e-ISSN: 2248-9126
Vol 4 | Issue 2 | 2014 | 87-93. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

# FORMULATION, EVALUATION AND SPECTROSCOPIC VALIDATION OF TERBUTALINE SULPHATE MOUTH DISSOLVING DRUG DELIVERY SYSTEMS

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**ABSTRACT**

Recent advances in Novel Drug Delivery Systems (NDDS) aim for designing dosage forms, convenient to be manufact ured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patie nt compliance. Orally disintegrating tablets (ODTs) are gaining prominence as new drug delivery systems and emerged as one of the popular and widely accepted dosage forms, especially for the pediatric and geriatric patients. To obviate the problem of dysphagia and to improve patient compliance, ODTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations. Terbutaline Sulphate is a beta-2 agonist and has action similar to that of Isoproterenol. The basic aim of this formulation was to decrease the onset time of the drug by decreasing the disintegration time of the tablet by formulating fast melting tablet. In the present study fast melting tablets of Terbutaline Sulphate was prepared. The tablets were evaluated for percentage friability, hardness, weight variation, disintegration, and percentage drug content and evaluation results shows tablet to be within the official limits. Dissolution profile of the tablet shows that the excipients used in the tablet had no negative influence on the release pattern of the drug. It was thus possible to formulate mouth melting tablets of Terbutaline Sulphate using simple and cost effective technique.

**Keywords:** Mouth dissolving drug delivery system, X-Ray diffraction study, Analytical validation, spectroscopy.

## INTRODUCTION

A bronchodilator is a substance that dilates the bronchi and bronchioles, decreasing resistance in the respiratory airway and increasing airflow to the lungs. Bronchodilators may be endogenous (originating naturally within the body), or they may be medications administered for the treatment of breathing difficulties. They are most useful in obstructive lung diseases, of which asthma and chronic obstructive pulmonary disease are the most common conditions. Although this remains somewhat controversial, they might be useful in bronchiolitis. They are often prescribed but of unproven significance in restrictive lung diseases. Bronchodilators are either short-acting or long-acting. Short-acting medications provide quick or "rescue" relief from acute broncho constriction. Long-acting bronchodilators help to control and prevent symptoms.

Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Terbutaline sulfate is a direct acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta2 receptors (a beta2 agonist) [1-7].

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Terbutaline is given as the sulfate for its bronchodilating properties in reversible airways obstruction, as occurs in asthma and in some patients with chronic obstructive pulmonary disease.

The research carried out by the author is to formulate a mouth dissolving tablet of Terbutaline sulfate as a novel drug delivery system followed by its quantitative and qualitative analysis and UV spectroscopic validation.

## MATERIALS AND METHODS

### Materials

Terbutaline sulphate was collected as a gift sample from Caplin Point Laboratories Ltd., Chennai. Gelatin, Sodium Starch Glycolate, Aerosil, mannitol, Magnesium stearate, Sucrose, Vanilla Flavour, MCC and PVP used are of analytical reagent grade.

### Methodology

Drug and all other ingredients were passed through desired sieve separately. The drug and diluents mixed by taking small portion of both each time and blending thoroughly to get uniform mixture kept a side for 30 minutes. Then ingredients are mixed by using distilled water using as a solvent and gelatin to get dough which was passed through mesh number 20 to get granules were dried at $45^0$ c for one hour followed by regranulation through 20 mesh sieve. The disintegrant added by passing wet granules (or) 50% added before granulation and 50% after granulation (Dry powder). The lubrication materials all passed through 60 meshes and finally added, mixed for 15 minutes thoroughly to get free flowing granules. The granules were compressed using die of 7.4 mm size to get tablet of 150 mg using fluid pack single compression machine. The weight was adjusted to 150 mg tablets using the formula in the above tablet. All the batches were prepared using the same procedure. According to standard formula each tablet of terbutaline sulphate contains 2mg of ssg (or) ccs and 2mg of gelatin. This combination is taken as 100% in the ratio of 50% ssg (or) ccs + 50% gelatin. For various batches this combination was changed by altering the concentration of the components but keeping the total weight of both components as 4mg tablet [8-12].

### Qualitative and Quantitative Evaluation

Mouth dissolving tablets of all formulations were evaluated for weight variation, content uniformity, hardness, friability, disintegration and wetting Time.

### X-Ray Diffraction study

The X-Ray diffraction study is important from the point of any conversion of crystallinity of the drug to the amorphous form which was carried out in Department of Instrumentation Science, Jadavpur University Calcutta.

