

Spectrophotometry Method for the Determination of Terazosin in Tablet Formulation

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Abstract Terazosin (TRZ) is indicated in the symptomatic relief of benign prostatic hyperplasia. The presented study is spectrophotometry method for the determination of terazosin in tablet dosage forms. Bromophenol blue was used for ion pair complex with the drug in 1:1 ratio. The linear range, limit of detection (LOD) and limit of quantitation (LOQ) were found to be 1-10, 0.001 and 0.012 $\mu\text{g/ml}$ respectively. The method was found to be specific when applied with some excipients and accurate enough to be applied in tablet formulation.

Keywords: Terazosin, Spectrophotometry, method validation, ICH guidelines, Bromophenol blue

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1. Introduction

Male lower urinary tract symptoms (LUTSs) affect millions of people worldwide and represent an important part of daily practice [1]. Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate caused by cellular hyperplasia. It is a bothersome and potentially severe condition that may lead to lower urinary tract symptoms (LUTS) involving weak urinary stream, hesitancy, intermittency, frequent urination, and urgency. The prevalence of BPH increases markedly with age, ranging from about 8% in men aged 31 to 40 years to approximately 80% in those aged over 80 years [2].

Alpha-adrenergic antagonists, or alpha blockers, relieve LUTS by reducing smooth muscle tone in the prostate and bladder neck. Alpha blockers have been demonstrated to significantly improve symptom scores (both irritative and obstructive symptoms), quality of life, and urinary flow rates, but they do not reduce the risk of AUR or risk of requiring BPH-related surgery [3].

Terazosin hydrochloride dehydrate RS-1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl) carbonyl]- piperazine monohydrochloride [Figure 1] is a α_1 -adrenoceptor blocker with a long lasting action [4]. This is official in European Pharmacopoeia [5], USP [6] and BP [7].

Terazosin is rapidly absorbed following single oral doses, achieving peak plasma concentrations in one to two hours, and has a bioavailability of approximately 90 percent. The consumption of food close to the time of terazosin administration had no appreciable effect on the absorption or excretion of the drug. Terazosin is approximately 90 to 94 percent bound to plasma proteins and, in concentrations up to 1,000 ng/ml, there is no evidence that saturation of binding sites occurred [8].

Terazosin is extensively metabolised by the liver, and the biliary tract is the major route of elimination: the drug

is also excreted in the urine. The relatively long terminal phase plasma elimination half-life (8 to 13h) of terazosin allows once daily administration [9].

Terazosin has been shown to have 400-fold greater affinity for α_1 - than α_2 -adrenoceptors. Terazosin is generally well tolerated, but caution is recommended at treatment initiation and when dosage adjustments are made due to an increased risk of postural hypotension and related adverse effects at these times; such a risk has also been observed with several other α_1 adrenoceptor antagonists. Adverse effects reported are dizziness, headache, asthenia, nasal congestion and cold symptoms [10]. In a recent study terazosin was found to be effectively used to treat nightmares as a second-line agent after prazosin failure [11].

The acid-dye method can provide a more sensitive technique for certain amines and quaternary ammonium compounds that absorb weakly in the ultraviolet region. In such methods addition of an amine in its ionized form to an ionized acidic dye, yields a salt (ion-pair) that may be extracted into an organic solvent such as chloroform or dichloromethane. The indicator dye is added in excess and the pH of the aqueous solution is adjusted (if necessary) to a value where both the amine and dye are in ionized forms. The ion-pair is separated from the excess indicator by extraction into the organic solvent, and the absorbance is measured at the λ_{max} of the indicator in the solvent [12].

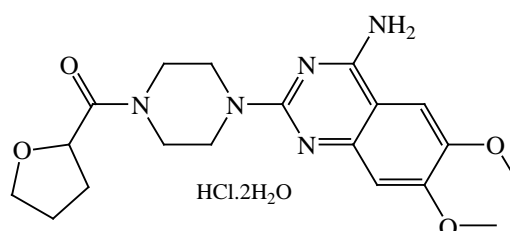


Figure 1. Structure of Terazosin

This is well evident from its structure that TRZ exist as primary ammonium salt, thus acid-dye method can be developed. Validation of the proposed method was planned to be performed as per ICH guidelines [13].

