INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

PREFORMULATION STUDIES OF TERBUTALINE SULPHATE WITH POLYMERS USED FOR SUSTAIN RELEASE APPROACH

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ARTICLE INFO

Article history
Received 10/11/2019
Available online
30/11/2019

Keywords
Asthma,
Preformulation Studies,
Terbutaline Sulphate,
Polymers,
Solubility,
Ethyl Cellulose,
Eudragit RS 100.

ABSTRACT

The major objective of the preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physico-chemical parameter of the drug. Among these properties drug solubility, drug excipients interaction, polymorphic forms and stability plays important role in preformulation study. The solubility of terbutaline sulphate in different solvents was studied. The calibration curve of the drug was prepared in phosphate buffer pH 7.4 by determining absorbance by UV visible spectrophotometer at 276 nm. The compatibility studies if the terbutaline sulphate with the excipients viz. eudragit RS100 and ethyl cellulose was performed using FTIR. The observed data complies for a sustained release formulation. Ethyl cellulose and Eudragit RS 100 may be used to prepare a matrix system for slow release profile formulations. These polymers have compatibility with terbutaline sulphate. The results provide promising baseline information that both ethyl cellulose and eudragit RS 100 are compatible with terbutaline sulphate and suitable to prepare a matrix formulation for sustained release action.

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*Please cite this article in press as **Mr. Vijay Kumar** et al. Preformulation Studies of Terbutaline Sulphate with Polymers Used for Sustain Release Approach . Indo American Journal of Pharmaceutical Research.2019:9(11).*

INTRODUCTION

Asthma

Asthma is defined as a chronic inflammatory disease of the airways. The chronic inflammation is associated with airway hyper responsiveness (an exaggerated airway narrowing response to triggers, such as allergens and exercise), that leads to recurrent symptoms such as wheezing, dyspnea (shortness of breath), chest tightness and coughing. Symptom episodes are generally associated with widespread, but variable, airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment in which the sleep-related worsening of asthma is common. [1, 2] Additionally, asthmatic deaths and respiratory arrests occur more frequently during the night. It is possible that these findings are related to the increase in bronchial responsiveness that has been demonstrated to occur in asthmatics at night. It is known that during the daytime hours, increased bronchial responsiveness is associated with producing airways inflammation. For instance, after ozone exposure or antigen challenge in humans, there is an increase in both bronchial reactivity and inflammatory cells in the bronchoalveolar lavage fluid. Because nocturnal asthma is associated with increased bronchial reactivity, it is hypothesized that inflammatory cells in the bronchoalveolar lavage would be increased at night. [3, 4]

Terbutaline is a selective β-2 adrenoceptor agonist. At therapeutic doses it acts on the β-2 adrenoreceptors of bronchial muscle, with little or no action on the β-2 adrenoreceptors of the heart. Selectivity is further increased by inhaling the drug**.** It is suitable for the management and prevention of attack of asthma. The elimination half-life of terbutaline was approximately 3-4 hours. About 90% of the drug was excreted in the urine at 96 hours after subcutaneous administration, with about 60% of this being unchanged drug. The sulphate conjugate is a major metabolite of terbutaline, and urinary excretion is the primary route of elimination. The dose of terbutaline sulphate is up to 15mg per day, it means dose frequency of the drug is 4-5 time in day. This sustained release formulation is used two times in a day and maintained the level of drug in body and prevent asthmatic attack and prevent night time asthma. [5]

MATERIAL AND METHODS

Terbutaline sulphate (TS) was obtained as a gift sample from Ananta Drugs & Pharmaceutical Pvt. Ltd., Sri Ganganagar (Rajasthan), Eudragit RS 100 provided by Alembic Pharmaceutical Ltd., Vadodara and ethyl cellulose provided by Lab Chemicals Pvt. Ltd., Bhubaneshwar.