### Differential Scanning Calorimeter Study

To study the drug polymer interaction in different ranges temperature, the author analyzed the formulation by Differential Scanning Calorimeter, carried out in Department of Instrumentation Science, Jadavpur University Calcutta which shows no interaction in form of independent graphs.

### FTIR Study

The approach carried out by the author for the interaction in drug and other in gradients in the formulation FTIR study was carried out in the Department of In organic Chemistry, Indian Association for Cultivation of sciences, Kolkata and the study interprets no super imposable curve for interaction or any availability of other matters [13-17].

### *In-vitro* dissolution study

In-vitro dissolution rate studies of the micro spheres were performed using USP XX type-II (electro lab TDP- 06T) apparatus [21]. Drug release was studied in 900ml of 7.2 pH phosphate buffer 37± 0.5ºC at 100 rpm. 1ml sample was withdrawn at regular intervals and the same quantity of pre warmed fresh dissolution medium was replaced. The samples withdrawn were assayed spectrum photo metrically at 284 nm using shimadzu 1700 UV visible spectrophotometer [18-21].

### Analytical validation of Terbutaline sulphate mouth dissolving tablets [22-25]

### Instrument

The instrument used was UV visible recording spectrometer (Schimadzu – chemito) with 1cm matched Quartz cuvettes were used for all absorbance measurements. The detector was set a wavelength of 284nm.

### Reagents and Solutions

All the solvents and reagents used are of analytical reagent grade.

**Standard drug (100µg/ml):** Accurately weighed 50mg of terbutaline sulphate was transferred into a 50ml calibrated flask, dissolved and completing to volume with distilled water. The solution was further diluted suitably with distilled water to get a solution of 100µg/ml concentration.

**TRIS buffer solution (0.3m):** Requisite amount of TRIS (hydroxyl methyl) amino methane buffer (TRIS buffer) pH 9.5 was dissolved in distilled water.

**Antipyrine solution:** 2% w/ L-amino antipyrine in solution was prepared in distilled water. Potassium ferric cyanide solution: 8% w/v potassium ferric cyanide was dissolved in distilled water.

**Hydrochloric acid solution (0.1M):** Requisite volume of concentrated hydrochloric acid was diluted with distilled water.

**Samples solution:** Accurately weighed tablet equivalent to 2.5 mg of terbutaline sulphate was taken and suspended in 10ml of water which is in separating funnel. The aqueous layer was extracted with four 30 ml portion of chloroform and discarded the organic layers. Then the aqueous layer was collected into a 25ml calibrated flask. To the aqueous layer 5 ml of 0.1M hydrochloric acid was added and shaked for 15 minutes and then made up the volume up to 25 ml with distilled water.

**Procedure:** To 5ml of each of blank sample and standard, about 35ml of TRIS buffer, 1ml of Antipyrine reagent followed by 1 ml of ferric cyanide solution was added. It was mixed and the volume was made up to 50 ml with TRIS buffer. The absorbance was measured at 550nm exactly 3 minutes from the addition of ferric cyanide solution against reagent blank. A calibration curve was plotted between concentration and absorbance. Aliquots of sample solutions were treated similarity and the amount of drug present in the sample was determined from the calibration curve.

**RESULT AND DISCUSSION**

The prepared mouth dissolving tablets and its quality control tests reveal that all the tablets are meeting the official Pharmacopeias requirements extensive and intensive the experimental data with regard to the weight variation test the feasibility of pilot plant study with regard to the scale of technique which is quite encouraging. The content uniformity is in the range of 95% to 99% followed by wetting time in seconds, some cases up to 4 seconds also.

It is of paramount important to study the drug-polymer interaction which is carried out by DSC, DTA & TGA of the compound. The data obtained clearly indicate that no interaction is evident by the appearance of new peak which assumes that has been no emergent of new drug.

The disintegration profile of the uncoated tablet indicates the range 2 to 3.5 min, which is suitable to prove it a mouth dissolving tablet. The hardness test of all the formulations were tested by Monsanto type as well as fizer type hardness testers and the values are more than 4 kg and up to 6 kg by both the tester.

The dissolution profile of various formulations by eight station USPTYPE-II (paddle) apparatus was carried out. From the obtained data it is evident that all the formulations showing higuchi order kinetics having very fast drug release which is near to bench mark of marketed formulation. To prove the formulation more reliable qualitatively the author carried out standard quality control test of friability by roche friablitor, the obtained data of various formulation is very relevant towards pharmacopeias values to prove it a NDDS of conventional type.

