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Simultaneous determination of amlodipine and lisinopril dihydrate using fourth derivative spectroscopy

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ABSTRACT

A new fast and simple selective method for the simultaneous determination of lisinopril dihydrate and amlodipine in combined drugs was developed using the fourth derivative spectrum method, based on the zero-crossing-point technique for the determination of compounds in drugs. The wavelength values for lisinopril dihydrate and amlodipine in solvent medium were found to be (203, 207, and 231 nm) and (215, 254, and 277 nm), respectively, with the average obeying Beer's law in the range of lisinopril dihydrate 2.0 to 45.0 µg/mL and amlodipine 2.0 to 35.0 µg/mL. Lisinopril dihydrate has molar absorptivity regions (9227.76-11700.28 L/mol.cm, 203 nm), (15320.74-20795.59 L/mol.cm, 207 nm), and (2207.60-3311.40 L/mol.cm, 231 nm), while amlodipine (5886.72-10914.96 L/mol.cm, 215 nm), (5518.8-6418.16 L/mol.cm, 254 nm) and (1676.08-1921.36 L/mol.cm, 277 nm). The recovery rate of lisinopril dihydrate in the pharmaceutical dosage forms range was 95.13 to 102.60% and amlodipine 95.14 to 102.80%. The results of the relative error showed that the interferences did not affect the method of estimating these compounds. The proposed method has been successfully applied to estimate pharmaceutical dosage forms.

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1. Introduction

Lisinopril dihydrate (LSD) is one of the long-acting angiotensin-converting enzyme (ACE) inhibitors allowing drugs with the chemical name 1-[6-amino-2-(1-carboxy-3-phenylpropylamino)-hexanoyl]-pyrrolidine-2-carboxylic acid (Scheme 1) [1]. Where it is considered a competitive inhibitor of angiotensin-converting enzyme (ACE) prevents the conversion of angiotensin I to angiotensin II, which works doing decrease sodium and water retention in the body, thus reducing angiotensin II-stimulated aldosterone secretion [2,3].

Amlodipine (ALP), 3, 5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl, 3-ethyl 5-methyl ester, is a calcium channel blocker (Scheme 1). It is used to treat chronic angina, hypertension, and myocardial infarction, as well as a specific type of chronic angina [4-6]. It prevents coronary arterial contraction and narrowing of the arteries, leading to increased blood flow and myocardial oxygenation [7]. Pharmaceutical formulations with the combination of amlodipine as a calcium channel blocker channel blocker and lisinopril as a long-acting ACE inhibitor have been made available on the market to treat hypertension [8].

Several analytical methods for the determination of LSD and ALP are revealed in the literature review, such as high performance thin layer chromatography (HPTLC) for the simultaneous quantification of LSD and ALP with other antihypertensive drugs [9]; Based on the absorption ratio method and the isoabsorptive point, these methods enable the determination of LSD and ALP in the same tablet dosage forms [10,11], at 25 °C, Column C18, 5 µm, 150 mm × 4.6 mm id as stationary phase and mixture solution from acetonitrile: sodium dihydrogen phosphate (50:50, *v:v*) has been succeeded in estimating simultaneous estimation of LSD and ALP in pharmaceutical dosage forms [12]. Furthermore, the first or second derivative spectrum method was used to determine LSD and ALP, which were prepared in 0.1 M HCl solution and gave accurate results without interference [13]. The derivative spectroscopic techniques are considered simple and direct for the simultaneous determination of mixtures in their pharmaceutical preparation [14]. Thus, the fourth derivative method achieved the desired purpose and has been utilized to determine LSD and ALP mixtures in their pharmaceutical preparations simultaneously.

