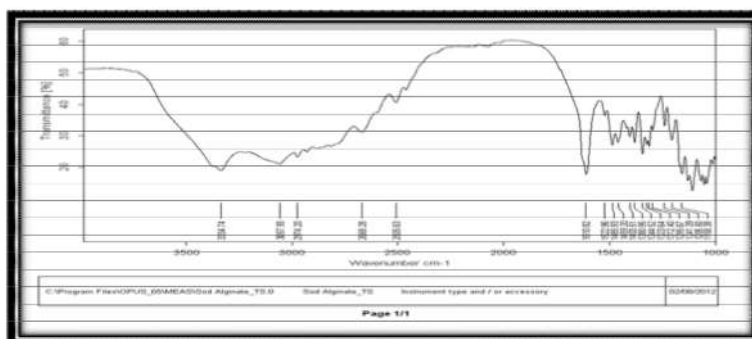


**Figure 2: FTIR of Terbutaline sulphate + Sodium Alginate**

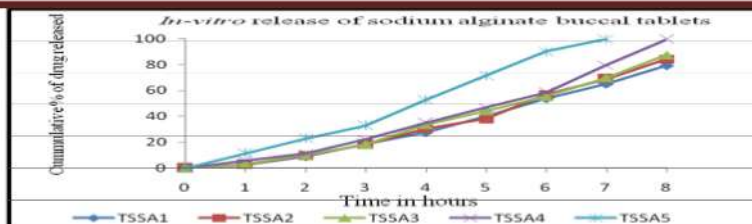


Figure 3: In-vitro studies of formulations TSSA1 to TSSA5

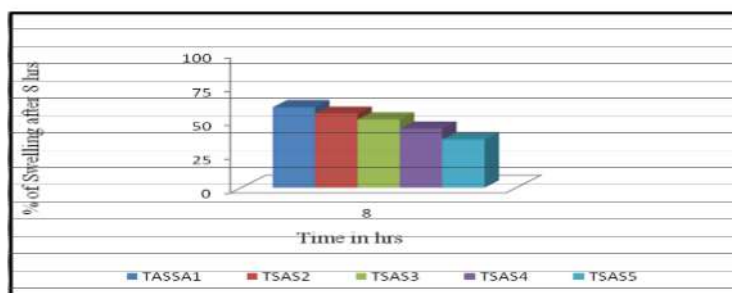


Figure 4: % of Swelling Sodium Alginate mucoadhesive buccal tablets

## RESULTS AND DISCUSSION

In the present work, an attempt was made to develop mucoadhesive buccal dosage form. tablets of TS as an improved and better patient compliant. From the study conducted, the following conclusions are drawn:

Mucoadhesive Buccal tablets of TS were developed to a satisfactory level, in parameters of bioadhesive strength, content uniformity, swelling index, surface pH, friability, in-vitro drug release. Pre compression studies drug polymer interaction by FTIR & UV spectrophotometer indicated, there is no interaction between drug and polymers.

Percentage of swelling index was increasing with time and with increase in hydrophilic polymer sodium alginate content. Buccal tablets containing sodium alginate with highest concentration (TSG1) showed better swelling index. In-vitro study showed that higher the polymer concentration the lesser the drug release in specified time. Formulation TSG4 can be selected as optimized formulation as its physical parameters and in-vitro release results were best among formulations.

## CONCLUSION

Conclusion of this study was, the results of mucoadhesive buccal tablets of TS were encouraging, and it needs for further study for reproducibility. Therefore, TS can be given by this route for better availability and can be minimized contraindications of drug.

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## Cite this article as:

Gururaj S.Kulkarni, N.G RaghavendraRao, D.Narasimhareddy. Formulation development and evaluation of terbutaline sulphate mucoadhesive buccal tablets. *Int. Res. J. Pharm.* 2013; 4(3):189-192