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Assessment of Aliskiren Hemifumarate and Amlodipine Besylate in combined Tablet Dosage form by Three Simple UV Spectrophotometric Methods

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: For a cardiovascular patient's blood pressure to be effectively controlled, more than one drug is required. When coupled with amlodipine besylate (AMLO), a calcium channel blocker, Aliskiren hemifumarate (ALI) is the 1st nonpeptide, low molecular mass, orally active transition state rennin inhibitor to efficaciously normalize blood pressure and cardiac ailments.
Objective: Three innovative, easy, sensitive, exact, and accurate UV spectrophotometric approaches, including simultaneous equation method (SEM), absorbance ratio method (ARM) and 1st derivative (zero-crossing) spectroscopic approach (FDR), were created and authenticated by validation for synchronized estimation of ALI and AMLO in tablet formulation.
Materials and Methods: The SEM was used to measure the absorbance of both medicines at 237 and 280 nm. ALI and AMLO were calculated using 237 and 271 nm, respectively, in the ARM. ALI and AMLO, on the other hand, used the FDR technique to transform UV spectra to first derivative spectra, with the first derivative signal captured at 237 and 254 nm, respectively. The wavelength

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interval (Δλ) was kept at 2 and the scaling factor was kept at 1 when transforming zero-order spectra using the first derivative approach. Validation of the proposed processes was done in compliance with the "International Conference on Harmonization" (ICH) recommendations. **Results:** SEM and ARM both showed a linear outcome in the range of 1-50 µg/ml for ALI and AMLO. FDR, on the other hand, was shown to be more sensitive and linear between 0.5 and 50 µg/ml for both medications. The results of the method validation parameters were within the allowed ranges of the ICH guidelines.
Conclusion: The proposed procedures were shown to be relatively quick, sensitive, simple, and cost-effective, and can thus be used for scheduled quality control analysis of ALI and AMLO in the mixed tablet.

Keywords: Aliskiren hemifumarate; amlodipine besylate; simultaneous equation; absorbance ratio; 1st derivative (zero-crossing) spectrophotometric methods; tablet formulation.

1. INTRODUCTION

The IUPAC name of Aliskiren hemifumarate (ALI) is specified as (2S,4S,5S,7S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate, a direct renin inhibitor that is commonly used to treat essential hypertension. ALI is highly hygroscopic and looks like white to slightly yellowish powder. It is highly soluble in water, whereas freely soluble in ethanol, methanol and isopropanol [1-3]. Amlodipine besylate (AMLO), IUPAC name benzenesulfonic acid;3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate, goes to the calcium channel blocker class of medicines, which are used to decrease blood pressure and prevent heart attacks, strokes, and other kidney issues. AMLO is a crystalline powder that is white to pale yellow and is easily soluble in methanol, ethanol, water, and 2-propanol. Fig. 1 depicts the chemical constructions of both medicines [4-7].

