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SPECTROPHOTOMETRIC SIMULTANEOUS DETERMINATION OF ASPIRIN AND ESOMEPRAZOLE MAGNESIUM IN SYNTHETIC MIXTURE BY RATIO DERIVATIVE METHOD.

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ABSTRACT

A sensitive, precise, accurate and simple UV spectrophotometric methods have been developed for the Simultaneous determination of Aspirin and Esomeprazole magnesium in API and Dosage form. The method depends on first derivative of the ratio-spectra by measurements of the amplitudes at 221 nm for Aspirin and 291 nm for Esomeprazole magnesium. In ratio derivative spectroscopy, analytical signals were measured at wavelengths corresponding to either maximums or minimums for both drugs in first derivative spectra of ratio spectra obtained by using either spectrum as divisor. Methanol was taken as a solvent. Calibration graphs were established for 20 -50 µg/ml for Aspirin and 5-30 µg/ml for Esomeprazole magnesium. The %R.S.D. values for intraday precision study and inter-day study were <1.0%, confirming that the method was sufficiently precise. The method can be successfully applied for the simultaneous analysis of both drugs in pharmaceutical dosage forms and statistical analysis of the data revealed that both the methods are precise, accurate, reproducible and suitable for the routine quality control analysis.

KEYWORDS: Aspirin, Esomeprazole magnesium, Spectrophotometric, Ratio derivative spectroscopy method.

INTRODUCTION

Aspirin (ASP) is chemically 2-(acetyloxy)-benzoic acid (Figure 1). It is non-selective cyclo-oxygenase inhibitor used as an antipyretic, analgesic, anti-inflammatory and antithrombotic agent. It reduces non-fatal myocardial infraction.[1-8] It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United states pharmacopoeia (USP) and European Pharmacopoeia (EP). It is estimated by acid-base titration method as per IP, BP, USP & EP.[9*-11]

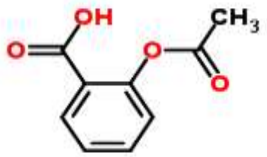

Fig. 1: Structure of Aspirin (ASP)

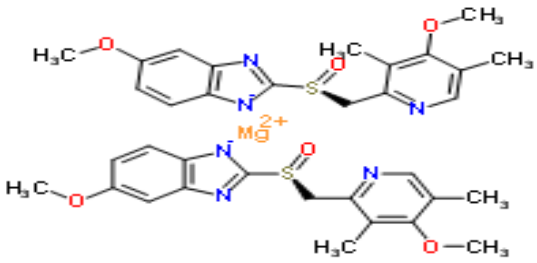

Fig. 2: Structure of Esomeprazole magnesium (ESO)

Literature review reveals that HPLC[13,14], UV spectrophotometric[15] methods has been reported for estimation of ASP in pharmaceutical dosage forms. Esomeprazole Magnesium[1-8] (ESO) is S-isomer of omeprazole and Proton pump inhibitor. It is chemically Di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2 pyridinyl)methyl]-sulfinyl]-1Hbenzimidazolemagnesium trihydrate (Figure 2). It is used in treatment of pepticulcer disease, NSAIDS- associated ulceration and Zollinger- Ellison syndrome used as Anti-ulcerative. ESO and its tablet dosage form is official in IP, USP & EP and estimated by Liquid Chromatographic method.[8] Literature review also reveals that UV spectrophotometric[16], HPLC[17-20] methods has been reported for the estimation of Esomeprazole in pharmaceutical dosage forms. Literature survey does not reveal any Ratio Derivative UV spectrophotometric method for simultaneous determination of ASP and ESO

in Pharmaceutical dosage form. The present developed method is simple, rapid, precise and accurate for simultaneous determination of both drugs in binary mixture as per International Conference on Harmonization (ICH) guidelines.[12]

MATERIALS AND METHODS

Apparatus and Instrument

A Double beam UV-Visible spectrophotometer (Shimadzu, model pharmaspec 1800) having two matched quartz cells with 1 cm light path and Electronic analytical balance, (Shimadzu AUX-220) was used. Corning volumetric flasks, pipettes of borosilicate glasses were used in the study.

Spectophotometric Conditions

Mode: Spectrum

Scan speed: Fast

Wavelength range: 400-200 nm

Absorbance scale: 0.00A – 2.00A

Initial base line correction: Methanol

Chemicals and reagents

Pure drug samples of Aspirin and Esomeprazole magnesium were provided as a gift sample by West coast pharma, Ahmedabad, Gujarat, India. Methanol and all other chemicals were provided by Sardar patel university,vallabh vidyanagar, Gujarat, India.

