Research Article

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Spectrophotometric Determination of Mesalazine in Pure Form and Pharmaceutical Formulations by Diazotization and Coupling With 2,7-Dihydroxynaphthalene As a New Coupling Agent

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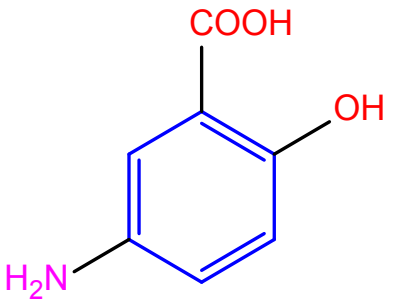
ABSTRACT

A simple, specific and sensitive spectrophotometric method is presented for the determination of Mesalazine (MZN) based on diazotization in an acidic medium through reaction with sodium nitrite ($NaNO_2$) to form a diazonium salt that coupling reaction in a base medium with 2,7-Dihydroxynaphthalene (DHNP) to form an azo dye. The dye intensity was measured at 501 nm after optimization of the experimental parameters. Beer's law was applied to the proposed method, valid within a concentration range of 0.25–10 µg.mL^{-1}, and the linear regression was $R^2 = 0.9974$. The limit of detection (LOD), the limit of quantification (LOQ), the molar absorptivity coefficient were 0.074 µg.mL^{-1},0.249 µg.mL^{-1} and 1.85x104 L.mol^{-1}.cm^{-1}, respectively. Sandell's sensitivity was 0.0082µg.cm^{-2}. There is no interference from excipients found in the tablet. The data were statistically compared with the British Pharmacopeia using two statistical methods (t-test and F-test).

Keywords: Mesalazine (MZN), 2,7-Dihydroxynaphthalene (DHNP) , Diazotization , Coupling Reaction

1. Introduction

Mesalazine (MZN) is chemically known as 5-aminosalicylic acid. It is a therapy for ulcerative colitis and Crohn's disease. As an anti-inflammatory medication [1-3], it plays an important function in eliminating oxygen-derived free radicals, which are abundant in inflammatory bowel disease (IBD) patients [4] (Scheme 1).



Chemical Formula: $C_7H_7NO_3$
Molecular Weight: 153.14

Scheme 1. Structure of Mesalazine

In the literature review, various analytical methods for assaying MZN were used, including voltammetric [5-6], spectrofluorometric [7], HPLC [8], flow-injection analysis method [9] Also, charge transfer complex reactions [10] and oxidative coupling reactions [11], in addition to spectroscopic methods [12-18], the aim of this work is to develop the sensitivity of a method for the determination of MZN as pure and pharmaceutical formulations based on the diazotization and coupling reaction of MZN with 2,7-Dihydroxynaphthalene (DHNP) in an alkaline medium from sodium carbonate solution, forming an orange-red azo dye with a maximum absorbance of 501 nm.

2. Materials and Methods

2.1. Apparatus

All spectrophotometric measurements were recorded on a JASCOV-360 digital spectrophotometer equipped with 1-cm glass cells. A Gilson micropipette with disposable tips was used to add samples; a HANNA pH211 pH meter was employed to monitor the pH, and a BEL-sensitive balance was employed to perform the appropriate weighing procedures.

2.2. Materials and standard solutions

All the reagents employed were of the highest purity available and obtained from Merck and Fluka companies.

Stock solution (100 µg. mL^{-1} = 6.530 × 10^{-4} M) of MZN as diazonium salt: 0.01 g of pure MZN was dissolved in exactly 5 mL of distilled water, transferred to a volumetric flask with a capacity of 100 mL, and placed in an ice bath, waiting for the next step.

Sodium nitrite solution, $NaNO_2$ (6.530 × 10^{-4} M): 0.00449 g of sodium nitrite was dissolved in exactly 5.00 mL of distilled water and transferred to the same volumetric flask, existing in an ice bath, waiting for the next step.

The corresponding diazonium salt: Transfer 3.00 mL of concentrated hydrochloric acid (11.80 M) to the same volumetric flask containing MZN and sodium nitrite (prepared in the previous step), followed by simple stirring for 20 minutes to complete the reaction. The same solvent was used to complete the volume to mark in a 100 mL volumetric flask. The corresponding diazonium salt resulted. It is kept in the dark bottle. A working solution was prepared by transferring 50.00 mL from it and diluting it with distilled water in a 100 mL volumetric flask, finally resulting in (50.00 µg.mL^{-1}) MZN as diazonium salt..