The available methods for the determination of TRZ are Spectrophotometry [14-24], HPLC [25-40], TLC [41] HPTLC [40,42,43,44], and Electrochemical methods [21,45,46,47,48,49] for the determination of TRZ in different matrices. But there is no method available in which bromophenol blue dye is available for its determination in pharmaceutical tablets. This forms basis of our study.

2. Material and Method

UV-Visible spectrophotometer, modal no. UV-1800 manufacture: Shimadzu Corporation was used for the study. Chloroform and concentrated hydrochloric acid and chloroform were purchased from Merck. Bromophenol blue was purchased from Loba chemie pvt limited. Terazosin Hydrochloride was kindly gifted by Noche laboratories, Hyderabad. Terapress 2 mg tablets were purchased from the local market.

2.1. Preparation of Reagent and Solution

Dye solution: 0.05% of dye solution was freshly prepared by dissolving the dye in distilled water.

HCL-KCL Buffer: Buffer was prepared by according to I.P. method by mixing 0.2 M KCL and 0.2 M HCL to obtain the buffer of different pH for optimization.

Standard solution of drug: Standard solution of drug was prepared by dissolving 50 mg of pure drug in water up to 10 ml water to obtain 5000ug/ml of this solution. 1 ml of this solution was diluted up to 50 ml of water to obtain 100 ug/ml of a working standard solution.

Procedure for estimation of drug as ion-pair: Terazosin exist as a ammonium salt, thus acid dye method is suitable for increasing the sensitivity of drug. A suitable aliquot 10ug/ml of working standard was transferred to a separating funnel, buffer was added to ionize the drug and dye, then in excess quantity of dye solution was added and finally 10 ml of chloroform was added. The mixture was shaken thoroughly and allowed to stand for separation of layer. The yellow colored ion- pair separated in organic layer was collected in 10 ml volumetric flask and volume was made up to the mark with chloroform. The solution was scanned against blank which consists of chloroform treated in same way and buffer and dye sol. The maximum absorbance of ion- pair was found at 415 nm.

2.2. Optimization of Reaction Condition

Choice of concentration of dye: From the literature it was revealed that in acid dye complexation method the amount of dye should be in excess. The ion-pair between the drug and dye formed is in 1:1 ratio. Thus, 2 ml of 0.05% w/v solution of dye will be sufficient for the proposed method.

Shaking time: As the drug and dye were soluble in water, so ion-pair was formed in aqueous layer. Therefore, the shaking time should be sufficient enough to extract the ion-pair of drug and dye from the aqueous layer to organic layer and 2 min shaking time was selected for extraction.

Volume and pH of buffer

HCL-KCL buffer was selected for the purpose, different pH and volume was used to optimize this parameter. The condition showing maximum absorbance and stability is the basis of selection of optimized condition. For optimization of buffer following 12 experiments were performed with different set of volume and pH of buffer ranging from 1 ml to 4 ml and 2.2 to 2 pH respectively.

The overlay UV spectra of pure and ion pair complex with dye is presented under Figure 2.