Drug Profile

Terbutaline Sulphate

Chemical Name: Terbutaline Sulphate is *(RS)*-2-(*tert*-butylamino)-1-(3,5-dihydroxyphenyl) ethanol sulphate**.**

Chemical Structure: The structure of terbutaline sulphate shown in figure no. 1.

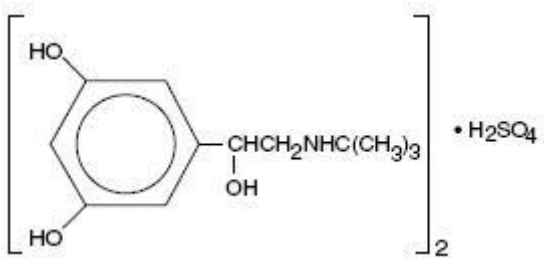

Figure 1: Chemical structure of terbutaline sulphate.

TS is a selective β2 adrenergic causing bronchodilator; increase in mucociliary clearance; suppression of edema and anti-allergic effects. The pharmacologic effects of beta-adrenergic agonists, including terbutaline, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme which catalyses the conversion of Adenosine triphosphate (ATP) to Cyclic 3', 5'-adenosine monophosphate (cAMP). The oral dose of TS is up to 15 mg per day.

After oral administration, peak plasma concentration is reached within 1-4 h. The plasma protein binding of terbutaline sulphate is low (14-25%). The main metabolite of terbutaline is the sulphate conjugate, which is formed in the liver and, after oral administration, predominantly in the gut wall. The elimination half-life of terbutaline was approximately 3.4 hours. During subcutaneous administration about 90% of the drug was excreted in the urine at 96 hours and about 60% of this being unchanged drug. The sulphate conjugate is a major metabolite of terbutaline, and urinary excretion is the primary route of elimination. [6]

METHODS

Organoleptic Properties

The sample of drug was observed for colour, odour and taste.

Color: It is determined by naked eye or magnifying glass.

Odour: It is determined by smell with human sensory organ.

Taste: It is determined by human taste buds.

Drug Identification (λ_{max})

Absorption spectrum method

Accurately weighed 10 mg of Terbutaline sulphate was dissolved in phosphate buffer pH 7.4 to prepare 100µg/ml solution. This solution was scanned between 200-400nm to determine absorption maxima (λ_{max}) for the pure drug. [7]

Infra-red spectra method

Accurately weighed 25 mg of TS was taken in vials, scanned in FTIR for identification. The scan was also taken for drug and polymers after 15 days of incubation at 50°C for confirmation of stability of drug & polymers. [7]

Standard calibration Curve of TS

10mg of TS was dissolved in 100ml of phosphate buffer pH 7.4 to prepare 100µg/ml of solution and scanned using UV-Visible Spectrophotometer to obtained λ_{max} . From this solution different strength viz 10, 20, 40, 60, 80 and 100µg/ml were prepared. Afterward absorbance of these solutions was measured at λ_{max}. [6]

Drug Excipients Compatibility Studies by FTIR

Before formulating a dosage form it is necessary to confirm that drug is not interacting with the polymer under certain experimental studies. Interacting among drug and polymer may affect the efficacy of final dosage form. Fourier transform infra-red spectrum of pure drug, eudragit RS 100, ethyl cellulose and their physical mixture were recorded. Drug and different excipients were taken in 1:1 ratio. Accurately weighed drug and excipients mixed, resulting mixtures were scaled in screw glass vials and kept at 50°C for 15 days Table 6. The changes regarding appearance, colour and odour were observed.

