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# Concurrent Determination of Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride Development and Validation by UV-VIS Spectrophotometry in Bulk and Pharmaceutical Dosage Form.

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***Abstract - An easy, precise, exact, cost effective, reproducible and economical UV spectrophotometric methods was developed and validated for the simultaneous determination Teneligliptin Hydrobromide hydrate and Metformin Hydrochloride in tablet dosage form and pharmaceutical formulations. The method is based on choice of wavelengths; someplace one drug shows identical absorbance or variation between absorbance is zero and additional drug shows some reply. The wavelengths selected for use of Teneligliptin were 243 nm. While, wavelengths select for use of Metformin were 233 nm. Water was in used as solvent. Beer's law was observing in the absorption range of 1.4 – 2.6 µg $mL^{-1}$ for Teneligliptin and 35-65 µg $mL^{-1}$ for Metformin. Development study for Teneligliptin and Metformin were performed and the percentage recovery for both the drugs were obtained in the range of 98.40-100.20% confirms the accuracy of the proposed method. The outcome woes verified that the procedure is accurate, precise and reproducible while being easy, not expensive and less time consuming and hence can be suitably applied for the estimation of Teneligliptin and Metformin in different dosage forms and successfully applied to determination of these drugs in commercial tablets.***

***Keywords: - UV spectrophotometric, Teneligliptin Hydro bromide hydrate, Metformin Hydrochloride,***

## I. INTRODUCTION

Asia accounted for 60% of the world's diabetic population. Diabetes affects more than 8.8% of the world's population and it is a significant public health concern. Type 2 diabetes is a global crisis that threatens the health and economy of all nations, particularly developing countries. Lots of oral anti-diabetic drugs with different mechanisms of action (MOA) have developed to decrease glucose level and delay the possibility of grave complication in patients with type 2 diabetes.[1] For the sort out of diabetes, treatment with a solitary oral enemy of diabetic specialist isn't sufficient to control the glucose level. Subsequently, mix treatment approaches including drugs with corresponding and distinctive MOA are suggested for the type 2 diabetics. In a perfect world, blend treatments have a few points of interest like they are decent, simple attractive, have relatively less contraindications and have a diminished danger of hypoglycemia and weight gain. The mix treatment can be compelling over the short and long haul, for example, the mix of biguanide (metformin) an insulin sensitizer and the dipeptidyl peptidase-4 (DPP- 4) inhibitors which go about as an insulin secretagogue. It helps in giving progressively useful and sense treatment with diminished tablet trouble than their monotherapy for debilitated β cell work [2, 3] Metformin (MET) N, N-dimethylbiguanide, is a biguanide class oral anti-hyperglycemic agent.[4] There are many analytical methods based on LC-MS/MS reported for MET. [1, 5-8] Teneligliptin (TEN) (3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-ylcarbonyl] thiazolidine) is a new high potent, long lasting and selective orally active DPP-4 inhibitor for use in the management of type 2 diabetes.[9] There are only few LCMS/ MS analytical methods report for TEN alone [10]. Several LC-MS/ MS based 5 bioanalytical methods have also been reported for the simultaneous estimation of MET and DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, alogliptin) combinations.[3, 11-13] Dried blood spots analyses of MET and DDP-4 inhibitors were also reported.[14, 15] Only one study has been reported for the pharmacokinetic (PK) interaction in healthy adults after the oral administration of MET and TEN.[16] The above study reports shows, mild pharmacokinetic interaction of biguanide and gliptins is common and there are however no preclinical reports for the combination of MET and TEN. Also, there is a need to develop a more efficient and sensitive analytical method for the Simultaneous detection and estimation of MET and TEN. The main objective of the study was to utilize the high resolution mass spectrometry (HRMS) as a quantitative tool for the study of preclinical pharmacokinetic interaction study.[17] The HRMS has emerged as a sensitive, stable and excellent tool in quantitative bioanalytical research. The advantages of Q-TOF instruments including quantitative analysis have been reviewed and highlighted in the following scientific 6 reviews.[18, 19] The current status of HRMS for drug quantification in the clinical and forensic toxicology was reviewed by Meyer et al 2014.[20] There are several reports showing excellent application of HRMS in quantitative bioanalysis.[10, 21, 22] Even though literature survey reveals that various methods were reported for Teneligliptin and Metformin both for single estimation and in combination with others drugs, but current study was to develop fast, accurate, reproducible, validated and

economical first derivative and ratio first-derivative analytical methods for the simultaneous determination of Teneligliptin and Metformin from pure and tablet formulations.

