IJPSR (2015), Vol. 6, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 June 2014; received in revised form, 12 August, 2014; accepted, 22 September, 2014; published 01 January, 2015

FACILE SPECTROPHOTOMETRIC DETERMINATION OF METRONIDAZOLE AND SECNIDAZOLE IN PHARMACEUTICAL PREPARATIONS BASED ON THE FORMATION OF DYES

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Keywords:

Spectrophotometry, Metronidazole, Secnidazole, Diazotization, naphthylamine, 2,5-Dihydroxy α- Benzoic Acid

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ABSTRACT: A rapid and sensitive spectrophotometric method is proposed for the determination of Metronidazole and Secnidazole drugs. The method depends on the reduction of Metronidazole and Secnidazole molecules with zinc dust and hydrochloric acid followed by diazotization and coupling with α-naphthylamine to give red colored chromogens easily measured spectrophotometrically at λ_{max} = 510 nm or coupling with 2,5- dihydroxy benzoic acid at λ_{max} = 518nm. The Sandell's sensitivity, the molar absorptivity, correlation coefficient and the regression equation were calculated. Under optimized experimental conditions Beer's law is obeyed in the concentration range 3-30 and 2-12 µg/ml for Secnidazole and Metronidazole; respectively with α-naphthyl amine as a coupling agent. Also, by using 2, 5-dihydroxybenzoic acid as a coupling agent, the concentrations obtained were 5-50 µg/ml for both Secnidazole and Metronidazole. Both techniques were applied successfully for the analysis of Metronidazole and Secnidazole in tablets form. These methods are recommended for quality control and routine analysis where time, cost effectiveness and high specificity of analytical techniques are of great importance.

INTRODUCTION: Nitroimidazoles are a class of veterinary drugs used for the treatment and prevention of certain bacterial and protozoal diseases in poultry as well as for swine dysentery. Their main compounds include metronidazole (MNZ), ornidazole (ONZ) and secnidazole (SNZ) [1]. Metronidazole (2-methyl-5- nitroimidazole – 1 - ethanol) and secnidazolel - (2-mehyl - 5 nitroimidazole – 1 - yl propan – 2 - ol) are used as antiprotozoal, antiamebic and antibacterial drugs [2]. Excellent reviews have been published on the activity and pharmacokinetics of these drugs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(1).103-10

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(1).103-10

Recently, spectrophotometric methods have been widely used in pharmaceutical analysis successfully [3]. Several methods have been reported for determination of both Metronidazole and Secnidazole which includes potentiometric [4, 5], polarographic [6, 7], CPG [8], supercritical Fluid Chromatography [9], TLC [10], HPLC [11-14], Voltammetric [15], derivative spectrophotometry [16-18], flow injection analysis [19] and Spectrophotometry [20-30].

Most of the spectrophotometric methods reported suffer from the disadvantage, like narrow range of determination, requires heating or extraction, long time for the reaction to complete, use of non-aqueous systems and stability of the colored product formed, etc. The purpose of our present investigation is to develop and validate a new simple, selective accurate and rapid

spectrophotometric assay for the determination of Metronidazole and Secnidazole in either pure form or in its pharmaceutical formulations. The method is based on the reduction of Metronidazole and Secnidazole molecules with zinc dust and hydrochloric acid followed by diazotization and coupling with coupling agents 2, 5-dihydroxybenzoic acid or α-naphthyl amine.

The advantages of the present work that the reagents used are easily available and the chemistry of these reagents is already well established. The reactions involved with these reagents are simple, rapid and sensitive in the range of determination compared with other established spectrophotometric methods. The present work which gives thoroughly comparable data is simple, accurate, rapid and precise. The common excipients used as additives in pharmaceuticals do not interfere in the proposed methods.

MATERIALS AND METHODS:

Apparatus

- An evolution 300 UV-VIS. spectrophotometer with 1.0 cm matched cells fitted with Vision Pro software of Thermo Electron Corporation (Cambridge, UK) was used for electronic spectral measurements.
- To obtain pH readings throughout the experimentation, a microprocessor pH meter (HANNA HI 211) was used.

MATERIALS AND REAGENTS:

All chemicals used were of analytical - reagent grade. α-naphthylamine and 2, 5-dihydroxybenzoic acid were purchased from Sigma. Metronidazole and Secnidazole were obtained from Aldrich Company. Sodium nitrite and sodium hydroxide was purchased from prolabo. All other reagents and solvent were of analytical-reagent grade.