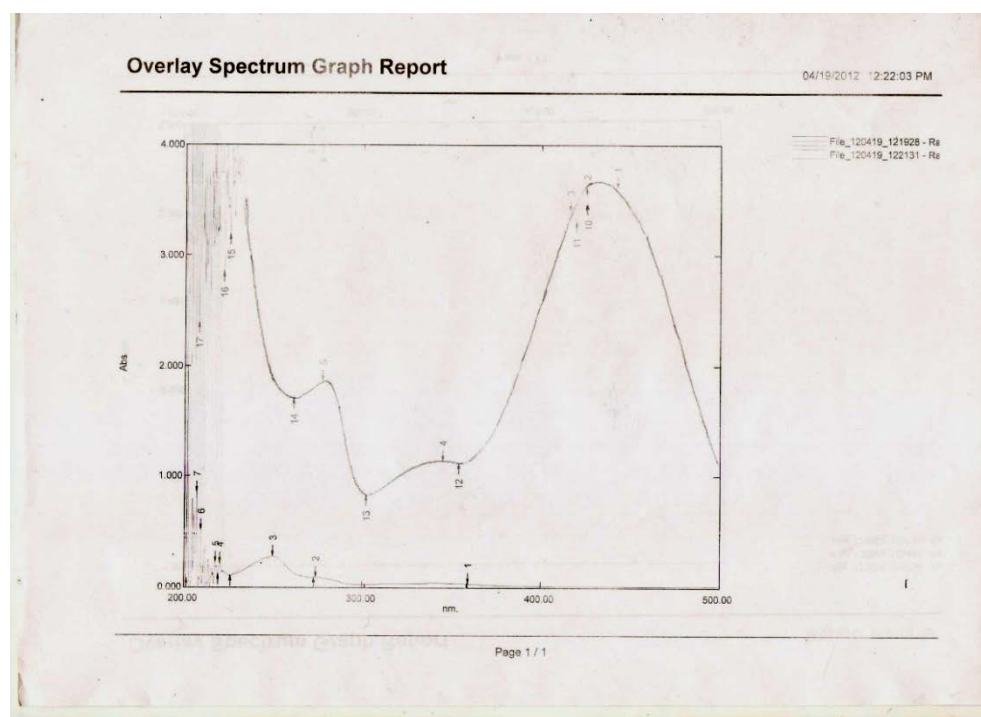


Figure 2. Overlay spectra of pure Terazosin 100 μ g/ml in water and as ion pair complex 50 μ g/ml with BPB in chloroform

2.3. Preparation of Calibration Curve

Preparation of calibration curve for terazosin: In a series of separating funnel, aliquots of standard drug solution (20 µg/ml) of terazosin (0.05, 0.1, 0.2, 0.3, 0.4, 0.5 ml) were transferred, 3 ml of buffer (pH 2.0) was added for ionization and 2 ml of dye solution was added, 10 ml of chloroform was transferred to each separating funnel, shaken for 2 min and allowed to stand for 5 min

for complete separation of aqueous and organic layers and yellow-colored ion-pair complex in organic layer was extracted and final volume was made upto 10 ml with chloroform in 10 ml volumetric flask to obtain 1, 2, 4, 6, 8, 10 µg/ml concentration. Same procedure was repeated two times in a day for 3 days. Calibration curve was plotted by using mean absorbance of these 3 days. The obtained calibration curve was presented under [Figure 3](#).

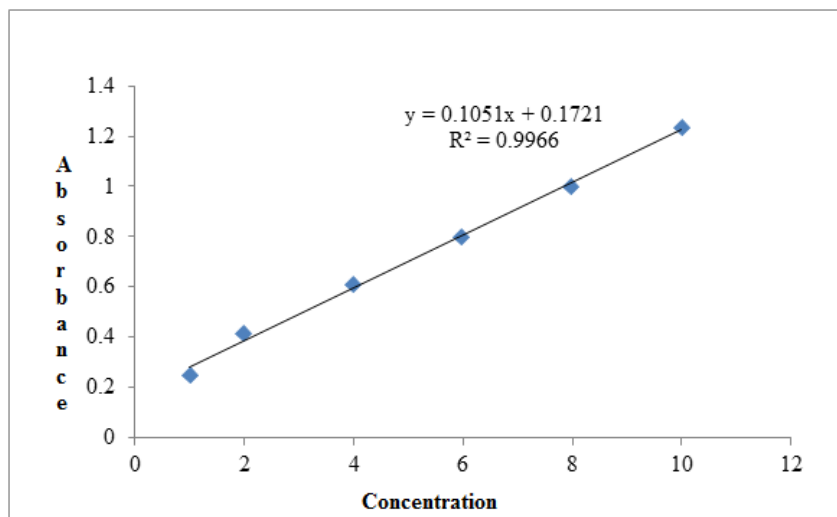


Figure 3. Calibration curve of Terazosin HCl by the proposed method

2.4. Validation of Proposed Method

Specificity

Various generally used excipient like MCC, Lactose, Talc and magnesium stearate were mixed in a definite proportion. They were mixed in 10 ml volumetric flask with methanol then 2 ml of supernatant mixed in each 2, 4, and 6 µg/ml of stock solution and shaken for while. The mean % interference found is 0.480 shows the method is specific in nature.

Linearity

Linearity is accessed by visualizing method. With r^2 value is 0.996 shows calibration curve in linear. The regression equation found was $Y = 0.105x + 0.172$.

Precision

Precision of analytical procedure express the closeness of agreement between a series of measurement obtained from multiple sampling of the same homogeneous sample under the prescribed condition.