The UV spectroscopic validation of the formulation for specificity, Linearity, Accuracy, Precision and intermediate precision and stability of the solution over desired period of time is highly appreciable and is within the limit. As per specificity interference from Placebo should not be more than 2.0 % where the obtained result is 1.39 %. From stability point of view the absorbance of analyte in test solution should not differ by more than 2.0 % from initial absorbance for the accepted storage time and the result is 0.71 %. From 50 % to 150 % of targeted concentration of the formulation, the linearity correlation coefficient ($r^2$) should not be less than or equal to 0.995 and the obtained result is 0.999. Accuracy in terms of recovery from 50% to 150% of targeted concentration, The recovery at each level should be between 98.0 % – 102.0 % and the % RSD should not be more than 2.0 and the result is quite inspiring of recovery 98.3% to 100.0% and % RSD is 0.78% to 1.71%. Method precision and intermediate precision reveals that the % assay shall be between 95.0 % and 105.0 % of label claim and % RSD for assay of preparations shall not be more than 2.0 followed by the difference between Average assay of Method precision and Intermediate precision shall not be more than 2.0%. The datas obtained for precision and intermediate precision are assay is 98.3 %, 97.5 % and % RSD are 0.62 %, 1.30 % respectively followed by 0.9 % difference between average assay of method precision and intermediate precision which is quite negligible.

**Table 1. Qualitative analysis of various formulations**

| Formulation | Weight Variation (mg) | Content Uniformity (% purity) | Hardness by Monsanto (kg) | Hardness by Pfizer (kg) | Wetting time (seconds) | % Friability | Disintegration time (min) |
|---|---|---|---|---|---|---|---|
| F1 | 148.8 | 98.40 | 4.2 | 4.3 | 55 | 0.51 | 3.2 |
| F2 | 149.4 | 98.65 | 4.7 | 4.9 | 56 | 0.42 | 2.3 |
| F3 | 148.5 | 98.62 | 5.5 | 5.7 | 54 | 0.23 | 3.6 |
| F4 | 149.4 | 98.61 | 5.7 | 5.4 | 53 | 0.33 | 2.2 |
| F5 | 149.1 | 98.78 | 5.4 | 5.1 | 51 | 0.17 | 2.7 |
| F6 | 148.8 | 98.97 | 5.2 | 5.0 | 53 | 0.11 | 2.1 |

**Table 2. Dissolution profile of Formulation 6 (F6)**

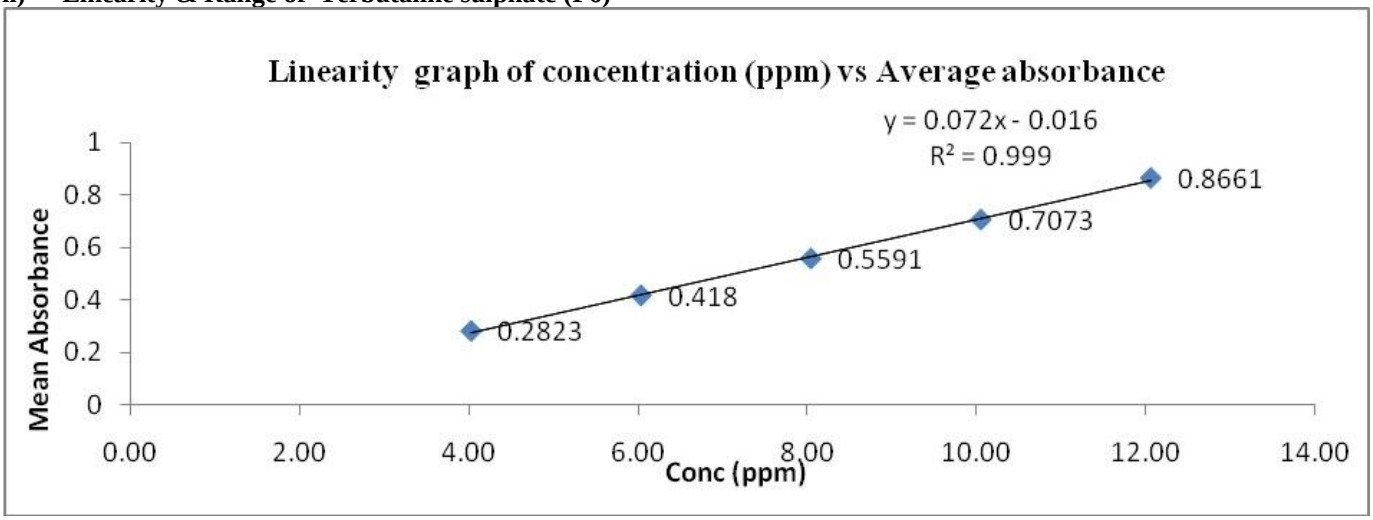
| Time (min) | Log [con$^n$] | SQRT | %CDR | W01/3-W1/3 |
|---|---|---|---|---|
| 0 | | 0 | 0 | 0 |
| 05 | 1.483637 | 5.477226 | 30.45349 | 0.529222608 |
| 10 | 1.55377 | 7.745967 | 35.7907 | 0.637233113 |
| 15 | 1.689061 | 9.486833 | 48.87209 | 0.93006143 |
| 20 | 1.736582 | 10.95445 | 54.52326 | 1.072178678 |
| 25 | 1.800781 | 12.24745 | 63.2093 | 1.315662126 |
| 30 | 1.877679 | 13.41641 | 75.45349 | 1.735359196 |
| 35 | 1.906798 | 14.49138 | 80.68605 | 1.958569964 |
| 40 | 1.951202 | 15.49193 | 89.37209 | 2.442973522 |
| 45 | 1.979262 | 16.43168 | 95.33721 | 2.970952302 |
| 50 | 1.995176 | 17.32051 | 98.89535 | 3.607855824 |