Standard Solutions:

Accurately (100 mg) Metronidazole or Secnidazole was transferred to a 100 ml beaker. 1 g of zinc dust was added along with 20 ml of 1M hydrochloric acid. The solution was stirred and left for 1 hour at room temperature. The filtrate was diluted with water to 100 ml in a volumetric flask. The working standard solution of the reduced Metronidazole and Secnidazole containing 100µg/ml was prepared by further dilution. A 1 % α-naphthylamine or 1% 2, 5-dihydroxybenzoic acid in 1M HCl and 10 % sodium hydroxide solution were kept in amber-glass volumetric flasks. A 1% sodium nitrite solution was prepared separately in double distilled water.

General Procedure:

Aliquots of the working standard solution of reduced Metronidazole or Secnidazole were transferred into 10 ml calibrated flasks. 1 milliliter of 1 M HC1 was added, cooled in an ice bath then 1ml of 1% $NaNO_2$ was added. The solution was stirred for 2 minutes and 1 ml of 1% α-naphthylamie, 1.5 ml of NaOH and 3 ml of absolute ethanol was added then the solution was diluted using double distilled water.

While, the above procedure was carried out in case of 2, 5-dihydroxybenzoic acid as described. Aliquots of the working standard solution of reduced Metronidazole or reduced Secnidazole were transferred into 10 ml calibrated flasks, 1.5 ml of 1 M HC1 was introduced then 1 ml of 1% $NaNO_2$ was added after cooling in an ice bath. The solution was stirred for 2 min. and 1ml of 1% 2, 5-dihydroxybenzoic acid, 1ml of 10% NaOH and 2 ml of absolute ethanol was added then the solution was diluted using double distilled water.

Analysis of Pharmaceutical Preparations:

Ten tablets were powdered and mixed thoroughly. An amount equivalent to 100 mg of the drug was reduced as mentioned before and the filtrate was made up to 100 ml and an aliquot of this solution was treated as described above for pure sample. The amount of each drug was calculated from the calibration graph.

Interferences from Excipients:

The effect of interfering common excipients such as uric acid, vitamin C, glucose, carboxy methyl cellulose and lactose on 50 mg Metronidazole or 50 mg Secnidazole was studied. The procedure was carried out as described under general procedure.

RESULTS AND DISCUSSION:

Metronidazole and Secnidazole showed weak absorption bonds in UV-range. For this reason, the proposed spectrophotometric method for the

determination of Metronidazole and Secnidazole is based on the reduction of the nitro group to an amino group with zinc dust and hydrochloric acid followed by diazotization and coupling with 2, 5-dihydroxbenzoic acid or with α-naphthylamine to give red colored products.

Spectral characteristics and Reaction Mechanism:

The absorption spectra of the red colored product with λ_{max} = 510 nm in case of α-naphthylamine or with λ_{max} = 518 nm in case of 2, 5-dihydroxybenzoic acid. The stability of colored azo products lasts for 3 days in case of α–naphthylamine or 2, 5-dihydroxybenzoic acid compared with 2 days in case of β-naphtol as reported in literature [29]. Indicating high stability of colored azo products for our proposed methods. The absorption spectra of reduced form of Metronidazole and the spectrum of the red azo product obtained at λ_{max} = 518 nm were showed in **Figure 1**. The reagent blank has practically negligible absorption at this wave length.

