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SIMULTANEOUS ESTIMATION OF NORFLOXACIN AND TINIDAZOLE IN COMBINED TABLET DOSAGE FORM BY USING RP- HPLC METHOD

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Keywords:

RP- HPLC,
Gradient method, Simultaneous, Norfloxacin, Tinidazole

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ABSTRACT: Simultaneous estimation method for Norfloxacin and Tinidazole in tablet dosage form had been developed by RP- HPLC. Both the drugs come under the category of antimicrobials and prescribed frequently in combination. The developed method is a gradient method which gives retention time of Norfloxacin and Tinidazole as 3.8min and 4.8min respectively. The separation was carried out on Supelco C18 (25cm × 4.6mm, 5µ) column using 0.05M phosphate buffer (pH 3 adjusted with ortho- phosphoric acid) and acetonitrile as a mobile phase. The flow rate was 0.8mL/min and wavelength used was 300nm. The method was validated as per ICH guideline and found to be linear between the range of 1- 6µg/mL for Norfloxacin and 1.5- 9µg/mL for Tinidazole. The developed method was found to be rapid, accurate and reproducible and therefore can be applied for simultaneous estimation of both the drugs as API or tablet dosage form effectively.

INTRODUCTION: Now a day's lot of drugs come in the market as in combination form, which creates difficulty to the analyst for their estimation and also estimation of related substances likely to be present in those dosage formulations. This research focuses onto the simultaneous estimation of Norlfoxacin and Tinidazole in API or combined tablet form by RP- HPLC.

Drug profile:

1. Norfloxacin:

It is a first generation synthetic flouroquinolone which is used as a synthetic chemotherapeutic antibacterial agent [1, 2]. It is used to treat common as well as complicated urinary tract infections [3].

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Molecular Formula: $C_{16}H_{18}FN_3O_3$

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Chemical Name: 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinolinecarboxylic acid

Molecular Weight: 319.33 g/mol

Description: White to light-yellow crystalline powder

Solubility: Slightly soluble in ethanol, methanol. Very slightly soluble in water.

Melting Point: 220-221 °C

Category: Antibacterial

Mechanism of action: It is a broad spectrum antibiotic showing activity against gram negative and gram positive bacteria. It inhibits bacterial cell division by inhibiting DNA gyrase, topoisomerase II and IV which are necessary enzymes for causing separation of bacterial DNA [4]. A number of methods like capillary electrophoresis [5], HPLC [6], TLC [7], LC [8], voltammetry [9], ISE [10], differential

pulse polarography [11], fluorimetry [12] and potentiometric titration [13] have been widely used for the detection in pharmaceuticals.

2. Tinidazole: It is a derivative of 2-methylimidazole, which belongs to the class of nitroimidazole antibiotics. It is an anti-parasitic drug and used for a treatment of various amoebic and parasitic infections [14].

Molecular Formula: $C_8H_{13}N_3O_4S$

Chemical Name: 1-(2- ethylsulfonylethyl)-2-methyl-5-nitro-imidazole

Molecular Weight: 247.27 g/mol

Description: White or pale yellow crystalline powder

Solubility: Practically insoluble in water, soluble in aetone and in methylene chloride, sparingly soluble in methanol

Melting Point: 127-128 °C

Category: Antiprotozoal, Antibacterial

Mechanism of action: Tinidazole is a prodrug and antiprotozoal agent. The nitro group of Tinidazole is reduced in Trichomonas by a ferredoxin-mediated electron transport system. The free nito radical generated as a result of this reduction is believed to be responsible for the antiprotozoal activity. It is suggested that the toxic free radicals covalently bind DNA, causing DNA damage and leading to cell death. The mechanism by which Tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known, though it is probably similar.

Literature survey reveals that Tinidazole is official in USP [15] and BP [16]. Tinidazole was determined by high performance liquid chromatography [17], spectrophotometry [18], voltammetry [19], capillary electrophoresis [20], flow injection analysis [21] and gas chromatography with FID [22].

