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Spectrophotometric Determination of Loratadine Drug by New 6-hydrazineyl-3-(pyridiin-4-yl)-[1,2,4] triazolo[3, 4-b][1, 3 ,4]thiadiiazole A1 Derived from Isonicotinic Acid in Pure and Pharmaceuticals Formulation

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Abstract

A novel, sensitive, simple, and accurate spectrophotometric technique for the determination of Loratadine (LD) drug in pure and pharmaceutical formulations was developed. It was created by the reaction of (LD) and a new organic reagent (A1) prepared from (TCH) and (A) in a base medium. TCH was prepared by heating at reflux of a mixture of carbon disulfide and aqueous hydrazine, while (A) was prepared by thermal melting of a mixture of TCH and nicotinic acid. The absorption of the product of LD and A1 was measured at 466 nm. Linearity ranged between (0.625-30µg.mL^{-1}), molar absorptivity was (17918.92 L / mol.cm), limits of detection and quantification were (0.0705, 0.213 µg.ml^{-1}), respectively. The method was applied successfully for the determination of LD in pure and pharmaceutical formulations.

Keywords: Determination; Isonicotinic acid; Loratadine; Spectrophotometric; Thiocarbohydrazide.

1. Introduction

Loratadine (LD or LOR) is a tricyclic antihistamine that acts as a selective inverse agonist of peripheral histamine H1-receptors [1]. Its structure includes ethyl 4 -(8-chloro-5 ,6-dihydroo-11-H-benzo-[5,6] cycloohepta [1,2-b] pyridin-11-ylidenee) -1-piperidinne-carboxylate (see Fig. 1) [2].

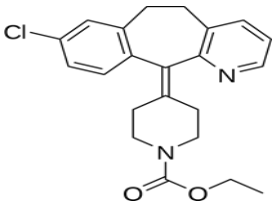

Figure 1. the structure of LD drug

Its molecular weight is 382.883g/mol and its chemical formula is $C_{22}H_{23}ClN_2O_2$ [3]. LD is a powder that is off-white in color. It is nearly water soluble and just slightly soluble in methanol and ethanol [4].The occurrence of confrontational medication effects, such as sedation, is greatly reduced as a result of selectivity. The fact that the majority of these combinations are zwitterionic at pH 7.4 explains their periphery selectivity. They are polar in nature, do not pass the blood-brain barrier, and perform mostly outside the central nervous system; therefore, they create very little effects [5]. Several analytical procedures were used to determine the quantitative amount of LD in dosage forms and biological fluids. They included UV spectrophotometry [6-11], High Performance Liquid Chromatography [4,12-19], voltammetry using cathodic stripping [20], electrical and chemical sensors [21], square-wave voltammetry and a boron-doped diamond electrode cathodically pre-treated [22], FIA [23], LC/MS/MS [24], Raman Excipient Spectrum [25], and Titrimetric Assay in Non-Aqueous Medium [26].

Antimalarials, oncolytics, and viruses are some of the biological applications of heterocyclic thiosemicarbazide derivatives (particularly pyridine derivatives) [27]. The goal of this study is to develop an improved spectrophotometric method for determining LD drug concentrations using a novel 6-hydrazineyl-3-(pyridin-4-yl)-[1,2,4,]triazolo[3,4b][1,3,4,]thiadiazole A1 generated from isonicotinic acid.

2. Organic Experimental Part

Flucka and BDH Chemicals Com. Ltd provided all the chemicals utilized.

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2.1. Instruments

Infrared measuring device (FT.I.R), KBr discs with a range (400-4000cm-1) was used. The measurement was taken in the laboratory of Tikrit University, College of Education for Pure Sciences, Chemistry Department. The degree of melting (M.P.) was measured by using electro thermal melting point apparatus (9300). In addition to using other devices including ultrasonic homogenizer (model: 300 V/T, 230 Volts/50 Hz), electronic sensitive balance (Sartorius Lab_BL219) with an accuracy of up to +010.00.

2.2. Preparation Methods

1- Preparation of thiocarbohydrazide (TCH)

In a cold bath, 20 ml of 80 percent aqueous hydrazine was introduced to a round flask with a capacity of 100 ml. Then, 5 mL carbon disulfide was added gradually over 10 minutes with magnetic stirring at (0 ℃). After that, the mixture was refluxed for 30 minutes until a yellow variety was formed. In an ice bath, the mixture was chilled. Separation was used to collect the deposited product, which was then washed with diethyl ether and ethanol until it turned white. It was recrystallized and dried at 50 °C using distilled water. The melting point ranged between (170_172) °C, consisting with previous research [28]. The product's proportion was (66 %) (Table 1).

