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# AN IMPROVED CHEMOMETRIC ASSISTED TECHNIQUE WITH QBD APPROACH FOR ESTIMATION OF TELMISARTAN AND HYDROCHLOROTHIAZIDE FROM COMBINED FORMULATION

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## ABSTRACT

Various pharmaceutical processes including analytical methods are designed and developed by Quality by design approach. Chemometric based analytical method was developed by using principles of QbD for the estimation of telmisartan (TST) and Hydrochlorothiazide (HCTZ) on the UV-VIS spectrophotometer. Ecological suitable solvent 0.1 N HCl was utilised to make solutions; 271.5 nm and 291 nm was the wavelength for absorbance measurement. Effect of input variables on spectrum characteristics were studied for selection of critical parameters and developed method was validated as per ICH Q 2 R1 regulatory guidelines. Linearity of both the drugs was ascertained over the conc range 0-24 mcg/ml. The accuracy was found with SD 1.62621for TST and 1.89292 for HCTZ; and the precision study data % RSD 1.73061 for TST and 0.91855 for HCTZ was found in the acceptable range. The developed method is rigid, robust and efficient for the estimation of TST and HCTZ, from their combined dosage form. QbD was applied to build rigid robust method through risk assessment at early stage and defining the design space at the later stage.

**KEYWORDS:** QbD, Telmisartan, Hydrochlorothiazide, ICH, simultaneous equation, chemo metric method.

## INTRODUCTION

The purpose for selection of antihypertensive with diuretic action drugs in the management of cardiovascular diseases is due to unique crisis with a higher prevalence of hypertension and related causes. Telmisartan (TST) chemically 4' {[4-Methyl-6-(1-Methyl-1*H*-benzimidazol-1-yl)-2propyl-1*H* benzimidazol-1-yl] Methyl}-2-biphenyl carboxylic acid[1,2], is an angiotensin II receptor antagonist with actions similar to those of losartan. It is used in the management of hypertension and for the prophylaxis of cardiovascular events.[3]

For estimation of TST methods such as HPLC[4], titrimetric method[5], chemometric and Spectrophotometric method[6,7], micellar liquid chromatographic method[8] and novel approach HPLC method[9] have been reported for the estimation of TST alone or in combination with other drugs.

Hydrochlorothiazide (HCTZ) chemically is 6-Chloro -3, 4 dihydro- 2 H-1, 2-4 benzothiadiazine-7-sulphonamide 1,1- dioxide[1, 2] used as thiazide diuretic. HCTZ and the other thiazide diuretics are used in the treatment of hypertension either alone or with other antihypertensive such as ACE inhibitors and beta blockers. They are also used to treat oedema associated with heart failure and with renal and hepatic disorders.[3,10]

Various analytical methods have been reported for the detection of HCTZ alone or in combination with other anti - hypertensive agents in pharmaceutical dosage form

includes chemometric assisted UV method [11] and UV spectroscopic method.[12,13]

Both drugs are official in recently published British Pharmacopoeia[14] and Indian Pharmacopoeia.[15] Chemical structure of both drugs is shown in (Fig No 1).

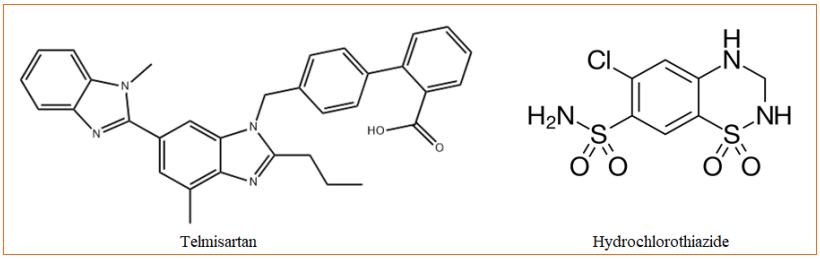


**Fig. No. 1: Chemical structure of Drug molecule.**

Quality by design concept is applied for the development of pharmaceutical processes to assure a predefined product quality. QBD concepts are mentioned in ICH guidelines Q8 (R1) (Pharmaceutical development), Q9 (Quality risk management), and Q10 (Pharmaceutical quality system).[16-18] ICH guidelines Q8 (R2) defines QBD as a "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[19] QBD approach in analytical method summarizes a complete understanding of how the analytical technique attributes and operating conditions affect the analytical performance.[20,21] Factors to study in analytical quality by design (AQbD) approach may include the type of analytical technique chosen; reagents used and instrument parameters.[22,23]

