Research Article

Ternary Complexation Process for New Spectrophotometric Assay of Levodopa using Ni(II) and 2,3-Diaminopyridine

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A novel, accurate, precise, inexpensive, and sensitive spectrophotometric approach is established to assay levodopa (LD) in both bulk drug and its pharmaceutical formulations. The method depends on the reaction of the ternary complex of a mixed-ligand type among LD, nickel(II) (Ni(II)), and 2,3-diaminopyridine (DAP) to form a stable complex of Ni-LD-DAP which is not extractable. The complex showed maximum absorption at 478 nm, with the apparent molar absorptivity of $4.93 \times 10^3 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ and Sandell's sensitivity of $0.04 \mu\text{g} \cdot \text{cm}^{-2}$. Beer's law is obeyed within the concentration range of $2\text{--}58 \mu\text{g} \cdot \text{mL}^{-1}$, and the regression line equation is as follows: $Y = 0.0251X + 0.0045$ ($R^2 = 0.9990$; $n = 5$). The detection limit and quantitation limit are found to be $0.1388 \mu\text{g} \cdot \text{mL}^{-1}$ and $0.4207 \mu\text{g} \cdot \text{mL}^{-1}$, respectively. The present study achieved reasonable accuracy (average recovery of 100.17%) and good precision (RSD did not exceed 1.71%). The developed method has been validated according to the current ICH guidelines (2013). The results of pure LD and pharmaceutical preparations using the recommended spectrophotometry are promising.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the extrapyramidal neuronal system, and the pathogenesis of the disease is due to deterioration of the cerebral dopaminergic pathways and the graduated degradation of dopamine (DA) in the black substance (substantia nigra). Mobility and control of the skeletal muscle system will be affected and major symptoms in people with PD are shown in the form of tremor, muscle stiffness, bradykinesia, and postural instability. Levodopa (L-3,4-dihydroxyphenylalanine, LD) (Figure 1) is a direct chemical precursor of DA and neurotransmitter modulator and is used as an effective drug

to treat PD, it penetrates the blood-brain barrier unlike DA, and it will metabolize as soon as it enters and undergoes a rapid decarboxylation by aromatic L-amino acid decarboxylase (AADC) to give DA [1–4].

However, not more than 1% of LD can be reached to the central nervous system because the metabolism of LD to DA by peripheral AADC will be outside the brain that releases amounts of DA in the circulatory system, which will exhibit undesirable side effects including vomiting, nausea, and hypotension, so it is necessitated that LD is combined with AADC inhibitors such as carbidopa, which reduces the effects of DA and increases the abundance of LD to the brain, hence increasing the kinetic benefit of the doses given of LD

FIGURE 1: Chemical structure of levodopa.

[5–8]. Several methods such as HPLC, electrochemistry [9, 10], and spectrophotometry [11, 12] are used to determine LD, despite the diversity of techniques used in the determination, but there are many obstacles (Table 1), for example, the chromatography and techniques connected with it are of high cost in terms of materials and tools used, need to experience in the operation system, sample preparation, and specific conditions in separation, and on the other hand, electrochemical methods are quick to accomplish the analysis, but it displays some errors in the analysis unless it provides a special environment such as the need to clean or polish the electrodes. Therefore, spectroscopic methods were used for ease, speed, accuracy, and low cost [13–18].

The investigated study characterizes the color reaction of LD by utilizing a mixed-ligand complex formation in an aqueous media, where there is no need for solvents or surfactants for its extraction. In previous works, dyes were exploited in the ternary complexes for the spectrophotometric analytical field, such as drugs [19], metals [20], biological molecules [21], and surfactants [22]. With the current pharmaceutical compound, the reagent phenyl-fluorone [23–28] was previously used. But herein, 2,3-diaminopyridine (DAP) is used as a chelating ligand, and Ni(II) is represented as the central metal. We noticed no previous work that used the same method of determining the LD in our literature review.

2. Experimental

2.1. Apparatus. All spectrophotometric measurements were carried out by using a Shimadzu UV-Vis Spectrometer (Model UV-1800, Tokyo, Japan) double beam and E-Chrom Tech single beam (Taipei, Taiwan), and Balance Kern Abs 120-4N four-digit balance (North Lincolnshire, United Kingdom) was used.