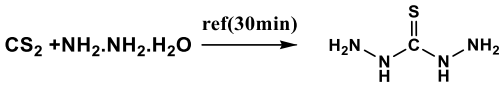


Table 1. Physical properties of the prepared compound

Comp. No	TCH
Molecular Formula	CH_6N_4S
M.P (C)	172-174
Yield	66%
Color	Pearl White
Solvent	D.W

2-Preparation of 4-amino-5-pyridine-4-yl-4,2,1-triazole-3-thiol (A)

Without using a solvent, (0.01 mol, 3 gr.) of TCH was mixed with (0.01 mol, 2.5 gr.) nicotinic acid. Then, the mixture was placed on a sand bath and stirred with a glass rod for 3-4 minutes or until a change in its thickness and color. The product was treated with a 10% sodium bicarbonate solution. Then, the precipitate was filtered, rinsed with distilled water, and dried at 50 °C [29-30]. It was recrystallized with ethanol. The prepared compound was calculated using the equation below (see Table 2).

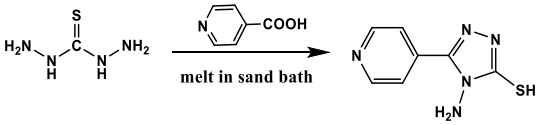


Table 2. Physical properties of the prepared compound (A)

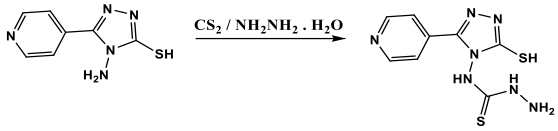
Comp No	Molecular Formula	M.P	Yield	Colour	Solvent
A	$C_7H_7N_5S$	208	%60	Pink	EtOH

3- **Preparation of N-(3-mercapto-5-(pri-yl)-4,2,1-triazole-4-yl)hydrazine carbothiamide (A1)**

(0.004 mol, 0.85 gr.) of prepared triazole (A) was dissolved in (50 mL, 96%) ethanol. Then, (20 mL) ammonium hydroxide (NH_4OH) and (20 mL) carbon disulfide (CS_2) were gradually added for 15 minutes with stirring. The solution was left for 1 hour, and then added to a combination of (40 mL) hydrazine hydrate ($N_2H_4.H_2O$) (80 %), cooled in an ice bath, where a white precipitate was formed, filtered, and recrystallized from a mixture of ethanol and water at a ratio of (1:3) [31] (as shown Table 3).

Table 3. Physical properties of the prepared compound A1

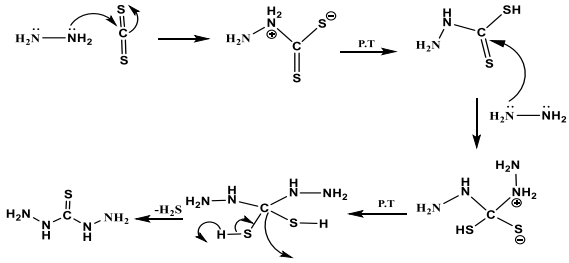
Comp. No	A1
Molecular Formula	$C_8H_9N_7S$
M.P (C)	120-123
Yield	85%
Color	Light yellow
Solvent	Dioxane



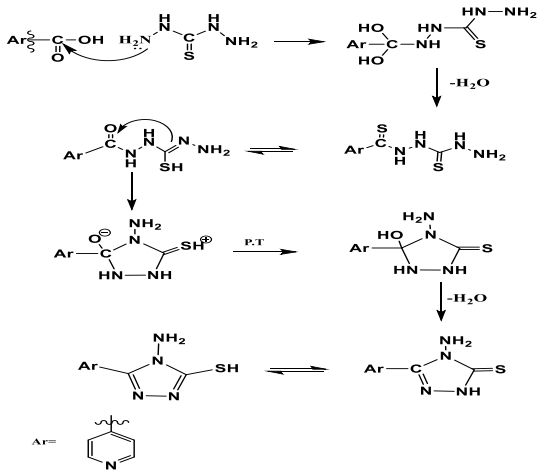
2.3. Discussion

1- Identification of thiocarbohydrazide TCH

The following mechanism was used to make thiodicarbohydrazide by heating a combination of carbon disulfide and aqueous hydrazine to produce unique crystals with a yield of (66 %) [32].