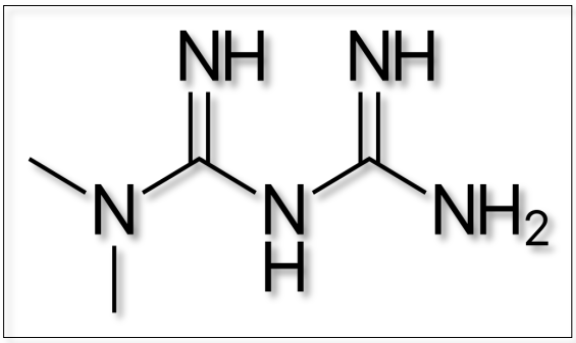
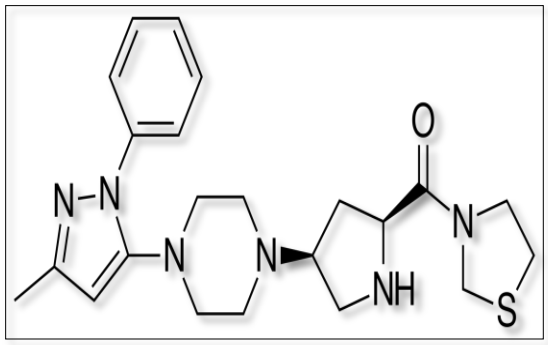



*Fig. 1 Metformin (MET)*




*Teneligliptin (TEN)*

## II. MATERIALS AND METHODS

### A. Instrument

ELICO SL-244 double beam UV-VIS spectrophotometer is used 1 cm matched quartz cell was used to measure absorbance of all the solutions.

### B. Chemical and reagents

Teneligliptin Hydro bromide hydrate (TEN) with purity (>99.54%) and Metformin Hydrochloride (MET) and (> 99.00%) were kindly provided a sample by Unison Pharmaceuticals Pvt. Ltd (Ahmedabad, India). Teneligliptin (TEN) was obtained from Ajanta Pharma Limited (Mumbai, India). All solvents and reagent use of A.R grade high purity demonized water

### C. Preparation of Standard Stock Solutions

**Teneliglipftin:**
Take 29.5 mg of Teneligliptin Hydro bromide hydrate (equivalent to 20 mg of TEN) in 100 mL volumetric flasks. Add sufficient amount of diluents and sonicated to 10 min. and dissolved it. Make up with diluents and mix it.

**Metformin:**
Take 50 mg of MET in 50 mL volumetric flasks. Add sufficient amount of diluents and sonicated to10 min. dissolved it. Make up with diluents and mix it.

**Standard Solution:**
From the above solution take 1 mL of TEN solution and 5 mL of MET solution In 100 mL volumetric flasks. Make up with diluents and mix well. To get concentration For TEN 2 µg $mL^{-1}$ and MAT 50 µg $mL^{-1}$ the wavelength of the drugs were obtained solutions were scanned in the UV region 200 nm to 400 nm using diluents as blank.

### D. Sample Solution

20 Tablets (Marketed tablets of TEN and MET), containing 20 mg and 500 mg with TEN and MET were accurately weighed and finely crushed with mortar and pestle. About 995.5 mg of the tablet powder containing about to 20 mg of TNE 500 mg of TEN and MET was weigh and transferred to 100 mL volumetric flask dissolved in water sonicated for 15 min. and volume was complete up to the mark used whattman filter paper (No.1) filtered the Solution. Pipette out 1.0 mL into a 100 mL volumetric flask and volume was complete up to mark with diluent. The resulting solution is use for absorbance and results were record.