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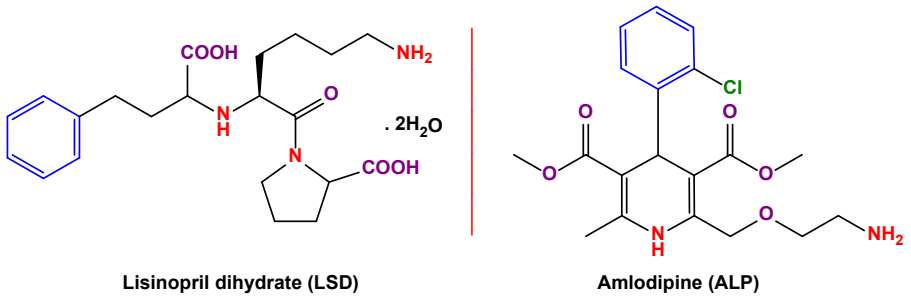

Scheme 1. Structures of lisinopril dihydrate (LSD) and amlodipine (ALP).

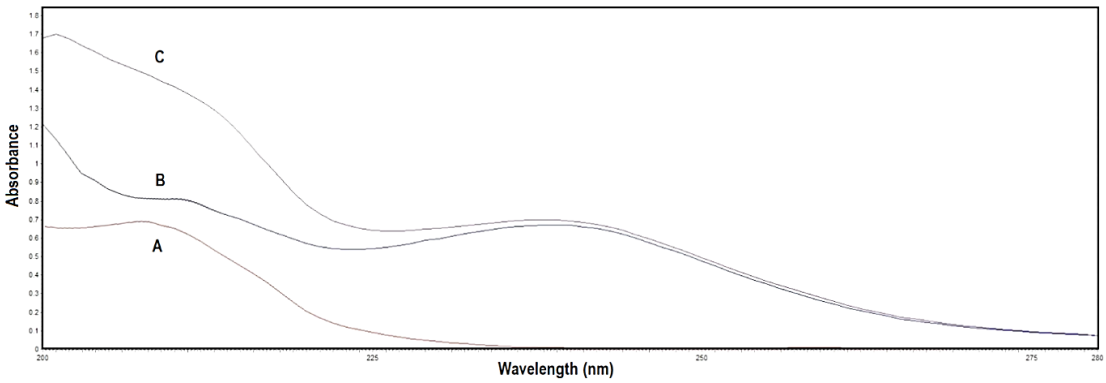

Figure 1. Zero-order order spectrums of (A) LSD, (B) ALP, and (C) overlap LSD and ALP.

2. Experimental

2.1. Apparatus

All spectrophotometric absorbances were measured using the Labomed Inc. 2602-UV-vis spectrophotometer using 1-cm quartz cells. pH measurements were taken using a HANNA brand pH211 model pH meter.

2.2. Chemicals

All chemical reagents used in this work were of high purity (Lisinopril dihydrate (99% purity, CAS 83915-83-7) supplied by Meryer Company, China and amlodipine (99% purity, CAS 88150-42-9) supplied by Energy Chemical Company, China.

2.3. Derivative spectrophotometry measurement

Standard solutions of LSD and ALP were scanned in the wavelength range of 200-300 nm, where distilled water was used as a blank solution. The zero-order and fourth-derivative spectra were measured using UVWin7 software (V5.2.0.1104), and no smoothing was required.

2.4. Preparation of standard solutions

Lisinopril dihydrate: A stock solution of LSD (500 µg/mL) was prepared in a 100 mL volumetric flask by dissolving 0.05 g of raw LSD in the appropriate amount of distilled water containing 1 mL of 1 M HCl. The volume was completed in the 100 mL volumetric flask. A standard working solution of LSD (100 µg/mL) was prepared by diluting 20 mL of the stock solution with distilled water in a 100 mL volumetric flask.

Amlodipine: A stock solution of ALP (500 µg/mL) was prepared by dissolving 0.05 g of raw ALP in the appropriate volume of distilled water containing 1 mL of 1 M HCl and then transferring it to a 100 mL volumetric flask, completing the volume by distilled water. A standard working solution of ALP (100 g/mL) was prepared by transferring 20 mL of the stock solution in a 100 mL volumetric flask and diluting it with distilled water to mark.