2- Identification of the compound 4- amino-5-pyridin-4- yl -4hydrogbin-4, 2 ,1-triazole -3-thiol (A)
The compound was prepared by applying thermal melting from the reaction of TCH with monocarboxylic acid. It was observed that the physical properties changed, such as color and melting point, as the reaction proceeded according to the following mechanism [33]:



The spectrum of compound A1 showed two bands of the primary amine group (3240, 3415) cm^{-1} with a clear bandwidth compared to the spectrum of compound A. This indicates the presence of a thioamidic N-H bond that increased the hydrogen bonds in the compound, due to its expected ability to participate in the tautomerism phenomenon, as it appeared C=S-stretching at (1348) cm^{-1}, with the appearance of C-S stretching at (763) cm^{-1} (see Fig. 2).

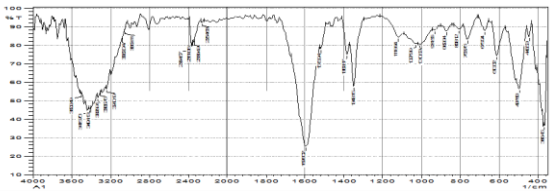


Figure 2. FT-IR spectrum of compound A1

3. Analytical Experimental Part

3.1. Apparatus

PG Instrumental Ltd UV-Visible Spectrophotometer, UK T90 using 10-3 m quartz cell for all spectrophotometric quantities, 210 S kern sartorius balance using all weight measurements were used.

3.2. Chemicals

Flucka and BDH Chemicals Com. Ltd provided all the chemical substances and solvents utilized Without further purification, Loratadine was provided by the state Company for Drugs Industry and Medical Appliances Samarra-Iraq. The solutions were prepared by using distilled water; as 1000 µg/ml of A1 was prepared by dissolving 0.05 gm in 50ml of hot distill water with a stirrer in volumetric flask 50mL.

A 1000 µg/ml of LD solution was prepared by dissolving in 10ml 1M HCl and adding distilled water to a volumetric flask 100mL. More dilute solutions of the LD were prepared via serialized dilutions with distilled water. Solutions of potassium ferricyanide and potassium periodate (with 0.01M for each) were prepared and used.

Sample Preparation

From 10 tablets Largactil (Pioneer Pharmaceutical Industries- Sulaymaniyah/ Iraq containing 10 mg of LD), a homogenized powder of 1.223 gm was obtained. About 0.6115gm weight of five tablets was dissolved in 100 ml water. Dissolution of the drug was supported by magnetic stirring and an ultrasonic bath. The solution was filtered through a Whatman filter paper (No.1.) with a volume up to the mark using distilled water in 100ml a volumetric flask to get 500 ppm solution and prepare 250ppm by dilution.

Interference Solutions of 1000 µg/ml

These solutions were prepared by dissolving 0.1gm of (maltose, lactose, sucrose and sulfamethoxazole) in a suitable solvent (water or ethanol) and then the volume was made up to 100ml with distilled water.

3.3.General procedure for determination of Loratadine (LD) drug with A1

0.1ml was transferred from 250ppm of LD drug to 10ml volumetric flask containing 0.1ml $K_3Fe(CN)_6$, 0.2ml KIO_4 of $1x10^{-2}M$ and 0.3ml of A1 250ppm. The mixture was diluted to create a brown-orange solution absorbance at 466 nm.

3.4 Discussion and Results

While LD was treated according to the recommended method, displaying band was in the expanse of (400-600 nm) and the noted absorption spectrum of the formed reaction product was at 466nm. Still the blank has no important absorbance in the region (see Fig. 3).

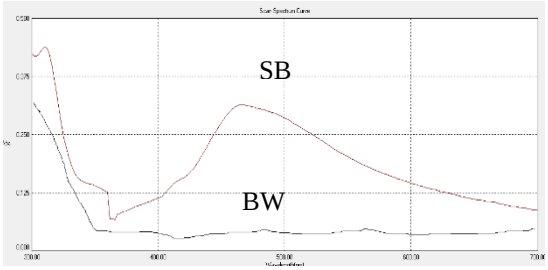


Figure 3. SB: Spectrum of sample solution against blank, and BW: Spectrum of blank against water.

3.5. Reaction conditions optimization

To acquire optimal reaction conditions, the impact of various factors on the absorption was studied.

