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Review Article

Development and Validation of Analytical Methods for Simultaneous Estimation of Terbinafine and Itraconazole in Bulk and Pharmaceutical Dosage Form.

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ABSTRACT

Two new simple, accurate and precise UV- VIS spectrophotometric methods have been developed for simultaneous estimation of Terbinafine and Itraconazole in bulk and pharmaceutical dosage forms. The first method is simultaneous estimation using vierodt's equation where absorption maxima found at 289nm and 282nm for Terbinafine (TER) and Itraconazole (ITZ) respectively. The second method is based on Q-method / Absorption ratio method using two wavelengths, at 285nm (Isobestic point) and 289nm(λmax for Terbinafine). Two methods follow Beer's linearity in the range of 10-35µg/ml for Terbinafine and 5-30µg/ml for Itraconazole with correlation coefficient $r^2$of 0.999 and 0.999 for Terbinafine and Itraconazole,(method 1); 0.999, 0.999 for Terbinafine and 0.999, 0.999 for Itraconazole(method 2). All LOD, LOQ, %RSD are less than 2.According to ICH norms the parameters linearity, precision, accuracy, limit of detection, and limit of quantification, robustness and ruggedness were studied. The proposed methods were simple, cost effective and were successfully applied to the determination of these drugs in quality control of combined pharmaceutical dosage.

KEYWORDS

Terbinafine, Itraconazole, Simultaneous Equation Method, Absorption Ratio Method, Ultraviolet Spectroscopy.

1. INTRODUCTION

Terbinafine hydrochloride is a synthetic allylamine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Chemically Terbinafine is N-(6, 6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine. It is used for the treatment of dermatophyte infections of the toenail or fingernail caused by susceptible fungi. Also for the treatment of tinea capitis (scalp ringworm) and tinea corporis (body ringworm) or tinea cruris (jock itch).[1, 2]

Itraconazole is the triazole antifungal agents that inhibit cytochrome P-450-dependent enzymes resulting in impairment of ergosterol synthesis. It has been used against histoplasmosis, blastomycosis, cryptococcal meningitis & aspergillosis. Chemically Itraconazole is1-(butan-2-yl)-4-{4-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]phenyl}-4,5 dihydro-1H-1,2,4-triazol-5-one 705.64 g/mol. It is used for the treatment of the following fungal infections in immune compromised and non-immuno compromised patients: pulmonary and extra pulmonary blastomycosis, histoplasmosis, aspergillosis, and onychomycosis.[3, 4]

Various analytical methods reported for determination of Terbinafine and Itraconazole using UV Spectroscopy, HPLC and other chromatographic methods in plasma and pharmaceutical formulation. However, there are no reported methods for simultaneous estimation of both drugs in combined pharmaceutical formulation. This paper presents two simple, rapid, accurate, precise methods for the simultaneous analysis estimation of both the drugs in bulk and from pharmaceutical dosage form.

2. MATERIALS AND METHODS

2.1. Instruments

IR Spectrophotometer (Jasco460 plus Spectrophotometer), UV-Vis Spectrophotometer (Jasco V-530Spectrophotometer) in R.D.'s College of Pharmacy, Bhor (Pune).

2.2. Materials

Standard gift samples of Terbinafine and Itraconazole were procured from (Sankalp Healthcare and Allied Products, Karad). Tablet formulation containing both drugs (Terbiface Plus) purchased from local market.

2.3. Preparation of Stock Solutions

10mg of Terbinafine and 10mg of Itraconazole were weighed accurately and transferred to a separate 10ml volumetric flask, dissolved in sufficient quantity of dichloro methane then sonicated for 15 min and diluted to 10ml with the same solvent so as to get the concentration of 1000 µg/ml.

2.4. Determination of λmax

The standard solutions of Terbinafine (25µg/ml) and Itraconazole (10µg/ml) were scanned separately in the wavelength range of 200 – 400 nm and the λ max was found to be 289 nm and 282nm respectively. Overlain spectra shows absorption maxima at 285nm. For simultaneous equation method, 289nm and 282nm were selected for analysis. For Q- method 289nm and 285nm were selected for analysis. UV spectra of Terbinafine, Itraconazole and overlain spectra of both drugs are shown in fig. 1.1, 1.2, 1.3.