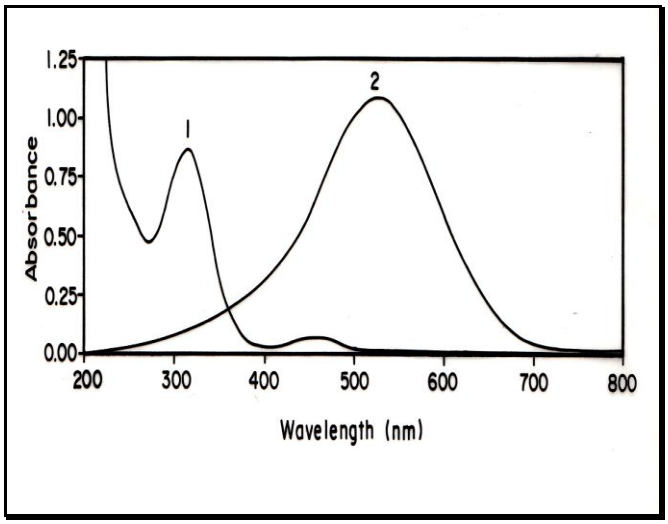
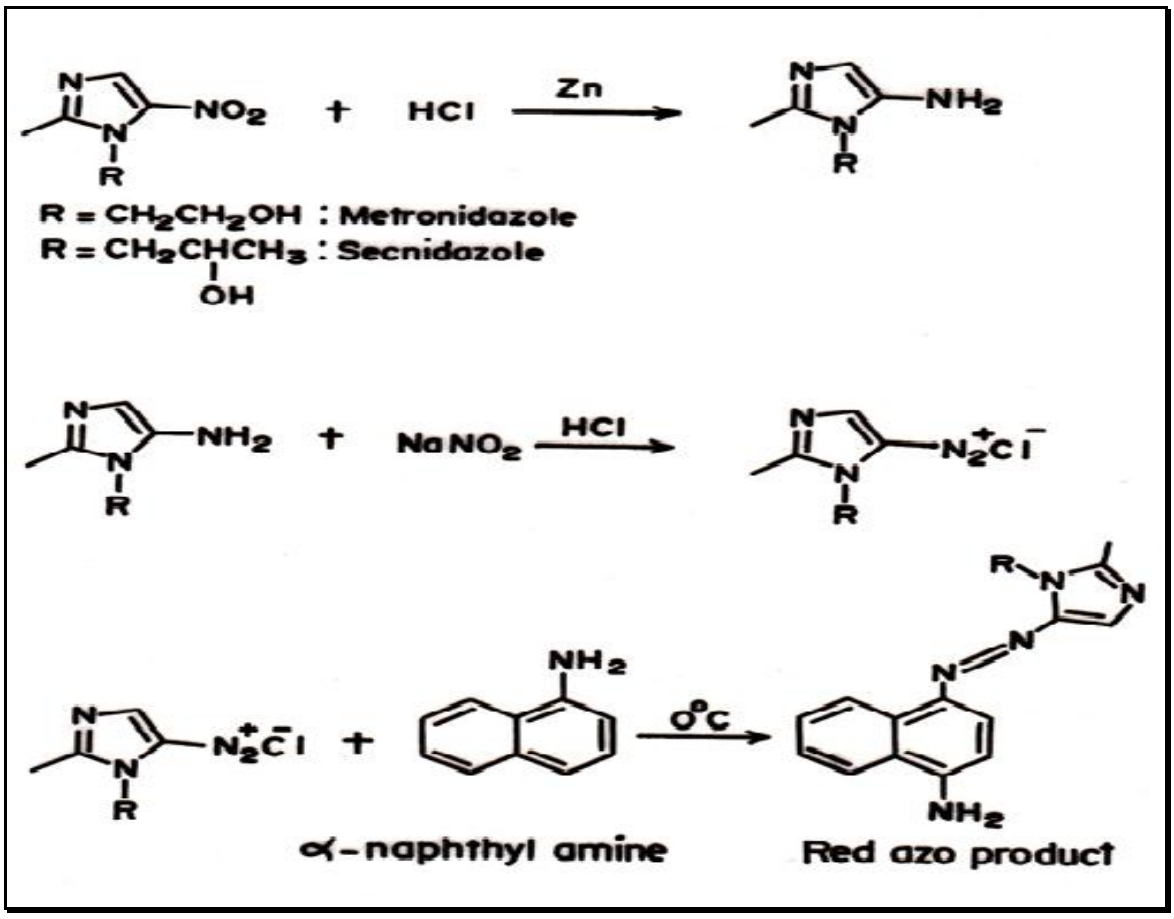
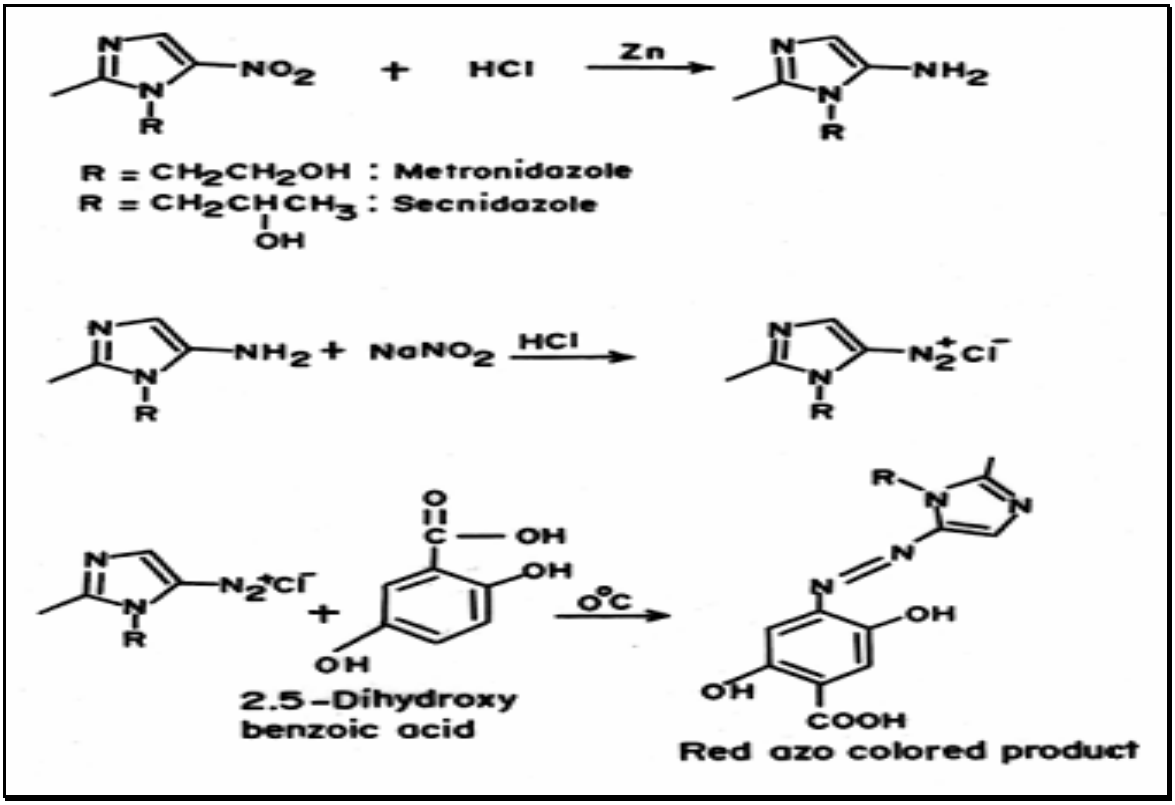