There are similar advantages of applying QbD principles to analytical methods as to manufacturing processes and product.[24] A QbD approach can be beneficial in the development of suitable, robust, low cost and eco-friendly (eco-friendly solvent, chemicals) method which is applicable at any stage of the lifecycle of the product. Also some regulatory guidelines have mentioned flexibility of changing analytical method without revalidation if the AQbD approach has been implemented during analytical method development. The first stage of AQbD approach is to fix an analytical target profile (ATP) for the method. ATP defines the goal of the analytical method development process and it is the sign of method performance [25, 26]. For analytical method validation ICH Q2 (R1) has given various method performance characteristics for an analytical method. Thus a QbD based UV spectrophotometric was developed, QbD approach was implemented with the study of the effect of method input variables on spectral shape, intensity of absorbance, and absorbance maxima $\lambda_{max}$ and critical parameters were selected for the proposed method and method was validated as per ICH guidelines Q2 (R1).

## MATERIALS AND METHODS

### Instrumentation

Analysis was performed with a Shimadzu Double beam UV - Visible spectrophotometer 1900i (Shimadzu, Kyoto, Japan) with spectral bandwidth of 1 nm and wavelength accuracy of ± 0.3 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was used for weighing and for degassing the solution Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

### Reagents and Chemicals

Pharmaceutically pure sample of HCTZ from Smruthi Organics Ltd Solapur Maharashtra and pharmaceutically pure sample of TST were procured from Micro Lab Bengaluru as a gift sample and the commercial formulation containing Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg was procured from the local market.

### AQbD approach application in method development

AQbD approach was applied to study the influence of input variable parameters on spectrophotometric analytical method performance shown in (Fig No 2).

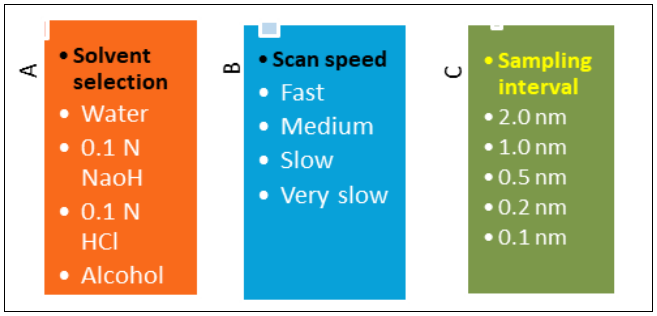


**Fig. No. 2: Analytical method performance parameters selection approach.**

**Solvent selection**

HCTZ is very soluble in water, soluble in acetone, sparingly soluble in ethanol, dissolves in dil solution of alkalies; whereas TST is sparingly soluble in alcohol, dichloromethane, slightly soluble in methanol and practically insoluble in water. Although the solubility of the procured drugs were studied in methanol, 0.1 N HCl and 0.1 N NaOH, separately; and each solution with known conc of analyte were scanned in UV range of 200 nm to 400 nm. The recorded overlaid spectra in respective solvent are shown in Fig No 3 and 4. The study summarises that suitable solvent is 0.1 N HCl with respect to low cost, robust and precise in producing result.