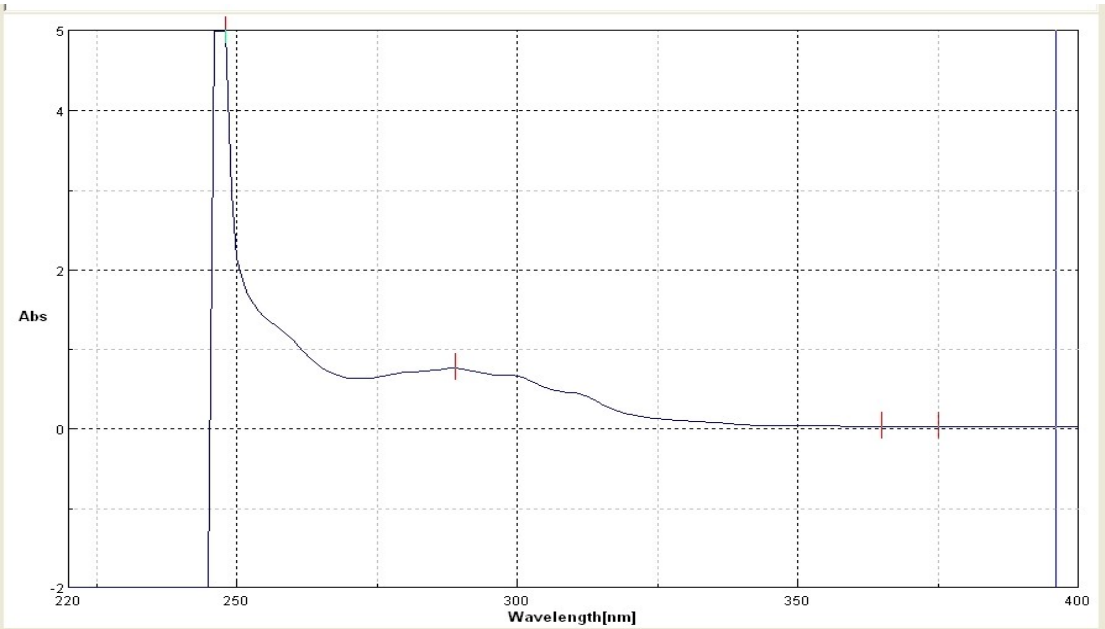

Fig. 1.1: UV Spectra of Terbinafine at conc. 25µg/ml.

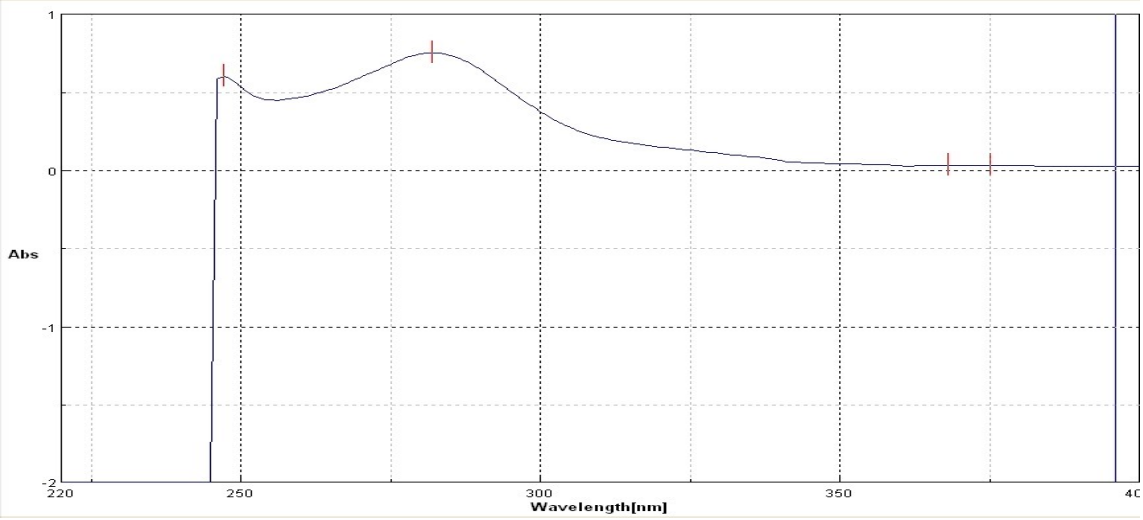

Fig. 1.2: UV Spectra of Itraconazole at conc. 10µg/ml.