Solubility Analysis

The solubility of the TS was determined to find the extent to which drug was soluble in different solvents such water, 0.1 N HCl, 0.1 N NaOH, Methanol, Ethanol, Acetone & Phosphate buffer pH 7.4. Excess amount of drug was added into different solvents (such as water, 0.1 N HCl, 0.1 N NaOH, ethanol, acetone, methanol etc) shaken for 72 hrs and solution were filtered using whatman filter paper to determine the solubility of the drug in different solvents with UV visible spectrophotometer. [8, 6]

Thermal Analysis

Melting point determination

Appropriate amount of drug was filled in capillary and placed in the Digital melting point apparatus. Observed the melting point of the drug when it just starts melting and when drug completely melted. Observations were taken for three samples of the drug. [6-7]

Micromeritics Study:

Successful formulation of suspensions, emulsions and tablets, from the viewpoints of both physical stability and pharmacologic response, depends on the particle size achieved in the product of terbutaline sulphate. In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders. The following parameters were observed. [14]

Bulk density

The bulk density of the formulated granules was evaluated using bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a graduated measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by following formula:

$$\text{Bulk Density } (\rho_b) = \frac{\text{Mass of the powder (M)}}{\text{Volume of the bulk powder } (V_b)}$$

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given as [9, 12]

$$\text{Tapped Density } (\rho_t) = \frac{\text{Mass of the powder (M)}}{\text{Tapped Volume of the powder } (V_t)}$$

Compressibility Index and Hausner's Ratio

The Compressibility index and Hausner's ratio are measures of the tendency of a powder to be compressed and the flow ability of granule. As such, they are measures of the relative importance of inter-particulate interactions. Carr's index and Hausner's ratio were calculated using following formula and the range of these parameters are shown in Table 1.

$$\text{Carr's Index (I)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_b}$$

Table 1: Range of Compressibility Index and Hausner's Ratio [10].

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of TS granules were passed through a funnel from a particular height onto a flat surface until a pile is formed, which touched the tip of the funnel. The height and radius of the pile were measured. The angle of repose was calculated using the formula and range are shown in Table 2. [11]

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Table 2: Range of angle of repose [10].

Flow Property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

RESULTS AND DISCUSSIONS

Oraganoleptic properties

The organoleptic properties were observed as shown in Table no 3.

Table 3: Results of organoleptic properties.

Name of Parameter	Observation
Colour	White to almost white
Odour	Odourless
Taste	Slightly bitter in taste

Drug Identification (λ_{max})

UV Spectrophotometer

Maximum wavelength for absorption in pH 7.4 phosphate buffer was 276 nm as shown in figure 2.

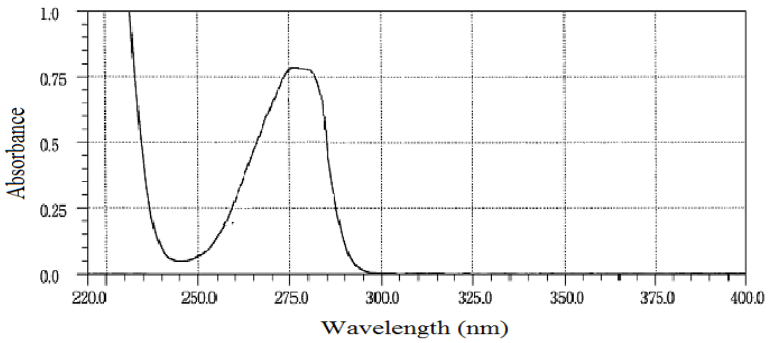

Figure 2: TS scan in pH 7.4 Phosphate Buffer.

Infra-red spectrum method

Drug identified by infra-red spectrum are compared with its standard IR given in pharmacopoeia. These IR spectrums given below shown that the peaks obtained in these spectrums are similar to that given in standards. Table 4 described the quantity per vial of drug used for the study. The results are shown in figure 3-5.

Table 4: Drug identification.