Objective:

- To develop a RP-HPLC assay method for the estimation of Norfloxacin and Tinidazole.
- To validate the developed RP-HPLC method as per ICH guidelines.
- To apply the developed RP-HPLC method on marketed formulation.

MATERIALS AND METHODS:

Instrumentation: This research was carried out on Shimadzu HPLC with the help of the software 'LC solution'. All the glass wares used were of 'A' grade.

Reagents and chemicals: The API of Norfloxacin was obtained from Cipla Pvt. Ltd. Vikhroli, Mumbai and Tinidazole was obtained from Aarti Pharma, Mumbai as a gift sample. The tablet formulation used was of a brand name 'Nor-TZ' containing norfloxacin (400mg) and tinidazole (600mg). All other chemicals used were of HPLC grade.

Instrumentation:

TABLE 1: INSTRUMENTS USED

S.no.	Name of the instrument	Company
1	HPLC	Shimadzu
2	Weighing balance	Premier weighing system
3	pH meter	DBK Digital pH meter
4	Sonicator	Oscar

Preparation of 0.05 M Potassium dihydrogen orthophosphate (pH 3.0): Accurately weighed 6.80 g of Potassium dihydrogen orthophosphate, dissolved in 1000 ml of water and adjusted the pH with o-phosphoric acid to 3.0 ± 0.05. The solution was filtered using 0.45 µ membrane filter.

Preparation of Mobile Phase: Phosphate buffer was prepared using Potassium dihydrogen orthophosphate (0.05 M) and pH was adjusted to 3.0 with Orthophosphoric acid. Then it was sonicated and filtered using 0.45 µ membrane filter. Different ports were used for buffer and acetonitrile to run the gradient mobile phase.

Preparation of diluents: 0.05M Phosphate buffer (ph=3.0) and acetonitrile were mixed accurately in the ratio of 50:50 (v/v) and degassed by sonication.

Preparation of standard stock solution (Norfloxacin 400 µg/ml and Tinidazole 600 µg/ml): About 40 mg of Norfloxacin and 60 mg of Tinidazole were accurately weighed and transferred into 100 ml volumetric flask respectively. The solution was sonicated to dissolve and diluted up to the volume with the diluent and filtered thrugh 0.45µ membrane filter for interference free solution.

Preparation of standard solution (Norfloxacin 4 µg/ml and Tinidazole 6 µg/ml): About 1 ml of standard stock solution was transferred into 100 ml volumetric flask and diluted up to the volume with diluent and the solution was then filtered through 0.45 µm membrane filter.

Preparation of Sample stock solution (Norfloxacin 400µg/ml and Tinidazole 600µg/ml): For sample stock preparation, tablet containing combination of Norfloxacin and Tinidazole was taken. Total 10 tablets were weighed and quantity equivalent to 400mg of Norfloxacin and 600mg of Tinidazole was weighed. This is transferred to 1000mL volumetric flask. Make up the volume with the diluents to prepare solution containing 400µg/mL of Norfloxacin and 600 µg/mL of Tinidazole.

Preparation of Sample Solution (Norfloxacin 4µg/ml and Tinidazole 6µg/ml): From the above stock solution 1mL was transferred in 100mL volumetric flask and diluted upto the mark with the diluent to prepare 4 µg/mL of Norfloxacin and 6 µg/mL of Tinidazole.

Final method:

Reagents:

1) Potassium dihydrogen orthophosphate (AR grade)
2) Orthophosphoric acid (GR grade)
3) Water (HPLC grade or equivalent)
4) Acetonitrile (HPLC grade)

TABLE 2: CHROMATOGRAPHIC CONDITIONS

Column	Supelco C18 (25cm X 4.6mm X 5µ)		
Wavelength	300 nm		
Flow Rate	0.8 ml/min		
Column Oven Temperature	30 °C		
Run time	7 minutes		
Injection Volume	10 µl		
Retention time of Norfloxacin	3.8 minutes		
Retention time of Tinidazole	4.8 minutes		
Mobile Phase (Gradient)	**Time(min)**	**A%**	**B%**
A: 0.05M Phosphate buffer (pH=3 adjusted with OPA)	0.01	60	40
	2.5	90	10
B: Acetonitrile (HPLC grade)	3.5	70	30
	4.0	60	40
	7.0	60	40
	7.01	Controller	Stop

Method Validation: [23]

Specificity: To ensure the absence of interference from blank in Norfloxacin and Tinidazole drug product. One blank solution of diluent was injected and Norfloxacin and Tinidazole were injected individually.