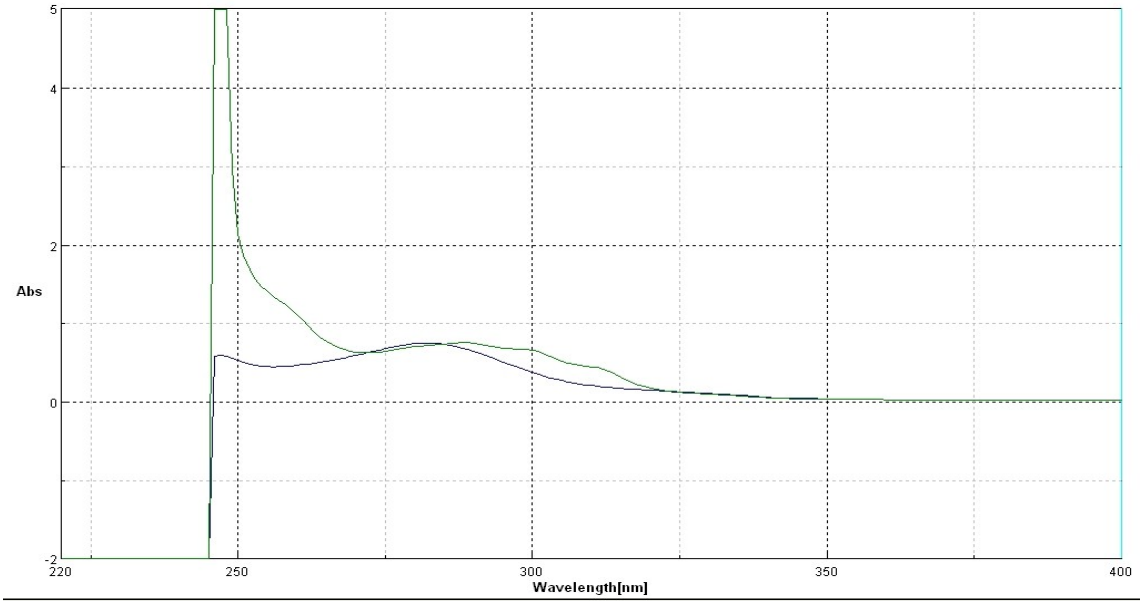

Fig. 1.3: Overlain UV-Spectra of Terbinafine and Itraconazole

2.5. Method A: Simultaneous Equation Method

If a sample contains two absorbing drug each of which absorbs at the λ max of the other, it may be possible to determine both drugs by the technique of simultaneous equation. Two wavelengths selected for the development of the simultaneous equations are 289 nm and 282 nm. The absorptivity values determined for Terbinafine at 289 and 282 are (ax1), and (ax2), and for Itraconazole are (ay1), and (ay2) at 289 nm and 282 nm respectively. The absorbance and absorptivity at these wavelengths were substituted in equation 1 and 2 to obtain the concentration of both drugs.

$$\mathbf{Cx} = \frac{\boldsymbol{A2ay1 - A1ay2}}{\boldsymbol{ax2ay1 - ax1ay2}} \mathbf{(1)}$$

$$\mathbf{Cy} = \frac{\boldsymbol{A1ax2 - A2ax1}}{\boldsymbol{ax2ay1 - ax1ay2}} \qquad \mathbf{(2)}$$

Where,

A1 and A2=Absorbance of sample at 289 and 282,
Cx and Cy=Concentrations of Terbinafine and Itraconazole in sample matrix,
ax1 and ax2=Absorptivity's of Terbinafine at 289 and 282
ay1 and ay2=Absorptivity's of Itraconazole at 289 and 282

2.6. Method B: Absorbance Ratio Method/ Q-Analysis

Absorbance ratio method of analysis is based on the absorbance at two selected wavelengths, one of which is an Isoabsorptive point and the other being the wavelength of maximum absorption of one drug. From overlain spectra of Terbinafine and Itraconazole 285 nm and 289 nm are selected for the formation of Q absorbance equation. The absorptivity values

determined for Terbinafine at 289 nm are (ax1), and 285 nm are (ax2) and for Itraconazole at 289 nm are (ay1), at 285 nm are (ay2). The absorbance and absorptivity at these wavelengths were substituted in equation 3 and 4 to obtain the concentration of drugs.

$$C_X = \frac{QM - QY}{QX - QY} * \frac{A1}{ax1} \qquad (3)$$

$$C_Y = \frac{QM - QX}{QY - QX} * \frac{A1}{ay1} \qquad (4)$$

Where,
A1 and A2 are absorbance of mixture at 289 and 285 nm respectively,
ax1 and ay1 are absorptivity of Terbinafine and Itraconazole at 237.5nm respectively, ax2 and ay2 are absorptivity of Terbinafine and Itraconazole at 258 nm respectively, QM=A2/A1, QX=ax2/ax1 and QY=ay2/ay1

2.7. Validation of UV- Visible Spectrophotometric Methods

Linearity and Range

From the standard stock solution of Terbinafine, appropriate aliquots were pipette out into 10 ml volumetric flasks and dilutions were made with dichloro methane to obtain working standard solutions of concentrations 10, 15, 20, 25, 30, 35 µg/ml. Similarly from the standard stock solution of Itraconazole subsequent dilution were made with dichloro methane to obtain working standard solution of concentration 5, 10, 15, 20, 25, 30, µg/ml. For simultaneous equation method solutions were scanned at 289nm and 285nm for Terbinafine and Itraconazole. The calibration curve of the drugs was plotted. For Q-Absorption ratio method solution were scanned at 285nm (isoabsorptive point) and 289nm (λmax of Terbinafine). The calibration curves were plotted. Linear regression equation of Terbinafine and Itraconazole at all wavelength were determined.

Accuracy and Recovery Studies

To check the accuracy of the proposed method, recovery studies were carried out by standard addition method at three different levels according to ICH guidelines. A series of solutions of Terbinafine and Itraconazole at 80%, 100%, and 120% of the standard preparation in the ratio of the formulation were prepared and checked for accuracy by determining the absorbance values at 289nm and 282nm (Method A) ,285nm and 289nm (Method B). To a fixed concentration of the formulation, varying concentrations of pure drug solutions were added and percentage recoveries calculated.

Precision

Precision of method was studied as intra-day precision and interday precision variation. Intra-day precision was determined by analysing 20, 25 and 30µg/ml of Terbinafine and 5, 10,15 µg/ml of Itraconazole solution for three times in the same day. Inter-day precision was determined by analysing 20, 25 and 30µg/ml of Terbinafine and 5, 10,15 µg/ml of Itraconazole solutions daily for three days in the week. In both intra and inter-day precision study for the methods %RSD were calculated.

Limit of Detection and Limit of Quantitation

The limit of detection and limit of quantification of Terbinafine and Itraconazole by proposed methods were determined using calibration standards. LOD and LOQ were calculated as 3.3σ/S and 10σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response.