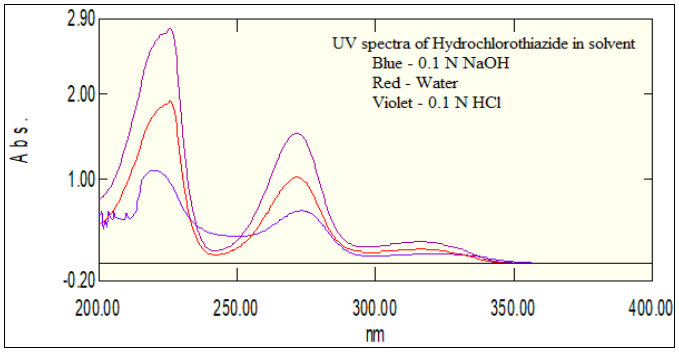


**Fig. No. 3: Overlaid spectra of HCTZ in solvents.**

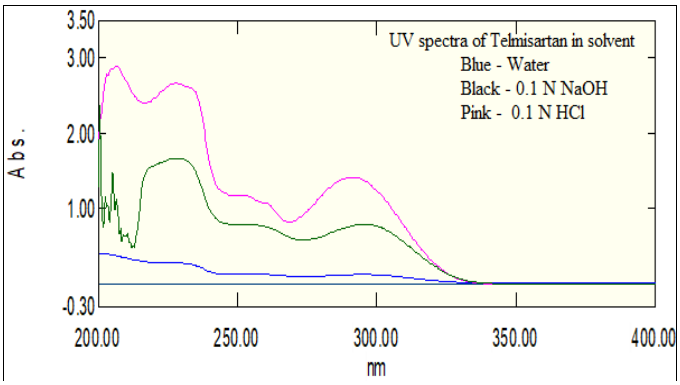


**Fig. No. 4: Overlaid spectra of TST in solvents.**

**Preparation of stock solutions and standard solutions**

10 mg each of drug TST and HCTZ were separately and accurately weighed; and transferred into separate 25 ml volumetric flask. Dissolved into 0.1 N HCl and volume was made to 25 ml with solvent. Subsequent standard solution of each drug with conc 10mcg/ml was prepared by diluting aliquot 0.5 ml of stock solution to 10 ml capacity volumetric flask.

**Selection of wavelength and conc range**

From UV spectra Fig No 5 it was found that TST has measurable absorbance at 291 nm; and HCTZ has maximum absorbance at 271.5 nm hence the $\lambda_{max}$ was located at 271.5 nm and 291 nm for HCTZ and TST respectively. Both drugs has reasonable absorbance at $\lambda_{max}$ of other drug which is interference and should be accounted in evaluation of combined formulation.

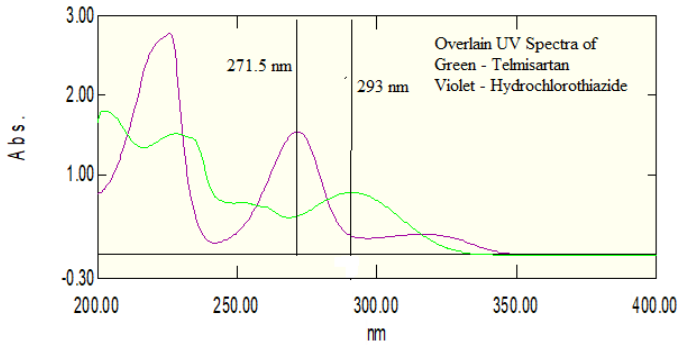


**Fig. No. 5: Overlaid spectra of TST and HCTZ spectra in 0.1 N HCl solvents.**

Chemometric method was applied and which was reasonable remedy to overcome interference of other drugs absorbance. From the nature of spectra working conc range 0 to 24mcg/ml for TST and 0 to 24mcg/ml for HCTZ was selected in 0.1 N HCl solvent. Also combined drug solution was prepared simulated to

marketed formulation. Selected critical parameters based upon above discussion, observations were listed in Table No 1 and by using these; method was validated as per ICH guidelines and by analysing marketed preparations.

**Table No 1: Selected critical parameters for UV-VIS analytical method of HCTZ and TST**

| Parameter | Selected variables of method I HCTZ | TST |
|---|---|---|
| Wavelength | 271.5 | 291 |
| Solvent | 0.1 N HCl | 0.1 N HCl |
| Scan speed | Fast | Fast |
| Sampling interval | 0.2 nm | 0.2 nm |
| Conc range | 0-24 mcg/ml | 0-24 mcg/ml |

**Experimental Method for estimation**

From the overlain spectra two methods simultaneous equation method and amplitude modulation method were applied for simultaneous estimation of both drugs in the combined dosage form.