### E. Selection of wavelength

Wavelength for the examination of TEN and MET (2 and 50 µg $mL^{-1}$ respectively) was selected from the UV spectrum. Solution was scan in the UV region 200 nm to 400 nm using diluent as blank. The absorption of the drugs was measured at 243nm (TEN) and 233 nm (MET) shown in Fig. 2

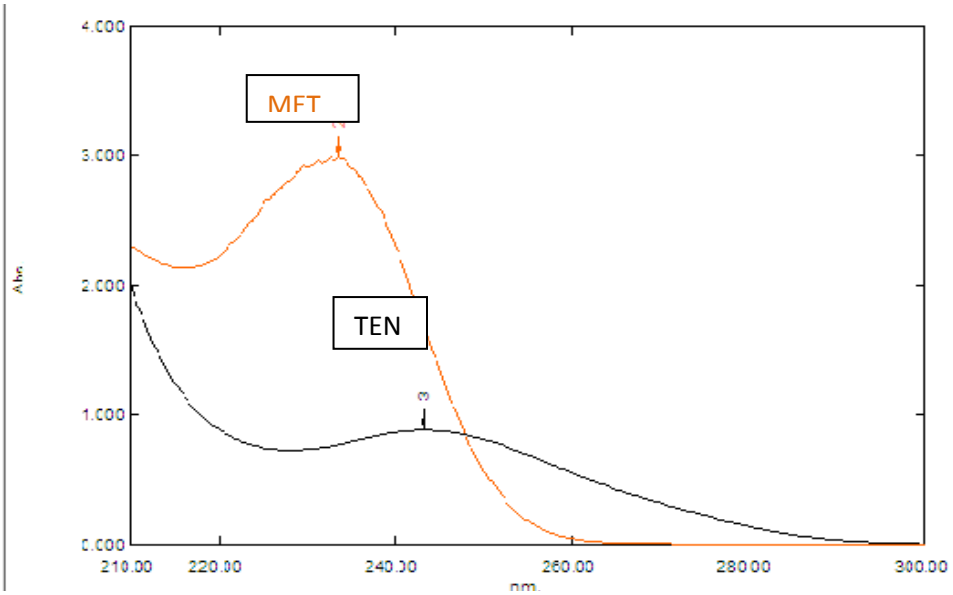



*Fig.2 Overlay spectra of both the drugs TEN and MET*

## III. Method validation

The strategy was created and approved by the investigative technique according to the ICH rules for approval of explanatory strategies so as to decide linearity, precision accuracy, ruggedness, and robustness for the analyzed.

### A. Linearity

The linearity was assessing by observance down the various convergence of the standard arrangement of TEN and MET. The Beer-Lambert's obsession run was experimental to be 1.4 to 2.6 and 35 to 65 µg $mL^{-1}$ for TEN and MET respectively. The linearity of the connection among absorbance's and obsession was dictated by plotting the adjustment bends for TEN and MET are appeared in Fig. 3,4 and Table 1.

**Table 1: Linearity study for TEN and MET**

| Sr. No | Concentration (%) | Concentration Range (µg/ml) | Absorbance | Concentration (%) | Concentration Range (µg/ml) | Absorbance |
|---|---|---|---|---|---|---|
| TEN | | | | MET | | |
| 1 | 70 | 1.4 | 0.0223 | 70 | 35 | 2.8452 |
| 2 | 80 | 1.6 | 0.0251 | 80 | 40 | 3.2377 |
| 3 | 90 | 1.8 | 0.0286 | 90 | 45 | 3.6425 |
| 4 | 100 | 2.0 | 0.0315 | 100 | 50 | 4.0470 |
| 5 | 120 | 2.4 | 0.0378 | 120 | 60 | 4.8564 |
| 6 | 130 | 2.6 | 0.0410 | 130 | 65 | 5.1452 |
| Mean | | | 0.0310 | Mean | | 3.9623 |
| SD | | | 0.0072 | SD | | 0.9034 |
| RSD | | | 0.2334 | RSD | | 0.2280 |
| %RSD | | | 23.350 | %RSD | | 22.800 |
| Correlation coefficient | | | 0.9990 | Correlation coefficient | | 0.9980 |
| Slope | | | 0.0150 | Slope | | 0.0770 |