Ruggedness

The ruggedness of the proposed method was determine for 25µg/ml concentration of Terbinafine and 10 µg/ml concentration of Itraconazole by analysis of aliquots from a homogenous slot by two analyst using same operational and environmental conditions .The result was indicated as% RSD.

Robustness

The robustness of the method was determined by introducing small changes in UV parameters, such as changing in the wavelength ± 5.

3. RESULTS AND DISCUSSION

3.1. Linearity and Range

For Simultaneous Equation Method, concentration range over which the drugs followed linearity was chosen as an analytical concentration range i.e. 10-35 µg/ml with correlation coefficient of 0.9998; Linear regression equation was found to be y = 0.0299x + 0.061 for Terbinafine. For Itraconazole analytical concentration range i.e. 5-30 µg/ml with correlation coefficient of 0.9997; Linear regression equation was found to be y = 0.0184x + 0.6647. The Calibration data is expressed in Table No. 1.1, calibration curve is shown in Figure No. 1.4 and 1.5

For Q- method ,concentration range over which the drugs followed linearity was chosen as an analytical concentration range i.e. 10-35 µg/ml with correlation coefficient of 0.9998 and 0.9999 ; Linear regression equation was found to be y = 0.0275x + 0.0775 and y = 0.028x + 0.1346 at 285nm,289nm respectively for Terbinafine. For Itraconazole analytical concentration range i.e. 5-30 µg/ml with correlation coefficient of 0.9999 and 0.9998; Linear regression equation was found to be y = 0.0483x + 0.3008 and y = 0.0532x + 0.365 at 285nm and 289nm respectively. The Calibration data is expressed in Table No. 1.2, calibration curve is shown in Figure No. 1.6,1.7,1.8,1.9.