2.2. Reagents. All chemicals and reagents used were of analytical grade and the deionized water was used to guarantee the absence of foreign ions. The pure LD compound was kindly donated by Pioneer Pharmaceutical (Iraq-Sulaymaniyah). A solution ($1000\text{ }\mu\text{g}\cdot\text{mL}^{-1}$, $4.21 \times 10^{-3}\text{ mol}\cdot\text{L}^{-1}$) of Ni(II) chloride hexahydrate (BDH, Pool, UK) and a solution ($0.1\text{ mol}\cdot\text{L}^{-1}$) of DAP (Merck, Darmstadt, Germany) were prepared. Approximate concentrations ($0.1\text{ mol}\cdot\text{L}^{-1}$) for both NaOH (BDH, Pool, UK) and HCl (37%) (Fluka, Switzerland) were also prepared. Pharmaceutical tablet Dopal Forte® labeled 100 mg of LD per tablet (Ibn Hayyan Pharmaceuticals, Syria) was purchased from local drug stores.

2.3. Preparation of Analytical Solutions

2.3.1. Standard Solution of Levodopa. A stock solution ($100\text{ }\mu\text{g}\cdot\text{mL}^{-1}$, $5.05 \times 10^{-4}\text{ mol}\cdot\text{L}^{-1}$) of LD standard was prepared by dissolving 10 mg of pure LD powder in 100 mL of deionized water.

2.3.2. Preparation of Tablet Solution. Ten tablets were weighed and finely pulverized, and then a quantity equivalent to 10 mg was dissolved for preparing a solution of $100\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ in a 100 mL volumetric flask and then made up to mark with water. The obtained solution was filtered and then further diluted according to its linearity range.

2.4. General Procedure for Levodopa Analysis

2.4.1. Calibration Curve. The color reaction is based on the chelation of both LD and DAP with Ni(II), aliquots of stock solution ($100\text{ }\mu\text{g}\cdot\text{mL}^{-1}$) measured accurately were transferred ($0.5\text{--}14.5\text{ mL}$ of $100\text{ }\mu\text{g}\cdot\text{mL}^{-1}$) into separate 25 mL volumetric flasks so that the final concentrations were in the range $2\text{--}58\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ of LD, and then, 1.0 mL of Ni(II) solution was added to each flask followed by 1.2 mL of DAP solution; the contents of each flask were shaken thoroughly, each mixture was diluted to 25 mL with water and placed in a water bath for 30 min at 65 C and then immediately cooled under the tap to room temperature, and the resultant absorbance of the colored complex was determined at 478 nm against a reagent blank prepared similarly without the addition of the analyzed drug.

2.4.2. Procedure for Determination of the Levodopa in Pharmaceutical Tablet. Aliquots of drug solution equivalent to $2\text{--}58\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ were transferred into a 25 mL volumetric flask and the assay was applied using the same procedure described above.

3. Results and Discussion

3.1. Optimization of Analytical Conditions. Various experimental parameters affecting the absorbance intensity were optimized (Figure 2) by changing each parameter while keeping all others constant. And the constant amount of LD, 2.5 mL of stock solution ($100\text{ }\mu\text{g}\cdot\text{mL}^{-1}$), was transferred into a 25 mL volumetric flask (to become $10\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ as final concentration), and then, the absorbance was measured at 478 nm.

TABLE 1: Comparative analytical results of the proposed approach with various previously described methods for determining levodopa.