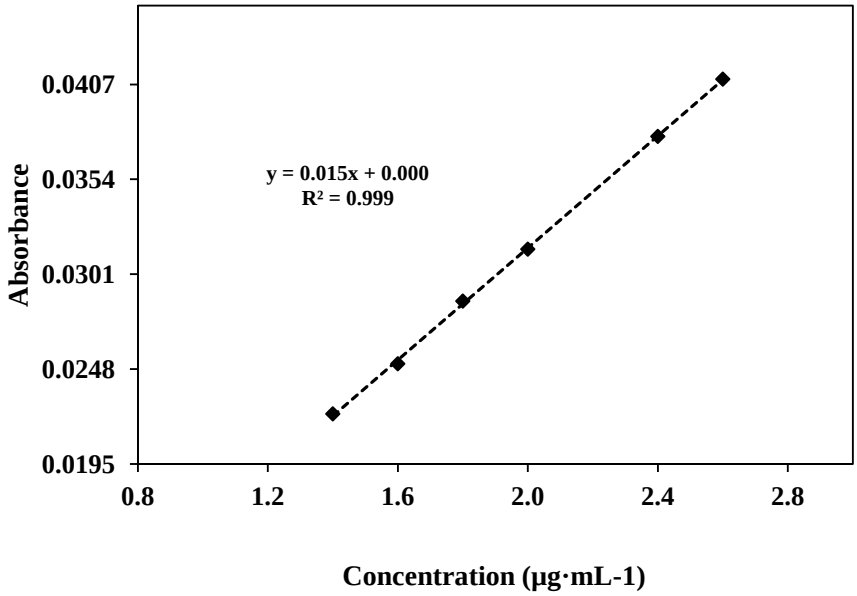



*Fig. 3: Calibration curve of TEN at 243 nm*

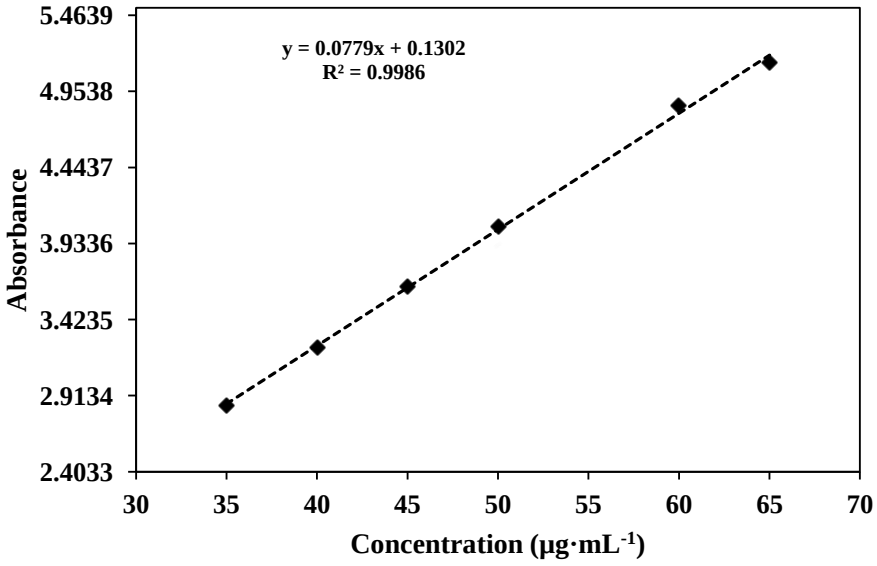



*Fig. 4: Calibration curve of MET at 233 nm*

**B. Accuracy (% Recovery)**

**Standard stock solution for accuracy**:
A Weigh accurately 29.5 mg of TEN (equivalent to 20 mg of TEN) and 500 mg MAT in 100 mL volumetric flasks. Add sufficient volume of diluents and dissolved it with sonicated for 10 min. Make up volume with diluents and mix well.