2,7 di-hydroxynaphthen solution 0.2% : 0.20 g of 2,7 di-hydroxynaphthen solution reagent was dissolved in a small amount of distilled water, and the same solvent was used to completed to mark in a 100 mL volumetric flask.

Sodium carbonate solution Na_2CO_3 (1.00 M): by dissolved 10.5988 g in a small amount of distilled water and completed with the same solvent to mark in 100 mL volumetric flask..

Pharmaceutical formulations prepared: An accurately weighed amount of tablets crushed to fine powder, equivalent to 0.01 g MZN, was transferred into an appropriate volumetric flask with about 10-20 mL of diluent and stirred for 30 min in a water bath; filtration after that, and the same methods used to prepare MZN pure.

2.3. Procedure

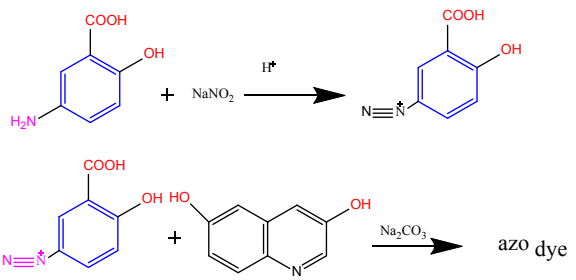
At installed conditions, in a series of (10 mL) volumetric flasks, (0.05-2.00 mL) of diazonium salt solution was added and followed by (1.25 mL) (0.2%)

DHNP solution. Finally, (1.00 mL) 1M Na_2CO_3 was added, The color azo-dye began to form, and after 15 minutes, the color stabilized, completing the volume to mark with distilled water. The absorbance of the diazonium salt solution was measured against a blank containing all material reacted without MZN; it gave a maximum absorbance of 501 nm.

3. Results and Discussion

3.1. Preliminary study

When mixed MZN and $NaNO_2$ solutions have the same molar concentration (molarity) in an acid medium for concentrated acid solutions, the corresponding diazonium salt is formed; in the alkaline medium, the diazonium salt formed was coupled with DHNP to form an azo dye complex scheme 2.



Scheme 2. The suggested mechanism of the azo dye complex

3.2. Optimal study conditions

3.2.1. Selected type of acid

The diazotization process requires the presence of an acid medium. Therefore, studied the effect of the various acids 1M (HNO_3, HCl, H_2SO_4, and CH_3COOH) on an azo dye formed and selected the appropriate one based on the resulting absorbance Table 1. It was shown that HCl gave the highest absorbance at 501 nm.

3.2.2. Amount of 2,7 dihydroxynaphthene reagent

For studied the effect of the different amounts of reagent on the intensity of absorbance of an azo dye, taken (0.50^{-1}.50 mL) from DHNP (0.2%) shown in Table 2 and Figure 1. (1.25 mL) of DHNP (0.2%) appears to be the optimum amount for giving high absorbance and reasonable coefficient R^2= 0.9901.

3.2.3. Effect of coupling reaction time on absorbance

At room temperature, monitoring the intensity of absorbance of azo dye versus change in time by transferring two concentrations of diazotized MZN (2.50 and 5.00 µg .mL^{-1}), studied the effect of time on the completion of the coupling reaction of diazotized MZN with DHNP before the addition of distilled water to complete the volume to the mark . The results are explained in Figure 2. It was shown that the reaction for azo dye needs 15 minutes to complete.

Table 1. Effect of the type acids on azo dye formed

1 mL acid/1M	HNO_3	HCl	H_2SO_4	CH_3COOH
Absorbance	0.3941	0.4358	0.1283	0.2471
λ_{max}	483	501	508	447

Table 2. Effect of the various amount DHNP (0.2%) on an azo dye formed

µg.mL^{-1} MZN	DHNP (0.2%) per mL			
	0.5	1	1.25	1.5
1.5	0.1777	0.228	0.2711	0.249
2.5	0.3053	0.3194	0.417	0.3714
3.5	0.4488	0.4606	0.4984	0.472
5	0.6101	0.6298	0.6221	0.6079
7.5	0.6335	0.8031	0.9487	0.8031
R^2	0.8578	0.9865	0.9901	0.9865