3.2. For Simultaneous Equation Method

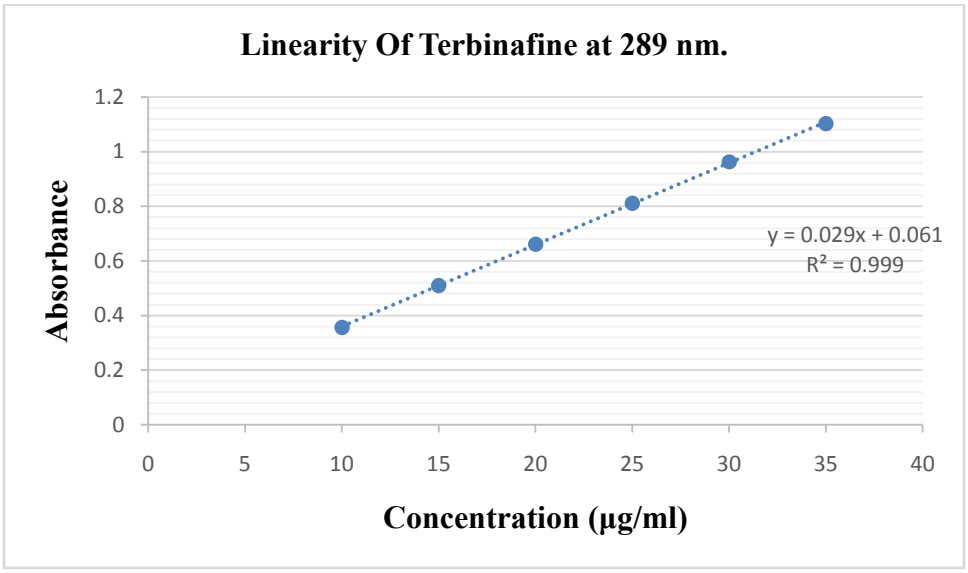

Fig. 1.4: Calibration curve of Terbinafine at 289nm

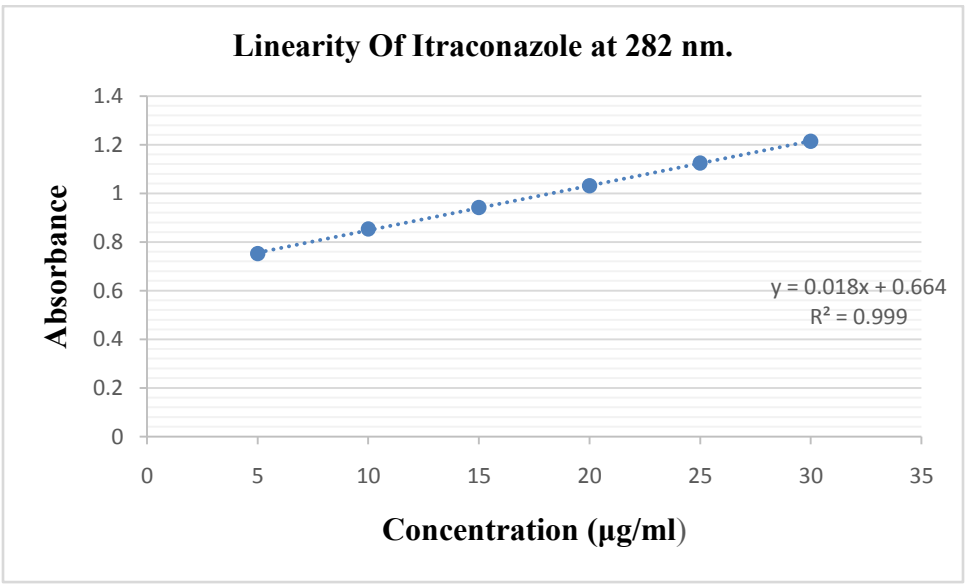

Fig. 1.5: Calibration curve of Itraconazole at 282nm

For Q Method-

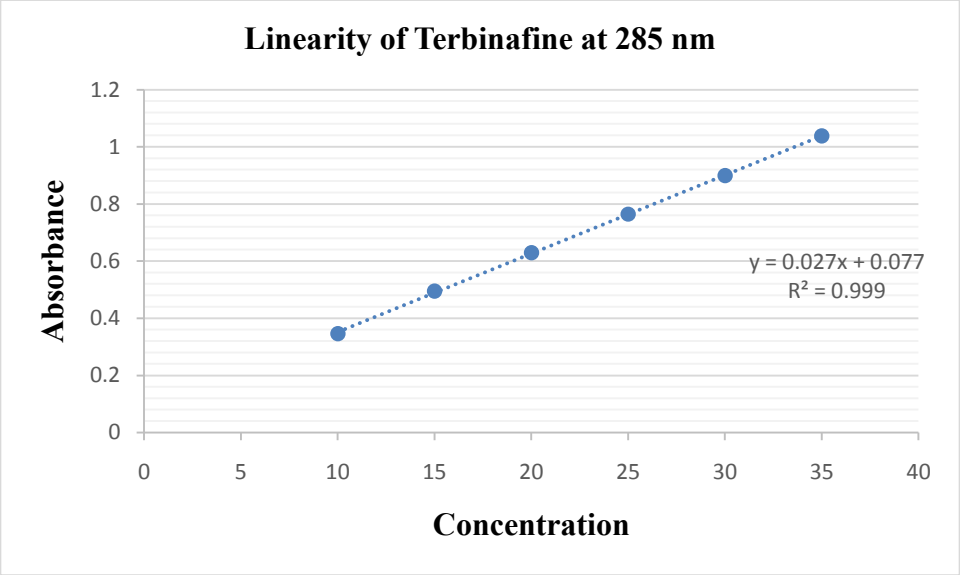

Fig. 1.6: Calibration curve of Terbinafine at 285 nm

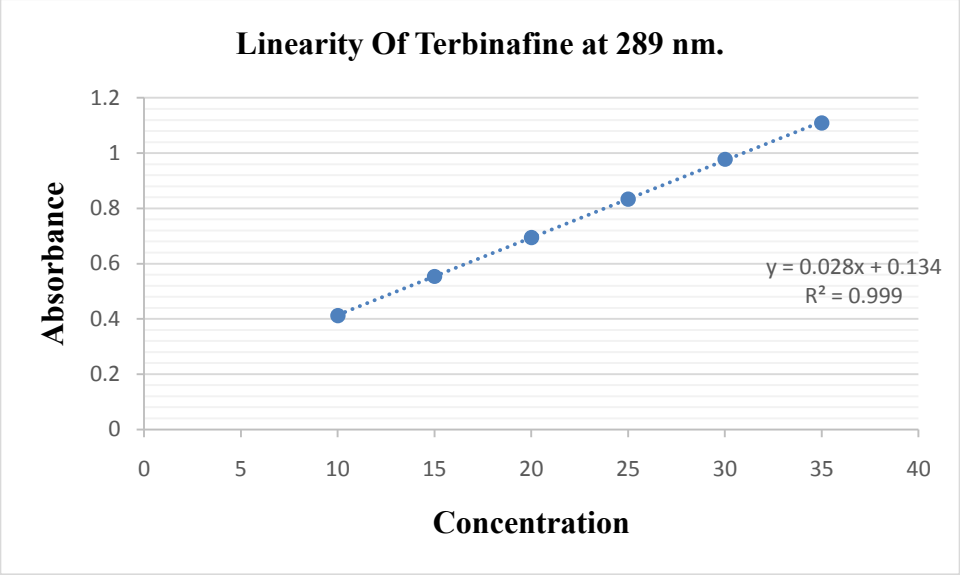

Fig. 1.7: Calibration curve of Terbinafine at 289 nm

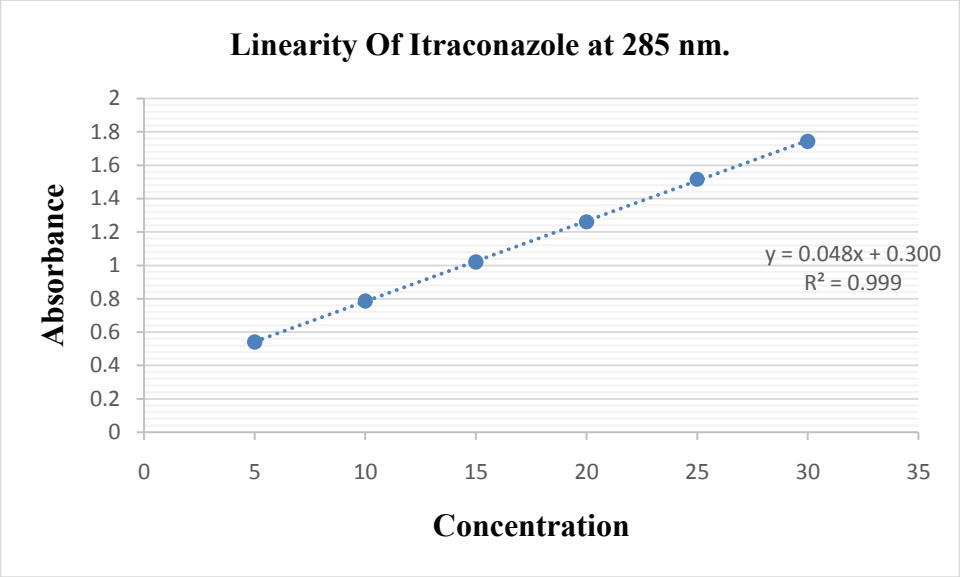

Fig. 1.8: Calibration curve of Itraconazole at 285 nm

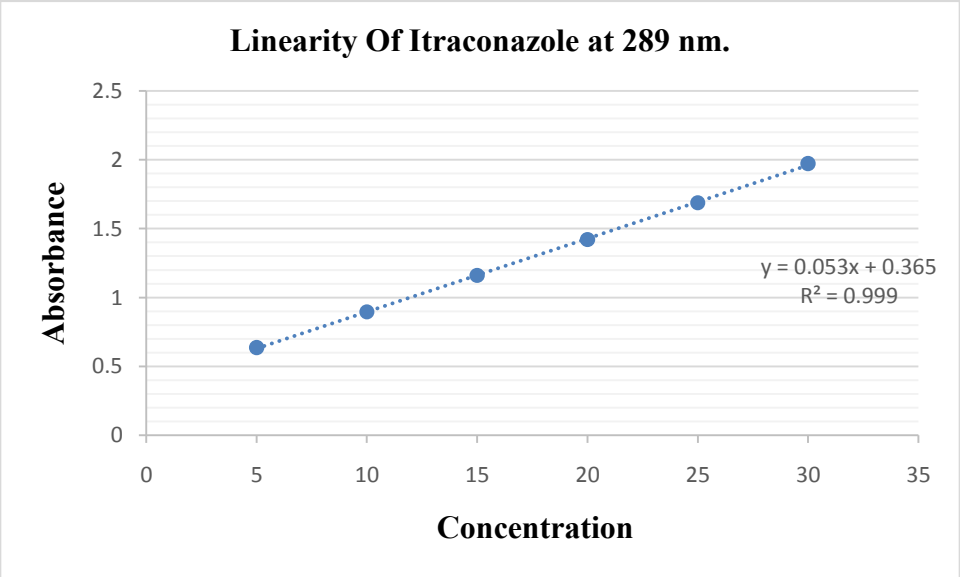

Fig. 1.9: Calibration curve of Itraconazole at 289 nm

Table 1.1: Calibration data for Terbinafine and Itraconazole simultaneous equation method

Sr. No.	**Terbinafine**		**Itraconazole**	
	Conc.(µg/ml)	**Absorbance at 289 nm**	**Conc.(µg/ml)**	**Absorbance at 282 nm**
1	0.0	0.0	0.0	0.0
2	10.0	0.3568	05.0	0.7521
3	15.0	0.5102	10.0	0.8532
4	20.0	0.6615	15.0	0.9412

5	25.0	0.8106	20.0	1.0306
6	30.0	0.9624	25.0	1.1243
7	35.0	1.1025	30.0	1.2139

Table 1.2: Calibration data of Terbinafine and Itraconazole acid for Q-method

Sr. No.	**Terbinafine**			**Itraconazole**		
	Conc.(µg/ml)	**Absorbance**		**Conc.(µg/ml)**	**Absorbance**	