**Sample preparation:**
An amount of 435.5 mg of placebo powder was weigh and moved into 3 sets of volumetric flasks, each set thusly comprising of 3 volumetric flasks of 100 mL. To the primary set (50% measurement), second set (100% measurement) and to the third set (150% measurement). To this 0.5, 1.0 and 1.5 mL of blended standard arrangement of medication was included. About 70

mL of refined water was added to all the 3 sets and sonicated for around 10 min. Volume was complete up to 100 mL with a similar diluent, and sifted through a Whatman filter paper. It's give a concentration of 1, 2 and 3 µg $mL^{-1}$ for TEN. And 25, 50 and 75 µg $mL^{-1}$ for MET absorbance of these was recorded at predetermined wavelengths. The test was performed in multiple times. The rate recuperation of the examples, % RSD and the rate were determined at every focus level appeared Table 2.

**Table 2: Statistical Validation for Recovery studies**

| Sr. No. | Concentration (%) | Concentration Range (µg/ml) | Absorbance | Mean | SD | %RSD | RSD | %Recovery |
|---|---|---|---|---|---|---|---|---|
| **TEN (Standard Absorbance: 0.0315)** | | | | | | | | |
| 1 | 50 | 1 | 0.0155 | 0.0155 | 0.0001 | 0.6451 | 0.006451 | 98.4 |
| | | | 0.0156 | | | | | 99.0 |
| | | | 0.0154 | | | | | 97.8 |
| 2 | 100 | 2 | 0.0311 | 0.0312 | 0.0001 | 0.3704 | 0.003704 | 98.7 |
| | | | 0.0311 | | | | | 98.7 |
| | | | 0.0313 | | | | | 99.4 |
| 3 | 150 | 3 | 0.0466 | 0.0466 | 0.0001 | 0.2145 | 0.002145 | 98.6 |
| | | | 0.0465 | | | | | 98.4 |
| | | | 0.0467 | | | | | 98.8 |
| **MET (Standard Absorbance: 4.047)** | | | | | | | | |
| 1 | 50 | 25 | 2.0252 | 2.0137 | 0.0004 | 0.017 | 0.00017 | 100.1 |
| | | | 2.0127 | | | | | 99.5 |
| | | | 2.0031 | | | | | 99.0 |
| 2 | 100 | 50 | 4.0413 | 4.0375 | 0.0055 | 0.13 | 0.0013 | 99.9 |
| | | | 4.0312 | | | | | 99.6 |
| | | | 4.0401 | | | | | 99.8 |
| 3 | 150 | 75 | 6.0712 | 6.0707 | 0.0063 | 0.1042 | 0.001042 | 100.0 |
| | | | 6.0809 | | | | | 100.2 |
| | | | 6.0601 | | | | | 99.8 |

### C. Precision

Repeatability estimation was done by examining six unique arrangements containing same concentration 2 and 50 µg $mL^{-1}$ (TEN, MET respectively) and % RSD was determined. Repeatability of the strategy was set up by analyzing different recreates tests of TEN and MET. Precision was done by performing inter-day and intra-day variety. In Inter day variety the example was investigated on three continuous days. In an intraday variation in the absorbance was estimated multiple times in multi day.

### D. Intra-day and inter-day Precision

The intra-day precision of the examiner was estimated by calculate the % RSD for the analysis of 2 µg $mL^{-1}$ and 50 µg $mL^{-1}$ TEN and MET respectively solutions in three replicates and inter-day precision was resolute by the analysis of three replicates of 2 µg $mL^{-1}$ and 50 µg $mL^{-1}$ TEN and MET solutions on three repeated days are shown in Table 3, 4.