3.5.1. Volume of Potassium Ferricyanide

By adding different volumes of 0.01M $K_3Fe(CN)_6$ solution, it was found that 0.3ml of 0.01M $K_3Fe(CN)_6$ is acceptable, but increasing the volume of solution causes the absorbance to decrease (Fig. 4).

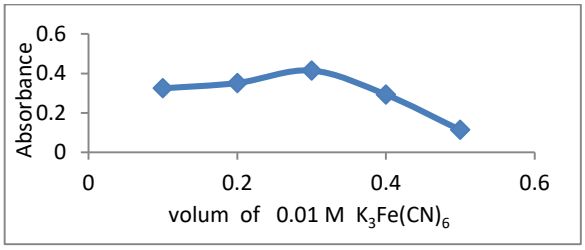


Figure 4. Volume of $K_3Fe(CN)_6$ in Absorbance intensity

3.5.2 Volume of Potassium Periodate

The effect of several volumes of potassium periodate solution (0.01M) on absorbance of the colored product was studied. It was found that 0.4 ml of 0.01M KIO_4 is acceptable; however, increasing the volume of solution decreases the absorbance of product (Fig. 5).

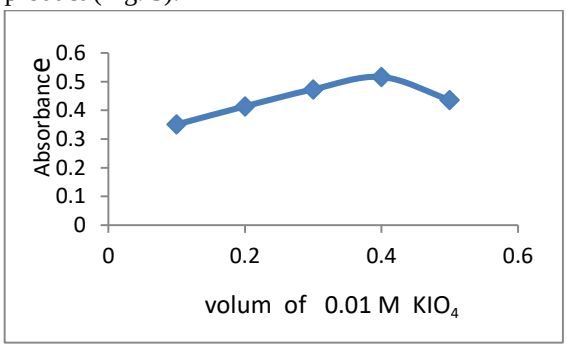


Figure 5. Volume of KIO_4 in Absorbance intensity

3.5.3. Volume of organic reagent A1 solution

The effect of different volumes (0.1- 1) ml of organic reagent A1 250ppm on absorbance of the colored product was studied.

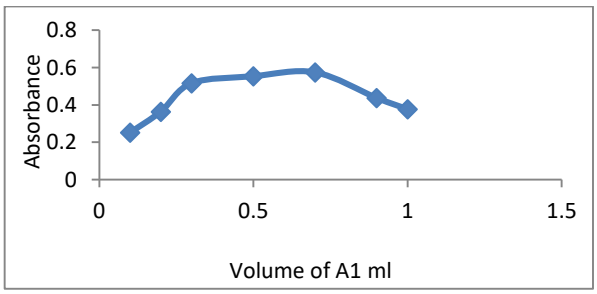


Figure 6. influence of volume of organic reagent (A1)

The maximum absorbance and constant color were recognized with 0.7 ml of A1 250 ppm; therefore, it was selected in subsequent experiments (Fig. 6).

3.5.4.The effect of addition order

Four orders of addition were examined. Table 4. shows that order No.1 was the optimum and recommended in the subsequent experiments.

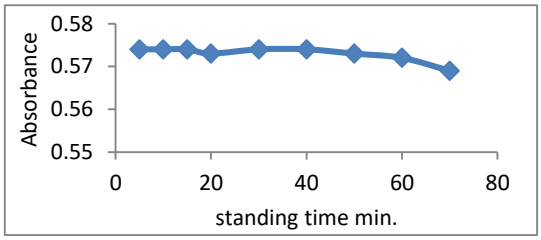
Table 4. The effect of addition orders

No	Addition order	Absorbance
1	**A+B+R+D**	**0.574**
2	D+A+B+R	0.431
3	R+A+D+B	0.268
4	D+B+A+R	0.426

A=$K_3Fe(CN)_6$ B= KIO_4 R = new organic Reagent(A1) D = Drug

3.6. The effect of time on stability of the colored product

The stability time was studied via taking 0.3 ml of $K_3Fe(CN)_6$ 10^{-2}M with the addition of 0.4 ml of KIO_4 10^{-2} M, then 0.7ml of new organic reagent A1 250ppm and 0.1ml from 250ppm of LD drug. The volume was completed to 10 ml in a volumetric flask using water. It was observed that the absorption