Method of analysis	Principle	Linearity	Limitation
Spectrophotometry	The method was based on the reaction of levodopa with vanadium(V) which was reduced to vanadium(IV) and the formed complex with eriochrome cyanine R to give the product has $\lambda_{\max}$ at 565 nm [11].	0.028–0.84 $\mu\text{g}\cdot\text{mL}^{-1}$	Nonselective among catecholamines
	The method was based on the reaction of alizarin red with the primary amino group present in the levodopa in basic medium; a purple color product has $\lambda_{\max}$ at 588 nm [12].	10–60 $\mu\text{g}\cdot\text{mL}^{-1}$	Also, nonselective among catecholamines
HPLC coupled with chemiluminescence	The method depends on the improved chemiluminescence (CL) signal of the online gold particle-catalyzed luminol- H_2O_2 system by levodopa, and the HPLC-CL detection system consists of an HPLC system and a CL detection system. The sample separation was achieved on an ODS column at 40°C with gradient elution at a flow rate of 1.0 $\text{mL}\cdot\text{min}^{-1}$. The mobile phase was composed of a mixture of methanol and 0.2% aqueous phosphoric acid (5:95, V/V) [7].	10–1000 $\text{ng}\cdot\text{mL}^{-1}$	Expensive method
HPLC coupled with mass spectrometry	Separation is achieved on a C_8 column set at 30°C, with a mobile phase consisting of a gradient of water and acetonitrile: methanol (90:10 v/v), both containing 0.1% formic acid, eluted at 700 $\mu\text{L}\cdot\text{min}^{-1}$ [8].	20–1000 $\text{ng}\cdot\text{mL}^{-1}$	Expensive method
Voltammetry	This electrochemical method is based on chloranil(CA) modified carbon paste electrode (CAMCPE) in the voltammetric determination of levodopa in an aqueous solution [9].	3–500 $\mu\text{mol}\cdot\text{L}^{-1}$	Lack of reproducibility because the electrochemical activity of CAMCPE decreased during successive scans due to the removal of the mediator by dissolving it into an aqueous solution, so the surface of the electrode must be renewed before each determination
	This method is based on adsorption stripping voltammetry by using a multiwalled carbon nanotubes-Nafion modified glassy carbon electrode [10].	3.5×10^{-7} – 1.5×10^{-5} $\text{mol}\cdot\text{L}^{-1}$	Some cations may have effect on the analysis of levodopa because they interact with anion sites SO_3^- in the Nafion film, which will reduce the signal of levodopa, so it needs certain conditions to get rid of this interfering as in Fe(III) which needs to add 1.0×10^{-3} $\text{mol}\cdot\text{L}^{-1}$ oxalic acid to eliminate it

3.1.1. Effect of First Ligand Amount (Ni(II)). Different amounts of 4.21×10^{-3} $\text{mol}\cdot\text{L}^{-1}$ Ni(II) solution in the range of 0.2–2.0 mL were added to a fixed mixture for 10 $\mu\text{g}\cdot\text{mL}^{-1}$ of LD and 1.0 mL of 0.1 $\text{mol}\cdot\text{L}^{-1}$ of DAP solution to predict the effect of Ni(II) amount on the absorbance. It was noted that 1.0 mL of 4.21×10^{-3} $\text{mol}\cdot\text{L}^{-1}$ of Ni(II) was used to produce a maximum absorbance, and this volume was chosen as the optimum value to examine other variables (Figure 3).

3.1.2. Effect of Second Ligand Amount (DAP). After the optimum quantity of the central metal was selected, the effect of the second ligand (DAP) was investigated. Different amounts of 0.1 $\text{mol}\cdot\text{L}^{-1}$ DAP solution in the range of 0.2–2.0 mL were added to the previous order (10 $\mu\text{g}\cdot\text{mL}^{-1}$ of LD + 1.0 mL of 4.21×10^{-3} $\text{mol}\cdot\text{L}^{-1}$ of Ni(II)). It was noted

that 1.2 mL of 0.1 $\text{mol}\cdot\text{L}^{-1}$ of DAP was used to produce a maximum absorbance, and this volume was chosen as the optimum value to check other variables (Figure 4).

3.1.3. Effect of Order of Addition. All sequence addition of reactants were studied to determine the order with the highest absorption, where it was at LD + Ni(II) + DAP (order III) as shown in (Table 2).

3.1.4. Effect of pH. A simple increase of acid or base into the solution makes the color of the solution disappear or turbid, and this negatively affects the shape and absorption of the ternary complex, so throughout all the experiments, the addition of acid or base to the solution was excluded.

FIGURE 2: Absorption spectrum at 487 nm of LD using the suggested procedure.

FIGURE 3: Effect of Ni(II) volume on the maximum absorbance signal of LD.

FIGURE 4: Effect of DAP volume on the maximum absorbance signal of LD.

TABLE 2: Order of addition.

Order number	Order of addition	Absorbance
I	LD + DAP + Ni(II)	0.187
II	DAP + Ni(II) + LD	0.193
III	LD + Ni(II) + DAP	0.231

3.1.5. Effect of Temperature. The effect of temperature on the absorption of the solution was studied and it has been observed that increasing the heat increases the absorption of the solution, as shown in Figure 5.

