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Accurate and Rapid Spectrophotometric Method Development for the Determination of Loratadine Drug Using O-Phenylenediamine by Oxidative Coupling Reaction

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Abstract
New simple, sensitive and accurate spectrophotometrice methods were developed for determining loratadine (LOR) drug in both pure forms and pharmaceutical preparations. The reaction depended on the oxidative coupling with O-Phenylenediamine via KIO_3 in acidic solution to create an orange-colored product that was stable and soluble in water with a maximum absorption at λ=453 nm. Linearity ranges of LOR were (1- 30 μg.mL^{-1}), the value of molar absorptivity was (11065.31 liter/ mol**.**cm) and Sandell's sensitivity was 0.0346μg/cm^2. As for the detection of limit (DOL) and quantification limit (DQL), they were (0.114 μg / mL) and (0.346 μg / mL), respectively. The results indicated that there were no interferences of excipients on the determination of LOR. The suggested method was successfully applied for the determination of LOR in pure and pharmaceutical formulations.

Keywords: Loratadine, O-Phenylenediamine, Potassium Iodate, Pharmaceutical Formulations

Introduction

Loratadine (LOR) is used as the second-generation antihistamine for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria and has no clinically significant sedative and anticholinergic effects [1]. Its IUPAC structure is 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene)-1-piperidinecarboxylic $C_{22}H_{23}ClN_2O_2$. Its molecular weight is 382.883g/mol [2] (see Fig 1).

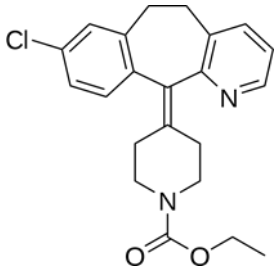


Fig 1: The structure of LOR drug

It is described as having a powerful effect when prescribed once-a-day, being a second-generation antihistamine, non-sedative and long-acting medicine. It has become a first-line agent for the treatment of allergic rhinitis, urticaria, and hay fever due to its excellent safety record. 6-3 LOR is rapidly absorbed when administered orally. The time for reaching peak plasma concentration of (0.5) is 2 hrs. Metabolic studies indicate that LOR suffers extensive first-pass metabolism to form [3].
Different analytical methods have been published for the determination of LOR including UV spectrophotometr [4], in the presence of Pseudoephedrine using Validated Spectrophotometric methods [5], Prussian Blue in pure and pharmaceutical formulations [6], visible spectrophotometry [7], the area under curve method [8], high performance liquid chromatography [9], RP-HPLC [10-12], HPLC using cation exchange column and experimental design optimization [13] HPLC/DAD from various dosage forms and biological samples [14-16] voltammetry using cathodic stripping [17], electrical and chemical sensors [18], square-wave voltammetry and a boron-doped diamond electrode cathodically pre-treated [19], FIA [20], LC/MS/MS [21], Raman Excipient Spectrum [22] and titrimetric assay in non-aqueous medium [23]. The present study aims to develop a spectrophotometric

method for the determination of LOR depending on the oxidative coupling of LOR with O-Phenylenediamine in the presence of potassium iodate as an oxidation reagent in acidic medium.

Experimental Part

Materials and Methods

Apparatus

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

Chemicals

Flucka and BDH Chemicals Com. Ltd provided all the chemical substances and solvents utilized. Without further purification, Loratadine was delivered by the state Company for Drugs Industry and Medical Appliances Samarra, Iraq. The solutions were prepared by using distilled water; as 500 µg/ml of LOR solution was prepared by dissolving in 10ml of 1M HCl, and then distilled water was added to a volumetric flask of 100mL. Other dilute solutions of the LOR were prepared via serialized dilutions with distilled water. 0.001 M of O-Phenylenediamine solution its prepare daily as a reagent, potassium periodate, potassium iodate, potassium dichromate, Copper (II) and sulfate pentahydrate (with 0.01M for each) were prepared and used in this study.