**Table 3. Analytical Validation of Terbutaline sulphate mouth dissolving tablet (F6)**

**i) % Interference of Drug and Placebo of Terbutaline sulphate(F6)**

| Sample No | Sample Abs. | Mean Sample Abs.-Blank | Mean Sample Abs. | % Interference |
|---|---|---|---|---|
| 1 | 0.0073 | 0.0070 | 0.0078 | 1.39 |
| | 0.0089 | 0.0086 | | |
| 2 | 0.5595 | 0.5592 | 0.56030 | |

**ii) Linearity & Range of Terbutaline sulphate (F6)**




**iii) Method Precision & Intermediate Precision of Terbutaline sulphate (F6):**

| Set 1(Method precision) | | Set 2(Intermediate precision) | |
|---|---|---|---|
| **Sample Set No.** | **% Assay of** | **Sample Set No.** | **% Assay** |
| 1 | 98.6 | 1 | 96.7 |
| 2 | 97.8 | 2 | 95.5 |
| 3 | 99.0 | 3 | 99.4 |
| 4 | 97.4 | 4 | 97.7 |
| 5 | 98.6 | 5 | 97.0 |
| 6 | 98.4 | 6 | 97.8 |
| Average | 98.3 | Average | 97.4 |
| SD | 0.59 | SD | 1.30 |
| % RSD | 0.60 | % RSD | 1.34 |
| Difference average assay of method and intermediate precision | | | 0.9 |

**iv) Accuracy Study of Terbutaline sulphate (F6) :**

| Level---> | 50% | 100% | 150% |
|---|---|---|---|
| % recovery | 99.3 | 98.0 | 98.0 |
| % recovery | 98.8 | 99.6 | 98.5 |
| % recovery | 102.0 | 98.9 | 98.3 |
| Average | 100.0 | 98.8 | 98.3 |
| SD | 1.713 | 0.768 | 0.216 |
| % RSD | 1.71 | 0.78 | 0.22 |

**v) Stability for solution of Terbutaline sulphate (F6) :**

| Stability in hrs. | % Assay | % Difference from initial absorbance |
|---|---|---|
| IMS | 97.31 | --- |
| 5.0 | 97.97 | 0.67 |
| 7.0 | 98.00 | 0.71 |
| 15.0 | 97.88 | 0.58 |
| 24.0 | 97.82 | 0.53 |

