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Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Pharmacy**

Preformulation Considerations of Terbutaline Sulphate: An Essential Component of Formulation Design

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DOI: https://doi.org/10.36348/sjmps.2025.v11i05.003 | **Received:** 03.04.2025 | **Accepted:** 08.05.2025 | **Published:** 12.05.2025

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Abstract

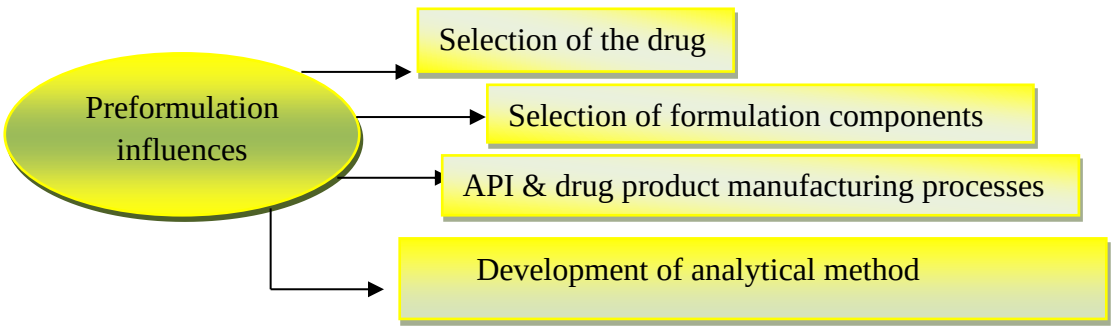
The preformulation study begins with the introduction of a novel chemical. It involves the analysis of physical, chemical, analytical, and medicinal properties related to molecules and provides guidance on suitable alterations to improve molecular efficacy. The examination of preformulation parameters pertains to the creation of effective, safe, stable, and reliable pharmaceutical formulations. Terbutaline is a selective β2 adrenergic receptor agonist often utilised in the acute and long-term management of bronchial asthma, chronic bronchitis, emphysema, and other chronic obstructive pulmonary disorders characterised by reversible bronchial hyperreactivity. Terbutaline sulphate is a short-acting bronchodilator that can be administered orally, parenterally, or by inhalation. The principal objective of the preformulation research of terbutaline is to generate knowledge that facilitates the creation of stable and bioavailable dosage forms.

Keywords: Preformulation study, Terbutaline sulphate, Solubility & Analytical methods.

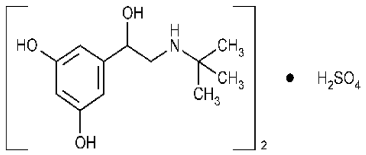
INTRODUCTION

Preformulation research is the essential stage in the methodical development of pharmaceutical dosage forms. The study involves an analysis of the physical and chemical characteristics of a pharmaceutical compound both independently and in combination with excipients. The main aim of preformulation testing is to generate data that aids the formulator in developing stable and bioavailable dosage forms appropriate for large-scale manufacturing. Preformulation research is undertaken to furnish critical data regarding the physicochemical, physico-chemical and biological characteristics of active pharmaceutical ingredients, excipients, and packaging materials [1]. This research should concentrate on the physicochemical properties of the novel molecule that may affect drug efficacy and the formulation of an appropriate dosage form. A thorough comprehension of these characteristics may eventually warrant formulation design or need molecular modification. This study sought to determine many physicochemical properties, including solubility, melting point, pKa, dissolution, assay development, and solution stability [2, 3].

Terbutaline sulphate (TBS), a selective β2 adrenergic agonist, is widely used in the treatment of bronchial asthma, chronic bronchitis and emphysema [4].



Terbutaline [5-7]

Molecular Formula	$C_{12}H_{19}NO_3$
Synonyms	Terbutalina
Molecular Weight	225.28 g/mol
Structure	
IUPAC Name	5-[2-(*tert*-butylamino)-1-hydroxyethyl] benzene-1,3-diol
Mechanism of action	Terbutaline is a selective agonist of the beta-2 adrenergic receptor. Activation of these receptors in bronchioles stimulates adenylyl cyclase, resulting in elevated intracellular levels of cyclic adenosine monophosphate (cAMP). Elevated cAMP reduces intracellular calcium, therefore activating protein kinase A, inhibiting myosin light-chain kinase, activating myosin light-chain phosphatase, and ultimately inducing relaxation of smooth muscle in the bronchiole.
Absorption	A 0.5 mg subcutaneous dose of terbutaline reaches a mean C_{max} of 9.6 ± ng/mL, with a median T_{max} of 0.5 hours, and a mean AUC of 29.4 ± 14.2 h*ng/mL.
Volume of distribution	Terbutaline has a mean volume of distribution of 1.6 L/kg.
Protein binding	Terbutaline is not highly bound to protein in plasma.
Half-life	An oral dose of terbutaline has an elimination half life of 3.4 hours

MATERIAL AND METHODOLOGY

Procurement of Drug:

Terbutaline sulphate was a gift sample obtained from Astrazeneca Pharma India limited, Bangalore, India.