Preparation of Reagents and Solutions

Preparation of standard solutions

To Prepare standard solution of ASP (1000µg/ml) and ESO (1000µg/ml), accurately weigh 10mg of each drugs were transferred in two different 10ml volumetric flasks, dissolve and diluted up to mark with distilled water, from these stock solutions, 1ml aliquots were transferred in two different 10ml volumetric flasks and were diluted up to mark with distilled water to get working standard solution having concentration of ASP and ESO of 100µg/ml.

Methodology

This method works on two mechanisms viz. (1) Ratio and (2) Derivatization. In this method, the mixture spectra are divided with the divisor and first derivative spectra of these ratio

spectra are generated. The main advantage of the ratio-spectra derivative spectrophotometry is the chance of doing easy measurements in correspondence of peaks so it permits the use of the wavelength of highest value of analytical signals (a maximum or a minimum). Moreover, the presence of a lot of maxima and minima is another advantage by the fact that these wavelengths give an opportunity for the determination of active compounds in the presence of other compounds and excipients which possibly interferes the assay.

The ratio spectra of different ASP standards at increasing concentration in Methanol were obtained by dividing each with the stored spectrum of the standard solution of 5µg/ml ESO by computer aid as divisor spectra; these ratio spectra are shown in Fig.3. The first derivatives of this spectrum traced with interval of $\Delta\lambda$ = 10 nm are illustrated in Fig. 4. As seen in Fig 4, one maximum (221nm) and one minimum (238 nm) exist and we found that both were suitable for determination of ASP in ASP and ESO mixture. The wavelength 221 nm was selected for the determination of this compound in the assay of mixture, due to its lower RSD values and more suitable mean recovery compared with other wavelengths.

For the determination of ESO, the ratio spectra of different ESO standards at increasing concentrations in Methanol, obtained by dividing each with stored spectrum of the standard solution of 20 µg/ml of ASP as divisor spectra by computer aid, are demonstrated in Fig. 5. The first derivatives of this spectrum traced with intervals of $\Delta\lambda$ = 10 nm are illustrated in Fig. 6. As seen in Fig. 6, there exist three minimum (221 nm, 270 nm & 331nm) and two maximum (245 nm & 291 nm) and in this both were suitable for the determination of ESO in ASP and ESO tablets. The peak at wavelength 291 nm was selected because of its lower RSD and more suitable mean recoveries.

Calibration curve for ASP and ESO

To check linearity of the method, working standard solution having concentration in range of 20- 50µg/ml of ASP and 5-30µg/ml of ESO were prepared from the standard stock solutions of both drugs. For this prepared aliquots of 2.0,2.5,3.0,3.5,4.0,4.5 and 5.0ml of standard stock solutions of ASP and 0.5,1.0,1.5,2.0,2.5,3.0ml of ESO were transferred separately to a series of 10 ml volumetric flasks and diluted to mark with Methanol and the absorbance was measured at 221 nm for ASP and at 291 nm for ESO respectively.. Calibration curves were constructed by plotting absorbance vs. concentration.

Analysis of ASP and ESO in synthetic mixture

Powder mixture equivalent to 80mg of aspirin and 20mg of Esomeprazole was transferred in volumetric flask containing 50ml methanol, sonicated for 5 min and diluted to mark with same solvent to obtain 0.8mg/ml of ASP and 0.2mg/ml of ESO. The resulting solution was filtered using Whatman filter paper. From the above solution 0.5ml was transferred into 10ml volumetric flask and diluted to mark with same solvent. So, Resultant solution was found to contain 10µg/ml of Esomeprazole magnesium and 40µg/ml aspirin. Note down the absorbance of this solution at 221 nm for ASP and 291 nm for ESO. The analysis was repeated for three times.

RESULTS & DISCUSSION

Selection of wavelength

In Ratio spectra Derivative Spectrophotometry Method, the absorption spectra of ASP prepared at increasing concentrations in Methanol were recorded in the spectral region of 200.0-400.0 nm and divided by the previously stored spectrum of 5.0µg/ml ESO in the same solvent and their ratio spectra were obtained as seen in the Fig. 3.

Then, the first derivatives of ratio-spectra were recorded as shown in Fig. 4, which were plotted with the interval of 10 nm and the values of the derivatives were measured at suitably selected wavelength for the determination of ASP. The concentration of divisor can be modified, and different calibration graphs are then obtained. A concentration of 5.0 µg/ml of ESO was considered as suitable .The calibration graph was established by measuring at the amplitude at 221 nm corresponding to a maximum wavelength.