2.5. Assay preparation of pharmaceutical formulations

The 10 tablets (Hipril-A; LSD 5 mg/ALP 5 mg) were accurately weighed (1.906 g; for ten tablets) and crushed to a fine powder. The portion equivalent to 0.05 mg for the pharmaceutical formulation was transferred to a 25 mL beaker, an appropriate amount of distilled water was then added containing 1 mL of 1 M HCl, and sonication was performed for 20 minutes with swirling. After that, the resultant solution was filtered through the Whatman filter paper, and the precipitate residue on the filter paper was washed several times with distilled water. Finally, the solution was transferred to a 100 mL volumetric flask and the volume was completed for a mark.

3. Results and discussion

When there is convergence in the absorbance spectrum of drugs when using zero-order spectra, and each compound spectrum interferes with the other spectrum, the derivative spectrophotometry technique is used [15]. LSD appears to have one maximum absorbance band at 205 nm. On the contrary, ALP has two maximum absorbance bands at 212 and 238 nm with the shoulder, while the spectrum of the mixture of the two medicinal compounds gave two bands for each of 216 and 235 nm (Figure 1). The derivative spectra technique can resolve compounds with the same or near-wavelength region that generates inseparable interference in zero-order spectrophotometry.

3.1. Fourth derivative spectrum of LSD

The fourth derivative spectrum of LSD is shown in Figure 2. LSD has a positive peak at 203, 207, and 231 nm with one negative peak at 221 nm.

Table 1. Regression analysis of LSD and ALP individually.

λ (nm)	Concentration (µg/mL)		Regression equation [19]	R^2
	LSD	ALP		
203	2.0-45	0	y = 0.0216x – 0.0045	0.9997
207	2.0-45	0	y = 0.0331x – 0.0102	0.9993
231	2.0-45	0	y = 0.0068x + 0.0102	0.9970
215	0	2.0-35	y = 0.0049x + 0.0202	0.9988
254	0	2.0-35	y = –0.0145x + 0.0015	0.9996
277	0	2.0-35	y = 0.0049x + 0.0035	0.9971

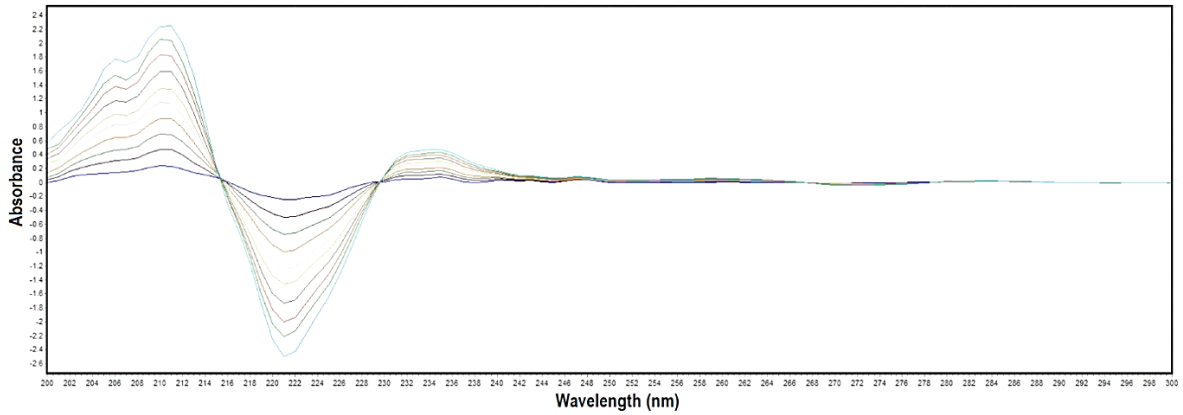

Figure 2. Fourth derivative spectrum of LSD (2-45 µg/mL).