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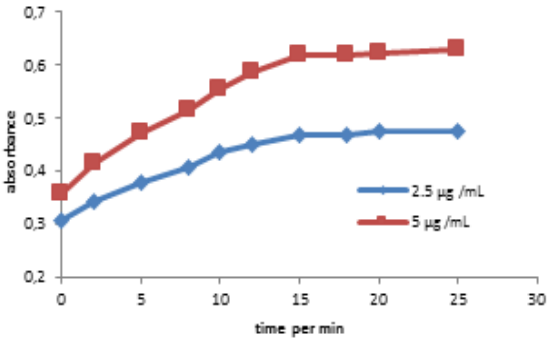

Figure 1. The effect of reaction time on absorbance 3.2.4. Selected type and amount of base

Amount of base was carried out by adding (5.00 µg.mL^{-1}) of diazonium salt solution and (1.00 mL) of reagent, followed by various bases (1M) from (NaOH, KOH,Na_2CO_3, and $NaHCO_3$) and waiting for 15 minutes, as shown in Table 3. Na_2CO_3 solutions had the highest absorbance of all the bases, and it was obtained that (1.00 mL) of Na_2CO_3 (1 M) gave the maximum absorbance when taken in various amounts from Na_2CO_3. Accordingly, it was selected for subsequent investigation Figure 2.

3.2.5. Stability of the product

After the reaction's optimum conditions were confirmed, The product's stability was investigated by measuring its absorbance at 501 nm by preparing two different MZN amounts (2.50 and 5.00 µg .mL^{-1}). The results are exhibited in Figure 3. It was shown that the reaction of azo dye at room temperature remains stable for at least 60 minutes.

3.3. Final absorbance spectra

The maximal absorbance of azo dye produced by (1.00 mL) diazotized MZN, and (1.25 mL) DHNP in (1.00 mL) alkaline Na_2CO_3 solution is 501 nm. Figure 5. While a blank that contains all material reacted without MZN has a little absorbance at this wavelength.

3.4. Calibration curve of MZN pure

An aliquot of diazotized MZN on a series of calibrated flasks with a capacity of (10.00) mL was added, and (1.25 mL) (0.2%) DHNP solution was added, followed by (1.00 mL) 1M Na_2CO_3, and waited for 15 minutes after completing the mark with distilled water. The absorbance of a diazonium salt solution was measured against blank. In Figure 5, it was shown that a straight line covers the concentration in the range of (0.25^{-1}0.00 µg.mL^{-1}). Several calculations were performed to determine the method's accuracy and precision [19,20]. The apparent molar absorptivity coefficient was 1.85×10^4 L.mol^{-1}.cm^{-1}, Sandell's sensitivity was 0.0082 , LOD and LOQ were 0.074 , 0.249 µg .mL^{-1}.

3.5. Stoichiometry of azo dye

Under the optimum conditions, the same molar concentration (molarit) of MZN and DHNP (6.5×10^{-4} M). Azo dye's complex composition has been identified using Job's continuous variation and mole ratio methods [21]. Concerning the job method, a series of the drug's opposite volumes (0.20-0.80 mL) and the reagent were taken in volumetric flasks. In the mole ratio method, several volumetric flasks containing (1.00 mL) of the drug and varying reagent volumes were used. The results obtained gave a stoichiometry of 1:1, shown in Figure 6.

3.6. Formation constant of complex(k_f)

Under the optimum conditions and same concentration for MZN and DHNP 6.5×10^{-4} M for both of them, the formation constant of complex was calculated by using the equation [22,23]:

$$K_f = K_f = \frac{1-\acute{\alpha}}{(\acute{\alpha})^2 - C} \qquad whereas\ \acute{\alpha} = \left(\frac{Am-As}{Am}\right)$$

Where As represents the absorbance of solutions of diazotized MZN with DHNP that were equivalent in molar concentration. In contrast, Am represents the absorbance when adding DHNP excess concen-

Table3. Effect of the basic solution on the absorbance of azo dye

bases	NaOH	KOH	Na_2CO_3	$NaHCO_3$
Absorbance	0.2115	0.2135	0.6221	0.2256
λmax	510	510	501	482