		285nm	**289nm**		**285nm**	**289nm**
1	0.0	0.0	0.0	0.0	0.0	0.0
2	10.0	0.3463	0.4123	05.0	0.5412	0.6374
3	15.0	0.4953	0.5543	10.0	0.7867	0.8967
4	20.0	0.6295	0.6946	15.0	1.0215	1.1612
5	25.0	0.7644	0.8334	20.0	1.2613	1.4216
6	30.0	0.8992	0.9776	25.0	1.5166	1.6886
7	35.0	1.0383	1.1089	30.0	1.7442	1.9730

Table 1.3: Data showing linearity of developed methods

Parameter	**Simultaneous equation method**		**Q-Absorption ratio method**			
	TER	**ITZ**	**TER**	**TER**	**ITZ**	**ITZ**
Linearity range (µg/ml)	**289nm**	**282nm**	**285nm**	**289nm**	**285nm**	**289nm**
	10- 35	5-25	10- 35	10-35	5- 25	5-25
Slope	0.0299	0.0184	0.0275	0.028	00482	0.0532
Intercept	0.061	0.6647	0.775	0.1346	0.3008	0.365
Regression coefficient (r^2)	0.9998	0.9997	0.9998	0.9999	0.9999	0.9998

3.3. Accuracy (Recovery):

Accuracy of the method was confirmed by recovery study from marketed formulation at three level of standard addition. The % recovery was found to be in the range 99.58%–99.88% for Terbinafine and 100.74% -100.93% for Itraconazole (method 1); 99.88% - 99.45% (TER 285 nm), 99.16% - 99.59% (TER 289 nm) and 99.96% - 100.08% (ITZ 285 nm), 99.65% - 99.88% (ITZ 289 nm) (method 2). The recovery studies are reported in Table No: 1.4,1.5, and 1.6.