Repeatability

Repeatability was accessed by using minimum of 6 replicates of extracted drug of strength 6 µg/ml solutions. The %RSD found was 0.612 shows method passes the repeatability test.

Intraday day precision

2, 4 and 6 µg/ml of standard solution extraction were used three times a day. The percentage RSD varies

between 0.024-1.229 which is less than acceptable value of less than two.

Inter day precision

2, 4, and 6 µg/ml of standard solution extraction were used in three days. The percentage RSD varies between 0.078-1.233 which is less than acceptable value of less than two.

Accuracy

Recovery studies were performed with Terapress 2 tablet formulation.

Powder terapress 2 tablet equivalent to 20 mg Terazosin was transferred to 100 ml volumetric flask and ultrasonication was done for 10 min. with approximately 50 ml water. Then 1 ml of this solution was diluted with 10 ml of water to obtained 20mg/ml of sol. 0.3 ml of this solution was spiked in three different separating funnel with 0.1, 0.2, 0.3 ml of standard stock solution. buffer was added to ionize the drug and dye, then in excess quantity of dye solution was added and finally 10 ml of chloroform was added. The mixture was shaken thoroughly and allowed to stand for separation of layer. The yellow colored ion- pair separated in organic layer was collected in 10 ml volumetric flask and volume was made up to the mark with chloroform. The solution was scanned against blank which consists of chloroform treated in same way and buffer and dye sol. The maximum absorbance of ion-pair was found at 415 nm. The results are produced under [Table 1](#).

Table 1. Recovery studies of Terapress 2 tablet

Conc. ug/ml	Conc. Before spiking(ug/ml) C_1	Conc. of std.added C_2	Conc. After spiking(ug/ml) C_3	% Recovery $(C_3-C_1)*100/C_1$	Mean SD
6	6.13	2	8.10	98.5	97.80
		4	10	96.75	
		6	12.02	98.16	

2.5. Limit of Detection and Limit of Quantification

The detection and quantification limit were calculated from the standard deviation of absorbance measurement in series of 6 blank solutions. LOD and LOQ was calculated with the help of following formula,

$DL=3.3 * S.D. \text{ of blank solution} / \text{slop of calibration curve}$

$QL=10 * S.D. \text{ of blank solution} / \text{slop of calibration curve}$

LOD and LOQ were found to be 0.001 and 0.012 ug/ml.

2.6. Stoichiometry of Reaction

For establishing stoichiometry of mole ratio method and job's method of continuous variation were selected. $0.1 * 10^{-4}$ M solution of Terazosin and dye solution were prepared by dissolving 4.59 mg of Terazosin in

100ml water then 1 ml of this solution was diluted in 10 ml of water to obtained $0.1 * 10^{-4}$ molar strength solution.

Mole ratio method: $0.1 * 10^{-4}$ M Terazosin standard solution was transferred in seven separating funnel in a constant volume 2ml, then 0, 0.5, 1, 1.5, 2, 2.5 and 3 ml of $0.1 * 10^{-4}$ M dye solution and buffer solution was transferred from 1st to 7th separating funnel followed by 2 ml buffer and 10 ml chloroform. Shaken for 2 min and allowed to stand for 5 min for separation of layer of two layer. The yellow colored ion- pair separated in organic layer was collected in 10 ml volumetric flask and volume was made up to the mark with chloroform. The solution was scanned against blank which consists of chloroform treated in same way and buffer and dye sol. The maximum absorbance of ion- pair was found at 415nm. and the absorbance was plotted against molar ratio of drug solution and total molar conc. of drug and dye.

On increasing the amount of dye absorbance increase up to ratio 1 after that it become constant. This proves that the drug bind with the dye in a ratio of 1:1 (Figure 4).