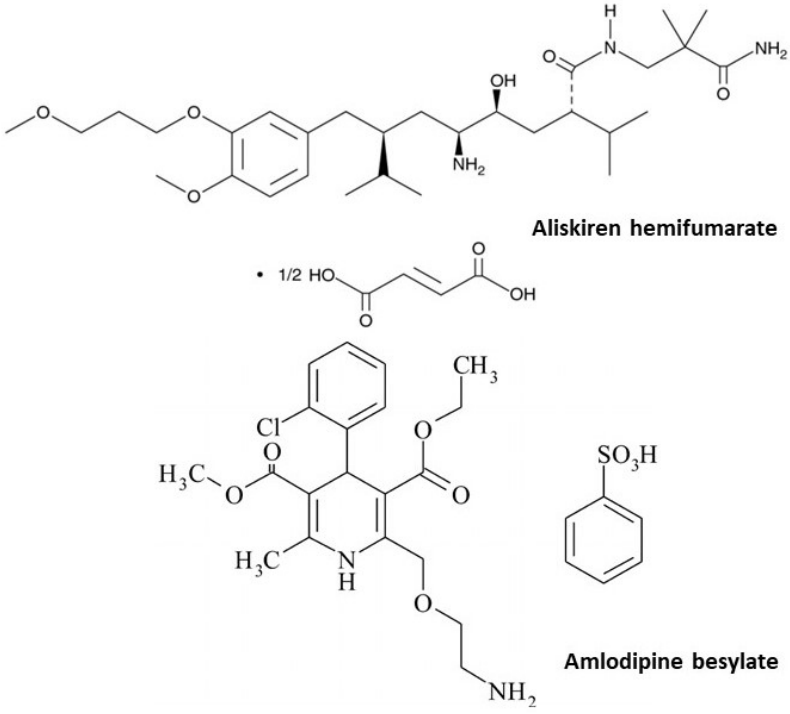

Fig. 1. Chemical structures of ALI & AMLO

One of the most prevalent and influential risk factors for cardiovascular ailment is hypertension. Normalizing blood pressure is vital in the handling of cardiovascular illnesses and their consequences. To adequately regulate blood pressure in a cardiovascular patient, multiple drugs are required. Aliskiren hemifumarate (ALI) is the first nonpeptide, low molecular mass, orally active transition state rennin inhibitor to effectively correct blood pressure and cardiac problems when combined with amlodipine besylate (AMLO), a calcium channel blocker [1-3,8]. A review of the literature indicates a variety of analytical approaches for estimating ALI and AMLO alone and in combination using UV spectrophotometry [8-10], fluorimetry [11-12], HPLC [13-16] and high-performance thin-layer chromatography [17]. As a result, the authors of this paper aimed to develop and validate several easier, sensitive, precise, accurate and economical UV spectroscopic approaches for the determination of ALI and AMLO in mixed tablet formulations that might be employed instead of the methods previously published. Projected methods have several advantages, including a straightforward standard and sample preparation approach as well as a broad range of applications.

2. MATERIALS AND METHODS

2.1 Materials, Chemicals and Reagents

Glenmark Pharmaceuticals Ltd. (Mumbai, Maharashtra, India) made available the active pharmaceutical ingredient of ALI, which was utilized throughout the study and IPCA Laboratories (Mumbai, Maharashtra, India) provided AMLO as a gift sample. Commercial sources were used to obtain the marketed formulation, Tekamlo® tablet (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey), which contains 300 mg of ALI and 10 mg of AMLO. Loba Chemie Pvt. Ltd. provided the Analytical grade (AR grade) methanol, which was employed as a solvent (Mumbai, India).

2.2 Instrument / Apparatus

A UV-1800 with UV Probe (Double beam UV visible spectrophotometer) from Shimadzu Corporation in Kyoto, Japan, and a quartz cell with a 1 cm path length was applied during the study. The weighing was executed with an Adventurer Pro AVG264C (Ohaus Corporation, Pine Brook, NJ, USA).

2.3 Standard Solution Preparation

Solutions comprising of ALI and AMLO were prepared by weighing appropriately 11.052 mg of ALI (11.052 mg of aliskiren hemifumarate is similar to 10 mg of aliskiren) and 10 mg of AMLO reference standard drug, which was then transferred to separate 10 ml standard flasks and diluted to 1000 µg/ml with AR grade methanol. To lower the concentration in the working range, necessary dilutions with methanol were made.

2.4 Detail Procedure

2.4.1 SEM and ARM

To obtain drug solutions containing 20 µg/ml of ALI and AMLO, standard solutions containing 1000 µg/ml of ALI and AMLO were properly diluted with AR-grade methanol. UV-Visible spectrophotometer (200-400 nm) was used to scan diluted ALI and AMLO solutions, and matching spectra were acquired and saved on the computer. Based on the spectral pattern, SEM and ARM [3,18-22] were preferred for the assessment of ALI and AMLO. Basis of the overlain spectra (Fig. 2A) of both the drugs, 237 nm (λ_{max} of AMLO) and 280 nm (λ_{max} of ALI) were chosen for SEM. However, in ARM, 237 nm (λ_{max} of AMLO) and 271 nm (isosbestic point) were picked, which exhibited an outstanding linear relationship and hence utilized for remaining studies. The resulting solutions were scanned using a double beam UV-Visible spectrophotometer and responses were recorded at 237 and 280 nm for SEM; 237 and 271 nm for ARM. Following that, absorptivity values for both medicines at their appropriate wavelengths were computed using the formula mentioned below:

$$\text{Absorptivity} = \frac{Absorbance}{Concentration\ (gm/100\ ml)}$$

The absorptivity value of each solution individually at its relevant wavelength was recorded and the mean value (Table 1) for that wavelength of each drug was used to calculate ALI and AMLO concentrations.