FIGURE 1: ABSORPTION SPECTRA OF 40µg/ml METRONIDAZOLE DRUG IN THE REDUCED FORM (1) AND THE SPECTRUM OF THE RED AZO PRODUCT OBTAINED (2) IN PRESENCE OF 0.5 ml OF 1 M HCl, 1ml OF 2% 2, 5-DIHYDROXYBENZOIC ACID, 1.5 ml OF 20% NaOH, 2ml ETHANOL AND 1 ml OF 2% $NaNO_2$ AT 25°C

The stoichiometric equations derived were shown in **schemes 1** and **2**.



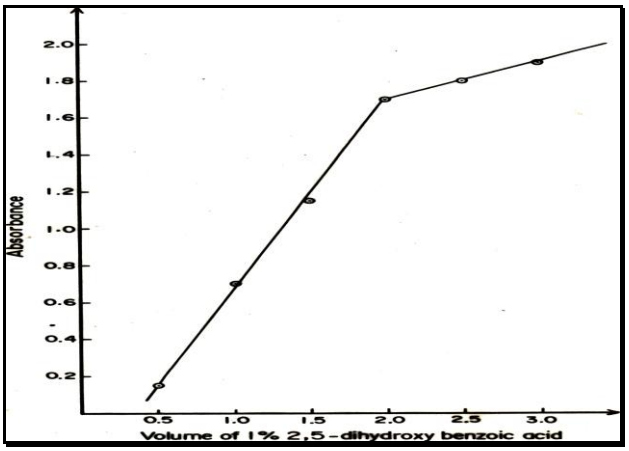
SCHEME 1: REACTION SEQUENCE FOR THE FORMATION OF AZO COLORED PRODUCT USING α-NAPHTHYL AMINE AS COUPLING AGENT