API and Excipient	Qty per vial (mg)	No: of Vials		Results
		Initial	50°C After 15 Days	
Terbutaline sulphate	25	1	1	Complies

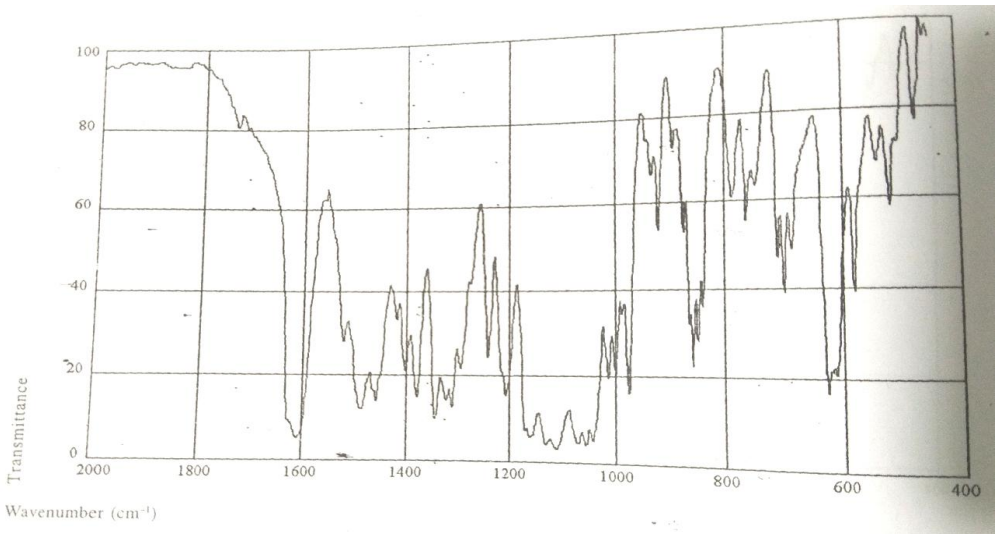

Figure 3: FT IR Spectra of TS [7].

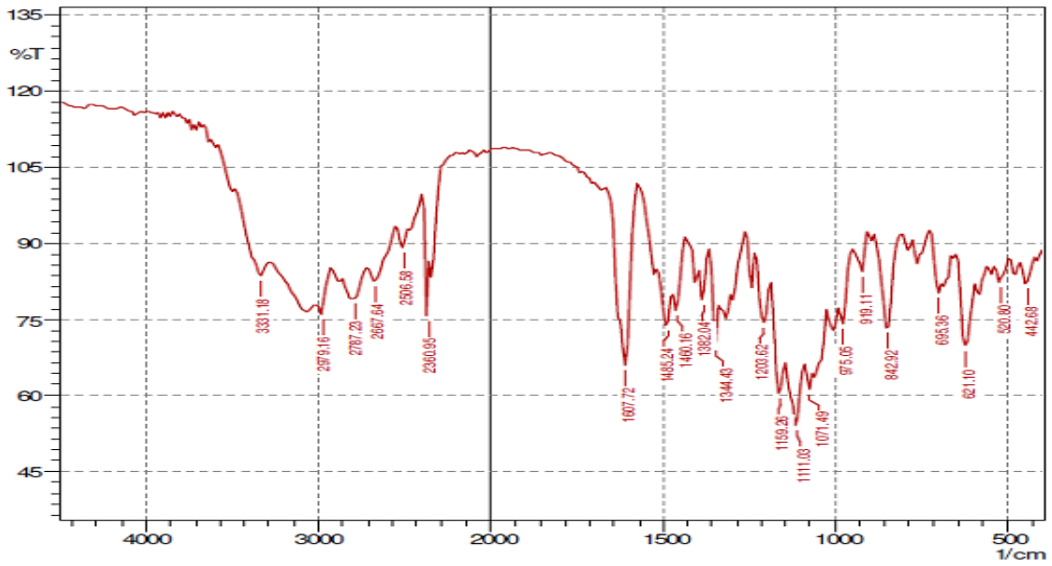

Figure 4: FT IR spectra of TS (Immediate).