Table 1. Mean absorptivity values for SEM and ARM

SEM				ARM			
Mean absorptivity*				Mean absorptivity*			
ALI		AMLO		ALI		AMLO	
237 nm	280 nm	237 nm	280 nm	237 nm	271 nm	237 nm	271 nm
96.44	43.77	332.35	13.39	96.44	31.19	332.35	31.19

**(n = 6) Mean of six determinations*

2.4.2 FDR

The recorded zero-order UV spectra of ALI and AMLO were converted into 1st and 2nd derivative spectra. However, based on the zero-crossing point and spectral pattern, FDR [3,18-22] was preferred for further study. When 2 nm was used as the wavelength interval (Δλ) and 1 as the scaling factor, 1st derivative spectra exhibited typical zero-crossing spots at 254 nm for ALI and 237 nm for AMLO. Following a thorough examination of overlain spectra, the wavelengths of 254 nm and 237 nm were chosen for further testing (Fig. 2B). For ALI and AMLO, a calibration graph was built in the range of 0.5-50 µg/ml employing the FRD method. The least square approach was applied to acquire the values of the slope, intercept and correlation coefficient post regression analysis.

2.5 Sample Solution Preparation

After the tablets were accurately weighed, the mean weight of 20 Tekamlo® tablets comprising 300 mg of ALI and 10 mg of AMLO was computed. The aforementioned formulations were grounded to a fine residue and a quantity equal to 150 mg of ALI and 5 mg of AMLO was weighed and put into a standard flask with a capacity of 50 ml. Standard flasks were shaken and sonicated (10 minutes) after the addition of 30 ml AR grade methanol, and the remaining volume was brought up to the capacity (50 ml) with the same solvent. The subsequent solution was filtered (Whatman filter paper no. 41) and proper dilutions were completed (ALI & AMLO 20 µg/ml).

2.6 Investigation of Sample Solution

2.6.1 SEM

Test solutions (formulation) were scanned in the wavelength range of 200 to 400 nm, and observed responses at specific wavelengths were recorded (237 and 280 nm). The following formula was used to assess the unknown concentration of ALI and AMLO existing in the test solution:

$$\mathrm{Cx} = \frac{A_2\, a_{y1} - A_1\, a_{y2}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

$$\mathrm{Cy} = \frac{A_1\, a_{x2} - A_2\, a_{x1}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

Where, Cx= concentration of ALI; Cy=concentration of AMLO; ax1 & ax2=absorptivities of ALI at 237 and 280 nm, respectively; ay1 & ay2= absorptivities of AMLO at 237 and 280 nm, respectively; A1 & A2= absorbances of the test solution at 237 and 280 nm, respectively.

2.6.2 ARM

In ARM, the unknown amount of ALI and AMLO that exists in the test solution was calculated by utilizing below stated formula:

$$\mathrm{Cx} = \frac{\mathrm{Qm} - \mathrm{Qy}}{\mathrm{Qx} - \mathrm{Qy}} \times \frac{\mathrm{A1}}{\mathrm{ax1}}$$

$$\mathrm{Cy} = \frac{\mathrm{Qm} - \mathrm{Qx}}{\mathrm{Qy} - \mathrm{Qx}} \times \frac{\mathrm{A1}}{\mathrm{ay1}}$$

The absorptivities of ALI at 237 and 271 nm are represented by ax1 and ax2, respectively. Whereas, absorptivities of AMLO at 237 and 271 nm are ay1 and ay2, respectively.

The absorbances observed at 237 and 271 nm for the sample solution are A1 and A2. The detected concentrations of both medicines (ALI and AMLO) in the sample solution are Cx and Cy.

$$\mathrm{Qm} = \frac{\mathrm{A2}}{\mathrm{A1}} \qquad \mathrm{Qx} = \frac{\mathrm{ax2}}{\mathrm{ax1}} \qquad \mathrm{Qy} = \frac{\mathrm{ay2}}{\mathrm{ay1}}$$

2.6.3 FDR

The spectrum of the test solution was noted between 200 and 400 nm (UV region), processed to 1st derivative spectra and the amplitude was evaluated at 237 and 254 nm. Utilizing a regression equation, the extent of ALI and AMLO present in the test solution was evaluated in terms of concentration.