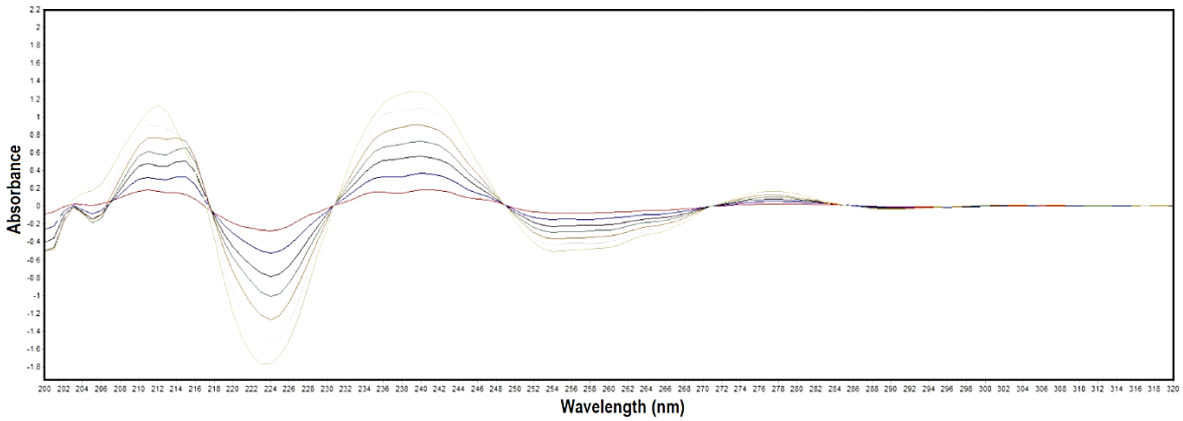

Figure 3. Fourth derivative spectrum of ALP (2-35 µg/mL).

These peaks could be estimated when LSD is present alone. LSD has more than one zero crossing point at 215 and 228 nm, where LSD has zero absorbance at any concentration.

3.2. Fourth derivative spectrum of ALP

Figure 3 shows the fourth derivative spectrum of ALP concentrations. ALP has appeared at more peaks that could be used to estimate when presenting alone, with three positive peaks at 215, 242, and 277 nm and one negative peak at 205, 223, and 254 nm. These peaks could be used to estimate when presented alone. ALP has more than one zero crossing point at 203, 207, 231, 251, and 271 nm. It has zero absorbance for any concentration.

3.3. Simultaneous determination of LSD and ALP

Figure 4 show the simultaneous determination of different concentrations of LSD at 203, 207, and 231 nm in the presence of 5-30 µg/mL ALP, where ALP has a zero-crossing point; therefore, LSD can be determined in the presence of ALP. Also, under the same condition, when the simultaneous determination of the different concentrations of ALP in the presence of 5-45 µg/mL LSD, we selected 215, 254, and 277 nm where LSD has a zero-crossing point at these wavelengths, as shown in Figure 5. The LSD and ALP concentration range was selected according to the zero-crossing point [16]. Based on this, the peak to baseline [17] can be used to measure LSD concentrations separately or simultaneously at 203, 207, and 231 nm and ALP at 215, 254, and 277 nm.

3.4. Calibration graphs for the analysis of LSD and ALP

The calibration curves were constructed using the fourth-order derivative response. Various concentrations can be used to analyze the drug separately or simultaneously. All calibration curve parameters are listed in Figure 6 and Table 1. Describe the compound individually. Table 2 shows the results of the calibration curve at variable concentrations of LSD in the presence of a fixed concentration of ALP, while Table 3 shows the reverse. Based on this, we determine the concentration range that obeys Beer's law [18]. Other characteristics, such as molar absorptivity and Sandell's sensitivity values, are given.

3.5. Accuracy and precision of the proposed method

To investigate the accuracy and precision of the proposed method, an aliquot (7 and 15 µg/mL) concentration of ALP and LSD, each concentration, was repeated three times individually (Table 4). The recovery% and error% were calculated as accuracy and the relative standard deviation as precision [20].