3.1.6. Effect of Reaction Time. The color of the complex does not settle immediately but continues to increase its intensity until the end of the reaction, and the process takes more than 80 minutes (Figure 6). Therefore, time and temperature variables were taken into consideration to facilitate the recording of absorbance value. A mixture was heated at 55, 60, 65, and 70 °C for 20–50 min where it was observed that the greatest and most stable absorbance was at 65 °C for 30 minutes, and the color of the solution remained stable for the next day after cooling.

3.2. Validity of the Method. The validity of the analytical method has been verified according to the ICH guidelines [24], with relating to the accuracy, precision, and others as follows.

3.2.1. Linearity Range. The calibration curve was drawn (Figure 7) using the optimum conditions mentioned above, and the linearity of the proposed method was evaluated by measuring the absorbance of fifteen concentrations covering the range $2\text{--}58\text{ }\mu\text{g}\cdot\text{mL}^{-1}$.

The analytical parameters for the determination of LD were collected statistically (Table 3), the regression equation was $A = 0.0251^\circ\text{C} + 0.0045$ ($n = 5$; $R^2 = 0.9990$). The mean recovery percentage of twelve LD standard solutions within the range of $14\text{--}58\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ was calculated for the proposed spectrophotometric method to ensure accuracy. Each solution was measured for three replicates (Table 4).

3.2.2. Limit of Detection (LOD) and Limit of Quantitation (LOQ). The proposed spectroscopic system displayed high sensitivity to the studied analyte with LOD ($3.3\sigma/s$) and LOQ ($10\sigma/s$) of 0.1388 and $0.4207\text{ }\mu\text{g}\cdot\text{mL}^{-1}$, respectively. The obtained analytical data revealed high sensitivity for the determination of LD using a ternary complexation procedure with Ni(II) and DAP.

3.2.3. Precision and Accuracy. The accuracy of the recommended spectrophotometric method was evaluated by calculating the average recovery (%) of nine LD solutions in the range of 2 to $58\text{ }\mu\text{g}\cdot\text{mL}^{-1}$. The final result is $99.6 \pm 0.4\%$, which shows that the accuracy of the proposed method is very high (Table 4). In addition, to study the precision of the proposed method, intraday precision and interday precision were applied, and three different concentrations of LD were determined in pure form through three consecutive occasions or repeated analyses over three consecutive days (Table 5). The estimated RSD percentage is between 0.2 and 0.7% in the interday test and between 0.2 and 0.8% in the

FIGURE 5: Effect of temperature for the maximum absorbance signal on the determination of LD.

FIGURE 6: Effect of time per min on the maximum absorbance signal of LD.

intraday test, which indicates that the proposed method has good accuracy in the determination of LD.

3.2.4. Selectivity. The selectivity of the suggested method against the assay of LD was measured by the determination of LD in the presence of some possible interfering substances. Among these, cations, anions, and other additive substances are K^+ , Na^+ , Mg^{2+} , Ca^{2+} , and SO_4^{2-} , glucose, starch, lactose, citric acid, and magnesium stearate. Under optimal conditions, the detection of $10\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ LD in the presence of $1.0\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ of each interfering substance was studied using the recommended method. Table 6 shows that no significant interference was found. Therefore, the recommended procedure can be considered as an alternative method to determine LD.

3.2.5. Reaction's Stoichiometry. The reaction ratio of LD with Ni(II) and DAP was measured using the method of continuous variations (Job's method). Several equimolar ($5 \times 10^{-3}\text{ mol}\cdot\text{L}^{-1}$) solutions, including varying quantities of LD ($0.1\text{--}0.9\text{ mL}$) and the DAP reagent ($0.9\text{--}0.1\text{ mL}$) in volumetric flasks of 10 mL , are utilized in this technique. The extra solutions are added according to the optimum working procedure, and the absorbance is measured at 478 nm

FIGURE 7: Calibration graph of LD determination using the proposed procedure.

TABLE 3: Analytical parameters for the determination of LD (Ni-LD-DAP).

