Research Article

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Formulation development and evaluation of terbutaline sulphate mucoadhesive buccal tablets

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ABSTRACT

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. In this work, the attempt has made to develop and evaluate the Mucoadhesive Buccal tablets of Terbutaline sulphate with natural polymers gaur gum, with ethyl cellulose as back layer of bilayer tablets. Terbutaline sulfate is a white to gray-white crystalline powder. It is odorless or has a faint odor of acetic acid. Terbutaline sulfate is indicated in for the prevention and reversal of bronchospasm in patients 12 years of age and older. With asthma, COPD and reversible bronchospasm associated with bronchitis and emphysema. Because of its first pass metabolism its bioavailability is in the range of 30 to 50% by orally. 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 Gaur gum, 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 37^0C. 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 80.57 to 100.81%.

Key words: Buccal tablets, *in-vitro*, Gaur gum, pH, COPD, TS, Gaur gum.

INTRODUCTION

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 controlled drug effect and dose of the drug can also 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[4]. 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 synthetic polymers have been used in various bioadhesive drug delivery systems. such as acrylic-based hygrogels i.e. synthetic polymers such as Carbopol 934.

The objective of the present study was (a) to prepare mucoadhesive buccal tablets Terbutaline sulphate (TS) using natural mucoadhesive polymer gaur gum in different concentrations. The targeting of drug TS and better control of systemic drug delivery. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the blood stream thus avoids the first pass metabolism.

The mucoadhesive drug delivery system gaining appreciation for the fabrication of pharmaceuticals with uniform drug release characteristics. Drug release property of matrices is preceded by polymer hydration and the rate of drug release from polymer carrier can be tailor-made by selecting a suitable polymer-blends composition and drug concentration.

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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. In acute attack of asthma, it will be difficult for patient to take oral medications repeatedly in short period. Hence, it is rational to administer Terbutaline sulphate (TS) in a sustained release dosage form, which will minimize repeated administration of drug1.

MATERIALS AND METHODS

Materials

Terbutaline sulpahate received as a gift sample from Astra geneca Ltd, Bangalore, gaur gum received from Himalaya laboratories Ltd, Bangalore. Other chemicals used are analytical grade, purchased from S.D Fine chemicals Mumbai.

Methodology

Preparation of Mucoadhesive Bilayer Tablets

Mucoadhesive buccal tablets of TS were prepared by direct compression techniques using gaur gum polymer with varying concentration (Table I).

Table1: Formulation of mucoadhesive buccal tablets of TS

Ingredients (Mg)	TSG1	TSG2	TSG3	TSG4	TSG5
Terbutaline Sulphate	4	4	4	4	4
Gaur gum	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

The tablets were compressed using 9 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 pure TS I.R spectroscopy was done, and the TS with formulation polymer IR was recorded by a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

Ex- vivo bioadhesion strength

The study of bioadhesive strength of TS buccal tablets is important to know the strength of the tablet to stay attached to the buccal later. 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 37^0 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 ± standard deviation.

Drug Content

The Drug content of TS prepared tablet of each batch of the formulation 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 and analyzed on Shimadzu UV spectrophotometer at 276 nm. The results are given in Table 2.

Hardness

The hardness of tablets is directly proportional to friability loss and convenient in handling the tablets. Breaking under the condition of storage, 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/ cm2. The results are given in Table 2.

Friability

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 for a time of 2 minutes. After the specific time the tablets were collected and removed any loose dust was with the help of a soft brush before weighing. The tablets were weighed again as final weight (W^2). The percentage friability was then calculated by,

$F = [(W^1 - W^2)/ W^1] X 100.$

Percentage Friability of tablets less than 1% is considered acceptable. The results are given in Table 2.

Surface pH:

The objective of study of surface pH of buccal tablet was to know whether the TS tablet causes any irritation to mucus membrane of buccal region. The Buccal tablets were allowed to swell at 37 ± 1^0 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:

Swelling study of buccal tablets was done on 1% agar gel plates. Ten tablets of all the formulations are weighed and average weight of each tablets were calculated. The tablets were placed on the gel surface in Petri dishes, which were placed in an incubator at 37°C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed. The swelling index was calculated by using formula,

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

The results are given in Table 2.

In vitro residence time12:

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°C. A segment of rabbit buccal mucosa 3 cm length was glutted to glass slab. The tablet surface was hydrated using 15 ml pH 6.8 and then hydrated surface 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 determined.