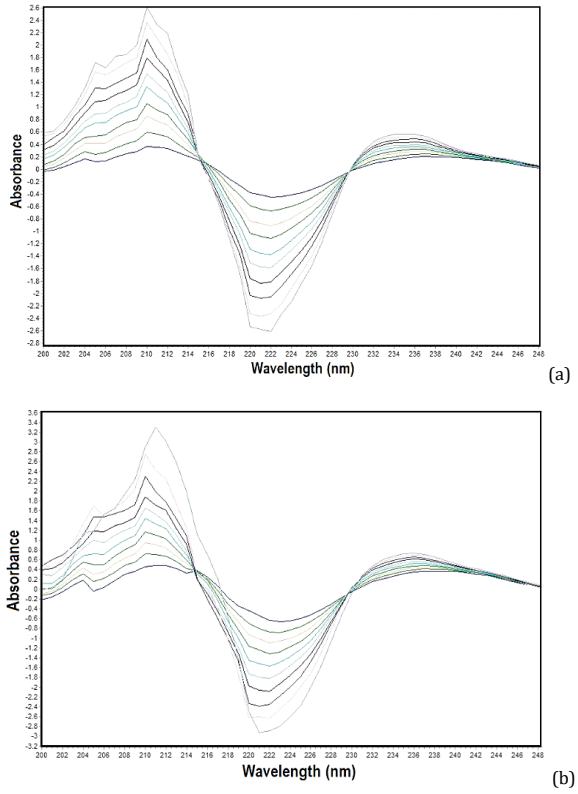

Figure 4. Simultaneous determination of LSD in the presence of (a) 5 µg/mL and (b) 30 µg/mL ALP.