Table 1.4: Result of % Recovery and % RSD of Terbinafine and Itraconazole for simultaneous equation method

Drugs	Recovery level	Initial conc.(µg/ml)+ Conc. of std. drug added.(µg/ml)	Amount Recovered (n=3)	%Recovery	%RSD
TER	80%	25+20	44.81	99.58	0.17
	100%	25+25	49.83	99.67	0.43
	120%	25+30	54.93	99.88	0..42
	80%	10+8	18.16	100.93	0.30
ITZ	100%	10+10	20.14	100.74	0.32
	120%	10+12	22.18	100.83	0.21

Table 1.5: Result of % Recovery and % RSD of Terbinafine and Itraconazole for Absorbance ratio method (285 nm)

Drugs	Recovery level	Initial conc.(µg/m+ Conc. of std. drug added.(µg/ml)	Amount Recovered (n=3)	%Recovery	%RSD
TER	80%	25+20	44.95	99.88	0.50
	100%	25+25	49.72	99.45	0.44
	120%	25+30	54.93	99.87	0..21
	80%	10+8	18.01	100.08	0.13
ITZ	100%	10+10	19.99	99.96	0.12
	120%	10+12	22.07	100.3	0.13

Table 1.6: Result of % Recovery and % RSD of Terbinafine and Itraconazole for Absorbance ratio method (289 nm)

Drugs	Recovery level	Initial conc.(µg/m+ Conc. of std. drug added.(µg/ml)	Amount Recovered (n=3)	%Recovery	%RSD
TER	80%	25+20	44.62	99.16	1.13
	100%	25+25	49.79	99.59	0.47
	120%	25+30	54.72	99.49	0..57

	80%	10+8	17.97	99.87	0.22
ITZ	100%	10+10	19.97	99.88	0.24
	120%	10+12	21.92	99.65	0.50

3.4. Precision:

The precision of the method was expressed in terms of % relative standard deviation (%RSD). The %RSD values found to be less than 2 for intra-day and inter-day precision, which indicate that the proposed method is precise for analysis. The result is expressed in Table No:1.7, 1.8, 1.9 and 1.10.

Table 1.7: Result of Intra-day precision of Terbinafine and Itraconazole for Simultaneous equation method

Sr. No	**Concentration (µg/ml)**		**Absorbance* Mean ± S.D. (n = 3)**		**%RSD**	
	TER	ITZ	TER(289nm)	ITZ (282nm)	TER	ITZ
1	20	5	0.6855±0.0127	0.5595±0.0048	1.85	0.87
2	25	10	0.8486 ±0.0093	0.8480±0.0033	1.09	0.39
3	30	15	1.0173±0.00606	0.9224±0.0028	0.59	0.31

Table 1.8: Result of Inter-day precision of Terbinafine and Itraconazole for Simultaneous equation method

Sr. No	**Concentration (µg/ml)**		**Absorbance* Mean ± S.D. (n = 3)**		**%RSD**	
	TER	ITZ	TER(289nm)	ITZ (282nm)	TER	ITZ
1	20	5	0.6915±0.0050	0.5706±0.0029	0.72	0.51
2	25	10	0.8408 ±0.0045	0.8398±0.0104	0.54	1.24
3	30	15	1.0214±0.0052	0.9472±0.0076	0.56	0.81

Table 1.9: Result of Intra-day precision of Terbinafine and Itraconazole for Absorbance ratio method

Sr. No	**Concentration (µg/ml)**		**Absorbance* Mean ± S.D.**		**%RSD**	
	TER	ITZ	TER	ITZ	TER	ITZ

1	20	5	0.5094±0.0023(285nm)	0.5671±0.0045(285nm)	0.46(285nm)	0.80(285nm)
			0.6896±0.0044(289nm)	0.6677±0.0046(289nm)	0.64(289nm)	0.70(289nm)
2	25	10	0.7689±0.0049(285nm)	0.7667±0.0046(285nm)	0.64(285nm)	0.60(285nm)
			0.8391±0.0073(289nm)	0.7362±0.0047(289nm)	0.87(289nm)	0.64(289nm)
3	30	15	0.8177±0.0034(285nm)	0.9229±0.0044(285nm)	0.42(285nm)	0.48(285nm)
			1.0521±0.0045(289nm)	1.0192±0.0035(289nm)	0.43(289nm)	0.34(289nm)

Table 1.10: Result of Inter-day precision of Terbinafine and Itraconazole for Absorbance ratio method

Sr. No	**Concentration (µg/ml)**		**Absorbance* Mean ± S.D.**		**%RSD**	
	TER	ITZ	TER	ITZ	TER	ITZ
1	20	5	0.5132±0.0035(285nm)	0.5678±0.0039(285nm)	0.69(285nm)	0.69(285nm)
			0.6826±0.0035(289nm)	0.6309±0.0031(289nm)	0.52(289nm)	0.49(289nm)
2	25	10	0.7658±0.0051(285nm)	0.7671±0.0032(285nm)	0.67(285nm)	0.42(285nm)
			0.8019±0.0106(289nm)	0.7365±0.0032(289nm)	1.33(289nm)	0.43(289nm)
3	30	15	0.8185±0.0043(285nm)	0.9212±0.0048(285nm)	0.52(285nm)	0.52(285nm)
			1.4806±0.0047(289nm)	1.0224±0.0057(289nm)	0.32(289nm)	0.55(289nm)

3.5 .LOD AND LOQ

The LOD and LOQ for Terbinafine and Itraconazole were found in µg/ml and the result is expressed in Table No: 1.11 and 1.12.