Sample Preparation

From 10 tablets of Laritin (Pioneer Pharmaceutical Industries/ Iraq containing (10 mg) of LOR), a homogenized powder of 1.240 gm was obtained. About 0.372gm as weight of three tablets was dissolved in 10ml of 1M HCl, and then distilled water was added to a volumetric flask of 100mL. Dissolution of the drug solution was supported by magnetic stirring in an ultrasonic bath. The solution was filtered through a Whatman filter paper (No.1.) with a volume to the mark using distilled water in a 100ml volumetric flask to get 300 µg/ml of solution.

Solutions of Interference 1000 µg/ml

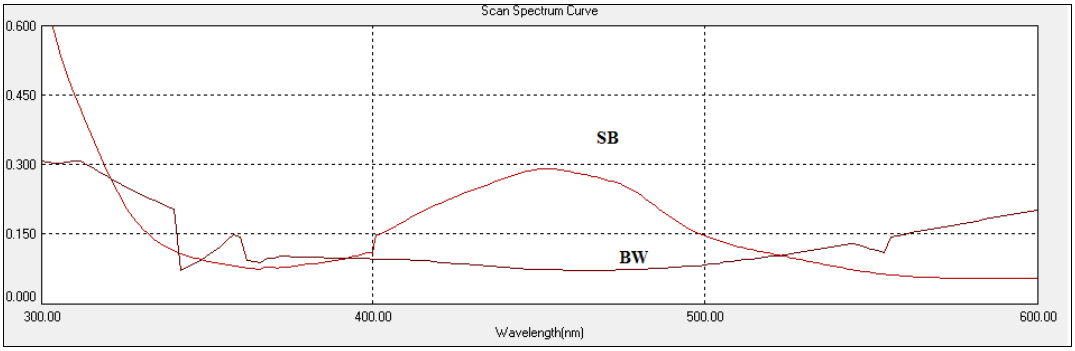
Interference solutions were prepared via dissolving 0.1gm of (vanillin, glucose, lactose, starch, sucrose) in an appropriate solvent (water or ethanol), and then the volume was made up to 100ml with distilled water.

A General Procedure for Determining Loratadine (LOR) Drug with O-Phenylenediamine

In this step, 0.5ml was transferred from 300µg/ml of LOR drug to a 10ml volumetric flask containing 0.5ml of $CuSO_4.5H_2O$ 0.01M, and 0.5ml of O-Phenylenediamine of 0.001M. The mixture was diluted to create orange solution absorbance at 453 nm.

Results and Discussion

While LOR was treated agreeing to the recommended method, displaying a band region of (400-600 nm). There was an absorption spectrum that formed the reaction product at 453nm. Yet, the blank had no important absorbance at this region (see Fig 2).



SB: Absorption spectrum of colored solution versus blank
BW: Absorption of blank versus distilled water

Fig 2: Final absorption spectrum of the determination of LOR

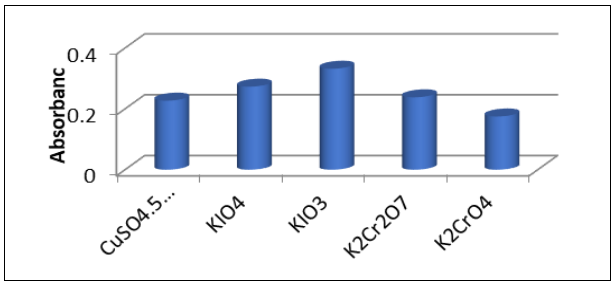


Fig 3: Types of oxidation reagents 0.01M

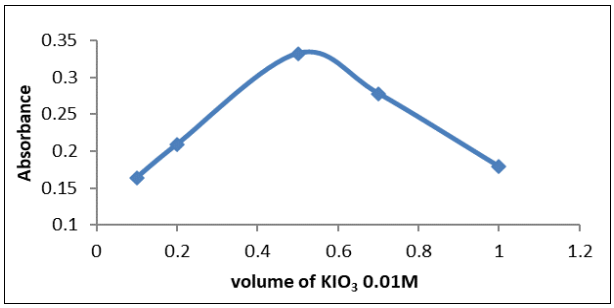


Fig 4: Volume of KIO_3 in Absorbance intensity

Reaction Conditions Optimization

To obtain the optimal reaction conditions, the various factors on the absorption were studied.