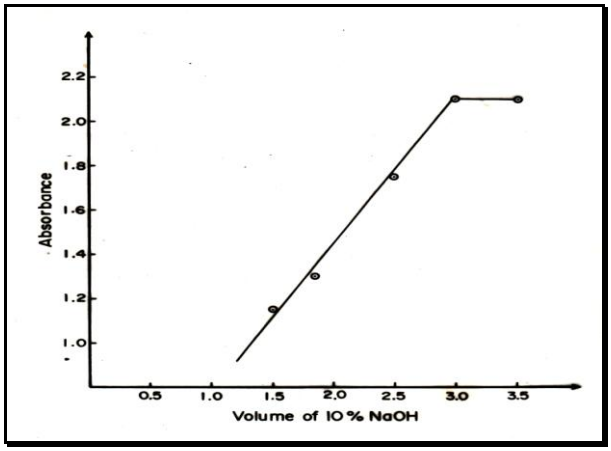
SCHEME 2: REACTION MECHANISM FOR THE FORMATION OF AZO COLORED PRODUCT USING 2, 5-DIHYDROXYBENZOIC ACID AS COUPLING AGENT

Optimization of reaction conditions

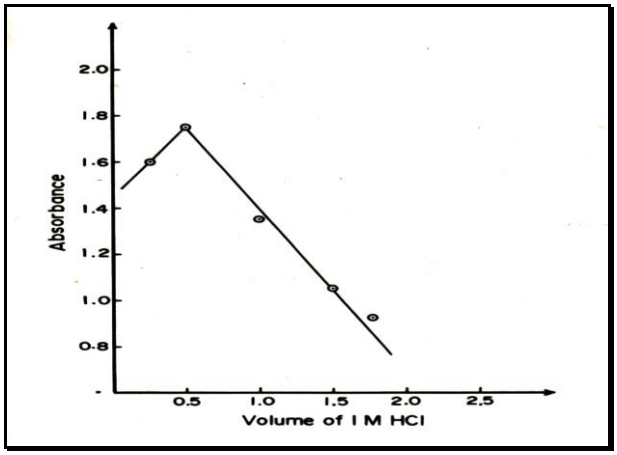
In order to optimize the conditions, we have investigated number of parameters such as the coupling agent concentrations, effect of HCl, effect of $NaNO_2$ and effect of NaOH as shown in **Figure 2**. The optimal conditions were established by changing one variable and observing its effect on the absorbance of the colored product. The investigations were carried out to achieve maximum color development in the quantitative determination of studied drugs. The factors affecting color development reproducibility, sensitivity and conformity with Beer's law were studies. It was found that, 0.5–3 ml of 1 M HC1, 0.2–1.5 ml of 1 % $NaNO_2$ solution, 0.4–2 ml of α-naphthylamine 1%, 0.5–2.5 ml of 10 % NaOH solution were necessary in case of α-naphthylamine as coupling agent. While, the use of 2,5-dihydroxy benzoic acid as a coupling agent required, 0.5–2.0 ml of 1 M HC1, 0.5–3 ml of 1% $NaNO_2$ solution, 0.5–2.5 ml of 1% dihydroxy benzoic acid , 1–3 ml of 10% NaOH solution to achieve maximum colour intensity as shown in **Figure 2**.



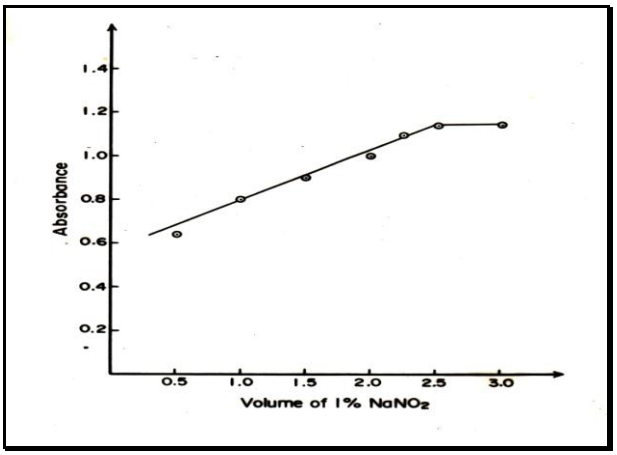
A- EFFECT OF VOLUME OF 1% 2, 5-DIHYDROXY BENZOIC ACID



B- EFFECT OF VOLUME OF 10% NaOH



C- EFFECT OF VOLUME OF 1 M HCl



D- EFFECT OF VOLUME OF 1% $NaNO_2$

FIGURE 2. REACTION CONDITIONS OF THE COLOR FORMATION OF METRONIDAZOLE WITH 2, 5-DIHYDROXY BENZOIC ACID AS A COUPLING AGENT.

