

## SIMULTANEOUS SPECTROPHOTOMETRIC ESTIMATION OF TELMISARTAN AND INDAPAMIDE IN CAPSULE DOSAGE FORM

DR. SUJIT PILLAI AND DEEPMALA MANORE\*

Department of Pharmaceutical Chemistry, GRY Institute of Pharmacy "Vidhya Vihar" Borawan (Khargone), M.P.- 451228, India.  
Email: deepmala30pharm@gmail.com

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### ABSTRACT

Simple, fast and precise simultaneous spectrophotometric methods for simultaneous estimation of two-component drug mixture of Telmisartan and Indapamide in combined capsule dosage form have been developed. The proposed first method is based on the formation and solving of simultaneous equations using 294.0 and 242.0 nm as two analytical wavelengths. The second method is absorbance ratio method, which uses 254.0 and 294.0 nm as two analytical wavelengths. Third method is based on multicomponent mode method. Developed method was applied to laboratory mixture and its marketed formulation. These methods were statistically validated and recovery studies confirmed the accuracy of the proposed method.

**Keywords:** Telmisartan, Indapamide, Simultaneous equations, Absorbance ratio and Multicomponent mode method.

### INTRODUCTION

Telmisartan is 2-(4-[[4-methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl] phenyl) benzoic acid (Fig.1) is a non-peptide molecule, angiotensin II receptor (type AT1) antagonist [1,2]. It acts by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II by selective blocking the binding of angiotensin II to AT1 receptor found in vascular smooth muscles [3]. It is not official in any pharmacopoeia. It is an effective agent for the treatment of hypertension and renal impairment. It has a lower incidence of cough than ACE inhibitors. It is white to off-white crystalline powder that is insoluble in water, freely soluble in methanol and acetonitrile [4].

Indapamide, 4-cholelo-N (2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoyl benzamide is a white to yellow white crystalline (tetragonal) powder, soluble in methanol, ethanol, acetic acid and ethyl acetate; very slightly soluble in ether, chloroform and benzene and practically insoluble in water is used as a diuretic. IND is the first of the new class of antihypertensive diuretics which is prescribed to treat the salt and fluid retention associated with congestive heart failure [5]. IND (thiazide like diuretic) act directly on the kidney and enhances excretion of sodium, chloride, and water by interfering with transport of sodium ions across renal tubular epithelium [6]. It also acts as a carbonic anhydrase inhibitor. Indapamide reaches maximum plasma concentration within 2-2.5 hours and half life is about 14-18 hours.

Many methods have been reported in the literature for the estimation of TEL and IND, individually or in combination with other drugs [7-19]. However, there is no method reported for the simultaneous estimation of TEL and IND. The multicomponent dosage form includes multiple entities and excipients; and poses considerable challenge to the analytical chemist during the development of assay procedure. The present study was aimed at the simultaneous estimation of TEL and IND by simultaneous equation, absorbance ratio and multicomponent mode analysis method. These methods were validated according to the ICH guidelines.

### MATERIALS AND METHODS

#### Equipment

Shimadzu UV-1700; UV/VIS double beam spectrophotometer with spectral bandwidth of 2 nm, wavelength accuracy  $\pm 0.5$  nm (with automatic wavelength correction) and wavelength readability 0.1 nm increment was employed for all measurements using a matched pair of 10 mm quartz cells.

#### Materials

Gift sample of TEL and IND were procured from Ipca Laboratories Limited Ratlam M.P., India and Mission Vivacare Limited Pithampur, M.P., India respectively. The commercial fixed dose combination product INDITEL-D SRcap label claim (Telmisartan 40mg, Indapamide 1.5mg) manufactured in India by Zydus Cadiva a division of Cadila Healthcare Limited was procured from the local pharmacy. Methanol used as a solvent.

#### Preparation of Stock Solutions

To prepare standard stock solution of TEL and IND, 100 mg of TEL and 100 mg of IND was transferred in two separate 100 ml volumetric flasks. Each drug was dissolved in 75 ml of methanol and shaken gently for 10 min. The volume was made up to the mark with methanol to get stock solution of 1000  $\mu$ g/ml. From above solution take 10 ml of the solution in volumetric flask and then diluted up to 100 ml with methanol to produce final stock solution of 100  $\mu$ g/ml of methanol.