**Method-I Simultaneous Equation Method**

TST was shown absorbance at ($\lambda_{max}$) 291 nm and HCTZ has maximum absorbance ($\lambda_{max}$) at 271.5 nm. The wavelength 271.5 and 291 nm were considered as 1 ($\lambda_1$) and 2 ($\lambda_2$) respectively. The equation A= abc was applied for x (HCTZ) and y (TST) determination. On rearranging the 2 generated equations, the conc of x and y was calculated by following formula. Working standard solutions of TST of conc 12 µg /ml and HCTZ of conc 12 µg /ml were separately prepared and used for the method.

$$Cx = \frac{A2\ .ay1 - \ A1.ay2}{ax2.ay1 - \ ax1.ay2}$$

$$Cy = \frac{A1\ .ax2 - \ A2.ax1}{ax2.ay1 - \ ax1.ay2}$$

Where Cx and Cy = Conc of HCTZ and TST in sample solution

$A_1$ and $A_2$ = absorbance of sample solution at 1 and 2 wavelength

$Ay_1$ and $ay_2$ = absorptivity of TST at 1 and 2 wavelength of standard solution

$Ax_1$ and $ax_2$ = absorptivity of HCTZ at 1 and 2 wavelength of standard solution

**Validation of the Method**

Selected critical parameters should meet the performance characteristics of the analytical method so as to attain analytical target profile of the method. An ICH guideline Q2 R1 was applied to study methods performance with critical parameters in order to implement AQbD approach. The method was validated as per ICH guidelines

**System suitability**

System suitability is studied to demonstrate the suitability of the developed procedure under consideration for the analytical method. Six replicates of working standard solutions with conc 10 mcg/ml each of TST and HCTZ were prepared separately and absorbance was recorded, and SD and % RSD of the response was calculated.

**Linearity**

The linearity of an analytical method is its ability to obtain response i.e. absorbance which is directly proportional to the conc of analyte. series of working standard solutions were prepared in conc. range of 0 to 24 mcg/ml for both TST and HCTZ and scanned in 200 to 400 nm range in spectrum mode of the spectrophotometer, absorbance of the standard solutions were recorded at 271.5 nm for HCTZ and 291 nm for TST in spectrum order. Microsoft office excel software tool was used to obtain the standard regression curve and its analysis as slope, intercept, and correlation coefficient.

**Assay of formulation**

Assay was carried out by proposed methods and assay was validated by statistical parameters.

**Estimation of formulations by Simultaneous equation method**

Tablet powder equivalent to 12 mg TST and 6.25 mg HCTZ was weighed and transferred into 50 ml volumetric flask. Dissolved into 0.1 N HCl and volume was made to 50 ml with solvent. Solution was filtered through whatman filter paper and aliquot of solution was further diluted to obtain sample. Solution was scanned in the range of 200 to 400 nm to obtain absorbance and record at 271.5 and 291 nm in spectrum order. Obtained absorbance was utilised to estimate unknown conc of formulation; and results were statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

**Accuracy and Precision**

The accuracy of an analytical method expresses the closeness of an agreement between test result and true result. Accuracy study was performed by recovery study i.e. standard addition method; diluted standard solutions of TST and HCTZ were prepared and standard solutions added in 80,100 and 120% proportionate to the tablet solution. Three replicates at each of these three levels were prepared, measured and % of conc, SD and RSD of replicates were calculated.

The precision study was carried out by performing assay of tablet six times; also the reproducibility in result was ascertained by interday and intraday precision.

**Limit of Detection (LOD) and Limit of Quantitation (LOQ)**

The LOD and LOQ of HCTZ and TST by the proposed method were determined using calibration graph method and calculated as 3.3σ/s and 10 σ/s for LOD and LOQ respectively, where σ is the standard deviation of calibration curve and s is the slope of regression line.