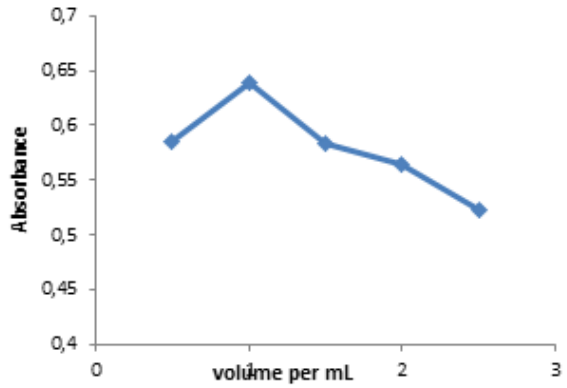

Figure 2. Effect of a basic solution (Na_2CO_3) on absorbance

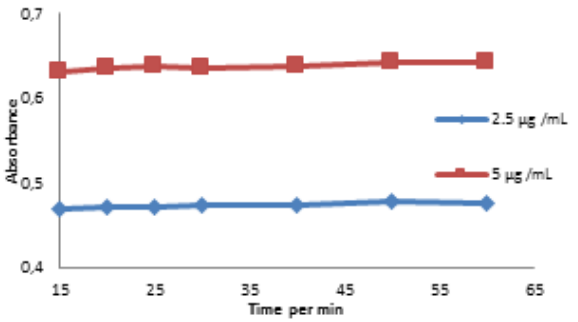

Figure 3. Stability of azo dye at room temperature.

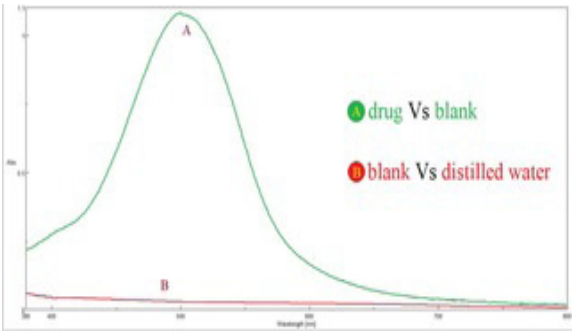

Figure 4. Absorbance Spectra of MZN vs. blank and blank vs. Distilled water

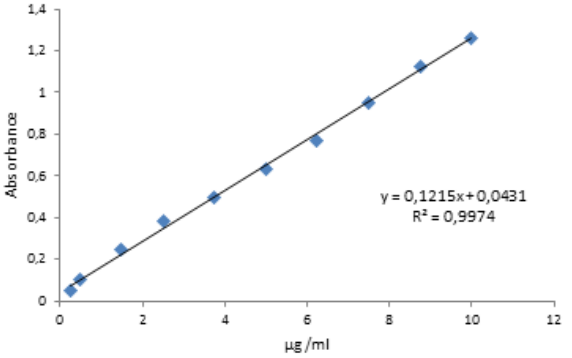

Figure 5. The calibration curve for MZN pure

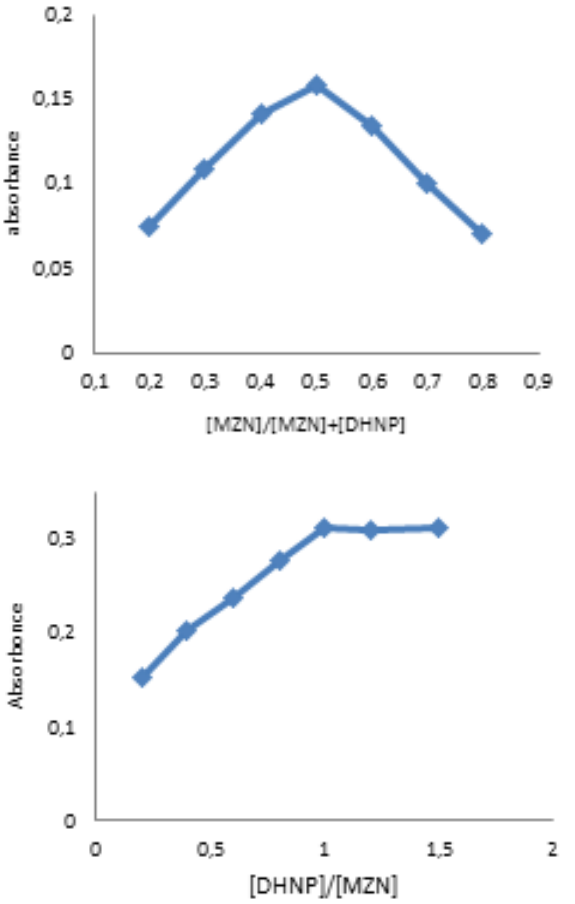

Figure 6. the stoichiometry of the reaction by a) job's method b) mole ratio.

tration to a fixed concentration of diazotized MZN. From the results in Table 4. The average formation was constant of complex (K_f) 4.3×10^4 l.mol^{-1}.