Types of Oxidation Reagents

By adding different oxidation reagents of 0.01M ($CuSO_4.5H_2O$, KIO_4, KIO_3, $K_2Cr_2O_7$, K_2CrO_4 solution, it was found that KIO_3 of 0.01M was acceptable. However, increasing the volume of solution over 0.5 ml caused the absorbance to decrease (see figures 3 and 4).

Effect of the Amount O-Phenylenediamine

The effect of O-Phenylenediamine was studied by adding different volumes (0.2-1ml) of (1×10^{-3}M) to the volumetric flasks till reaching 10ml with distilled water.

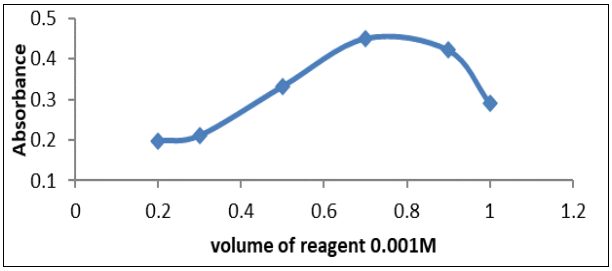


Fig 5: Volume of O-Phenylenediamine 0.001M in Absorbance intensity

Fig 5 shows that the volume of 0.7 ml of coupling reagent 1×10^{-3}M was the optimum quantity because it gave the highest absorption rate. Therefore, it was accepted in the subsequent experiments.

Acidic Solution Effect

This study was carried out using different volumes ranging between 0.1- 1mL of 1.0 M hydrochloric acid. Fig 6 clarifies the acid effect.

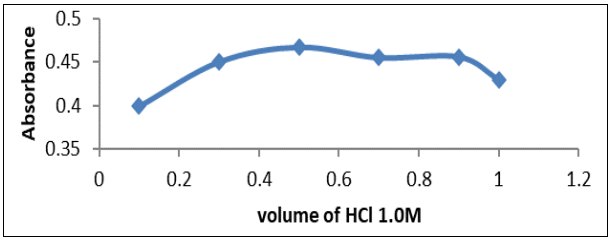


Fig 6: Volume of HCl 1.0M in Absorbance intensity

Oxidation Time Effect

To have a sequence of volumetric flasks, each flask had 0.5 ml of LOR (300 $\mu g.ml^{-1}$) and 0.5 ml of KIO_3 1×10^{-2}M. The solutions were left for different periods of time. Then, 0.7ml of O-Phenylenediamine reagent (1×10^{-3}M) **0.5** ml of **1.0**M hydrochloricacid solution were added till the volume reached 10ml with distilled water. The absorption of solutions was measured at 453 nm. The results are shown in Fig 7.

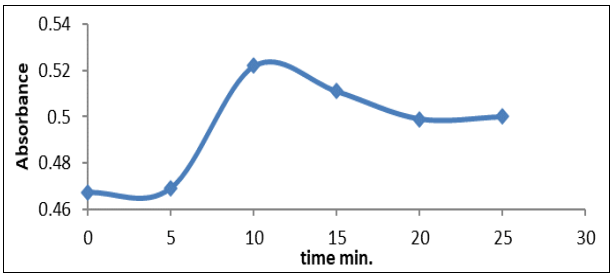


Fig 7: The effect of oxidation time

Effect of Temperature

The temperature (5-60°C) on the absorption of colored product was studied. The results are shown in Fig 8. The optimum temperature was 20-30. Thus, it was considered in the following experiments.