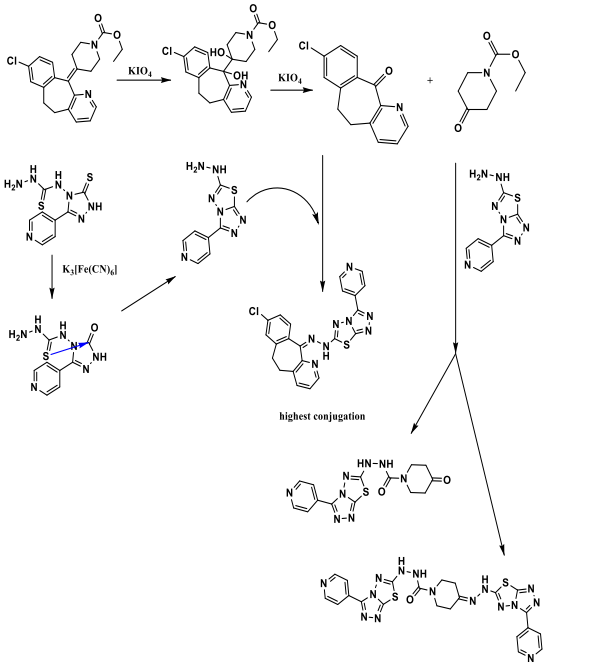
becomes constant directly and remains for 60 min. (Fig. 7).

Figure 7. Stability time of the colored product

3.7. Suggested reaction mechanism

The mechanism showed the ability of K_3 [$Fe(CN)_6$] to oxidize compound A1 in position 5 from thiooxo to oxo, allowing cyclization and transformation into a combined dicyclic hydrazine system. While KIO_4 converted the compound into a ketone derivative that reacted with the hydrazine derivative to form a highly conjugated compound. The oxidation process of the olefin-oxocyclic bond between the non-aromatic rings in the drug occurred by converting the compound into a ketone derivative that reacted with the hydrazine derivative. With the possibility of consuming a portion of the hydrazine derivative in reaction with the second part of the drug after the oxidation process, forming a

hydrazone-thiosemicarbazide derivative or only a thiosemicarbazide derivative, as in the steps below:



3.8. The calibration graph

In a chain of volumetric flasks (10ml), volumes of 0.3 ml $K_3Fe(CN)_6$ 10^{-2}M, 0.4 ml of KIO_4 10^{-2} M and 0.7ml of new organic reagent (A1) 250ppm at concentrations of 0.625-30µg/ ml of (LD) (0.025 – 1.2 ml of 250 µg . ml^{-1}) were added and then completed with distilled water. The absorption of solutions against the blank was measured at 466 nm (Fig. 8). The value of the molar absorbance was 17918.92 $L.mol^{-1}.cm^{-1}$ with the correlation coefficient of 0.9993.

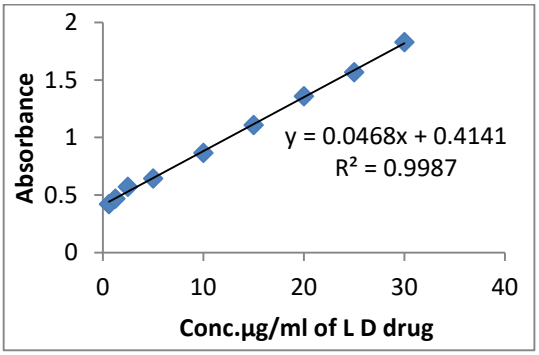


Figure 8. Calibration graph for determination of LD drug

3.9. Precision and Accuracy

Precision and accuracy were studied n=6 at 466 nm for 3 various concentrations of the LD in the limits of Beer's law. The average recovery (97. 18%) showed that the method was of high precision and accuracy. The results are shown in Tables (5 and 6).

Table 5. Results of precision and accuracy

Conc.LD µg.ml^{-1}	Conc. LD Observe*	Recovery,*%	RSD*,%
1.25	1.19	95.55	0. 024
10	9.72	97.2	1.02
25	24.69	98.79	1.89

n=6*(Rec%=RE+100)

Table 6. Results of Detection limits

Concentration µg /ml	P	S	LOD [34-35] µg/ml	LOQ [34-35] µg/ml
0.625	0.0468	0.001	0.0705	0.213

3.10. Applications

3.10.1. Direct process

Different concentrations of a pharmaceutical formulation (1.25, 10, 25 ppm) were treated based on the calibration graph, measured at 466 nm for 6 times. Relative error was calculated (Table 7).