Table 1.11: Result of LOD & LOQ of Terbinafine and Itraconazole for Simultaneous equation method

Sr. No.	**Drugs**	**LOD(µg/ml)**	**LOQ (µg/ml)**
1.	TER	0.445	1.35
2.	ITZ	0.629	1.90

Table 1.12: Result of LOD & LOQ of Terbinafine and Itraconazole for Absorbance ratio method

Sr. No.	**Drugs**	**LOD(µg/ml)**	**LOQ (µg/ml)**
1.	TER	0.539 (285nm)	1.636(285nm)
		0.374(289nm)	1.135(289nm)
2.	ITZ	0.418(285nm)	1.268(285nm)
		0.521(289nm)	1.579(289nm)

3.6. Ruggedness

The ruggedness of the proposed method was determined for 25µg/ml concentration of Terbinafine and 10µg/ml concentration of Itraconazole. The result was indicated as % RSD. The result expressed in Table No.1.13 and 1.14.

Table 1.13: Result of Ruggedness of Terbinafine and Itraconazole for Simultaneous equation method

Sr. No.	Drugs	Conc. (µg/ml)	Analyst I		Analyst II	
			SD	%RSD	SD	%RSD
1	TER	25	0.0062	0.74	0.0057	0.68
2	ITZ	10	0.0092	1.09	0.0058	0.68

Table 1.14: Result of Ruggedness of Terbinafine and Itraconazole for Absorbance ratio method

Sr. No.	Drugs	Conc. (µg/ml)	Analyst I		Analyst II	
			SD	%RSD	SD	%RSD
1	TER	25	0.0056(285nm) 0.0066(289nm)	0.73(285nm) 0.77(289nm)	0.0068(285nm) 0.0048(289nm)	0.89(285nm) 0.57(289nm)
2	ITZ	10	0.0040(285nm) 0.0038(289nm)	0.52(285nm) 0.52(289nm)	0.0045(285nm) 0.0045(289nm)	0.59(285nm) 0.61(289nm)

3.7. Robustness

The robustness of the method was determined by introducing small changes in UV parameters, such as changing in the wavelength ± 5.The result was indicated as % RSD. The result expressed in Table No.1.15, 1.16, 1.17.

Table 1.15: Determination of Robustness of Terbinafine and Itraconazole for Simultaneous Equation Method.

Sr. No.	Drugs	Wavelength	Mean Absorbance	SD	%RSD
1	TER	289	0.8550	0.014	1.68
2		284	0.7360	0.005	0.72
3		294	0.7613	0.009	1.21
4	ITZ	282	0.8335	0.011	1.35
5		277	0.7655	0.004	0.62

6	287	0.7443	0.004	0.53

Table 1.16: Determination of Robustness of Terbinafine and Itraconazole for Q- Method at 285 nm

Sr. No.	Drugs	Wavelength	Mean Absorbance	SD	%RSD
1	TER	285	0.7666	0.004	0.57
2		280	0.7250	0.003	0.50
3		290	0.8072	0.005	0.69
4	ITZ	285	0.7670	0.004	0.55
5		280	0.8199	0.003	0.40
6		290	0.7181	0.005	0.76

Table 1.17: Determination of Robustness of Terbinafine and Itraconazole for Q- Method at 289 nm

Sr. No.	Drugs	Wavelength	Mean Absorbance	SD	%RSD
1	TER	289	0.8388	0.003	0.41
2		284	0.7486	0.002	0.32
3		294	0.7633	0.003	0.46
4	ITZ	289	0.7354	0.004	0.67
5		284	0.7731	0.003	0.50
6		294	0.6986	0.003	0.56

3.8. Analysis Of Marketed Formulation (Terbiface Plus) By UV Spectrophotometric Methods

The percentage of Terbinafine and Itraconazole in the formulation was found to be 99.66% and 99.49% for Terbinafine and Itraconazole respectively for simultaneous equation method. For Q-method the percentage of Terbinafine and Itraconazole in the formulation was found to be 100.65% and 99.27% respectively as shown in Table 1.18.

Table 1.18: Results of analysis of tablet dosage forms containing Terbinafine and Itraconazole

Methods	**Simultaneous equation method**		**Absorbance ratio method**	
Drugs	**TER**	**ITZ**	**TER**	**ITZ**
Amount Recovered	24.91	9.94	25.16	9.92
% Assay	99.66	99.49	100.65	99.27

4. CONCLUSION

Two new, simple, sensitive and economical UV spectrophotometric methods were developed for the simultaneous analysis of Terbinafine and Itraconazole in bulk and in pharmaceutical

formulations. The developed methods were validated and from the statistical data, it was found that the methods were linear, accurate and precise and can be successfully applied for the analysis of pharmaceutical formulations without interference of excipients.

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