Organoleptic properties

Organoleptic properties of the drug sample were studied by visual inspection.

Preformulation studies [8-10]

Identification of Drug

Identification of drug: The drug was identified by, Ultraviolet spectroscopy (UV) and Melting point, Solubility.

Ultraviolet Spectroscopy

A stock solution of Terbutaline sulphate (1000µg/ml) was prepared in distilled water and scanned spectrophotometrically between 270-280nm. The recorded UV-spectra were compared with the UV-reference spectra of Terbutaline sulphate to trace the λmax.

Melting Point

The melting point of Terbutaline sulphate sample was determined by melting point apparatus and compared with the melting point of reference sample of Terbutaline sulphate.

Melting Point Determination

To determine the M.P. of drug powder, it was filled in a capillary tube with one end open and the other end closed and then the capillary was placed in a digital melting point apparatus.

Solubility

The solubility of terbutaline was assessed in various solvent systems and buffers. An excess quantity of the medication was combined with 10 ml of each solvent in screw-capped glass tubes and agitated on a continual water bath shaker for 24 hours at 25 ℃. The solutions were physically analyzed for the presence or absence of the medication.

Partition coefficient

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 276 nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

FTIR spectroscopy studies

FTIR (ATR Bruker, Germany) was used. The IR spectrum was obtained by scanning it in the range 4000-500nm and compared with the reference pharmacopoeia.

Preparation of calibration curve

Preparation of 0.2 M Potassium dihydrogen phosphate

Dissolve 27.218 gm of Potassium dihydrogen phosphate in distilled water and diluted the volume to 1000 ml with distilled water

Preparation of 0.2 M Sodium Hydroxide

Dissolve 8.0 gm of Sodium Hydroxide in distilled water and diluted the volume to 1000 ml with distilled water.

Preparation of pH 6.8 phosphate buffer (Simulated saliva pH)

Place 50 ml of 0.2 M Potassium dihydrogen phosphate in a 200ml volumetric flask, added 22.4 ml of 0.2M Sodium Hydroxide, mixed, and volume was made upto 200 ml with distilled water.

Preparation of Calibration Curve of Terbutaline Sulphate

From the standard stock solution of Terbutaline Sulphate (Stock I),1ml was pipette out and volume was made up to 10 ml in a 10 ml volumetric flask (Stock II). From this stock II, again aliquots of samples pipette out ranging from volumes 1,2,3,4,5 and 6 ml into 10 ml volumetric flasks and volume was made up using distilled water to produce concentrations 10, 20, 30, 40, 50 and 60 g/ml respectively. The absorbance was measured at 276 nm against distilled water as blank. Plotted a calibration curve of Terbutaline Sulphate using concentration and absorbance on X and Y-axis respectively.

RESULT AND DISCUSSION

Preformulation testing constitutes the initial phase in the systematic creation of pharmacological dosage forms. It is described as an examination of the physical and chemical characteristics of a drug ingredient both in isolation and in conjunction with excipients. The primary aim of preformulation testing is to create information that aids the formulator in creating stable and bioavailable dosage forms suitable for mass production. Preformulation research aim to provide comprehensive data, particularly about the physicochemical, physico-chemical, and biopharmaceutical characteristics of medicinal ingredients, excipients, and packaging materials. The solvent medium was chosen based on solubility, revealing that Terbutaline Sulphate is easily soluble in distilled water (Table 1). The organoleptic characteristics of terbutaline sulphate were documented in Table 2. The melting point and partition coefficient were determined to be 2470°C and 0.03 respectively (Table 3). A Standard Stock Solution was produced and analyzed using a UV Spectrophotometer. The λ max was determined to be 276 nm using distilled water as the blank. The Calibration Curve and the data were acquired by the technique outlined in the preformulation studies section. The findings are presented in Table 4 and Figure 1. The linear plot of concentrations vs absorbance indicated a concentration range of 10-60 µg/ml. The IR spectra of Terbutaline sulphate, both alone and in conjunction with polymers, are presented in the figures. The IR spectra of pure Terbutaline sulphate exhibited peaks at 1601 cm^{-1} and 907 cm^{-1}. The peaks identified are typical of Terbutaline sulphate and were distinctly visible in the IR spectra of Terbutaline sulphate in conjunction with polymers, as illustrated in Figure 2, indicating no interaction between Terbutaline sulphate and the polymers.