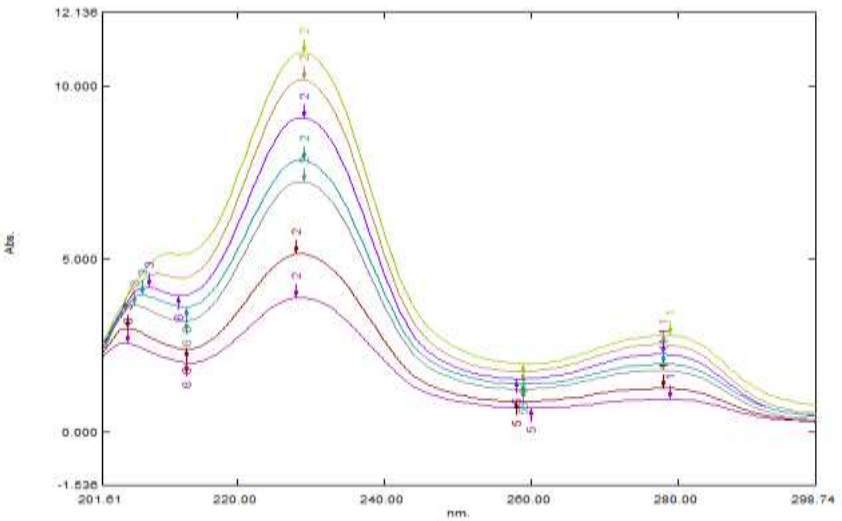

Fig. 3: Ratio Spectra of ASP when 5 µg/ml solution of ESO used as divisor

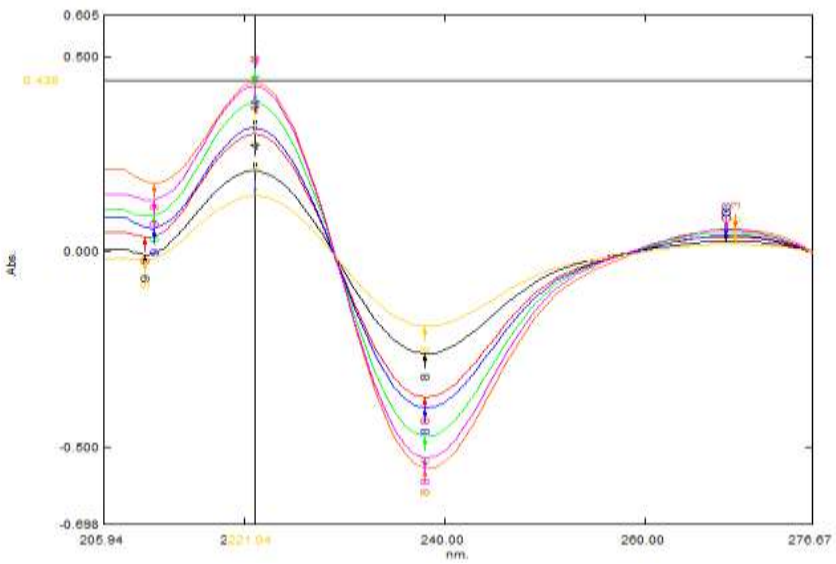

Fig. 4: First Derivative Ratio Spectra for ASP at 221 nm

For determining ESO, an analogous procedure was followed. The ratio spectra were obtained by dividing the spectra of ASP with previously stored spectrum of a 20 µg/ml ASP solution as shown in Fig. 5 and their first derivatives were calculated with the interval of λ=10 nm as shown in Fig. 6. The values of the derivatives were measured at suitably selected wavelength for the determination of ESO. A concentration of 5.0 µg/ml of ASP was considered as suitable. The calibration graph was established by measuring at the amplitude at 291 nm corresponding to a maximum wavelength.