**Table 3: Intra-day Precision for TEN and MET (n = 6).**

| Sr. No | Concentration Range (µg/ml) | Abs. I | Abs. II | Abs. III |
|---|---|---|---|---|
| **TEN** | | | | |
| 1 | 2 | 0.0315 | 0.0311 | 0.0309 |
| 2 | 2 | 0.0311 | 0.0307 | 0.0304 |
| 3 | 2 | 0.0309 | 0.0303 | 0.0299 |
| 4 | 2 | 0.0318 | 0.0313 | 0.031 |
| 5 | 2 | 0.0306 | 0.0301 | 0.0299 |
| 6 | 2 | 0.0319 | 0.0314 | 0.0308 |
| Average | | 0.0313 | 0.0308 | 0.0305 |
| SD | | 0.0005 | 0.0005 | 0.0005 |
| %RSD | | 1.6540 | 1.7465 | 1.6260 |
| RSD | | 0.0165 | 0.0175 | 0.0163 |
| Average %RSD | | 1.6755 | | |
| **MET** | | | | |
| Sr. No | Concentration Range (µg/ml) | Abs. I | Abs. II | Abs. III |
| 1 | 50 | 4.0491 | 4.0484 | 4.0475 |
| 2 | 50 | 4.0345 | 4.0338 | 4.0321 |
| 3 | 50 | 4.0085 | 4.0079 | 4.0061 |
| 4 | 50 | 4.0412 | 4.0401 | 4.0391 |
| 5 | 50 | 4.0532 | 4.0527 | 4.0514 |
| 6 | 50 | 4.0125 | 4.0117 | 4.0103 |
| Average | | 4.0332 | 4.0324 | 4.0311 |
| SD | | 0.0187 | 0.0187 | 0.0189 |
| %RSD | | 0.4647 | 0.4650 | 0.4647 |
| RSD | | 0.0046 | 0.0047 | 0.0046 |
| Average %RSD | | 0.4649 | | |

**Table 4: Inter-day Precision for TEN and MET (n = 6).**

| Sr. No | Concentration Range (µg/ml) | Abs. I | Abs. II | Abs. III |
|---|---|---|---|---|
| **TEN** | | | | |
| 1 | 2 | 0.0311 | 0.0301 | 0.0307 |
| 2 | 2 | 0.0309 | 0.0312 | 0.0303 |
| 3 | 2 | 0.0307 | 0.0308 | 0.0313 |
| 4 | 2 | 0.0314 | 0.0303 | 0.0308 |
| 5 | 2 | 0.0304 | 0.0313 | 0.0314 |
| 6 | 2 | 0.0312 | 0.0305 | 0.0299 |
| Average | | 0.0310 | 0.0307 | 0.0307 |
| SD | | 0.0003 | 0.0004 | 0.0005 |
| %RSD | | 1.1694 | 1.5824 | 1.8711 |
| RSD | | 0.0117 | 0.0158 | 0.0187 |
| Average %RSD | | 1.5410 | | |
| **MET** | | | | |
| Sr. No | Concentration Range (µg/ml) | Abs. I | Abs. II | Abs. III |
| 1 | 50 | 4.0552 | 4.0485 | 4.0078 |
| 2 | 50 | 4.0501 | 4.0301 | 4.0473 |
| 3 | 50 | 4.0296 | 4.0475 | 4.0379 |
| 4 | 50 | 4.0422 | 4.0154 | 4.0504 |
| 5 | 50 | 4.0139 | 4.0621 | 4.0103 |
| 6 | 50 | 4.0725 | 4.0245 | 4.0754 |
| Average | | 4.0439 | 4.0380 | 4.0382 |
| SD | | 0.0204 | 0.0175 | 0.0257 |
| %RSD | | 0.5058 | 0.4342 | 0.6379 |
| RSD | | 0.0051 | 0.0043 | 0.0064 |
| Average %RSD | | 0.5259 | | |

### E. Robustness

The Robustness of the technique was controlled via doing the examination by the diverse examiner in various research centers utilizing different UV spectrophotometer and the particular absorbance of µg $mL^{-1}$ and 50 µg $mL^{-1}$ was well-known. % RSD was resolute. The Ruggedness information and explanatory execution parameters of TEN and MET were appeared Table 5.