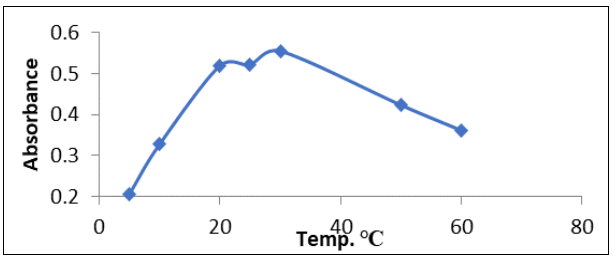


Fig 8: The effect of temperature

Stability Time Effect

The effect of stability time on the formed product was studied. It was detected that absorption remained constant directly after dilution for 60 min. The results in Fig 9.

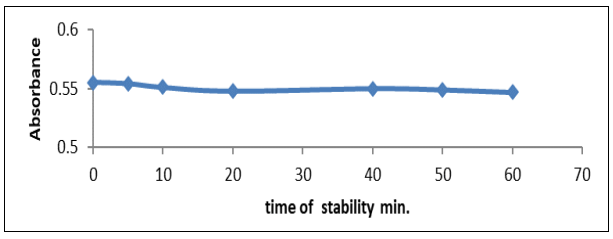


Fig 9: Stability time effect

Calibration curve

A calibration curve was built to obtain the optimum conditions. Fig 10 shows that the product obeyed Beer's law

in the range of 1–30 µg.ml^{-1} of LOR. Table 1 illustrates the statistical information of calibration curve of spectrophotometric determination of drug.

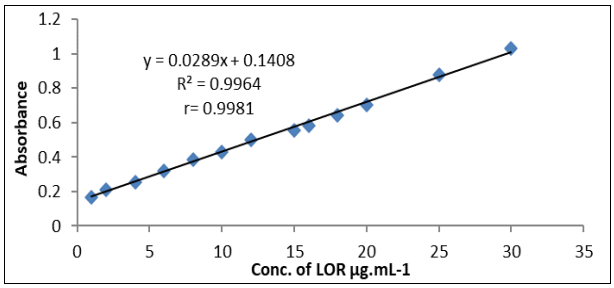


Fig 10: Calibration curve of LOR determination

Table 1: Statistical data for calibration curve for LOR

Parameter	Value
λmax nm	453
Color	Orange
Linear range (µg/mL)	1-30
Regression equation	A = 0.0289 [LOR] + 0.1408
Molar absorptivity L/mol.cm	11065.31
Correlation coefficient	0.9981
Intercept	0.1408
Slope	0.0289
Sandell's sensitivity (µg/cm^2)	0.0346

Precision and Accuracy

Precision and accuracy were studied by evaluating the absorption (n=6) at 453 nm for three concentrations of LOR in the limits of Beer's law. The average recovery of (100.11%) showed that the method was of great accuracy and precision. The results are shown in Table 2.

Table 2: Results of precision and accuracy

Conc. of LOR µg .ml^{-1}	Conc. of LOR Observed*	RE	%Recovery
6	6.13	2.19	102.19
15	14.33	-4.4	95.6
30	30.76	2.56	102.56

*n = 6

Detection Limits

Detection limits were considered by evaluating the absorption of blank at optimum conditions (eleven times) at 453 nm. shown in Table 3.

Table 3: Detection limits

Solution	b*	S**	LOD µg.ml^{1-}	LOQ µg.ml
blank	0.0289	0.001	0.114	0.346

*n=11, b= Slope, **S= Standard deviation.

Study of Interference

In pharmaceutical analysis, it is significant to test the selectivity towards excipients added to the pharmaceutical preparations, such as (glucose, vanillin, starch, lactose, sucrose), which do not interfere the determination of LOR and do not affect the reaction (15µg.ml^{-1}) of LOR. Thus, interference was analyzed. The results are shown in Table 4.