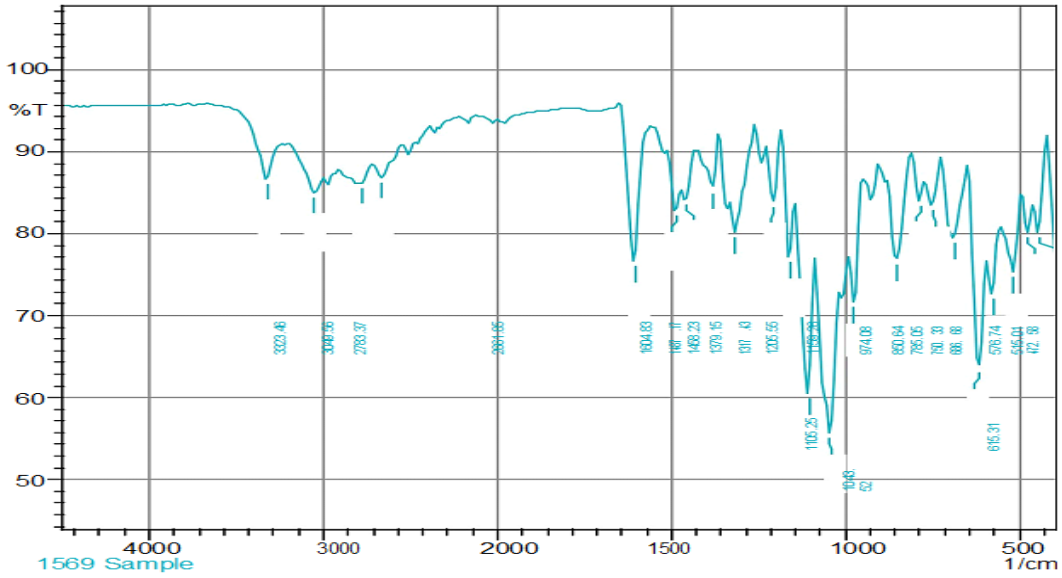

Figure 5: FT IR spectra of TS (after 15 days).

FT-IR of TS in standards showed that peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standards.

Standard calibration curve of TS

The standard calibration curve of TS was observed at 276 nm & the observations are shown in Table 5. It indicates that the value of r^2 was near about 1 that was 0.999 as shown in figure 6.

Table 5: Absorbance of TS in Phosphate buffer pH 7.4.

Concentration (µg/ml)	Absorbance *
10	0.082
20	0.173
40	0.337
60	0.494
80	0.650
100	0.829

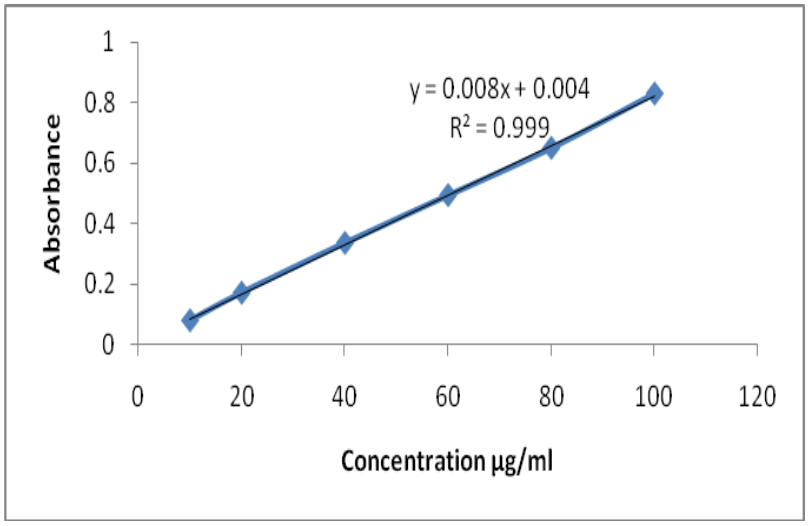

Figure 6: Standard calibration curve of TS in Phosphate buffer pH 7.4.

Drug Excipient Compatibility Studies

The possible interaction between the drug and excipients were studied by IR spectroscopy. Below spectra shows the peaks of pure drug sample and polymers as compare to standard drug sample that is no chemical reaction occurs between polymers and drug samples. Table 6 described the quantity per vial of drug and polymers used for the study. The results are shown in figure 7-10.