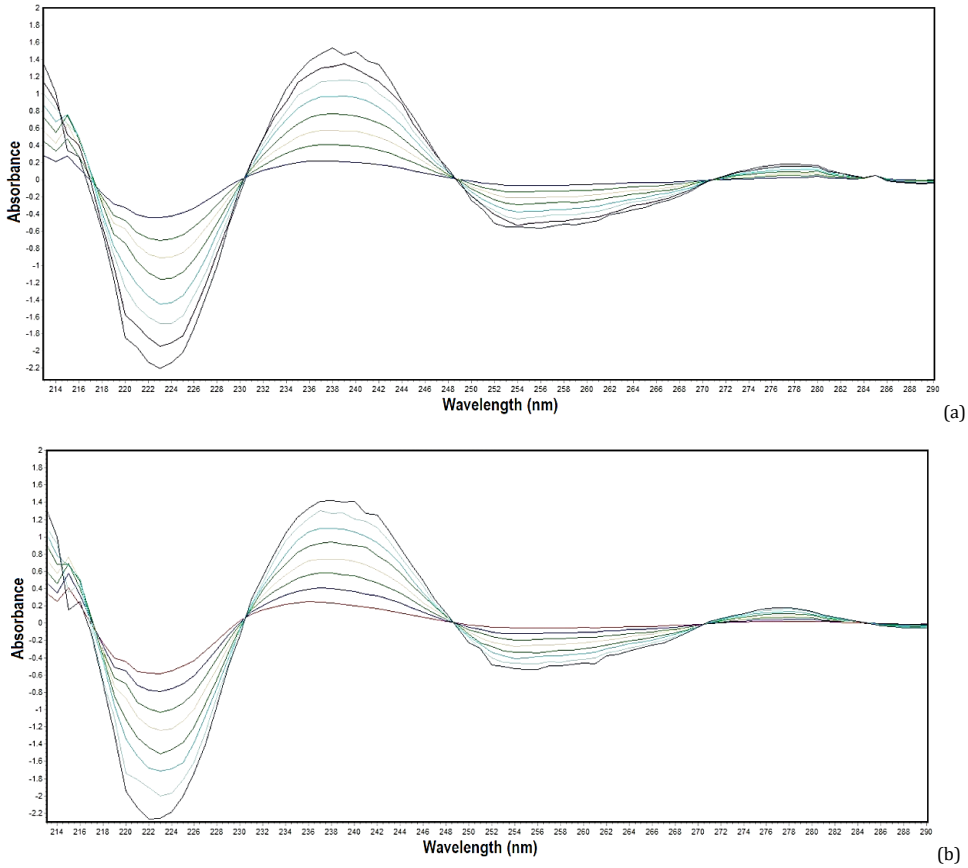

Figure 5. Simultaneous determination of ALP in the presence of (a) 5 µg/mL and (b) 45 µg/mL LSD.

Table 2. Regression analysis of LSD and ALP in a mixture solution.

λ (nm)	Concentration (µg/mL)		Regression equation	R^2	Molar absorptivity (L/mol.cm)	Sandell's sensitivity (µg/cm²)
	LSD	ALP				
203	2-45	5	y = 0.0209x – 0.0085	0.9979	9227.76	0.047
	2-45	10	y = 0.0215x – 0.0257	0.9976	9492.68	0.046
	2-40	15	y = 0.0224x – 0.0513	0.9888	9890.05	0.044
	2-35	20	y = 0.0241x – 0.0548	0.9906	10640.63	0.041
	2-30	25	y = 0.0265x – 0.0891	0.9918	11700.28	0.037
	2-35	30	y = 0.0258x – 0.0134	0.9877	11391.21	0.038
207	2-45	5	y = 0.0347x – 0.0027	0.9979	15320.74	0.028
	2-45	10	y = 0.0380x – 0.0428	0.9963	16777.76	0.026
	2-45	15	y = 0.0405x – 0.1294	0.9859	17881.56	0.024
	2-35	20	y = 0.0428x + 0.0034	0.9877	18897.06	0.023
	2-40	25	y = 0.0399x – 0.1247	0.9901	17616.65	0.025
	2-45	30	y = 0.0471x + 0.0904	0.9966	20795.59	0.021
231	2-45	5	y = 0.0063x + 0.0114	0.9969	2781.57	0.158
	2-45	10	y = 0.0062x + 0.0184	0.9962	2737.42	0.158
	2-45	15	y = 0.0052x + 0.0405	0.9806	2295.90	0.192
	2-35	20	y = 0.0058x + 0.0354	0.9678	2560.82	0.172
	2-30	25	y = 0.0050x + 0.0370	0.9857	2207.60	0.200
	2-35	30	y = 0.0075x + 0.1523	0.9797	3311.40	0.133

Table 3. Regression analysis of LSD and ALP in a mixture solution.

λ (nm)	Concentration (µg/mL)		Regression equation	R^2	Molar absorptivity (L/mol.cm)	Sandell's sensitivity (µg/cm²)
	LSD	ALP				
215	5	2-35	y = 0.0223x + 0.0945	0.9846	9116.24	0.044
	10	2-30	y = 0.0248x + 0.0490	0.9839	10138.24	0.040
	15	2-35	y = 0.0267x + 0.0057	0.9933	10914.96	0.037
	25	2-30	y = 0.0144x + 0.0652	0.9572	5886.72	0.069
254	5	2-35	y = -0.0157x + 0.0139	0.9986	6418.16	0.063
	10	2-35	y = -0.0137x + 0.0078	0.9989	5600.56	0.072
	15	2-35	y = -0.0142x + 0.0099	0.9991	5804.96	0.070
	25	2-35	y = -0.0136x + 0.0103	0.9988	5559.68	0.073
	35	2-35	y = -0.0135x + 0.0185	0.9973	5518.8	0.074
	45	2-35	y = -0.0140x + 0.0260	0.9958	5723.2	0.071
277	5	2-35	y = 0.0047x – 0.0022	0.9988	1921.36	0.212
	10	2-35	y = 0.0044x – 0.0023	0.9983	1798.72	0.227
	15	2-35	y = 0.0043x – 0.0057	0.9989	1757.84	0.232
	25	2-35	y = 0.0043x – 0.0075	0.9965	1757.84	0.232
	35	2-35	y = 0.0043x – 0.0114	0.9912	1757.84	0.232
	45	2-35	y = 0.0041x – 0.0151	0.9831	1676.08	0.243

Table 4. The accuracy and precision of the proposed method.