**Figure 1. Drug- polymer interaction by FTIR Study graph for Terbutaline sulphate**

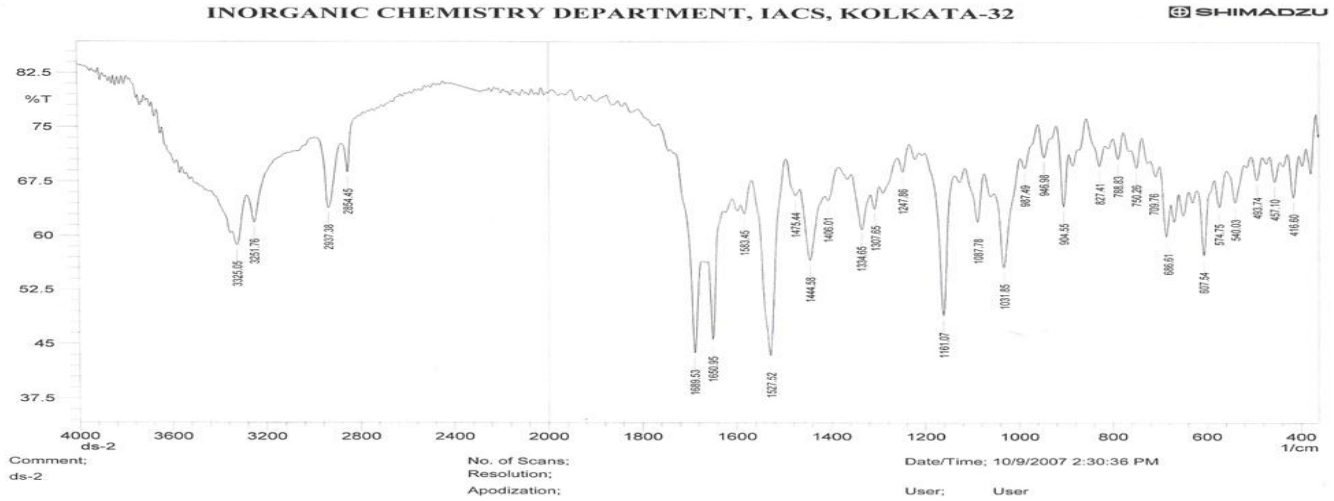
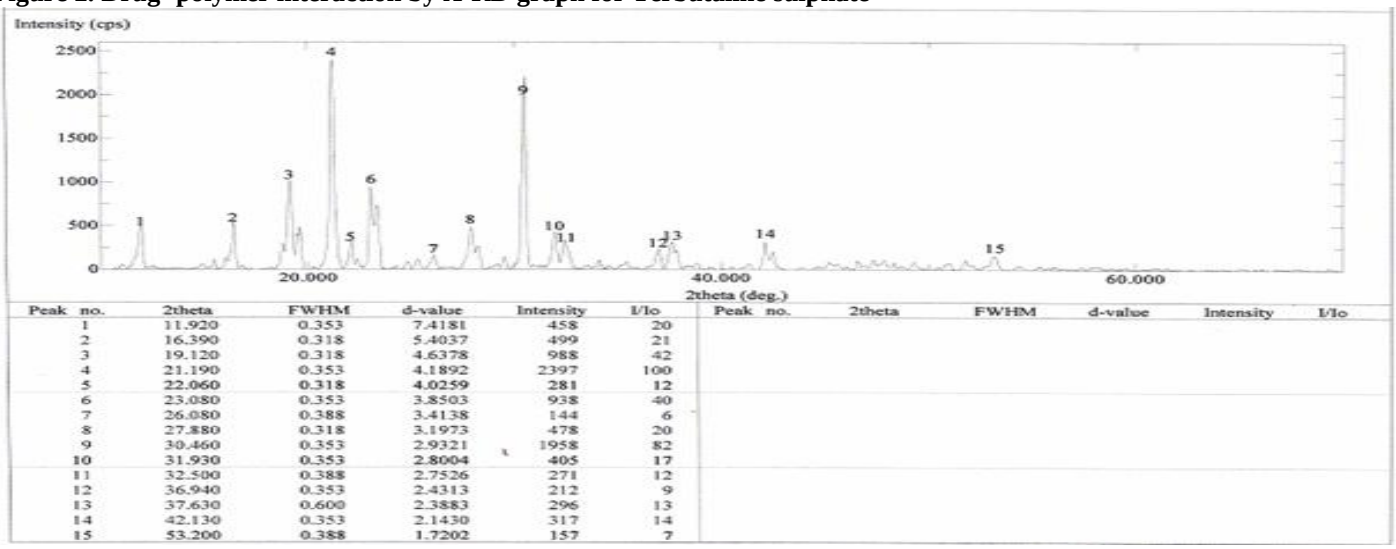