Table 6: Drug – Excipient Compatibility Studies.

API and Excipient	Drug: Excipient Ratio	Qty per vial (mg)	No: of Vials		Compatibility reaction
			Initial	50°C After 15 Days	
Terbutaline sulphate + Eudragit RS100	1:1	25 + 25	1	1	Compatible
Terbutaline sulphate + Ethyl cellulose	1:1	25 + 25	1	1	Compatible

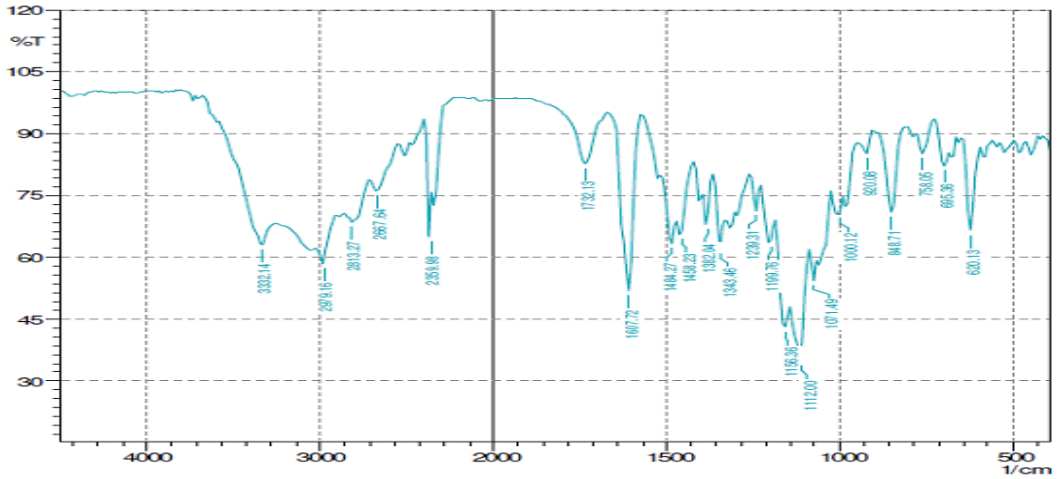

Figure 7: FTIR Spectrum of TS with Eudragit RS 100 (Immediate).

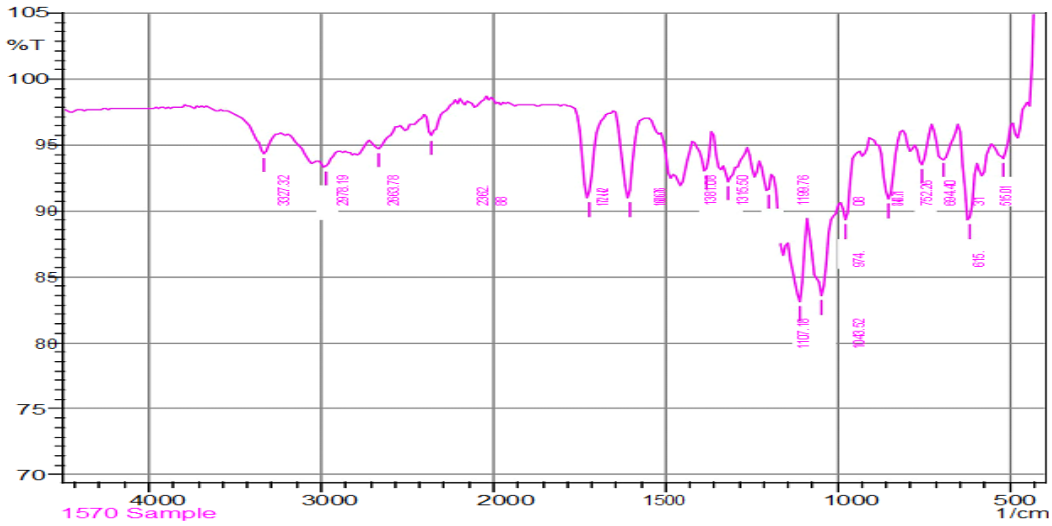

Figure 8: FTIR Spectrum of TS with Eudragit RS 100 (15 days).