#### Development of Method

##### Method 1: Simultaneous equation

From the stock solutions, 1 ml of TEL and 1 ml of IND was transferred to two separate 10 ml volumetric flasks and the volume was adjusted to the mark with methanol i.e. strength obtained was 10  $\mu$ g/ml for TEL and 10  $\mu$ g/ml for IND. Both the drug solutions were scanned separately between 200 nm to 400 nm. The overlain spectrum of both drugs was recorded (Shown in Fig.3) and two wavelengths 294.0 nm ( $\lambda$  max of TEL) nm and 242.0 nm ( $\lambda$  max of IND) were selected for estimation of drugs using simultaneous equation method and construction of calibration curves.

Two series of different concentration in range of 1-25  $\mu$ g/ml for TEL and 1-14  $\mu$ g/ml for IND were prepared from the working standard solutions. The calibration curves were plotted at 294.0 and 242.0 nm. The absorptivities ( $A_{1\%}$ , 1 cm) of both the drugs at both the wavelength were determined. These calculated values were the mean of five independent determinations. The absorbance and absorptivity value at the particular wavelength were calculated and substituted in the following equation to obtain the concentrations:

$$C_x = \frac{A_2 \times 101.12 - A_1 \times 684.4}{-269239.4792} \dots\dots\dots (1)$$

$$C_y = \frac{A_1 \times 507.04 - A_2 \times 468.31}{-269239.4792} \dots\dots\dots (2)$$

where  $A_1$  and  $A_2$  are absorbance of sample solution at 294.0 nm and 242.0 nm respectively  $C_x$  and  $C_y$  are concentration of TEL and IND

respectively (mole/lit) in sample solution the validity of formed equation was checked by preparing three mixed standards measuring there absorbance at respective wavelength and comparing these with the absorbance calculated using above formed equations.

### Method 2: Absorbance Ratio method

From the overlain spectra of TEL and IND, 294.0 nm was taken as  $\lambda_{max}$  for TEL and 254.0 nm as isoabsorptive point for estimation of IND. Series of different concentrations in range of 1-25  $\mu\text{g/ml}$  for TEL and 1-14  $\mu\text{g/ml}$  for IND were prepared from the working standard solutions. The calibration curves were plotted at 254.0 and 294.0 nm. The absorptivities ( $A_{1\%}^{1\text{cm}}$ ) of both the drugs at both the wavelength were determined. These calculated values were the mean of five independent determinations. The concentration of sample was measured by this equation,

$$C_{TEL} = Q_M - Q_Y/Q_X - Q_Y \times A_1/a_{x1} \text{-----} (3)$$

$$C_{IND} = Q_M - Q_X/Q_X - Q_Y \times A_1/a_{y1} \text{-----} (4)$$

### Method 3: Multicomponent Mode Method

In this method eight mixed standards of TEL and IND in the having concentrations in  $\mu\text{g/ml}$  of 5:4, 10:5.37, 15:6, 20:8 and 25:10 were prepared by appropriate dilution of the standard stock solutions and scanned in the region of 400 nm to 200 nm. Sampling wavelengths (294.0nm and 242.0 nm) were selected considering the peaks and valleys in the UV spectra of the individual components. The concentration of individual drug was feed to the multi-component mode of the instrument. The instrument collects and compiles the spectral data from mixed standards and the concentration of the various components of the formulation are directly recorded when the sample solution is scanned (Shown in Fig.4). The analysis was repeated for three times.

### Analysis of marketed formulations

Twenty capsules were weighed ingredients of capsule were taken and empty shell were weighed again, weight of empty shell was subtracted from total weight and then average weight of ingredients was calculated. Ingredients were crushed to obtain a fine powder. An accurately weighed sample equivalent to 40 mg of TEL and 1.5 mg of IND was taken in a stoppered volumetric flask (100.0ml); 75ml of methanol was added and sonicated for 5 min. The volume was then made up to the mark using same solvent. The solution was filtered through Whatmann filter paper (No 41). From this stock

solution, 0.5 ml of solution was transferred in 10 ml of volumetric flask. As the amount of IND pretend in the prepared dilution is below linearity range. The solution was spiked and pure drug sample solution of IND to give 5.37  $\mu\text{g/ml}$  of IND respectively. The final dilution contains 10  $\mu\text{g/ml}$  of TEL and 5.37  $\mu\text{g/ml}$  of IND. The concentrations of dilution were given by multicomponent mode because this concentration within the Beer's law limit ( $\mu\text{g/ml}$ ) for both drugs. The absorbances were noted at respective wavelengths. The concentration of each drug in capsule formulation was determined using above methods.