Acceptance criteria: There should be no interference from blank at the retention time of Norfloxacin and Tinidazole.

Accuracy: To evaluate the recovery at each level. Working standards of the drugs were prepared at three different concentrations (levels) 80 %, 100 % and 120 %. The measurements were done in triplicates. For Norfloxacin 4µg/mL was considered as 100%, therefore 80% became 3.2µg/mL and 120% of 4.8µg/mL. About 0.8mL, 1 ml and 1.2mL of standard stock solution was transferred into different 100 ml volumetric flasks and diluted up to the volume with diluent for preparing 80%, 100% and 120% solutions respectively.

Acceptance criteria: Individual % recovery of Norfloxacin and Tinidazole at each level should be between 98% - 102% and % RSD should not be more than 2.0 at each level.

Precision:

System precision: Prepared and injected six replicates of standard solution as per the proposed method of analysis into HPLC system. Calculated the mean, SD and % RSD for peak areas of Norfloxacin and Tinidazole. Standard solution was

of 4µg/mL Norfloxacin and 6µg/mL of Tinidazole mixture.

Method precision: Six samples of same strength as that of standard solution of Norfloxacin and Tinidazole were prepared and analyzed as per the test method. The % assay and % RSD for Norfloxacin and Tinidazole in six samples was calculated.

Intermediate precision or Ruggedness:
Ruggedness of the method was verified by analyzing six samples of the same concentration used for method precision as per proposed method by different analysts, different column serial number on different day. The % assay and % RSD of Norfloxacin and Tinidazole in tablets was determined.

Acceptance criteria: % RSD and cumulative % RSD should not be more than 2.0 and % assay should be within the specification limit.

Linearity: Linearity of Norfloxacin and Tinidazole was performed using standard solution in the range of 1-6 µg/ml and 1.5- 9 µg/ml for RP- HPLC.

Acceptance criteria: Correlation coefficient (R^2) should be not less than 0.999.

Range: For range, data shall be considered from linearity and accuracy.

Acceptance criteria: Correlation coefficient (R^2) should be not less than 0.999 and individual % recovery of Norfloxacin and Tinidazole at each level should be between 98 % - 102 %.

Robustness: Robustness of the method was evaluated by changing the flow rate by ± 10 %, by changing the column temperature by ± 5 °C and by changing the pH of buffer by ± 0.1 units.

Acceptance criteria: % RSD should be not more than 2.0

LOD (Detection limit): The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. For assay purpose limit of detection was not considered as the validation parameter as per ICH guideline.

LOQ: The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products. Therefore this is not considered as the validation parameter for assay purpose.

RESULT AND DISCUSSION: Before validation of the developed method, analysis of blank solution (only mobile phase), standard solution (mixed standard) and sample solution (tablet mixture) was carried out. Following were the results obtained.

Blank Solution:

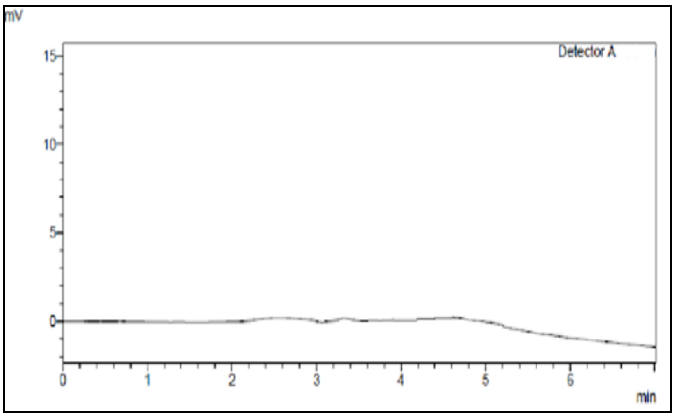

FIG. 1: CHROMATOGRAM OF BLANK SOLUTION

Observation: It was found that the blank solution does not show any interference of characteristic peak and therefore can be used for estimation of drugs.