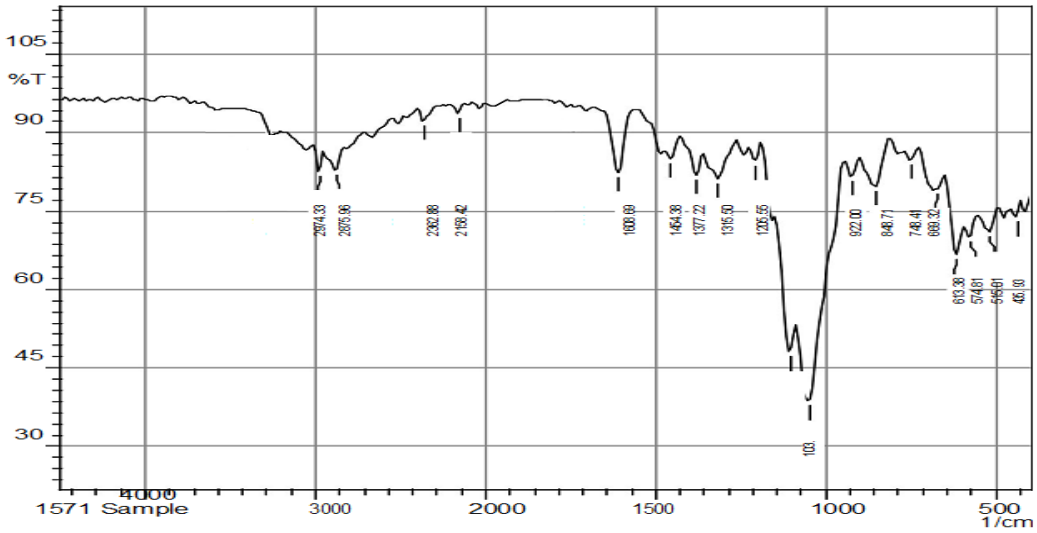

Figure 9: FTIR Spectrum of TS with Ethyl cellulose (immediate).

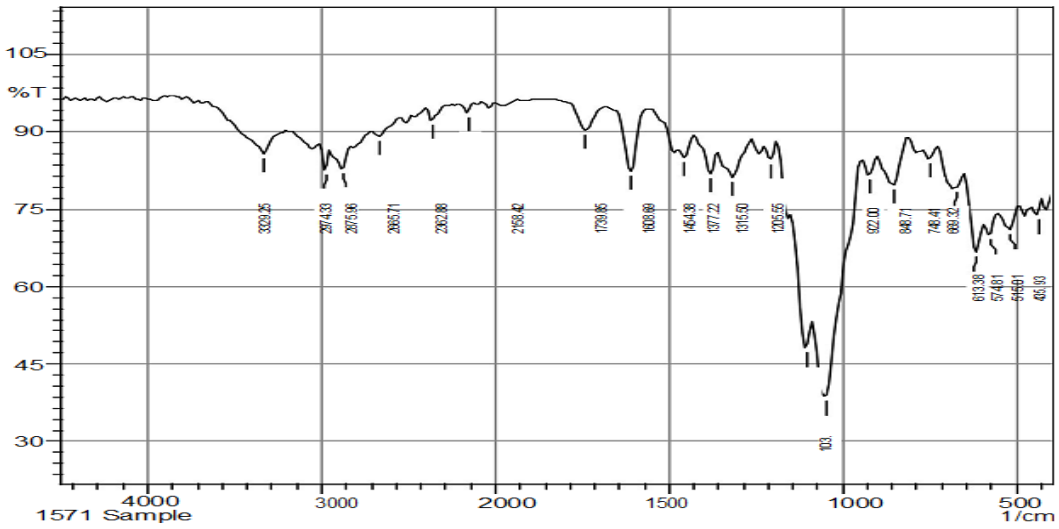

Figure 10: FTIR Spectrum of TS with Ethyl cellulose (15 days).