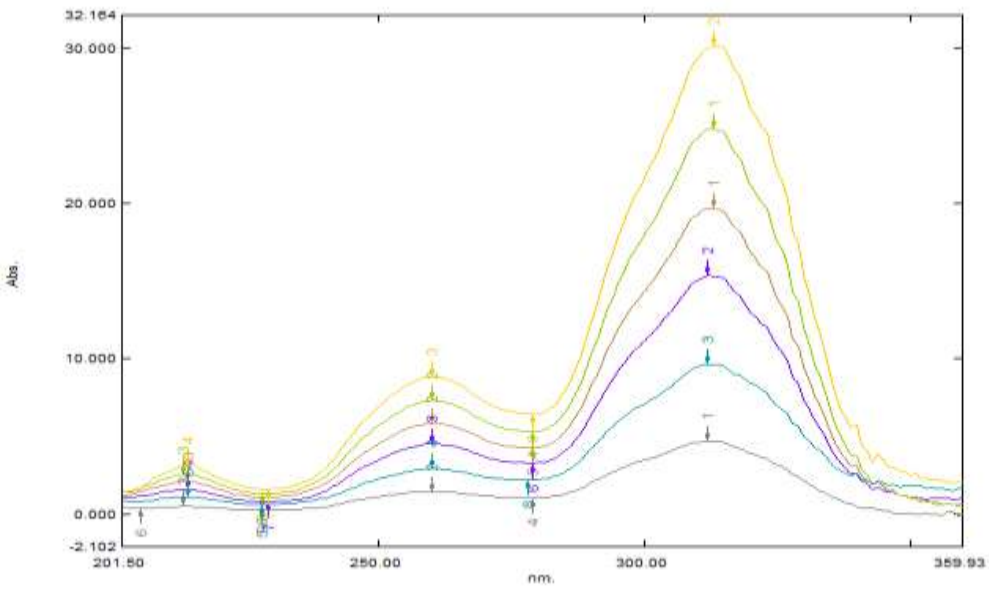

Fig. 5: Ratio Spectra of ESO when 20 µg/ml solution of ASP used as divisor

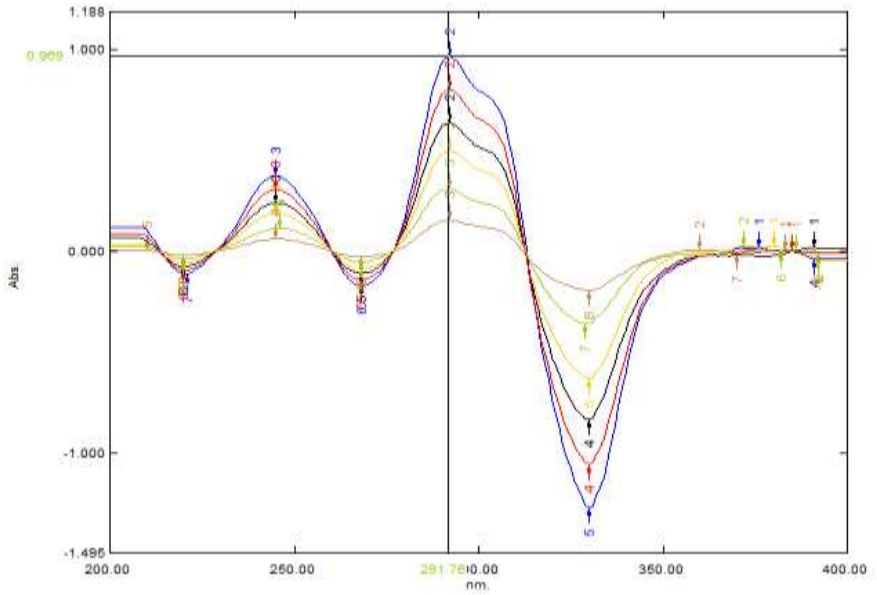

Fig. 6: First Derivative Ratio Spectra for ESO at 291 nm

Linearity

Linear correlation was obtained between absorbance Vs concentrations of ASP and ESO in the concentration ranges of 20-50µg/ml and 5-30µg/ml respectively. Regression parameters are mentioned in Table 7 and the Linearity spectra and calibration curves of ASP and ESO at 221 nm and 291 nm for Ratio Derivative Spectroscopy are shown in above Fig. 3, 4, 5, 6. The calibration curve was shown in Fig 7 and 8 for ASP and ESO respectively. Calibration curve data of ASP and ESO shown in Table 1 & 2.