Table 1: Solubility profile of Terbutaline Sulphate in different solvent

S. No	Solvent	Solubility
1	Ethanol	+
2	Chloroform	-
3	Methanol	++
4	Buffer solution pH6.8	+++
5	Water	+++
6	Hexane	+

+++ Freely soluble (1 to 10 of solvent)
++ Soluble (10 to 30 of solvent)
+ Slightly soluble
- Insoluble (more than 10,000 of solvent)

Table 2: Organoleptic properties

S. No.	Properties	Inference
1.	Colour	White
2.	Odor	Odurless
3.	Taste	bitter

Table 3: Melting point and Partition coefficient

M.P.	247^0C
P.C.	0.03

Table 4: Calibration curve data for Terbutaline Sulphate

Concentration (mg/ml)	Absorbance*
0	0.0000
10	0.0692
20	0.1292
30	0.1894
40	0.2491
50	0.3102
60	0.3594

- **Each value is an average of 6 determinations**

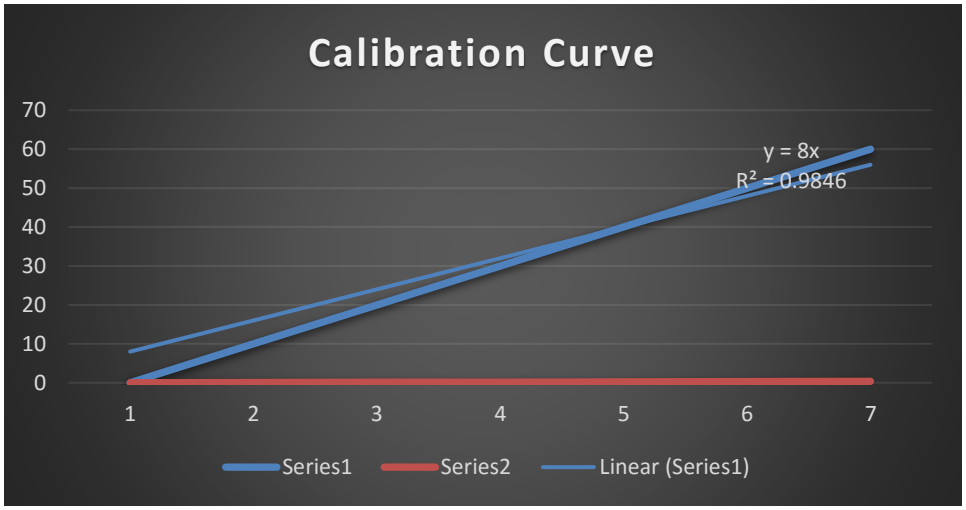


Figure 1: Calibration curve for Terbutaline Sulphate

Drug-polymer compatibility

Drug Polymer compatibility was studied by ATR.

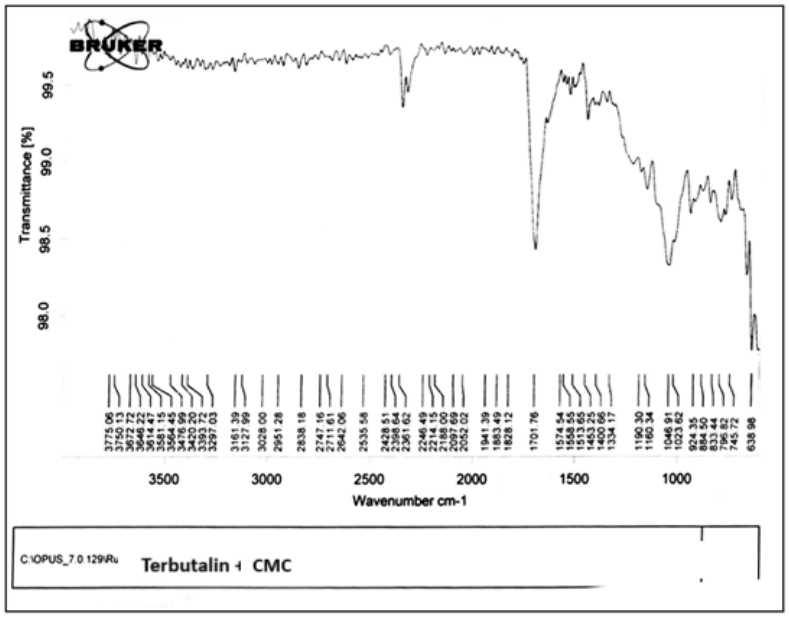


Figure 2: IR spectrum of Terbutaline Sulphate

CONCLUSION

The preformulation phase is essential for identifying the characteristics of a drug, enabling accurate risk evaluation for its development. It usually begins in the lead optimisation phase, continues during predominance, and extends into the early phases of development. Consequently, it is essential that preformulation is executed with the highest accuracy to facilitate informed decision-making. The preformulation study of terbutaline sulphate seeks to generate data advantageous for the creation of stable and bioavailable dosage forms.

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