**Table 5: Statistical validation for Robustness studies of TEN and MET.**

| Sr. No. | Set. No | Wavelength (nm) | Conc. | Absorbance | Average | SD | RSD | %RSD |
|---|---|---|---|---|---|---|---|---|
| **TEN** | | | | | | | | |
| 1 | I | 243 | 2 | 0.0319 | 0.0313 | 0.0005 | 0.0182 | 1.8186 |
| 2 | II | 243 | 2 | 0.0311 | | | | |
| 3 | III | 243 | 2 | 0.0308 | | | | |
| **MET** | | | | | | | | |
| 1 | I | 233 | 50 | 4.0392 | 4.0480 | 0.0083 | 0.0021 | 0.2060 |
| 2 | II | 233 | 50 | 4.0489 | | | | |
| 3 | III | 233 | 50 | 4.0558 | | | | |

## IV. Result and discussion

To advance the UV parameters, a several conditions were attempted to a complish a decent ingestion and peak shape for TEN and MET. A Several solvents of various compositions were attempted to give sufficient selectivity towards the medications. Refined water parts brought about better sensitivity. The techniques examined in the present work give an advantageous and exact route for the examination of TEN and MET from bulk and tablet measurement structure by UV Spectrophotometry strategy. The 243 nm and 233 nm wavelength was chosen for examination of TEN and MET (Fig. 2).The absorbance of TEN and MET was observed to be 1.4 to 2.6 and 35 to 65 respectively (Table 1). Chosen techniques linearity was seen in the absorption range of 70%-130%. In this method, the convergence of the drug was resolved at 243 nm and 233 nm utilizing the individual absorptive esteem appeared in (Fig. 2). A Linear relationship was acquired between absorbance Vs concentration. Calibration curve for TEN and MET indicated linearity in the concentration range 1.4 to 2.6 and 35 to 65 µg $mL^{-1}$. The linearity of the adjustment bend was approved by the estimation of relationship coefficients ($r^2$). The estimation of relationship coefficient for TEN and MET was observed to be 0.999 and 0.998 appeared Table 1 and Fig.2, 3.The standard expansion technique was utilized for accuracy measurement. The rate recuperations for TEN and MET were found in the range of 98-102 %. The estimations of the % Recovery and % RSD were appeared Table 2, which demonstrates the accuracy of the proposed technique.The precision of the technique was controlled by breaking down the medication definition by imitate infusions and precision of the framework was dictated by blended standard arrangements. % RSD of the analyze was observed to be inside the point of confinement of 2 %, appeared Table 3 and Table 4 along these lines the created technique was observed to be in the high level of precision. The low estimations of the % RSD demonstrate the repeatability of the proposed method. Ruggedness was determined by playing out the examiner with a similar condition on various days, by various investigators, distinctive instrument and diverse time. the test outcomes were found inside cutoff 98– 102% appeared. Robustness was dictated via doing the examiner amid change wavelength. The % RSD was found to be not more than 2 % which was inside the point of confinement appeared in Table 5.

## V. CONCLUSION

A classic and basic synchronized condition strategy has been produced for synchronous investigation of TEN and MET in bulk and in tablet formulation. The proposed strategy quantitatively assess as far as linearity, precision, accuracy, Robustness recovery. Every one of these components led to the end that the proposed UV-Spectrophotometric strategy is simple, precise, accurate, delicate and practical. This technique was received for the utilization of conservative and effectively accessible portable stage and for the UV detector and validation was done as per ICH guidelines. In this way the utilized versatile stage makes it an amazing strategy for the estimation of MET and TENT in bulk drug and its formulations.

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