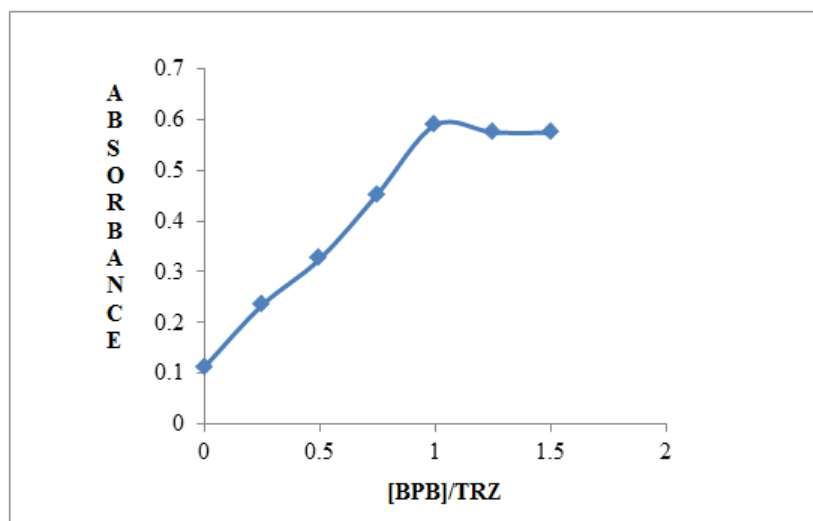


Figure 4. Mole ratio method of TERAZOSIN-BPB ion pair complex

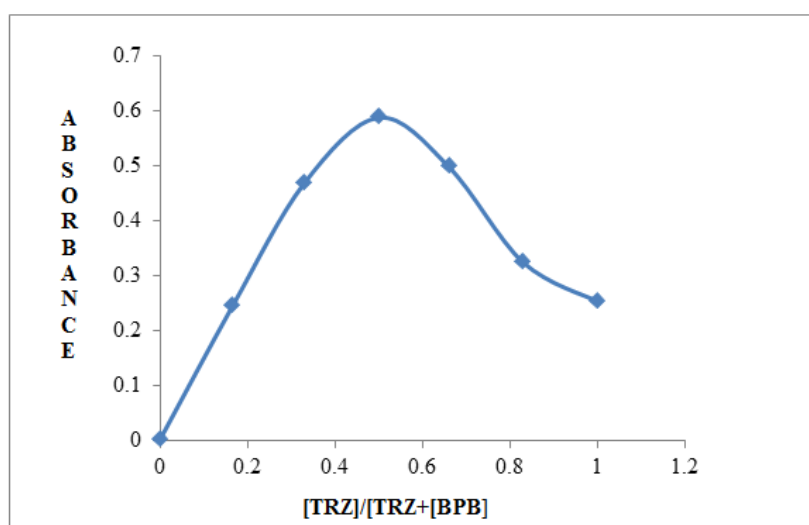


Figure 5. Job's method of continuous variation of TERAZOSIN-BPB system

2.7. Job's Method of Continuous Variation

Stoichiometry ratio of Terazosin to BPB in the complex was determined by Job's method of continuous variation.

Terazosin standard solution was transferred in seven separating funnel (0, 0.5, 1, 1.5, 2, 2.5 and 3ml) and aliquot of $2 * 10^{-4}$ M BPB (3, 2.5, 2, 1.5, 1, 0.5, 0) was added, respectively. Keeping the mole ratio constant. Then 2 ml

buffer and 10 ml chloroform. Shaken for 2 min and allowed to stand for 5 min for separation of layer of two layer. The yellow colored ion- pair separated in organic layer was collected in 10 ml volumetric flask and volume was made up to the mark with chloroform. The solution was scanned against blank which consists of chloroform treated in same way and buffer and dye sol. The maximum absorbance of ion- pair was found at 415nm and the absorbance was plotted against molar ratio of drug solution.

The absorbance increases up to 0.5 molar ratio with a positive slope show that till there Terazosin was a limiting factor after that change in slope from positive to negative show that after dye was a limiting factor. Thus, the change in slope at 0.5 molar ratio conclude that the drug react with dye in 1:1 ratio (Figure 5).

Procedure for analysis of Tablet formulations

Powdered terapress 2 tablet equivalent to 20 mg of terazosin was taken in 25 ml volumetric flask and ultrasonication was done using approximately 20 ml water and diluted upto the mark with the same. The content in the tablet was calculated by regression equation. The results are presented under Table 2.

Table 2. Table Estimation of Terazosin

Formulation	Conc. found ug/ml	Mean(mg) SD	RSD
Terapress 2	1.892	1.886 + 0.010	0.530

3. Conclusion

Simple, rapid, precise and cost saving spectrophotometric method was developed for the estimation of terazosin from tablet dosage form. Terazosin shows good regression values at their respective wavelength and the result of recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. Hence proposed method is new, simple, cost effective, accurate, sensitive and precise so can be adopted for routine analysis.

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