2.7 Method Validation

The proposed ideas were validated following the strategies of the "International Conference on Harmonization" [7,18-23].

2.7.1 Specificity

A specificity investigation was conducted to determine whether the tablet excipients employed in the formulation interfered with the medicinal substance. Before being filtered (Whatman filter paper no 41), all the formulation excipients (as given in the marketed formulation) were proportioned and diluted with methanol. Both solutions (placebo and standard) were scanned in the UV range and compared to see if excipients and medicines interfered.

2.7.2 Linearity and range

By assessing all of the standard solutions independently, which comprised ALI and AMLO (1, 5, 10, 20, 30, 40, and 50 µg/ml) in methanol and evaluating absorbances at 237 and 280 nm for SEM; 237 and 271 nm for ARM; 237 and 254 nm for FDR, all the three approaches were assessed for linearity and range. The absorbances of reference solution versus concentration were utilized to create calibration graphs in the SEM and ARM, whereas the 1st derivative response of standard drug solution versus concentration was utilized in the FDR. The slope, intercept and correlation coefficient was computed utilizing the least squares approach of regression analysis.

2.7.3 Precision

The repeatability, intra and inter-day precision of the procedures were assessed and expressed in terms of percent RSD (Coefficient of variation) of the acquired data. Precision experiments were completed in triplicate on the same day and 3 distinct days for both drugs at 2 dissimilar concentration levels (10 and 20 µg/ml).

2.7.4 Accuracy

To confirm the applicability and consistency of the proposed processes, recovery studies were conducted using the traditional addition approach. Standard medication solutions of ALI and AMLO (10, 15, and 20 µg/ml) were added to pre-analyzed sample solutions containing ALI and AMLO (10, 15, and 20 µg/ml) at 3 dissimilar levels, 50, 100, and 150 %. Finally, the RSD (%) and the proportion of medicines retrieved were calculated. The study's accuracy was assessed by utilizing the formula to evaluate the proportion of reference ALI and AMLO recovered from the formulation:

> % Recovery= [(Amt. of the drug found post addition of std. drug - Amt. of the drug found before the addition of std. drug) / Amount of std. drug added ×100

2.8 Limit of Detection (LOD) and Limit of Quantification (LOQ)

The sensitivity of the projected approaches was assessed using the parameters LOD and LOQ. The following equations were utilized to compute the LOD and LOQ of ALI and AMLO as specified in ICH guidelines.

$$\mathrm{LOD} = 3.3 \times \frac{\sigma}{S}$$

$$\mathrm{LOQ} = 10 \times \frac{\sigma}{S}$$

Where 'S'=Slope of the calibration curve; 'σ'= Standard deviation of the response.

2.9 Solution Stability

Solutions' stability was verified by supervising any fluctuations in absorbance and comparing the spectral pattern to newly created solutions while holding them at ambient temperature and evaluating them at regular intervals.

3. RESULTS AND DISCUSSION

For synchronized assessment of ALI and AMLO in marketed tablets, three UV spectrophotometric methods, SEM, ARM, and FDR, were created and tested. They are very accurate, precise, easy and responsive. Both medicines' response was noted in SEM at 237 and 280 nm. For the identification and quantification of ALI and AMLO in ARM, wavelengths of 237 and 271 nm were

employed (Fig. 2A). The FDR approach was based on converting stored zero-order UV spectra to first derivative spectra, then evaluating the first derivative signal at 237 and 254 nm (Fig. 2B) for ALI and AMLO, respectively. In FDR, a wavelength interval (Δλ) of 2 nm and a scaling factor of 1 was exercised. It was testified that there was no interference amongst excipients and typical pharmaceuticals after comparing the overlain spectra of placebo and drug solutions. SEM and ARM revealed a linear association with ALI and AMLO in the range of 1-50 µg/ml. In the concentration range of 0.5-50 µg/ml, the FDR approach, on the other hand, was found to be linear. The overlapping spectra of ALI and AMLO are shown in Fig. 2C and 2D.