**Figure 2. Drug- polymer interaction by X-RD graph for Terbutaline sulphate**




| Peak no. | 2theta | FWHM | d-value | Intensity | I/Io | Peak no. | 2theta | FWHM | d-value | Intensity | I/Io |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11.920 | 0.353 | 7.4181 | 458 | 20 | | | | | | |
| 2 | 16.390 | 0.318 | 5.4037 | 499 | 21 | | | | | | |
| 3 | 19.120 | 0.318 | 4.6378 | 988 | 42 | | | | | | |
| 4 | 21.190 | 0.353 | 4.1892 | 2397 | 100 | | | | | | |
| 5 | 22.060 | 0.318 | 4.0259 | 281 | 12 | | | | | | |
| 6 | 23.080 | 0.353 | 3.8503 | 938 | 40 | | | | | | |
| 7 | 26.080 | 0.388 | 3.4138 | 144 | 6 | | | | | | |
| 8 | 27.880 | 0.318 | 3.1973 | 478 | 20 | | | | | | |
| 9 | 30.460 | 0.353 | 2.9321 | 1958 | 82 | | | | | | |
| 10 | 31.930 | 0.353 | 2.8004 | 405 | 17 | | | | | | |
| 11 | 32.500 | 0.388 | 2.7526 | 271 | 12 | | | | | | |
| 12 | 36.940 | 0.353 | 2.4313 | 212 | 9 | | | | | | |
| 13 | 37.630 | 0.600 | 2.3883 | 296 | 13 | | | | | | |
| 14 | 42.130 | 0.353 | 2.1430 | 317 | 14 | | | | | | |
| 15 | 53.200 | 0.388 | 1.7202 | 157 | 7 | | | | | | |

**Figure 3. Crystallography and interaction study by DSC graph for Terbutaline sulphate**

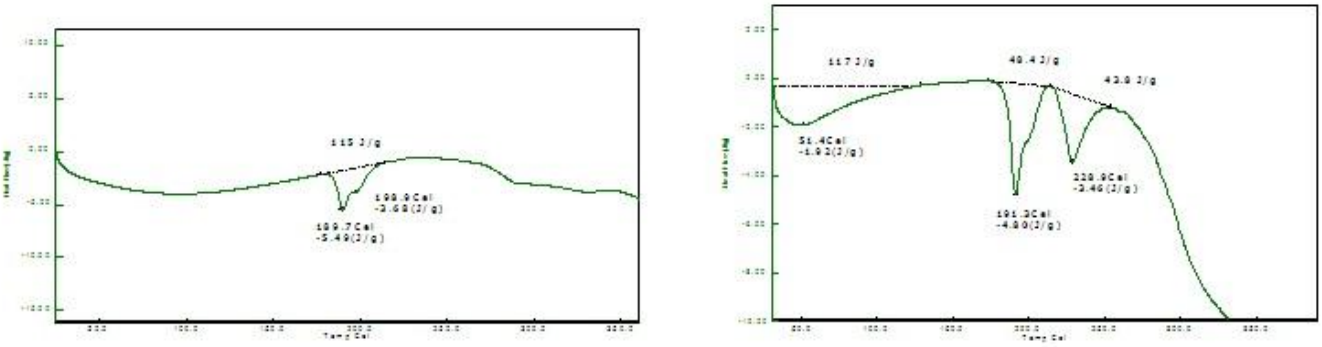
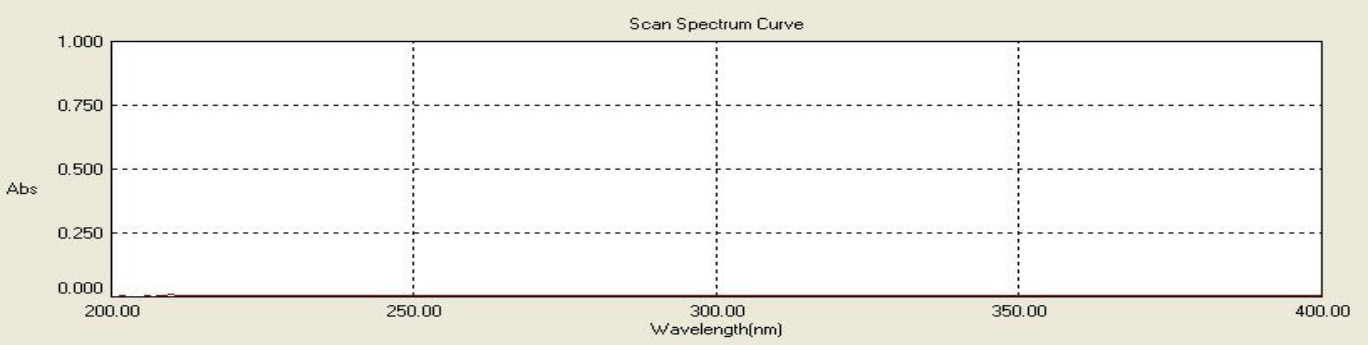
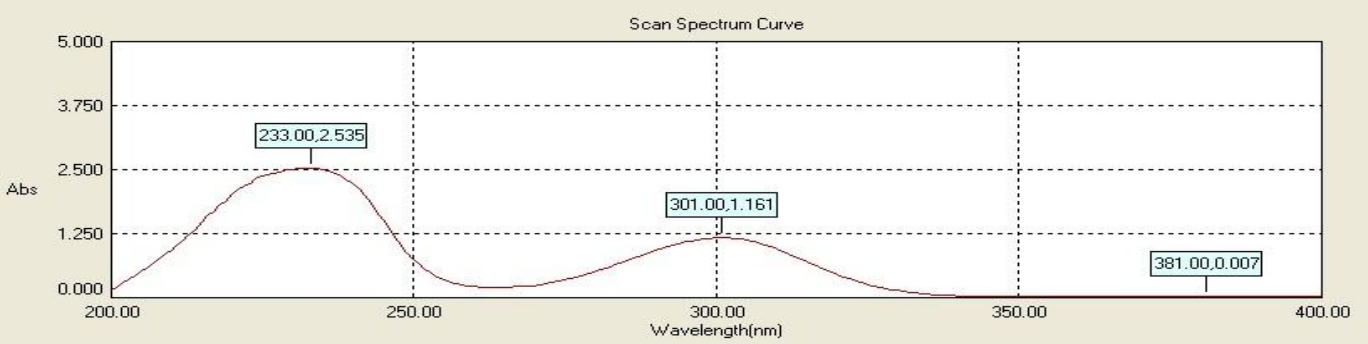