Standard Solution:

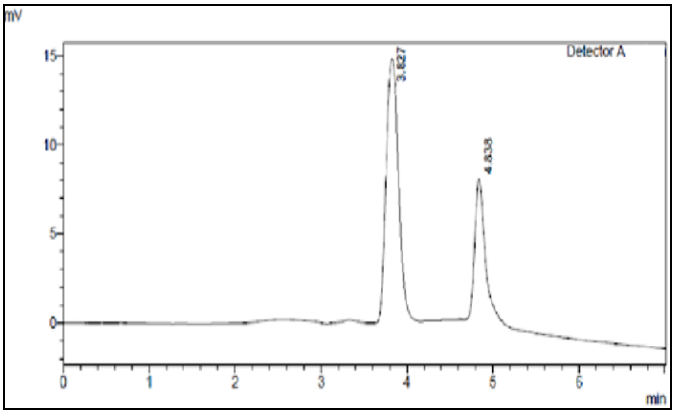

FIG. 2: CHROMATOGRAM OF STANDARD SOLUTION (NORFLOXACIN 4µg/mL AND TINIDAZOLE 6 µg/mL)

Sample Solution:

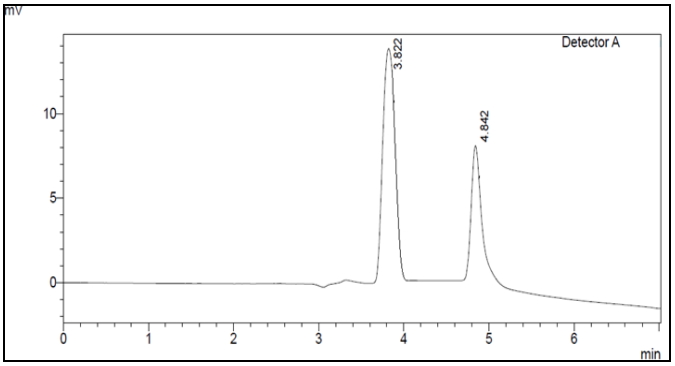

FIG. 3: CHROMATOGRAM OF SAMPLE SOLUTION (NORFLOXACIN 4µg/mL AND TINIDAZOLE 6 µg/mL)

Method validation: Specificity: Chromatograms of blank solution i.e. diluent and Norfloxacin and Tinidazole individually were compared.

DISCUSSION: From above chromatograms it was found that there were no interferences from the blank solution at the retention time of Norfloxacin and Tinidazole. Therefore it was concluded that the method was specific for the detection of Norfloxacin and Tinidazole.

Accuracy: Initially a standard solution was analyzed and for accuracy studies, 80%, 100% and 120% solutions of sample were prepared. From these areas of Norfloxacin and Tinidazole at all 3 concentrations were considered for the calculations and amount found was compared with the amount added for preparing these concentrations.

TABLE 3: ACCURACY STUDIES OF NORFLOXACIN

Level	Amount taken (mg)	Area	% Recovery	Mean % recovery	Amount found (mg)	%RSD
I (80%)	3200	149462	100.24	100.10%	3203.2	0.18%
	3200	149358	100.17		3205.4	
	3200	148960	99.90		3196.8	
II (100%)	4000	187106	100.35	100.36%	4014.4	0.03%
	4000	187211	100.40		4016	
	4000	187100	100.34		4013.6	
III (120%)	4800	222710	99.59	99.48%	4780.3	0.19%
	4800	222721	99.60		4780.8	
	4800	221988	99.27		4764.9	