For SEM and ARM, calibration graphs were created using the absorbance of a standard drug solution against concentration. The 1st derivative signal of a standard drug solution vs concentration was utilized to plot the calibration graph for the FDR. To compute values of the slope, intercept, and correlation coefficient for ALI and AMLO at their relevant wavelengths, regression analysis was executed by exploring the least square approach. Precision experimentations were assessed in terms of % RSD, which met the ICH guideline acceptable limits (<2) and demonstrated high repeatability and low intra- and inter-day variability, indicating exceptional precision of the outcomes (Table 2). Recovery rates for both drugs ranged from 98 to 103 percent, implying that the recommended approaches are effective (Table 2). There was no tablet excipient interference, based on the % recovery. Furthermore, the sensitivity of the projected approaches was supported by low LOD and LOQ values (Table 2).

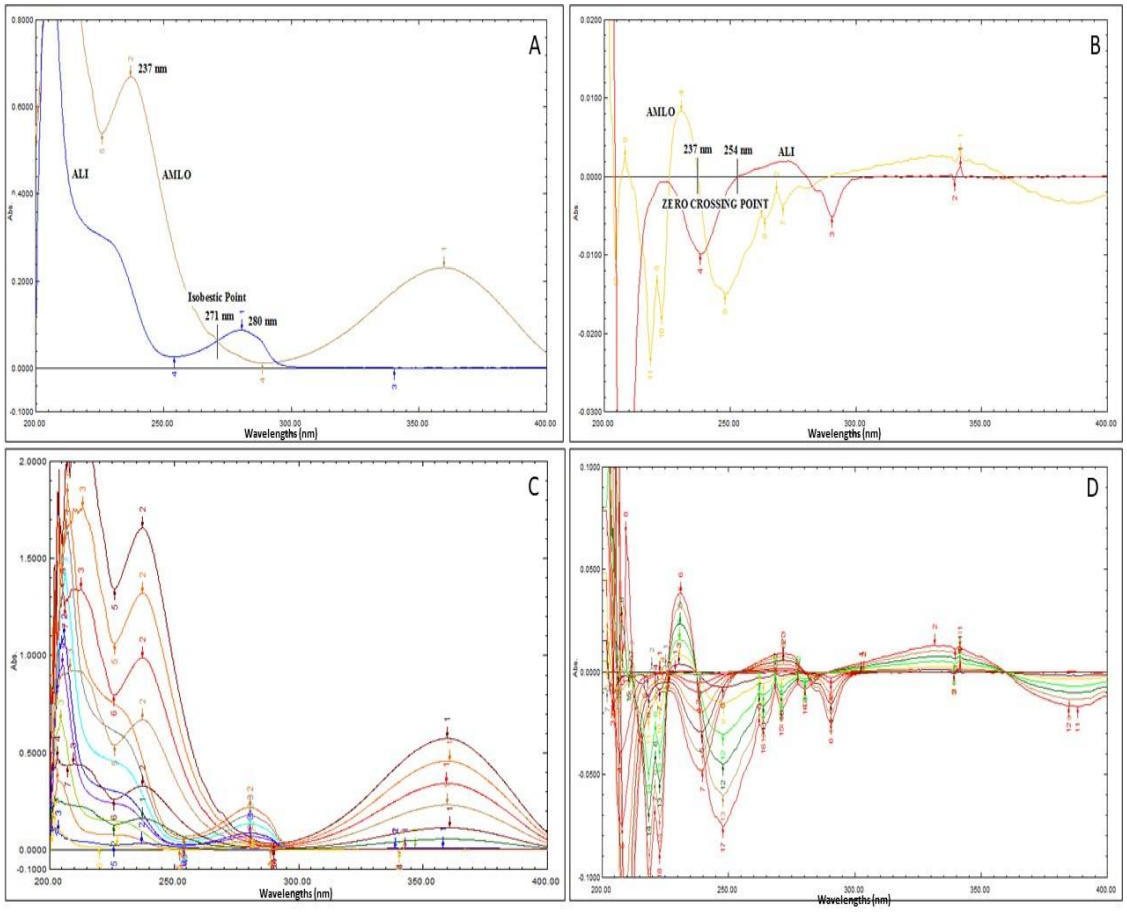

Fig. 2. A: Overlain UV Spectra of ALI and AMLO (20 µg/ml); B: Overlain 1st Derivative (Zero crossing) UV Spectra of ALI and AMLO (20 µg/ml); C: Overlain UV Spectra of ALI and AMLO (1-50 µg/ml) for SEM and ARM; D: Overlain 1st Derivative (Zero crossing) UV Spectra of ALI and AMLO (0.5-50 µg/ml) for FDR method