Table 7. Determination of LD in pharmaceutical formulation

Conc. of LD µg.ml^{-1}	Conc. of LD Observed *	RE
1.25	1.23	-1.6
10	10.22	2.2
25	25.44	1.76

*n=6

3.1.2. Method of standard additions

For determining LD in its pharmaceuticals, the developed method was free from interferences of standard additions method. 0.5 ml of a pharmaceutical formulation solutions 100 µg.ml^{-1} were transferred to 5 volumetric flasks (10 ml), then volumes were increased (0.1- 0.5 ml). 100µg.ml^{-1} of LD standard solution was added, but the fifth of flask was left without addition. The solution was treated based on the calibration graph and measured at 466nm (see Fig. 9 and Table 8).

3.11 Interference Study

In pharmaceutical analysis, it was important to test the selectivity towards the excipients added to the pharmaceutical preparations, such as vanillin, glucose, lactose, starch, sucrose, which did not interfere in the determination of LD and did not affect the reaction between LD and A1. (20µg.mL-1) of LD was analyzed. The design of experiment method was used for analyzing the data (Table 9).

3.12 Comparing proposed method with literature methods

The proposed method was compared successfully with other literature methods to demonstrate the excellent, rapid, precise, high selectivity, and sensitive spectrophotometric method for the determination of LD drug than other methods in the literature for the complex product of LD, as shown in table 10.

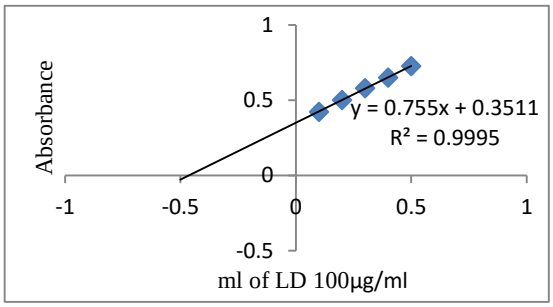


Figure 9. Determination of LD in pharmaceuticals via standard additions graph

Table 8. Standard additions method

Typeof Drug	LD present µg/ml	LD measured µg/ml	Recovery, (%)*
Tablets	5	5.01	100.2

*(Rec%=RE+100)

Table 9. Percent recovery for (20µg.mL^{-1}) of LD in the presence of different concentration of Excipients

Excipients	*Concentration* (µg.mL^{-1})	LD *Conc. Taken* (20 µg.mL^{-1})	
		Conc. Found µg.mL-1*	*Recovery* %*
Sucrose	1000	20.06	100.5
Vanillin	1000	20.08	100.66
Glucose	1000	20.04	100.33
Lactose	1000	19.97	99.75
Starch	1000	19.95	99.59

Table 10. Comparison of LD determination in proposed method and other literature method

Analytical Parameter	Literature(6) method	Literature(7) method	Literature(8) method	Literature(9) method	Literature(10)method	Literature[11] method	Present Method
Reagent	0.1N HCl	0.1M HCl	0.1N MeOH/HC	chloranilic acid	Area under curve method	Eriochrome Black T	A1
Beers law range	4-40	0.1-0.5	2-10	100-700	4-20	2.5-25	0.625-30
Molar absorptivity	99572	_____	---------	1.5×10^4	------	11524.688	17918.92
λ_{max} (nm)	275	339	275	538	244-264	530	466
RSD(%)	2.5803	_____	0.101087	_____	0.3266	0.3359	0.978
Solvent	Water	Water	Water	chloroform	methanol.	Water	Water
LOD µg.ml-1	1.678001	2.53 x 10^{-2}	0.009	11.62	0.4092	0.164	0.0705
LOQ µg.ml-1	5.084851	2.93 x 10^{-2}	0.027	35.21	1.24	0.498	0.213
Pharmaceutical Preparation	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet

4. Conclusion

The results found confirmed that the proposed method is simple with having a good sensitivity to the determination of LD. The method that was based on the reaction of LD and new organic reagent (A1) was prepared from (TCH) and (A) in a base medium. TCH was prepared by heating at reflux of a mixture of carbon disulfide and aqueous hydrazine, while (A) was prepared using thermal melting of a mixture of TCH and nicotinic acid with a good yield. The coloured product showed an absorption maximum at 466 nm. It was found that the proposed method was highly efficient and recoverable with a high linear range. It did not use organic solvents or solvent extraction. It could be applied successfully to the determination of LD in pharmaceutical formulations.

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