TABLE 4: ACCURACY STUDIES OF TINIDAZOLE

Level	Amount taken (mg)	Area	% Recovery	Mean % recovery	Amount found (mg)	%RSD
I (80%)	4800	50771	100.70	100.69%	4833.6	0.11%
	4800	50825	100.80		4838.4	
	4800	50712	100.58		4827.8	
II (100%)	6000	63659	101.06	101.14%	6063.6	0.10%
	6000	63741	101.16		6069.6	
	6000	63779	101.22		6073.2	
III (120%)	7200	74925	99.06	99.30%	7132.3	0.21%

Discussion:

1. % Recovery of Norfloxacin was found to be in the range of 99.48%- 100.10% and %RSD was found to be between 0.03%- 0.19%.
2. % Recovery of Tinidazole was found to be in the range of 99.30%- 101.14% and %RSD was found to be between 0.10%- 0.21%.
3. From the above observation it was concluded that the method is accurate for the simultaneous determination of Norfloxacin and Tinidazole in a tablet dosage form.

Precision: Precision was performed in three different levels as system precision, method precision and intermediate precision i.e. ruggedness.

System precision: System precision was performed by injecting six replicates of standard solution of 10µg/mL.

TABLE 5: RESULTS OF SYSTEM PRECISION

Drug Name	Sr. No.	Area	Mean	%RSD
Norfloxacin	1	186452		
	2	186880		
	3	186289	186142.5	0.37%
	4	184929		
	5	185855		
	6	186450		
Tinidazole	1	63551		
	2	63762		
	3	63924	63660.5	0.25%
	4	63577		
	5	63650		
	6	63499		

Discussion: The % RSD values indicate an acceptable level of precision of the analytical system for the assay of Norfloxacin and Tinidazole. The % RSD values on lower side indicate that there exists only minimum variation in the results and thus the system precision is validated.

Method precision: Method precision was performed by injecting six samples of same strength as that of standard solution of Norfloxacin and Tinidazole (10µg/ mL). Results obtained were as follows:

TABLE 6: RESULTS OF METHOD PRECISION

Drug Name	Sr. No.	Area	Mean	%RSD
Norfloxacin	1	187241		
	2	187168		
	3	187359	187265.5	0.06%
	4	187294		
	5	187105		
	6	187426		
Tinidazole	1	64658		
	2	64853		
	3	63765	64434.17	0.61%
	4	64684		
	5	64359		
	6	64286		

Intermediate precision (Ruggedness): For intermediate precision different analyst on different day analysis was carried out.

TABLE 7: PARAMETERS FOR INTERMEDIATE PRECISION

Sr. no.	Parameter	Specification
1.	Different analyst	Analyst II
2.	Different day	Interday precision

TABLE 8: % RSD CALCULATIONS FOR INTERMEDIATE PRECISION

Drug Name	Sr. No.	Area	Mean	%RSD
Norfloxacin	1	187049		
	2	187137		
	3	187164	187142.7	0.04%
	4	187281		
	5	187098		
	6	187127		
Tinidazole	1	63941		
	2	64268		
	3	63671	63914.5	0.76%
	4	63467		
	5	64684		
	6	63456		

Discussion: The % RSD values for intermediate precision were found to be within the specified limit. This indicated that the method is rugged and can be used to analyze the formulations containing Norfloxacin and Tinidazole effectively in any given condition.

Linearity: Linearity studies were performed at six different concentrations. The linearity data was calculated on individual drug basis and checked for the R^2 value.