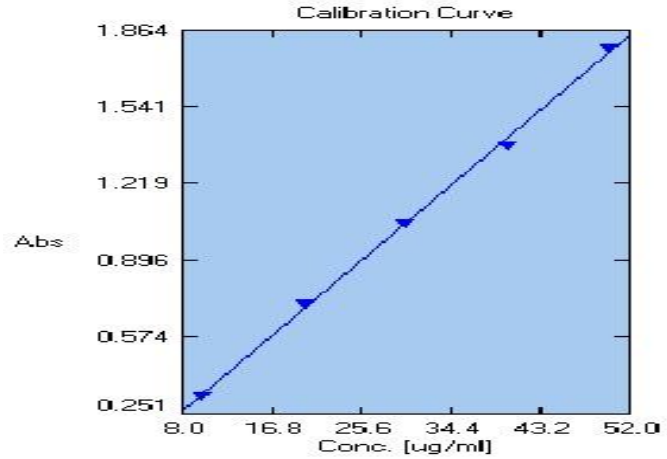
**Figure 4. Standard curve For Terbutaline sulphate**

**Blank sample spectrum**




**Standard Solution Spectrum**




| Conc. (mcg) | Abs | K0 | K1 | $R^2$ |
|---|---|---|---|---|
| 10.0 | 0.324 | -0.026 | 0.036 | 0.999 |
| 20.0 | 0.716 | | | |
| 30.0 | 1.053 | | | |
| 40.0 | 1.377 | | | |
| 50.0 | 1.790 | | | |

## CONCLUSION

The present drug carried out by author for preparation of mouth dissolving tablet of terbutaline sulphate and its evaluation qualitatively and quantitatively is highly appreciable. The obtained of various formulation by changing the polymer and other active ingredients in different formulations are quiet impressile towards bench mark. Out of six formulations the sixth formulation showing better response in qualitative, quantitative and invitro dissolution profile following higuchi model. The analytical validation for drug and placebo interaction by specificity is very less. The precision and intermediate precision carried out by two different analyst results similar assay value in all respect. The formulation is linear over 50 to150 percent and the recovery value is optimum within the same range. The stability study reveals that the absorbance of formulation in test solution is not differ significant from initial absorbance for the accepted storage time.

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