**Robustness and Ruggedness**

It is measure of capacity of analytical procedure to remain unaffected by small but deliberate variations in method parameter.

**RESULTS AND DISCUSSION**

Method development comprises numerous steps of which solvent selection, method for measurement selection are significant one. Uses of aqueous solvents, eco-friendly solvents like hydrotropic have got remarkable weightage due to low cost, readily available and environmentally sound. Drugs underlying analysis must have appreciable solubility in the selected solvent. Chemical structure of the drug and physico-chemical properties available in the literature guides about use of appropriate solvent in the method.

**System Suitability**

The absorbances of six replicates of standard solutions (10mcg/ml) are reported in Table No 2. The SD and % RSD was found for TST and HCTZ and meets the system suitability requirements indicates method was suitable for analysis.

**Table No. 2: System suitability study of TST and HCTZ.**

| Sr No | Conc in mcg/ml | Absorbance of TST (291nm) | Absorbance of HCTZ (271.5 nm) |
|---|---|---|---|
| 1 | 10 mcg/ml | 0.474 | 0.666 |
| 2 | 10 mcg/ml | 0.486 | 0.669 |
| 3 | 10 mcg/ml | 0.483 | 0.652 |
| 4 | 10 mcg/ml | 0.472 | 0.657 |
| 5 | 10 mcg/ml | 0.483 | 0.666 |
| 6 | 10 mcg/ml | 0.478 | 0.646 |
| | SD<br>RSD | 0.48265<br>0.03023 | 0.51781<br>0.04741 |

**Linearity**

The calibration curve of both drugs was found to be linear in the conc range of 4-24 mcg/ml for TST and 4-24 mcg/ml for HCTZ (overlain linear spectra shown in Fig No 6 and 7) as shown in Fig No 8 and 9. The regression equation of line and its parameters slope, $r^2$ value and intercept are tabulated in Table No 3, which proved the linear relationship between conc and obtained response.