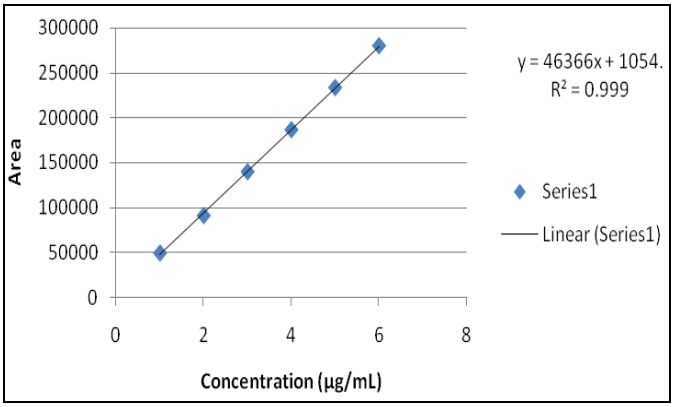

FIG.4: LINEARITY PLOT OF NORFLOXACIN

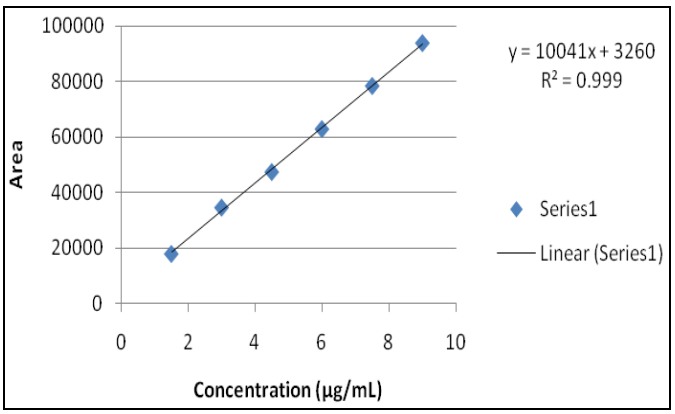

FIG.5: LINEARITY PLOT OF TINIDAZOLE

Discussion: The correlation coefficient (R^2) values for Norfloxacin and Tinidazole were found to be within acceptable limits. This indicated that the method is linear between the concentrations 1 µg/ml and 6 µg/ml for Norfloxacin and 1.5 µg/ml and 9 µg/ml for Tinidazole.

Range: It was inferred from the data of accuracy and linearity that the established range for the estimation of Norfloxacin and Tinidazole was between the concentration range of 25 % to 150 %. Thus, the range was established as 1 µg/ml and 6µg/ml for Norfloxacin and 1.5 µg/ml and 9 µg/ml for Tinidazole.

Robustness: Deliberate variations were made in the method and the % RSD was calculated. Plus flow rate, minus flow rate, plus pH, minus pH, plus temperature and minus temperature were the variations that were analyzed.

TABLE 9: ROBUSTNESS OF NORFLOXACIN

Sr. No.	Parameter	Area	Mean	%RSD
1	Plus pH (3.1)	187046		
		187083	187055.3	0.01%
		187037		
2	Minus pH (2.9)	187098		
		187076	187085	0.01%
		187081		
3	Plus	187214		
	Temperature	187245	187245	0.02%
	(35°C)	187276		
4	Minus	187286		
	Temperature	187257	187264	0.01%
	(25°C)	187249		
5	Plus Flow	187135		
	(0.9mL/min)	187168	187144	0.01%
		187129		
6	Minus Flow	187245		
	(0.7mL/min)	187267	187253.3	0.01%
		187248		

TABLE 10: **ROBUSTNESS OF TINIDAZOLE**

Sr. No.	Parameter	Area	Mean	%RSD
1	Plus pH (3.1)	64821		
		64764	64809.3	0.06%
		64843		
2	Minus pH (2.9)	64673		
		64764	64794.3	0.21%
		64946		
3	Plus	64483		
	Temperature	64975	64781.6	0.41%
	(35°C)	64887		
4	Minus	64798		
	Temperature	64999	64888	0.16%
	(25°C)	64867		
5	Plus Flow	64523		
	(0.9mL/min)	64258	64313.3	0.29%
		64159		
6	Minus Flow	64486		
	(0.7mL/min)	64376	64538.3	0.30%
		64753		

Discussion: Small but deliberate variations were made in the method parameters and it was found that % RSD values for all the variations were in acceptable limits. This indicated that the method is robust and that it can be used within small variations of flow rate, pH and temperature without having a major effect on the results of % assay values.

CONCLUSION: The method was developed and validated which concluded that the method is linear, simple, accurate, precise and rugged. Thus, the proposed method can be effectively applied for analysis of Norfloxacin and tinidazole in bulk dosage forms as well as in combined tablet dosage form.

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