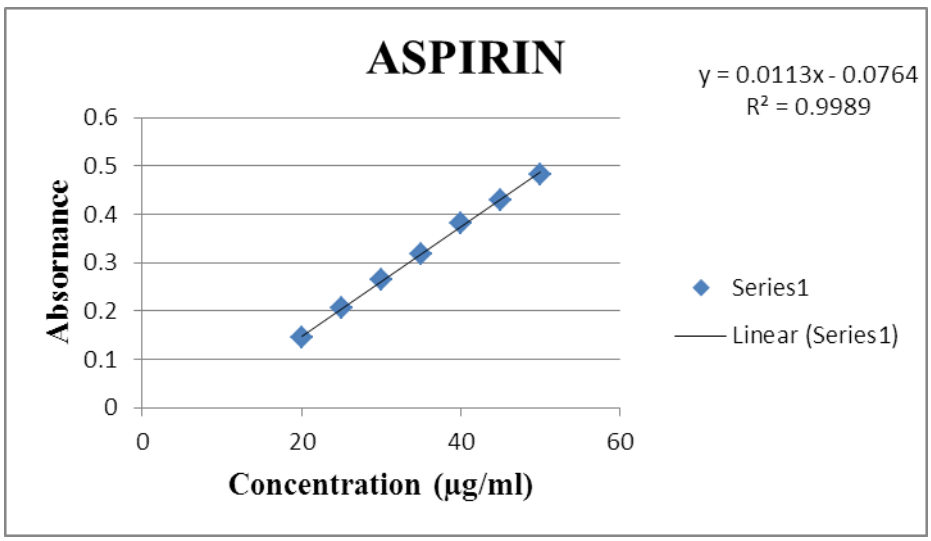

Fig. 7: Calibration curve of ASP at 221 nm

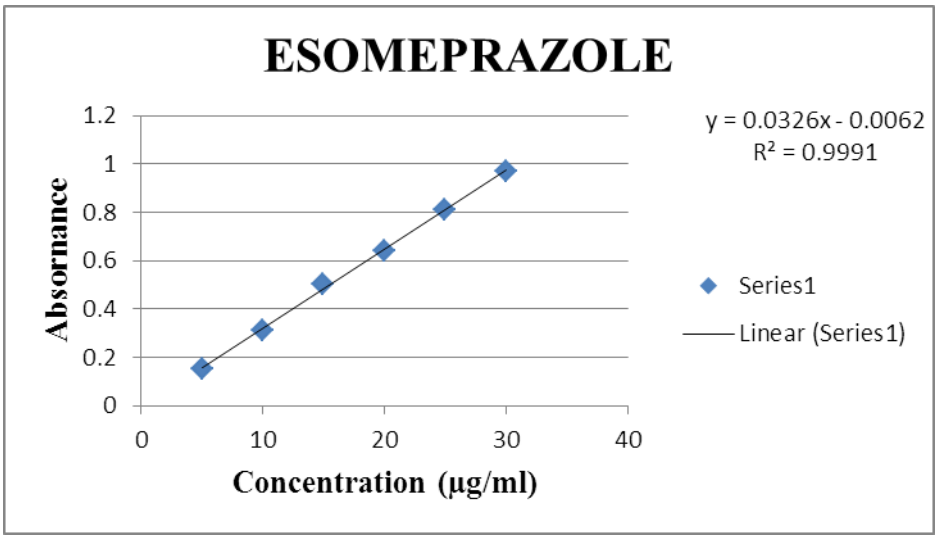

Fig. 8: Calibration curve of ESO at 291 nm

Table 1: Calibration curve data of ASP

Conc. (µg/ml)	Mean of Absorbance (At 221nm)	% R. S. D. [b]
20	0.144	1.210
25	0.206	0.567
30	0.265	0.553
35	0.318	0.540
40	0.380	0.318
45	0.430	0.416
50	0.482	0.242

[b] *% relative standard deviation*

Table 2: Calibration curve data of ESO

Conc. (µg/ml)	Mean of Absorbance (At 291nm)	% R. S. D. [b]
5	0.155	1.051
10	0.312	0.620
15	0.501	0.293
20	0.642	0.228
25	0.809	0.174
30	0.971	0.184

[b] *% relative standard deviation*

Accuracy

The accuracy of both the methods were determined by calculating recovery of ASP and ESO by the standard addition method. The mean recoveries were 99.31% - 100.3% and 99.13% - 100.4% for ASP and ESO, respectively. The low value of standard deviation indicates that the proposed methods are accurate. Results of recovery studies are shown in Table 3.