Quantifications of Drugs:

Under the optimum experimental conditions attained, the standard calibration curve as shown in **Figures 3** and **4** obeyed Beer's law over the Metronidazole and Secnidazole concentration range (5–50µg/ml) for both drugs in case of 2, 5-dihydroxy benzoic acid.

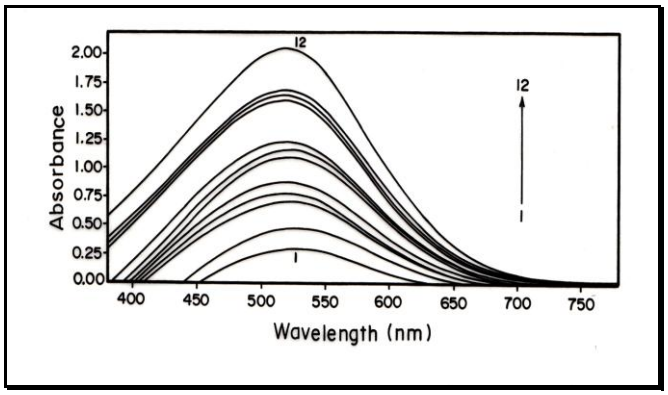


FIGURE 3. ABSORPTION SPECTRA OF SECNIDAZOLE DRUG IN THE CONCENTRATION RANGE FORM (5-50)µg/ml FROM (1 -12) IN PRESENCE OF 1 ml of 1 M HCl,1ml OF 2% 2, 5-DIHYDROXYBENZOIC ACID , 1ml of 10% NaOH, 2ml ETHANOL AND 1 ml of 2% $NaNO_2$ AT 25°C

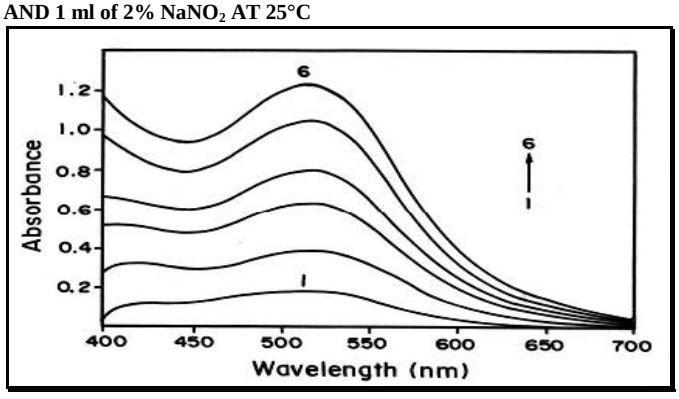


FIGURE 4: ABSORPTION SPECTRA OF METRONIDAZOLE DRUG IN THE CONCENTRATION RANGE FORM (5 – 50) µg/ml FROM (1 - 6) IN PRESENCE OF 0.5 ml of 1 M HCl, 1ml of 2% 2, 5-DIHYDROXYBENZOIC ACID , 1.5 ml of 10% NaOH, 2ml ETHANOL AND 1ml of 2% $NaNO_2$ AT 25°C

Similarly, Beer's law is obeyed over the metronidazole concentration range (2–12µg/ml) and over the Secnidazole concentration range (3–30µg/ml) in case of α-naphthylamine.

The details of optical characteristics were summarized in **Tables 1 and 2**. It was observed from these Tables that the proposed method was validated by determining various optical parameters, in case of two coupling agents used 2, 5-dihydroxy benzoic acid and α - naphthylamine. It was noticed that the two procedures have been valid for determination of drugs under consideration with two mentioned coupling agents.