To study the accuracy (percentage recovery), for both developed methods, recovery studies were carried out by the addition of standard drug solution to pre-analyzed capsule sample with proper dilutions at three different concentration levels (80, 100, and 120%) within the range of linearity for both the drugs.

## RESULTS AND DISCUSSION

The proposed methods developed for simultaneous analysis of TEL and IND in combined capsule dosage form was found to be simple, accurate, rapid, economical and sensitive to be applied in routine analysis of capsule. In the described methods there were no additional extraction or separation procedures to extract the drug from the formulation excipient matrix. The elimination of these procedures thereby reduces the error in quantitation. First method was developed by formation and solving of simultaneous equation based on absorptivity coefficient of two drugs at  $\lambda_{max}$ .

Once the equation is framed, the absorbance of sample solution at selected wavelengths was to be measured followed by simple calculation.

Framed equation was validated using laboratory prepared mixed standards of two drugs which gave satisfactory results.

In second developed method (absorbance ratio method) for estimation TEL and IND, two wavelengths were selected from overlain spectra. The spectra of TEL and IND when overlaid indicated that the isoabsorptive point was at 254.0 nm at which estimation of IND was done and estimation of TEL was done at its  $\lambda_{max}$  294.0 nm.

By observing the validation parameters (Table 2), methods found to be specific, accurate, precise, repeatable and reproducible. Methods can be employed for routine analysis of capsule for assay. The methods were found to be accurate, precise and rugged.

Table 1: Summary of Optical Characteristic

Parameters (Units)	Telmisartan			Indapamide		
	Method I	Method II	Method III	Method I	Method II	Method III
Linearity range ( $\mu\text{g/ml}$ )	1-25	1-25	1-25	1-14	1-14	1-14
$\lambda_{max}$ (nm)	294.0	294.0	294.0	242.0	254.0	242.0
$r^2$	0.9997	0.9997	0.9997	0.999	0.9982	0.999
Slope $\pm$ SD	0.0454	0.0454	0.0454	0.0726	0.0366	0.0726

SD is standard deviation

Table 2: Summary of Analytical Method Validation

Parameters (Units)	Telmisartan			Indapamide		
	Method I	Method II	Method III	Method I	Method II	Method III
LOD ( $\mu\text{g/ml}$ )	0.190	0.139	0.190	0.136	0.146	0.136
LOQ ( $\mu\text{g/ml}$ )	0.577	0.422	0.577	0.413	0.444	0.413
Recovery (%)	102.43	102.92	96.45	99.32	102.7	101.07
Precision (%RSD)						
Repeatability (n=5)	0.50	0.12	0.49	0.62	1.02	0.65
Interday (n=3)	0.73	0.96	0.76	1.02	0.30	1.02
Intraday (n=3)	1.12	0.70	1.12	0.96	0.54	0.96
Ruggedness(%RSD)						
Analyst 1	0.12	0.12	0.11	0.42	0.42	0.65
Analyst 2	0.44	0.84	0.32	0.84	0.82	0.44

LOD is limit of detection, LOQ is limit of quantitation, RSD is relative standard deviation for n = 3 observations.

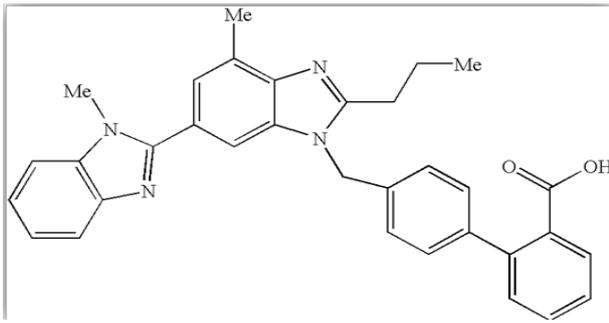


Fig. 1: Structure of Telmisartan (TEL)

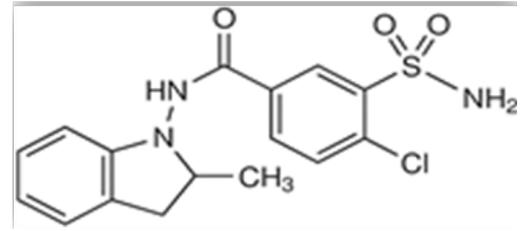


Fig. 2: Structure of Indapamide (IND)