Table 3: Recovery data for the proposed method

Drug	Conc. of Sample taken(µg/ml)	Conc. of pure API spiked(µg/ml)	Total Conc. (µg/ml)	Mean total Conc. Found (n=3) (µg/ml)	%Recovery Mean (n=3)	%R.S.D.[b]
ASP	40	20	60	59.58	99.31	1.36
	40	40	80	80.3	100.37	1.04
	40	60	100	99.46	99.46	0.75
ESO	10	5	15	14.87	99.13	1.54
	10	10	20	19.85	99.25	1.06
	10	15	25	25.12	100.48	1.08

[b] *% relative standard deviation*

Precision

Repeatability

The precision of the instrument was checked by repeated scanning and measurement of the absorbance of solutions (n = 6) of ASP (20µg/ml) and ESO (20µg/ml) without changing the parameters of the proposed method. The %RSD values for ASP and ESO were found to be 1.33% and 0.40%, respectively at 221 nm and 291 nm (Table 4). Low relative standard deviation (<1) indicates that the proposed method is repeatable.

Table 4: Repeatability Data for Proposed method

Sr no.	Concentration (µg/ml)	Absorbance of ASP at 221 nm	Abs of ESO at 291 nm
1	20 ppm	0.144	0.641
2	20 ppm	0.147	0.645
3	20 ppm	0.143	0.639
4	20 ppm	0.148	0.646
5	20 ppm	0.144	0.642
6	20 ppm	0.145	0.643
	Mean	0.1451	0.6426
	SD	0.0019	0.0025
	% RSD	0.1940	0.2581

Intermediate precision (Reproducibility)

Precision of both the methods were determined in the terms of intra-day and inter-day variation (%RSD). Intra-day precision (%RSD) was assessed by analyzing standard drug solutions within the calibration range, three times on the same day. Inter-day precision (%RSD) was assessed by analyzing drug solutions within the calibration range on three different days. The intra-day and inter-day precisions were determined and results of which are given in Table 5 & 6.

Table 5: Intra-day and Inter-day Precision Data of ASP for Proposed method

Sr.no.	Concentration (µg/ml)	Absorbance	%R.S.D.
Intra day			
1	20	0.145	0.689
2	30	0.265	0.377
3	40	0.38	0.401
Inter day			
1	20	0.146	1.71
2	30	0.266	0.78
3	40	0.382	0.54

Table 6: Intra-day and Inter-day Precision Data of ESO for Proposed method

Sr.no.	Concentration (µg/ml)	Absorbance	%R.S.D.
Intra day			
1	10	0.312	0.489
2	20	0.64	0.238
3	30	0.97	0.157
Inter day			
1	10	0.314	1.11
2	20	0.641	0.46
3	30	0.97	0.31

LOD and LOQ

LOD and LOQ of the drug were calculated as per ICH guideline. LOD values for ASP and ESO were found to be 0.43µg/ml and 0.16µg/ml and LOQ values for ASP and ESO were found to be 1.30µg/ml and 0.49µg/ml. The summary of validation parameter and its data was shown in (Table 7) which indicate proposed method is sensitive for the determination of ASP and ESO**.**

Table 7: Regression analysis data & summary of validation parameters for proposed methods

Parameters	Ratio derivative method	
	ASP at 221 nm	**ESO at 291 nm**
Linearity (µg/ml)	20-50	5 to 30
Slope	0.01123	0.03263
Intercept	0.07543	0.0053
Correlation coefficient	0.9989	0.9991
LOD (µg/ml)	0.43	0.16
LOQ (µg/ml)	1.3	0.49
%Recovery	99.31-100.37	99.13-100.48
Repeatability (RSD, n = 6) %	0.82	0.99

Precision (RSD), %		
Interday (n = 3)	0.54-1.71	0.31-1.11
Intraday (n = 3)	0.40-0.68	0.15-0.48

Analysis of ASP and ESO in synthetic mixture

Content of ASP AND ESO found in the synthetic mixture from the proposed method are shown in table 8. The % purity was 99.72% for ASP and 99.70% for ESO.

Table 8: Assay Result of Synthetic mixture

Parameters	ASP	ESO
Actual Concentration (µg/ml)	40	10
Concentration Obtained (µg/ml)	39.89	9.97
%Purity	99.02	99.70
%RSD	0.425	0.144

CONCLUSION

In this proposed method the linearity was observed in the concentration range of 20-50µg/ml and 5-30µg/ml with co-efficient of correlation, r^2 = 0.9989and r^2 = 0.9991 for ASP and ESO, respectively at 221nm and 291 nm. The result of the analysis of combined mixture by the proposed method was found to be highly reproducible and reliable. The additive present in the combined mixture of the assayed samples did not interfere with determination of ASP and ESO. So, the developed Ratio Derivative UV spectroscopy method is simple, precise, accurate and reproducible and can be used for simultaneous determination of ASP and ESO in pharmaceutical dosage forms. The method was validated as per International Conference on Harmonization (ICH) guidelines.

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