3.7. Accuracy and precision

Take three repetitions of each (2.50 and 3.75 µg.mL^{-1}) individually from diazotized MZN. The selected concentrations should be a linear part of the calibration curve, and the results are shown in Table 5.

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Table 4. The average formation Kf of diazotized MZN with DHNP

C/Mol.L^{-1}	As	Am	$\dot{\alpha}$	$\dot{\alpha}^2$	Ks
0.000026 0.0515		0.1549	0.667527	0.445593	28697.51
0.000039	0.099	0.2173	0.544409	0.296381	39414.94
0.000052	0.1221	0.2311	0.471657	0.222461	45672.97
0.000065	0.1521	0.2523	0.397146	0.157725	58802.75

$K_f = 4.3x10^4$ l.mol^{-1}

Table 5. Accuracy and precision of the proposed method.

added concentration	Found[a]	SD	RSD%	E%	REC%
2.5	2.48	±0.0036	0.9596	±0.6065	99.39
3.75	3.72	±0.0054	1.0994	±0.5982	99.40

[a]from the proposed method

3.8. Application of MZN in pharmaceuticals formulations

The suggested method's applicability for determining MZN in drugs was investigated by investigating two pharmaceuticals (Pentasa Germany and Pentasa Turkey) applied at (2.5 and 3.75 µg.mL^{-1}) with four replicates. Table 6 shows the results of determining MZN in pharmaceutical formulations, which were compared to the standard MZN and with British Pharmacopoeia [24] standard methods using t-test and F-test [25,26]. With degrees of freedom for four levels, it was shown in Table 6.

3.9. Evaluation of the procedure for determination of MZN

To verify the effectiveness and compatibility of the suggested method, used the standard addition method [27]. The method was carried out by taking increasing concentrations of diazotized MZN (0, 0.5, 1, 1.5, 2, and 2.5)and two fixed concentrations of pharmaceutical formulations (2.5 and 3.75 µg.mL^{-1}) each concentration individually (Figures 7a,b). The method successfully estimated the property without interference Table 7.

3.10. Comparison of the proposed method

Several currently available spectrophotometric methods have been employed previously to determine MZN in pharmaceutical formulations. The proposed method is in Table 8. It was compared with some of those other methods.

4. Conclusion

The proposed method was compared with the previous method of MZN determination and with British pharmacopeia by using two statistical methods (t-tests and F-test) and proved the accuracy and precision of the method.

In addition, the detection limit of 0.09 µg.mL^{-1}, molar absorptivity coefficient $1.85x10^4$ L.mol^{-1}.cm^{-1}, and Sandell′s sensitivity of 0.0082 µg.cm^{-2} . The results of standard addition methods for the suggested method showed success in estimating the MZN without interference.

Acknowledgement

The authors are thankful to College of science, University of Mosul, Mosul, Iraq for providing essential research facilities to carried out this research work.

Table 6. Application of the suggested method for determination of MZN in drugs and t, F-test

drugs	Amou-nt of drugs	added[a]	Found[a]	ER%	RE%	Measured	RSD%	Average[b] RE%	t, F-test
Pentasa tab. (Turkey)	500 mg	2.5	2.49	±0.58	99.42	498	0.26	100.37	±0.71[c] 0.01[d]
		3.75	3.79	±1.16	101.16	497	0.82		±1.93[c] 0.10[d]
Pentasa tab. (Germany)	500 mg	2.5	2.48	±0.53	99.47	496	0.1	98.22	±0.52[c] 1.14[d]
		3.75	3.73	±0.38	99.62	497	0.34		±0.31[c] 1.02[d]

a; diazotized MZN, b; British Pharmacopoeia standard method , * 95% Confidence Interval of the Difference degrees of freedom; t-test 2.776, F-test 6.39, **c**; t-test, **d**; F-test.