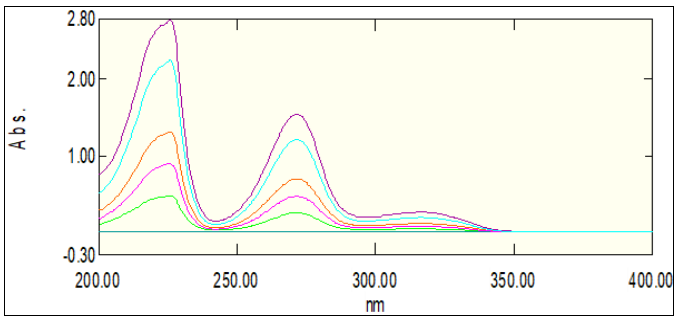


**Fig. No. 6: Overlaid spectra of HCTZ obtained in linearity study.**

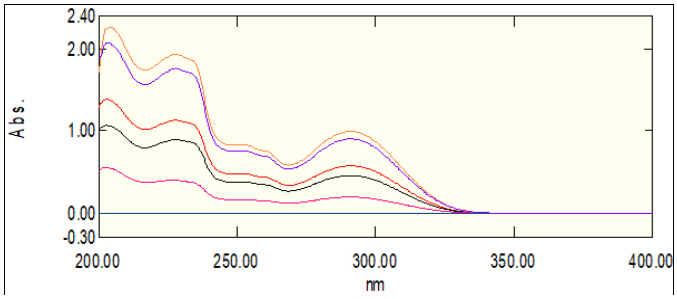


**Fig. No. 7: Overlaid spectra of TST obtained in linearity study.**

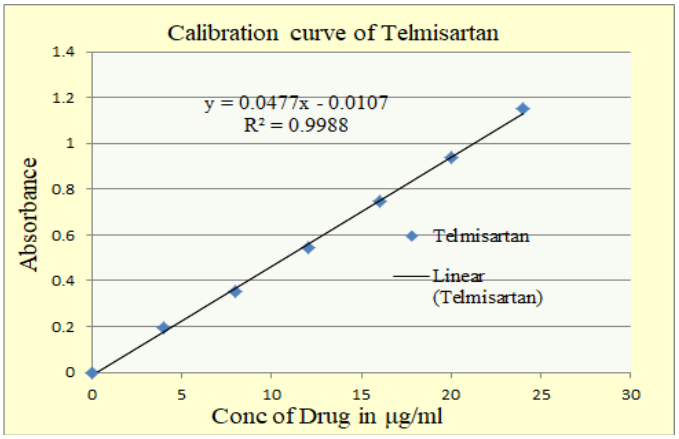


**Fig. No. 8: Calibration curve of TST obtained in linearity study.**

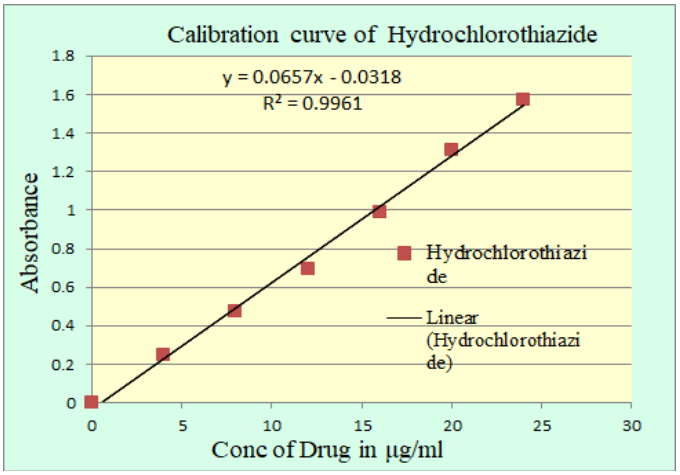


**Fig. No. 9: Calibration curve of HCTZ obtained in linearity study.**

**Table No 3: Parameters of regression equation obtained in Microsoft excel**

| Parameters | TST | HCTZ |
|---|---|---|
| Detection wavelength | 291 | 271.5 |
| Beer's law limit (µg/ml) | 4-24 mcg/ml | 4-24 mcg/ml |
| Correlation coefficient ($r^2$) | 0.9988 | 0.9961 |
| Regression equation (y = mx + c) | Y = 0.0477 X -0.0107 | Y = 0.0657 X - 0.0318 |

**Assay**

The assay was carried out by proposed method. The spectra of formulation by method I was shown in Fig No 10. The assay of formulation was carried out by proposed method and calculated % of nominal conc and RSD was found within acceptable limits are summarized in Table No 4. The results indicated applicability of the method for estimation of formulation.

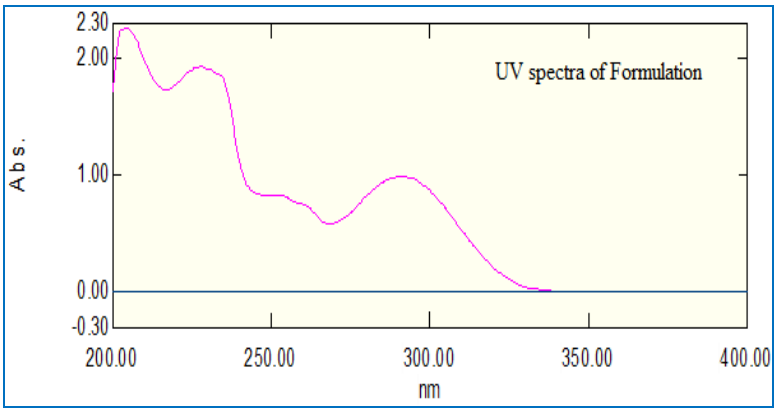


**Fig. No. 10: Spectra of formulation by method I.**

**Table No 4: Results of assay of formulation by proposed method**

| Formulation | Drug | Label Claim (mg/Tablet; n=6) | Amount found/mg | Drug Content % | Std Deviation | % RSD |
|---|---|---|---|---|---|---|
| Formulation Method -I | TST | 40 | 39.41 | 98.52 | 0.43219 | 3.13295 |
| | HCTZ | 12.5 | 12.32 | 98.61 | 0.15993 | 2.79699 |

**Accuracy and Precision**

The results of accuracy Fig No 11 are summarised in Table No 5, the obtained results were within acceptable limit; and methods accuracy was justified by calculating % drug content.