Table2: Physical parameters of mucoadhesive buccal tablets of TS

FC	Drug content (%)	Surface pH	Mucoadhesive Strength	Swelling Index (%)
TSG1	98.75 ±0.14	6.95±0.1	9.13±0.47	54.00±0.67
TSG2	93.75 ±5.44	7.05±0.1	8.25±0.10	52.08±0.66
TSG3	95.75±1.30	6.9±0.30	7.62±0.40	49.17±0.98
TSG4	95.75±1.14	6.83±0.41	6.41±0.37	46.05±0.55
TSG5	95.50±0.866	7.16±0.076	5.78±0.30	38.81±1.00

***Ex vivo* permeation studies16, 17**

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°± 1ºC. 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 dissolution13-15:**

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 $37^0 \pm 1^0$ 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 ± standard deviation (SD). (Figure 1)

Kinetic study

To analyze the mechanism of drug release form the tablets the in vitro dissolution data. Were fitted to zero order (K=kt), korsmeyer and peppas model (F=ktn), higuchi (F=kÖt) release models. Where F is the fraction of drug release, k is the release constant and t is time [20-21].

Table3: Physical parameters of mucoadhesive buccal tablets of TS

FC	Friability (%)	Weight variation	Thickness	Hardness
TSG1	0.636 ±0.015	125.81±0.30	3.39±0.073	4.01±0.11
TSG2	0.68 ±0.03	126.42±1.04	3.54±0.086	4.04±0.08
TSG3	0.683±0.035	124.95±0.26	3.55±0.1	4.02±0.15
TSG4	0.72±0.015	125.53±0.60	3.58±0.0.25	4.05±0.1
TSG5	0.73±0.0.03	125.18±0.49	3.65±0.25	4.15±0.05

Table 4: Kinetics

FC	Zero order R^2	First order R^2	Higuchi's R^2	Korsmeyer R^2
TSG1	0.976	0.921	0.976	0.904
TSG2	0.975	0.913	0.975	0.898
TSG3	0.983	0.885	0.983	0.853
TSG4	0.990	0.882	0.990	0.825
TSG5	0.993	0.911	0.993	0.809

Table 5: Comparison of the peak of functional groups observed in IR spectra

IR Spectra	Peak of functional groups [wave length (cm^{-1})] O H Stretch cm^{-1}	Methyl asymmetric stretch cm^{-1}	Aromatic ring Stretch cm^{-1}	t-butyl symmetric bend Stretch cm^{-1}
Terbutaline sulphate Pure (TS)	3334.37	2666.65	1610.35 &1486.72	1380.69
Terbutaline sulphate+ Gaur gum	3334.65	2669.69	1610.50 & 1484.87	1380.71

Stability study:[20]

The stability study of TS tablets was carried out according to ICH guidelines at 40^0 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.

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.