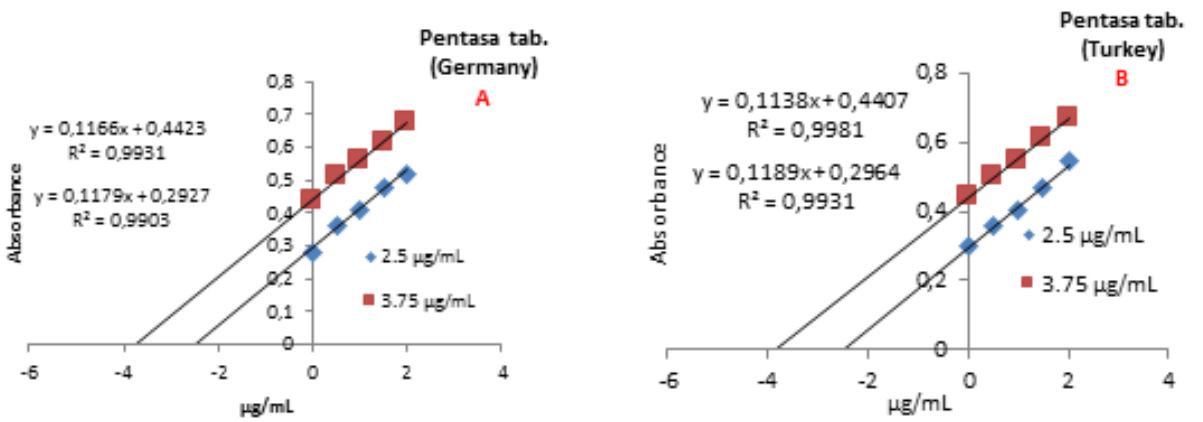

Figure7. Standard addition calibration graphs of MZN in the pharmaceuticals formulations of A)Pentasa Germany and B) Pentasa Turkey.

Table 7. The results of standard addition methods for determination of MZN

pharmaceutical formulations	MZN added	MESZ Measured	Recovery %
Pentasa tab. (Germany)	2.5	2.48	99.2
	3.75	3.79	101
Pentasa tab. (Turkey)	2.5	2.49	99.6
	3.75	3.87	103

Conflicts of Interest Statement

No conflicts of interest.

Statement of Contribution of Researchers

Concept: A. M.; Design: A. M.; prevision: A. M.; Resources: A. M.; Materials: M. A.; Data collection and/or processing: A. M.; Analysis and/or interpretation: A. M, M. A; Literature search: A. M.

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Table 8. Comparison of the proposed method with other methods

λ (nm)	LOD[a]; LOQ[b] µg.mL^{-1}	εmolar absorptivity L.mol^{-1}.cm^{-1}	RSD% (precision)	RE% (Accuracy)	Sandal's sensitivity µg.cm^{-2}	source
501	0.074[a]; 0.294[b]	1.85×10^4	0.38	99.42-101.16	0.0082	This work
659	1.48[a], 4.94[b]	0.49×10^3	1.42	97.72-98.82	0.31	[9]
346	0.053[a] 0.176[b]	6.5×10^3	1.70	98.04	-	[10]
500		0.52×10^3	0.81	-	0.29	[11]
655 510	0.004[a] 0.010[b] 0.006[a] 0.018[b]	1.087×10^4 1.48×10^4	0.31 0.92	99.14-101.12 98.95-100.15	0.0140 0.0103	[12]
430	-	3.02×10^4	0.63[c]	100.42-102.50	-	[13]
645	0.101[a]; 0.338[b]	2.2×10^4	3.50	95.98-102.35	-	[14]
552	0.113[a]	1.5×10^4	0.71	95.4 -102.3	0.0263	[15]
494	0.171[a]; 0.451[b]	1.96×10^3	0.14	-	0.0070	[16]
514	0.102[a]; 0.310[b]	4.6×10^3	0.26	97.31-103.14	0.0327	[17]
600 470	4.92[a]; 14.89[b] 0.56[a]; 1.68[b]	$1.18\text{x}10^3$ $7.73\text{x}10^3$	0.47 1.51	97.27-101.24 96.85-102.81	0.1290 0.0200	[18]

ε : molar absorptivity, RSD: relative standard deviation, RE: recovery, LOD: Limit of detection , LOQ: Limit of quantification, c; average

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