The FTIR of TS and all polymers show that all peaks obtained from drug and carrier combination were unchanged. This indicates that there is no interaction in between drug and the polymers employed in formulation.

Solubility Studies

The solubility of the TS found to be maximum in phosphate buffer pH 7.4. The solubility of TS in 0.1 N HCl and 0.1 N NaOH was found to be less than water & phosphate buffer pH 7.4. The solubility in acetone was found to be more than methanol but less than 0.1 N HCl. The solubility of TS found to be poorly soluble in methanol and ethanol shown in Table 7.

Table 7: **Saturation solubility of TS.**

Name of solvents	Solubility at 25°C (mg/ml)
Phosphate buffer pH 7.4	35
Water	28
0.1N HCL	22
0.1N NaOH	25
Methanol	2.2
Ethanol	1.7
Acetone	9.42

Thermal Analysis

Melting point *determination*

The melting point of TS was observed 249.33°C as per range provided in IP. The observations are shown in Table 8.

Table 8: **Melting point of TS.**

Name of Sample	Results	Average & S.D.
Sample A	249°C	
Sample B	250°C	249.33°C ± 0.577
Sample C	249°C	

Micromeritics Evaluations

The bulk density & tapped density of TS is determined by tapped density method. This value of bulk density indicates of good packing character. The compressibility index of TS found below 24.43 % and flow properties of the powder were analyzed by angle of repose it raged is found 39.04. All the observations are shown in Table 9-13.

Table 9: Results of Bulk density of TS.

Bulk Density (g/ml)	Average & S.D. (g/ml)
0.4351	
0.4402	0.4370 ± 0.002
0.4359	

Table 10: Results of Tapped density of TS.

Tapped Density (g/ml)	Average & S.D. (g/ml)
0.5802	
0.5724	0.5784 ± 0.005
0.5828	

Table 11: Results of Compressibility Index of TS.

Compressibility Index (%)	Average & S.D. (%)
25.0	
23.09	24.43 ± 1.164
25.20	

Table 12: Results of Hausner ratio of TS.

Hausner ratio	Average & S.D.
1.333	
1.300	1.323 ± 0.020
1.337	

Table 13: Results of Angle of repose of TS.

Angle of repose	Average & S.D.
39.09	
38.98	39.04 ± 0.055
39.05	

CONCLUSION

The preformulation study of terbutaline sulphate with pharmaceutical excipients viz ethyl cellulose and eudragit RS 100 was conducted. The result of drug excipients interaction shows that the TS is compatible with ethyl cellulose & eudragit RS 100TS and also these excipients can be use to develop a sustained release formulation of TS. The TS shows good flow properties & complies standards parameters of melting point, solubility and micromeritics study. Thus this research work concludes that ethyl cellulose and eudragit RS100 may be used to develop sustain release formulations of terbutaline sulphate for nocturnal asthma. .

ACKNOWLEDGEMENT

The authors are thankful to the principal and management for providing the facilities for research work. Authors are also thankful to M/s Anata Medicare Ltd., Sriganganagar for providing the drug and assistance in execution of the research work.

ABBRIVATIONS

ATP	:	Adenosine triphosphate
cAMP	:	Cyclic 3', 5'-adenosine monophosphate
hrs.	:	Hours
e.g.	:	Example
nm	:	Nanometre
mg	:	Milligram
ml	:	Millilitre
ρ_t	:	Tapped density of the powder
ρ_b	:	Bulk density of the powder
IR	:	Infra-red
θ	:	Angle of repose
h	:	Height of pile
r	:	Radius of the pile base
S.D.	:	Standard deviation
TS	:	Terbutaline Sulphate
*	:	Average of three

CONFLICT OF INTERESTS

The authors report no conflict of interest.

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