TABLE 1: REGRESSION ANALYSIS DATA AND SUMMARY OF PARAMETERS FOR THE SPECTROPHOTOMETRIC DETERMINATION OF METRONIDAZOLE AND SECINDAZOLE USING α–NAPHTHYL AMINE AS A COUPLING AGENT

Parameters / characteristics	Secnidazole	Metronidazole
Colour	Red	Red
λ_{max} (nm)	510	510
Stability (in days)	3	3
Beer's law range (µg/ml)	3–30	2–12
Ringbom range (µg m^{-1})	6-27	3-10
Limit of Detection (µg/ml)	0.049	0.1142
Limit of Quantification (µg/ml)	0.164	0.3805
Molar absorptivity (L. mol^{-1} cm^{-1})	3.56×10^3	15.02×10^3
Sandell's sensitivity (µg cm^{-2})	0.0529	0.0114
Regression equation[a]	--	--
Slope (a)	0.019	0.088
Intercept (b)	0.127	0.055
Correlation coefficient	0.9994	1.0009
RSD (%)[b]	0.1125	0.237

[a]y = a x + b where x is the conc. of Metronidazole or Secnidazole in (µg/ml)

[b]Ten replicates.

TABLE 2: REGRESSION ANALYSIS DATA AND SUMMARY OF PARAMETERS FOR THE SPECTROPHOTOMETRIC DETERMINATION OF METRONIDAZOLE AND SECINDAZOLE USING 2, 5-DIHYDROXYBENZOIC ACID AS A COUPLING AGENT

Parameters / characteristics	Secnidazole	Metronidazole
Colour	Violet	Violet
λ_{max} (nm)	520	518
Stability (in days)	3	3
Beer's law range (µg/ml)	5–50	5–50
Ringbom range (µg m^{-1})	10–45	10–45
Limit of Detection (µg/ml)	0.0091	0.0214
Limit of Quantification (µg/ml)	0.0303	0.0649
Molar absorptivity (L. mol^{-1} cm^{-1})	5.8×10^3	4.4×10^3
Sandell's sensitivity (µg cm^{-2})	0.0031	0.0114
Regression equation[a]	-	-
Slope (a)	0.024	0.188
Intercept (b)	0.683	0.319
Correlation coefficient	0.9997	0.9993
RSD (%)[b]	0.088	0.011

[a]y = a x + b where x is the concentration of metronidazole or secnidazole in (µg/ml)

[b]Ten replicates.

The apparent molar absorptivity (ε) of the resulting colored product in the proposed method with α–naphthyl amine as a coupling agent was found to be 3.50×10^3 and 15.02×10^3 $L.mol^{-1}cm^{-1}$ for Secnidazole and Metronidazole drugs; respectively as shown in **Table 1**. A comparison of these values with other values of molar absorptivities obtained in the literature which were 6.60×10^3 and 2.68×10^3 $L.mol^{-1}cm^{-1}$ for both Secnidazole and Metronidazole; respectively using β-naphtol as coupling agent [29]. Also, by comparing the molar absorptivity value (ε) of the resulting colored product in our proposed method with excellent and new coupling agent 2,5-dihydroxybenzoic acid were found to be 5.8×10^4 and 4.4×10^4 $L.mol^{-1}cm^{-1}$for Secnidazole and Metronidazole; respectively.

A comparison of our obtained values of molar absorpivities and Beer's law range obtained with other values reported in literature [29, 30] showed that our obtained values could be very satisfactory for the analysis of both Seccnidazole and Metronidazole drugs at concentration levels examined as shown in **Table 3**.

TABLE 3: APPARENT MOLAR ABSORPTIVITIES (ε) $\times10^3$($L.mol^{-1}$ cm^{-1}) OBTAINED BY THE PROPOSED METHODS COMPARED WITH OTHER REPORTED METHODS

Coupling agent used	Value of (ε)$\times10^3$ (L. mol^{-1} cm^{-1})		Beer's law range in (µg/ml)	
	SNZ	MNZ	SNZ	MNZ
β-naphtol [29]	6.60	2.68	2-30	5-50
8-quinolinol [30]	11.31	9.01	1-15	1-17
α-naphthyl amine (proposed method)	3.50	15.02	3-30	2-12
2,5-dihydroxybenzoic acid (proposed method)	58.03	44.07	5-50	5-50

Interferences: A detailed study on the interference of various concomitant substances on the determination of these drugs was made. The extend of interference by various excipients that often accompany the pharmaceutical formulations were tabulated in **Table 4**. Some of the common excipients, which often accompany the pharmaceutical preparations do not interfere in the proposed method. An error of 2.0% in the absorbance readings was considered tolerable.