Parameter	Values
Linearity, $\mu\text{g}\cdot\text{mL}^{-1}$	2–58
Calibration curve equation	$A = 0.0251^\circ\text{C} + 0.0045$
Slope	0.0251
Intercept	0.0045
Correlation coefficient, R	0.9995
Molar absorptivity, $\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$	4.93×10^3
Sandell's sensitivity, $\mu\text{g}\cdot\text{cm}^{-2}$	0.04
LOD, $\mu\text{g}\cdot\text{mL}^{-1}$	0.1388
LOQ, $\mu\text{g}\cdot\text{mL}^{-1}$	0.4207
RSD, %	1.71
Accuracy (rec% $\pm$ SD)	100.17 ± 1.71

TABLE 4: Analytical parameters for the determination of LD.

Sample	Taken, $\mu\text{g}\cdot\text{mL}^{-1}$	Found, $\mu\text{g}\cdot\text{mL}^{-1}$	% recovery
1	14	13.76	98.29
2	18	17.75	98.61
3	22	22.53	102.41
4	26	25.72	98.92
5	30	30.89	102.97
6	34	34.48	101.41
7	38	38.86	102.26
8	42	41.65	99.17
9	46	46.43	100.93
10	50	49.62	99.24
11	54	53.61	99.28
12	58	57.19	98.6
Mean $\pm$ SD		$100.17 \pm 1.71\%$	
n		12	
Variance		2.91	
SE%		0.17	
%RSD		1.71	

TABLE 5: Evaluation of the proposed method using intraday and interday assay.

Sample	LD determination using the proposed method			% RSD
	Taken, $\mu\text{g}\cdot\text{mL}^{-1}$	Found, $\mu\text{g}\cdot\text{mL}^{-1}$	% recovery $\pm$ SD, ($n = 3$)	
Intraday assay	81218	8.0111.9318.09	$100.13 \pm 0.899.42 \pm 0.3100.50 \pm 0.6$	0.80.30.2
				0.7
Interday assay	81218	7.9611.9517.93	$99.50 \pm 0.799.58 \pm 0.299.61 \pm 0.3$	0.2
				0.3

TABLE 6: Tolerable limits of $10 \mu\text{g}\cdot\text{mL}^{-1}$ LD using the proposed procedure.

Interferences	Tolerable values
Glucose, lactose, starch	280
Zn^{2+} , Mg^{2+} , Ca^{2+} , Na^{+} , and K^{+}	850
Citric acid, magnesium stearate	160

FIGURE 8: Stoichiometry of the reaction of the proposed method of LD determination using the ternary complexation procedure.

TABLE 7: Analytical results of LD in pure form and pharmaceutical preparations determined by spectrophotometry using the ternary complexation procedure.

Sample	Taken, $\mu\text{g}\cdot\text{mL}^{-1}$	Found, $\mu\text{g}\cdot\text{mL}^{-1}$	% recovery $\pm$ SD, ($n=6$)	% SE	Present method	t -test	F-test
Pure drug	51015	4.9210.0214.84	$99.4 \pm 0.6100.2 \pm 0.78.9 \pm 0.3$	0.240.290.12	100.01 ± 0.7	$1.78(2.228)^*$	$3.01(5.05)^*$
Tablets	51015	4.919.9714.95	$98.2 \pm 0.399.7 \pm 0.499.7 \pm 0.9$	0.120.160.37	$\text{SE} = 0.29$ $n = 6$	$1.91(2.228)^*$	$2.18(5.05)^*$

*Figures in parentheses are the tabulated values of t -test and F-test at 95% confidence limit.

against a blank. The ratio of the LD to the DAP is 1 : 1, as illustrated in Figure 8.

3.3. Analytical Application. The developed spectrophotometric approach was used for the assay of LD in the drug substance, with a recovery average of 100.01 ± 0.7 . In addition, an established approach was used to estimate the LD of its drug form. The data obtained (Table 7) were statistically evaluated and then compared with the data obtained in another previously published spectrophotometric article [25].

4. Conclusion

The present study introduced a low-cost, accurate, and precise spectrophotometric method based on a ternary complexation procedure to determine LD using Ni(II) and DAP as first and second ligands. The proposed method provided promising results for the assay of LD in its bulk drug and pharmaceutical formulations. The developed method exhibited a linear relationship over a concentration range of $2\text{--}58 \mu\text{g}\cdot\text{mL}^{-1}$. Also, the acquired results indicated that the present procedure is simpler and more flexible to determine LD without significant interference from other coformulated species or possible interfering compounds.

Data Availability

The data underlying the results presented in the study are available within the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this study.

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