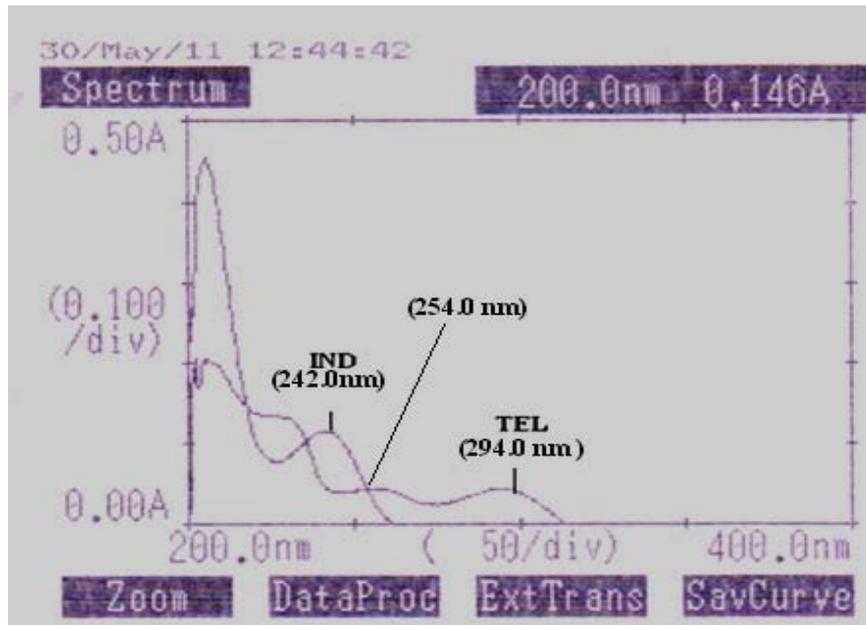


Fig. 3: Overlain spectra of TEL and IND

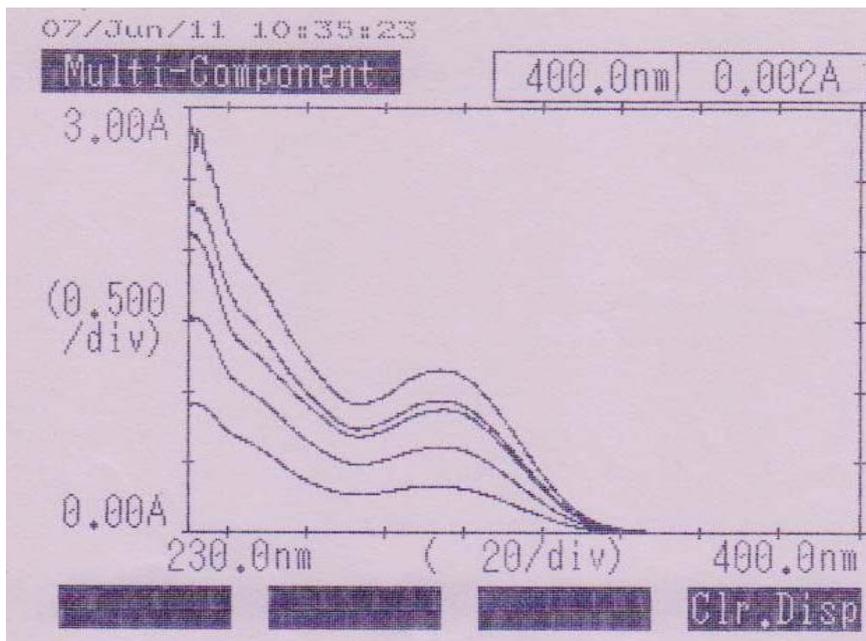


Fig. 4: Overlain Spectra of Mixed Standards

Telmisartan (TEL), Indapamide (IND), 254.0nm. (isobestic point), 294.0nm  $\lambda_{max}$  of TEL and 242.0nm  $\lambda_{max}$  of IND.

**CONCLUSION**

Methods were found to be simple, specific and easy to perform and require short time to analyze the samples. Low limit of quantification and limit of detection makes these methods suitable for use in quality control.

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