TABLE 4: RECOVERY OF METRONIDAZOLE (MNZ) AND SECNIDAZOLE (SCN) IN PRESENCE OF DIFFERENT EXCIPIENTS USING α–NAPHTHYL AMINE AND 2, 5-DIHYDROXYBENZOIC ACID

Excipients	Amount (mg)	Recovery % of (MNZ)[a] (%±RSD[b])		Recovery % of (SNZ)[a] (%±RSD[b])	
		α–naphthyl amine		2,5-dihydroxybenzoic acid	
		MNZ	SNZ	MNZ	SNZ
Uric acid	50	98.95±0.36	99.21±0.73	99.31±0.71	99.34±1.26
Vitamin C	50	99.71±0.29	98.98±0.45	97.83±0.88	99.44±1.16
Glucose	50	99.62±0.26	99.11±0.74	99.97±0.34	99.55±0.93
Carboxy methyl cellulose	50	99.47±0.27	99.28±0.92	98.93±0.83	99.47±1.09
Lactose	50	99.49±0.35	99.35±0.15	98.57±0.72	99.66±0.72
Cellulose	50	99.51±0.33	99.49±0.18	98.97±0.71	99.20±0.82

[a]10 µg/ml of metronidazole and secnidazole were taken.
[b]Average of ten determinations.

Applications:

The applicability of the spectrophotometric method to assay of pharmaceutical preparations was successfully made; the results were presented in **Table 5**. The tests showed that results of the proposed methods were very satisfactory compared with other reported methods in literature [29-30].

The applicability of the suggested methods for the assay of a wide variety of pharmaceutical preparations was examined. The results of the assay of tablets are given in **Table 5**. The results of the assay of the pharmaceutical preparations were cross checked by the official methods [21, 29–30]. The obtained results compared favorably with other data in literature and our obtained results were highly reproducible.

TABLE 5: APPLICATION OF THE PROPOSED METHODS FOR THE DETERMINATION OF METRONIDAZOLE (MNZ) AND SECINDAZOLE (SCN) IN DOSAGE FORM USING α–NAPHTHYL AMINE AND 2, 5-DIHYDROXY BENZOIC ACID

Commercial formulations Analyzed	Content	Label Claim (mg)	Recovery[a] %, (±RSD[b])	
			α–naphthyl amine	2,5-dihydroxy benzoic acid
[c]Secnidazole®500	SNZ	500 / tablet	97.80 ± 0.52	97.50 ± 1.01
[d]Senidal® 500	SNZ	500 / tablet	99.72 ± 0.34	99.33 ± 0.68
[e]Flagyl® 250	MNZ	250 / tablet	97.60 ± 0.83	98.29 ± 0.58
[f]Flagyl® 500	MNZ	500 / tablet	99.25 ± 0.48	98.00 ± 0.58

a: Average of ten determinations.
b: Relative standard deviation.
c: product of Egyptian Int. pharmaceutical industries CO., Egypt, Batch no. 1305303
d: product of Global Napi pharmaceuticals, Egypt, Batch no. A22506.
e: product of Sanofi Aventis, Egypt, under license of Sanofi Aventis, France, Batch no. 3EG114.
f: product of Sanofi Aventis, Egypt, under license of Sanofi Aventis, France, Batch no. 3EG011.

The excellent recoveries obtained indicated the absence of any interference from the common excipients.

CONCLUSION: The work evidenced that our proposed spectrophotometric methods were found to be simple, selective, economical, rapid and sensitive compared with available spectrophotometric methods in the concentration range of the determination. The statistical parameters and recovery study data clearly indicated the reproducibility and accuracy of the proposed method in the range of the determination concentration. Analysis of the authentic samples containing Metronidazole and Secnidazole showed no interference from the common excipients. Hence, the present work seemed to be very suitable for the analysis of Secnidazole and Metronidazole in tablet dosage forms.

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How to cite this article:
Youssef AK, Saleh MSS, Abdel-Kader DA and Hashem EY: Facile Spectrophotometric Determination of Metronidazole and Secnidazole in Pharmaceutical Preparations Based On the Formation of Dyes. Int J Pharm Sci Res 2015; 6(1): 103-10.doi: 10.13040/IJPSR.0975-8232.6 (1).103-10.

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