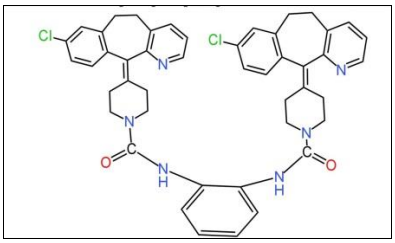
Table 4: recovery for (15µg.ml^{-1}) of LOR in the presence of diverse concentration of excipients

Excipients	Concentration (µg.ml^{-1})	LOR Conc. Taken (15 µg.ml^{-1})	
		Conc. Found* µg.mL-1	Recovery* %
Sucrose	1000	15.06	100.5
Vanillin		15.08	100.66
Glucose		15.04	100.33
Lactose		14.97	99.75
Starch		14.95	99.59

n = 3*

Stoichiometry of Reaction

Stoichiometry of reaction between LOR and the mixture was examined using Job's and mole- ratio methods. The values found through the two methods showed that the stoichiometry of coupling product drug and the reagent was 2:1 (see figures 11 and 12).



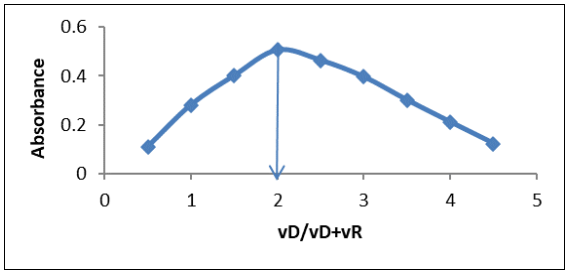


Fig 11: Job's method of oxidative coupling of LOR using reagent

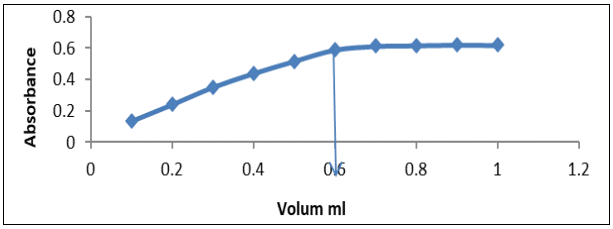


Fig 12: Molar ratio method of oxidative coupling of LOR using reagent

Applications

Direct Method

Different volumes (0.5,1 ml) of a pharmaceutical formulation solution 300 µg.ml^{-1} were transferred to 10 ml volumetric flasks. The resulting concentrations (15, 30 µg.ml^{-1}) were treated as in the construction of calibration curve. The absorbance was measured at 435 nm for 3 times. RE was calculated as shown in Table 5.

Table 5: Determination of LOR in pharmaceutical formulation

Conc. of LOR (µg/ml)	Conc. of LOR Observed*	RE
15	15.81	-2.5
30	30.03	0.32

*n = 3

Table 5 illustrates the success and efficiency of the developed method for the determination of LOR in pharmaceutical formulation.

Comparing the Proposed Method with Another Method

The present method was compared with another spectrophotometric method. The results of comparison are shown in Table 6.

Table 6: Comparison of the proposed method with other spectroscopic methods existing in literature

Analytical Parameters	Present method	Literature method [2]
Reagent used	O-Phenylenediamine	0.1N MethanolicHCl as solvent
λ max(nm)	453	275
Beer's law (µg/ml)	1-30	2-10
Molar absorptivity	11065	7905
Recovery (%)	100.11	100.15

Conclusion

A rapid spectrophotometric method was developed for the determination of microgram amounts of LOR using O-Phenylenediamine reagent at 453 nm based on the oxidative coupling reaction with good accuracy and agreement. The developed method showed a good agreement and was characterized by its easiness and sensitivity. It was carried out in an aqueous medium, without requiring any pre-treatment of sample. Certain working conditions were considered including organic solvents or temperature control. The method measured LOR in pure and pharmaceutical formulations.

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