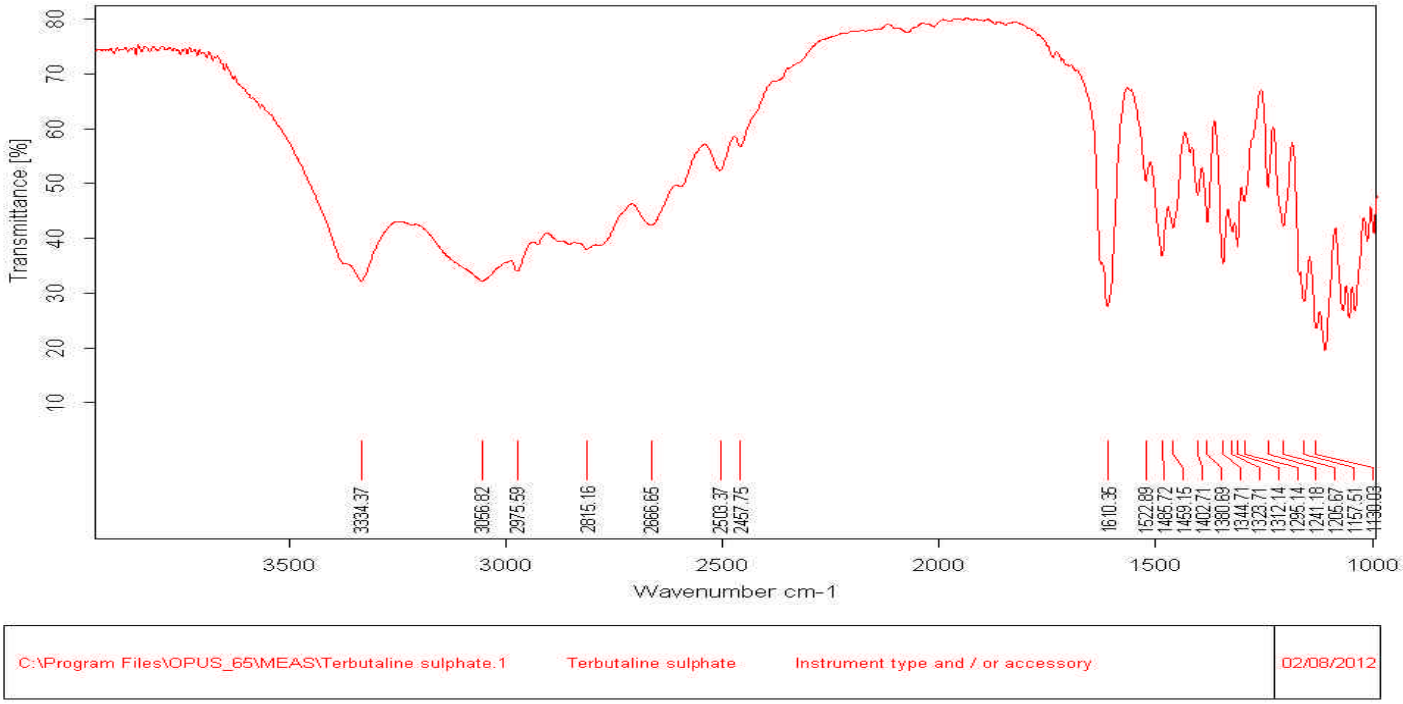

Figure 1. FTIR of Terbutaline sulphate

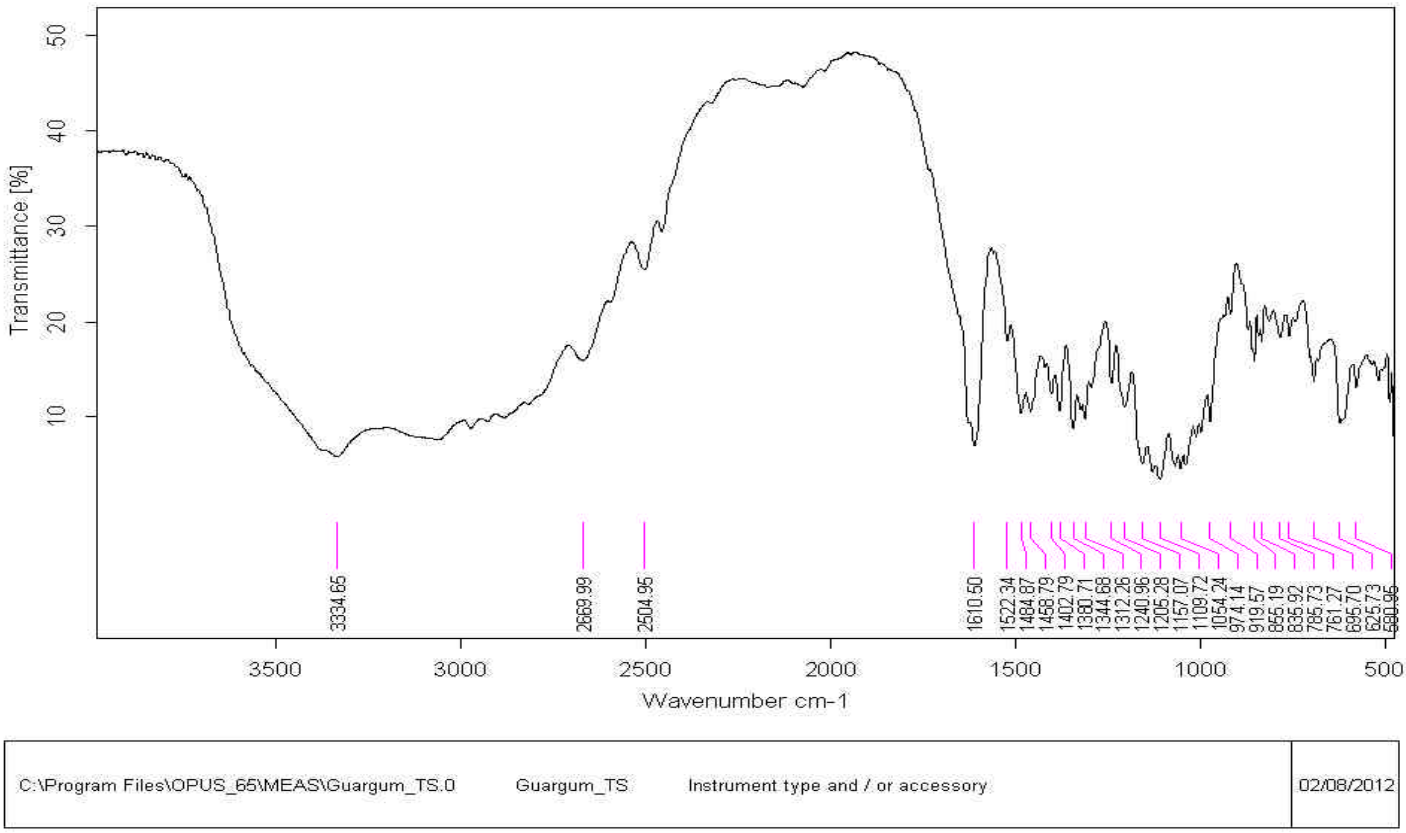

Figure 2: FTIR of Terbutaline sulphate+ Gaur gum

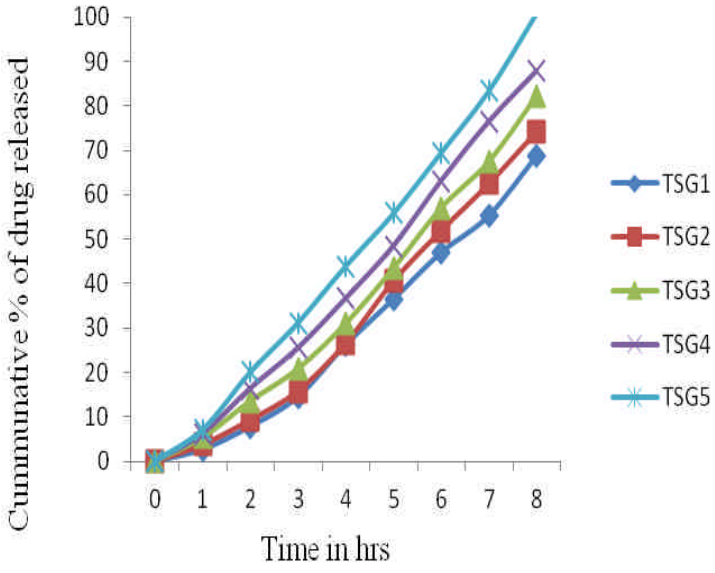

Figure 3: In-vitro studies of formulations TSG1 to TSG5

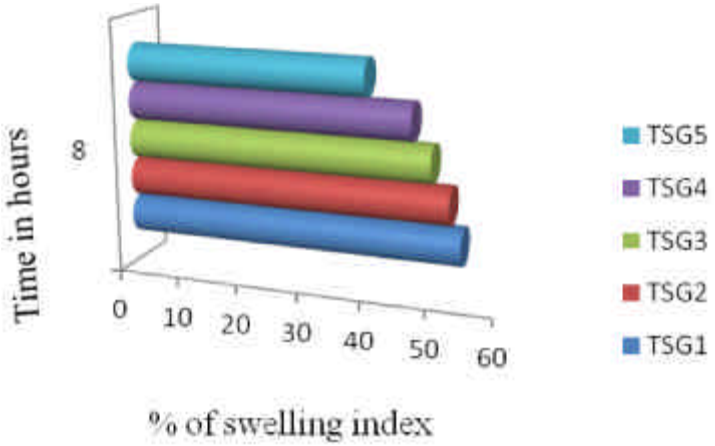

Figure 4: % of swelling index after 8 hours

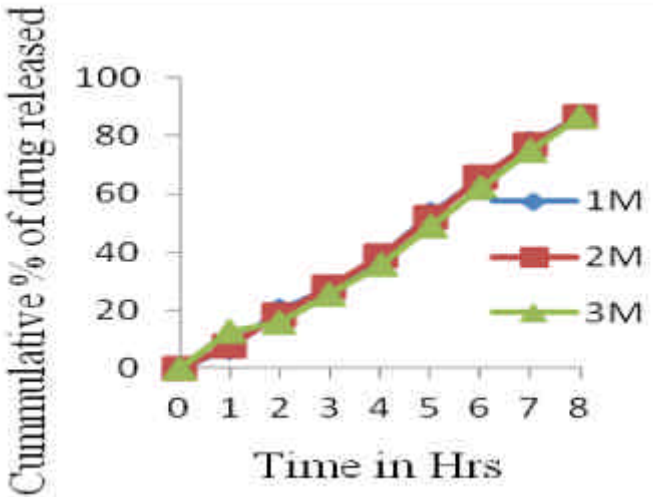

Figure 5: comparison in vitro studies of formulation TSG4 after stability time

Percentage of swelling index was increasing with time and with increase in hydrophilic polymer gaur gum content. Buccal tablets containing gaur gum 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 it physical parameters and in-vitro release results were best among formulations. Conclusion of this study was, these studies of mucoadhesive buccal tablets of TS were encouraging for further study and reproducibility. Therefore, TS can be given by this route for better availability and can be minimized contraindications of drug.

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