Table 2. Method validation and linear regression data for the proposed procedures

Parameters	SEM				ARM				FDR	
	ALI		AMLO		ALI		AMLO		ALI	AMLO
Wavelengths (nm)	**237**	**280**	**237**	**280**	**237**	**271**	**237**	**271**	**237**	**254**
Linearity range (µg/ml)	1-50								0.5-50	
Correlation coefficient	0.9999	0.9996	0.9999	0.9992	0.9999	0.9998	0.9999	0.9998	0.9998	0.9999
Regression equation:	y = 0.0097x - 0.0001	y = 0.0044x + 0.0002	y = 0.0331x - 0.0025	y = 0.0014x - 0.0005	y = 0.0097x - 0.0001	y = 0.0031x - 0.0001	y = 0.0331x - 0.0025	y = 0.0031x - 0.0001	y = 0.0009x + 0.0005	y = 0.0012x - 0.0002
LOD (µg/ml)	0.2329	0.1959	0.0959	0.1796	0.2329	0.1197	0.0959	0.1197	0.1366	0.1296
LOQ (µg/ml)	0.7059	0.5938	0.2908	0.5442	0.7059	0.3629	0.2908	0.3629	0.4141	0.3928
Specificity	**No interferences**									
Precision (% RSD)										
Repeatability (n=6)*	0.7833	1.0626	0.3913	1.1625	0.7833	0.9842	0.3914	1.1507	1.1257	1.6360
Intra-day (n=3)*	0.5958	0.8737	0.8322	1.2928	0.5958	1.3078	0.8322	1.3078	1.5165	1.2839
Inter-day (n=3)*	0.8087	1.1385	0.9209	1.2395	0.8087	1.4775	0.9209	1.4775	1.3451	1.6326
Accuracy (n=3)*										
% Recovery ± SD	99.85±1.16		100.29±0.72		100.95±1.54		99.78±1.14		100.45±1.35	100.60±1.50
% RSD	1.1643		0.7129		1.5265		1.1435		1.3463	1.4899

*Percentage relative standard deviation (% RSD), *n = No. of determinations*

Table 3. Results of formulation analysis by SEM, ARM and FDR

Drugs	Label Claim (mg/tab)	Amount Achieved (mg/tab)			Amount Achieved (%)*			RSD (%)		
		SEM	ARM	FDR	SEM	ARM	FDR	SEM	ARM	FDR
ALI	300	294.83	295.37	293.81	98.28±1.20	98.46±1.18	97.94 ± 1.51	1.22	1.20	1.54
AMLO	10	9.78	9.97	313.82	97.84±0.72	99.74±1.30	98.07 ± 1.50	0.73	1.30	1.53

*Percentage relative standard deviation (% RSD), *Mean ± SD (n = 6), Standard deviation (SD)*

The solution's stability was tested at room temperature and found to be two days stable. The proposed methods for quantifying ALI and AMLO in tablet formulation (Tekamlo® tablet: 300 mg of ALI and 10 mg of AMLO) were effectively executed. Because sample solutions were checked 6 times and investigational results were determined to be between 96 and 101 % for both medications, the recommended methodologies can be utilized for the synchronized assessment of ALI and AMLO in collective tablet formulations (Table 3).

4. CONCLUSION

Three novel UV spectrophotometric procedures have been developed that are effortless, responsive, accurate and precise. For synchronized assessment of ALI and AMLO in combination tablet dose form, spectrophotometric methods such as SEM, ARM and FDR were devised. According to ICH criteria, all of the procedures were validated. The proposed approaches were discovered to be extremely responsive, accurate, straightforward, and cost-effective. Furthermore, each of the established UV-spectrophotometric methods requires relatively little sample preparation and has a greater concentration range and sensitivity. As a result, the three described methodologies can be used to investigate the quality of ALI and AMLO in mixed formulations regularly.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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