λ (nm)	Concentration (µg/mL)		Found (µg/mL)	Precision	Accuracy	
	LSD	ALP		Relative standard deviation (%)	Percentage error	Percentage recovery
203	7	7	6.95	1.94	-0.72	99.28
	15	15	14.85	2.51	-0.86	99.00
207	7	7	6.90	0.52	-1.43	98.57
	15	15	14.93	0.21	-0.47	99.53
231	7	7	7.24	3.50	+3.42	103.42
	15	15	14.87	2.71	-0.87	99.13
215	7	7	6.87	0.90	-1.86	98.14
	15	15	15.97	0.41	-0.20	99.80
254	7	7	6.93	2.04	-1.00	99.00
	15	15	14.86	0.25	-0.94	99.06
277	7	7	7.05	2.93	+0.70	100.71
	15	15	14.81	2.19	-1.27	98.73

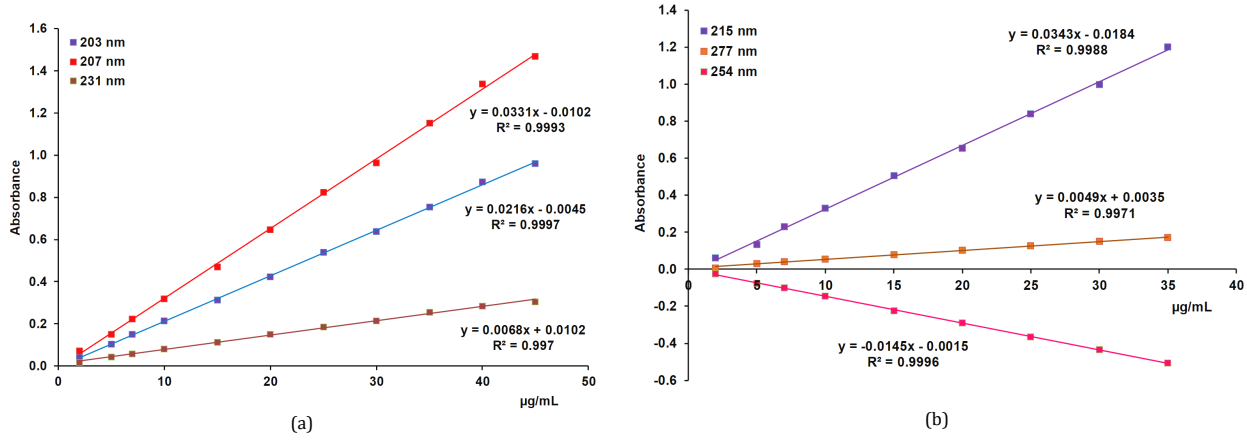

Figure 6. (a) Calibration curve of the LSD at 203, 207, and 231 nm and (b) Calibration curve of the ALP at 215, 254, and 277 nm.

Table 5. The limit of detection LOD and quantification LOQ.

λ (nm)	SD	LOD (µg/mL)	LOQ (µg/mL)
203	0.0021	0.1821	0.6073
207	0.0026	0.2373	0.7912
231	0.0008	0.371	1.2371
215	0.0040	0.3942	1.3141
254	0.0008	0.1703	0.5677
277	0.0005	0.3226	1.0756

Table 6. The effect of common excipients on the determination of drugs.