The precision study was carried out by performing assay of solutions; further the reproducibility in result was studied by interday and intraday precision. The values obtained SD and % RSD was shown methods precision and are summarised in Table No 5.

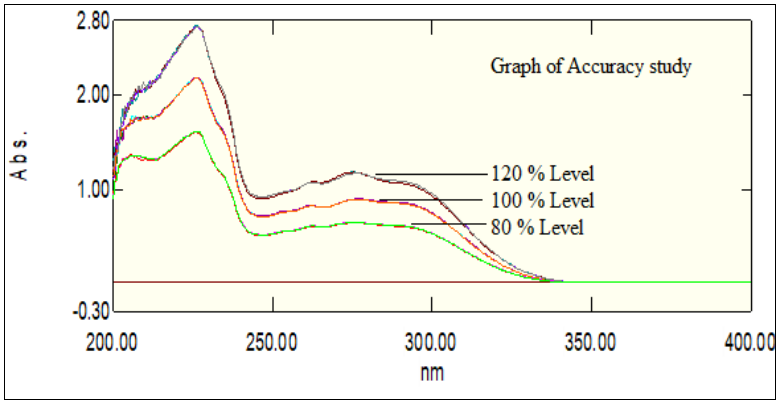


**Fig. No. 11: UV spectra obtained in accuracy study in method-I at 3 levels.**

**Table No 5: Results of accuracy and precision**

| S. No. | Parameter | Level of study | Drug Name | S.D. | % RSD |
|---|---|---|---|---|---|
| 1 | Precision of TST and HCTZ | Intraday Precision | TST | 0.18575 | 1.92758 |
| | | | HCTZ | 0.11045 | 6.88722 |
| | | Interday precision | TST | 0.16945 | 1.73061 |
| | | | HCTZ | 0.14873 | 0.91855 |
| 2 | Accuracy study of TST and HCTZ | 80% | TST | 0.42497 | 1.01849 |
| | | 100% | TST | 1.62621 | 2.84567 |
| | | 120% | TST | 0.84641 | 0.95291 |
| | | 80% | HCTZ | 0.79907 | 0.86199 |
| | | 100% | HCTZ | 0.47453 | 3.44318 |
| | | 120% | HCTZ | 1.89292 | 1.13613 |

**Limit of Detection (LOD) and Limit of Quantitation (LOQ)**

The LOD and LOQ of TST and HCTZ by the proposed method were shown in Table No 6. The standard deviation of the calibration curve was obtained in Microsoft excel word and found 0.000417 for TST and 0.000165 for HCTZ.

**Robustness and Ruggedness**

Robustness was studied and capacity of analytical procedure to measure analyte was remain unaffected by small but deliberate variations in method parameter. The analytical method was found rugged during development; similarity the result was produced by performing the analysis by different analyst.

**Table No. 6: Results of LOD and LOQ, robustness.**

| Parameters | | TST | HCTZ |
|---|---|---|---|
| LOD mcg/ml | | 0.288 | 0.0828 |
| LOQ mcg/ml | | 0.8727 | 0.2501 |
| Robustness | ± 2 nm | SD = 0.15399 (conc 10 mcg/ml) | SD = 0.02636 (conc 10 mcg/ml) |
| Ruggedness | Analyst 1 | SD ± 0.11544 | SD ± 0.02324 |
| | Analyst 2 | SD ± 0.53243 | SD ± 0.12941 |

**CONCLUSION**

Both the drugs were estimated from the combined formulation by simultaneous equation method. Chemometric equations are applied to determine amount of each drug from their combined dosage form; and

obtained results were within acceptable limits given in the pharmacopoeia.

The validated method was economical, precise, accurate, robust and reproducible hence can be routinely used for simultaneous estimation of Telmisartan and Hydrochlorothiazide from combined dosage form.

**Conflict of Interest**

All Authors declared that there is no conflict of interest

**ACKNOWLEDGEMENT**

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