Excipients		Concentration (µg/mL)	λ (nm) / The percentage of error					
			203	207	231	215	254	277
The relative error percentage ±5.0%	Arabic gum	100	0.45	2.23	0.86	2.73	0.75	0
		200	1.79	2.86	1.72	2.80	0.76	2.50
	Fructose	100	0	1.47	1.72	0.32	2.27	0
		200	1.86	1.64	1.73	3.55	3.03	2.50
	Sucrose	100	0.99	1.76	1.70	0.21	0.75	2.4
		200	0.89	4.71	3.44	1.07	1.51	2.56
	Potassium chloride	100	0.96	0.95	2.58	1.50	0	0
		200	0.89	1.97	0.86	2.84	0.76	2.50
	Glucose	100	0.48	0.33	0	0.53	1.51	2.50
		200	1.44	0.65	0.86	0.32	1.51	2.50

Table 7. The results of the proposed method on pharmaceutical drugs and the *t*-test for LSD and ALP.

λ (nm)	Hipril-A (5 mg:5 mg)		Found	Relative standard deviation (%)	Percentage error	Percentage recovery	t-Test
	LSD	ALP					
203_{LSD}	7	7	7.18	2.77	+2.57	102.57	±1.64
	15	15	14.27	3.57	-4.87	95.13	±2.51
207_{LSD}	7	7	6.96	2.06	-0.42	99.42	±0.37
	15	15	14.96	1.35	-0.27	99.73	±0.27
231_{LSD}	7	7	6.87	1.75	-1.86	98.14	±1.37
	15	15	15.39	0.60	+2.60	102.60	±0.73
215_{ALP}	7	7	6.66	2.58	-4.86	95.14	±3.17
	15	15	15.42	3.26	+2.80	102.80	±1.42
254_{ALP}	7	7	7.06	0.56	+0.85	100.85	±1.73
	15	15	14.93	1.79	-0.47	99.53	±0.30
277_{ALP}	7	7	6.82	1.88	-2.57	97.43	±0.02
	15	15	15.05	3.59	+0.33	100.33	±0.17

3.6. Limit of detection (LOD) and quantification (LOQ)

According to the ICH guidelines, the absorbance of ten samples of the same concentration of a mixed solution containing (2:2 µg/mL) LSD and ALP drugs (2:2 g/mL) was measured [21]. LOD and LOQ were calculated according to the ICH guidelines. Table 5. reveals the acceptable and sensitive values of the method.

3.7. Study of the effect of common excipients

The influence of different common excipients added to pharmaceutical drugs on the determination of 10 µg/mL of LSD and 10 µg/mL of ALP with the fourth derivative spectrophotometry method. The method was tolerable for different concentrations (100 and 200 µg/mL) of Arabic gum, fructose, sucrose, potassium chloride, and glucose. The relative error percentage was within ±5.0% (Table 6).

3.8. Applications on pharmaceutical drugs

LSD and ALP were determined in a pharmaceutical drug to evaluate the proposed method. The results for the two concentrations are listed in Table 7. The results of the proposed method revealed an acceptable recovery, and the relative standard deviation and a *t*-test (at three degrees of freedom, which is 3.182 and a 95% confidence level) [22] were appropriate.

4. Conclusions

A sensitive spectrophotometric method has been used to determine LSD and ALP in combined drugs simultaneously. Analytical data was based on the zero-crossing point technique using the fourth derivative spectrum method. Determining the accuracy and precision represents the best assessment of the proposed method in routine use. LOD and LOQ reveal the sensitivity of the method.

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Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Aws Maseer Nejres; Methodology: Aws Maseer Nejres, Moath Abdallah Najem; Software: Aws Maseer Nejres; Validation: Aws Maseer Nejres; Formal Analysis: Aws Maseer Nejres; Investigation: Aws Maseer Nejres; Resources: Aws Maseer Nejres, Moath Abdallah Najem; Data Curation: Aws Maseer Nejres; Writing - Original Draft: Aws Maseer Nejres; Writing - Review and Editing: Aws Maseer Nejres; Project Administration: Aws Maseer Nejres, Moath Abdallah Najem.

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