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# Simultaneous Spectroscopic Estimation of Ezetimibe and Simvastatin in Tablet Dosage forms

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Rajput, *et al.*: Simultaneous Estimation of Ezetimibe and Simvastatin

A simple, accurate and precise spectroscopic method was developed for simultaneous estimation of ezetimibe and simvastatin in tablets using first order derivative zero-crossing method. Ezetimibe showed zero crossing point at 245.4 nm while simvastatin showed zero crossing point at 265.2 nm. The  $dA/d\lambda$  was measured at 265.2 nm for ezetimibe and 245.4 nm for simvastatin and calibration curves were plotted as  $dA/d\lambda$  versus concentration, respectively. The method was found to be linear ( $r^2 > 0.9994$ ) in the range of 5-40  $\mu\text{g/ml}$  for ezetimibe at 265.20 nm. The linear correlation was obtained ( $r^2 > 0.9935$ ) in the range of 5-80  $\mu\text{g/ml}$  for simvastatin at 245.4 nm. The limit of determination was 0.39 and 0.12  $\mu\text{g/ml}$  for ezetimibe and simvastatin, respectively. The limit of quantification was 1.10 and 0.4  $\mu\text{g/ml}$  for ezetimibe and simvastatin, respectively. The method was successfully applied for simultaneous determination of ezetimibe and simvastatin in binary mixture.

**Key words:** Ezetimibe, simvastatin, simultaneous estimation, zero crossing method, antihyperlipidemic agents

Ezetimibe is a new antihyperlipidemic agent and chemically is, 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone<sup>1</sup>. It is a selective cholesterol absorption inhibitor that effectively blocks intestinal absorption of dietary and biliary cholesterol.<sup>2-6</sup> Simvastatin inhibits the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase<sup>7</sup>. Simvastatin when combined in low doses i.e. 10-20 mg/day; with ezetimibe can be a potent and safe combination for reduction of LDL-cholesterol<sup>8</sup>. A combination formulation Simvotin<sup>TM</sup>EZ 10, Ranbaxy, containing 10 mg of simvastatin and 10 mg of ezetimibe is available in the market. Simvastatin is official in BP and the official method is a LC method<sup>9</sup>. Other methods reported in literature are TLC<sup>10</sup>, HPLC<sup>10,11</sup>. One HPLC<sup>12</sup> method and GC<sup>10</sup> method are available for simultaneous estimation of simvastatin and Lovastatin. Similarly for ezetimibe, RP-HPLC<sup>13</sup>, HPLC<sup>14</sup>, LCMSMS<sup>15</sup> and TLC<sup>16</sup> methods are reported. But no official or reported procedure is present for simultaneous determination of ezetimibe and Simvastatin in pharmaceutical preparations. The

reported procedures are time consuming expensive and relatively complicated. Derivative spectroscopy provides a greater selectivity than common spectroscopy and offers a powerful approach for resolution of band overlapping quantitative analysis of multicomponent mixture<sup>17,18</sup>. The aim of this study was to develop a simple, fast and sensitive derivative spectroscopic method for simultaneous determination of ezetimibe and simvastatin in pharmaceutical preparations on the basis of zero-crossing measurement.

## MATERIALS AND METHODS

Ezetimibe and simvastatin were obtained as a gift samples from Sun Pharmaceutical Ltd. Baroda. Methanol used was of analytical grade and obtained from S. D. Fine Chemicals. A commercial tablet formulation (Simvotin<sup>TM</sup> EZ 10, Ranbaxy) each containing 10 mg of simvastatin and 10 mg of ezetimibe were procured from the local pharmacy. A Shimadzu UV-1700 double beam UV/Vis spectrophotometer with software of UVprobe was used for all measurements. The zero order absorption spectra were recorded over the wavelength range of 200–380 nm, against a solvent blank, in quartz

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cuvettes with 1 cm diameter. For all solutions, the derivative spectra were obtained over 200–380 nm range at 2 nm slit width ( $\Delta\lambda$ ).

### Standard and calibration solutions:

Standard stock solution of ezetimibe and simvastatin were prepared by separately dissolving 10 mg of ezetimibe and simvastatin, respectively in 100 ml methanol. Accurate volumes were transferred into two sets of 10 ml calibrated flask. The first series contained varying concentrations of ezetimibe (1–40  $\mu\text{g/ml}$ ). The second series contained varying concentration of simvastatin (1–40  $\mu\text{g/ml}$ ). The calibration curves for derivative spectroscopy were constructed by plotting drug concentration versus the absorbance values of the first derivative spectrum ( $D_1$ ) at 265.20 nm for ezetimibe and at 245.4 nm for simvastatin and regression equations were computed.

### Spectroscopic measurements:

The difference between spectra of standard solutions of ezetimibe and simvastatin versus their solvent blanks were recorded in the range of 200–380 nm. The first order derivative spectra of the standard solutions of each drug and those containing mixtures of both drugs were obtained in the same range of wavelength (200–380 nm) against blanks. The values of  $D_1$  amplitudes for ezetimibe in the presence of simvastatin and vice versa measured at 265.20 nm (zero-crossing of simvastatin) and 245.4 nm (zero crossing of ezetimibe), respectively.

### Accuracy and precision:

To establish the reliability of the proposed method, two series of solutions containing 10, 20, 30 and 40  $\mu\text{g/ml}$  of ezetimibe plus in each 10  $\mu\text{g/ml}$  of simvastatin and 10, 20, 30 and 40  $\mu\text{g/ml}$  of simvastatin plus in each 10  $\mu\text{g/ml}$  ezetimibe were prepared, respectively, and analyzed as discussed above. Precision of the procedure was calculated by within – day and between-day variations. Accuracy of the method was measured as percentage of deviation between added and measured concentrations (recovery study).

### Analysis of tablets:

Twenty tablets of Simvotin<sup>TM</sup> EZ 10, Ranbaxy, were powdered. The powder equivalent to 10 mg of simvastatin and 10 mg of ezetimibe was weighed accurately and transferred to 100 ml volumetric flask. Twenty milliliters methanol was added to the flash

and sonicated for 20 min. The solution was filtered through Whatman filter paper No. 41 and the volume was adjusted up to the mark with menthol. This solution is expected to contain 100  $\mu\text{g/ml}$  simvastatin and 100  $\mu\text{g/ml}$  ezetimibe. From the stock solution 1 ml was taken in to a 10 ml volumetric flask and the volume make up to the mark with methanol to get a final concentration of simvastatin (10  $\mu\text{g/ml}$ ) and ezetimibe (10  $\mu\text{g/ml}$ ). The concentration of ezetimibe and simvastatin in tablets were calculated using the corresponding calibrated curve.

### Results and discussion

Zero-order absorption spectra of ezetimibe and simvastatin showed overlapping peaks that interfere with the simultaneous determination of this formulation (fig. 1). Derivative spectroscopy, based on a mathematical transformation of the spectra zero-order curve into the derivative spectra, allows a fast, sensitive and precise resolution of a multicomponent mixture and overcomes the problem of overlapping of a multi-component system. Derivative spectroscopy on the basis of zero-crossing measurements involves measurement of the absolute value of the total derivative spectrum at an abscissa value corresponding to the zero-crossing wavelength of the derivative spectra of individual components, which should be only a function of the concentration of other component<sup>19</sup>. The spectroscopic parameters including derivative order, wavelength and  $\Delta\lambda$  values should be optimized to obtain maximum resolution, sensitivity and reproducibility<sup>19-21</sup>. In this study first-derivative technique ( $D_1$ ) traced with  $\Delta\lambda = 2$  nm was used to resolve the spectral overlapping. Zero-crossing points

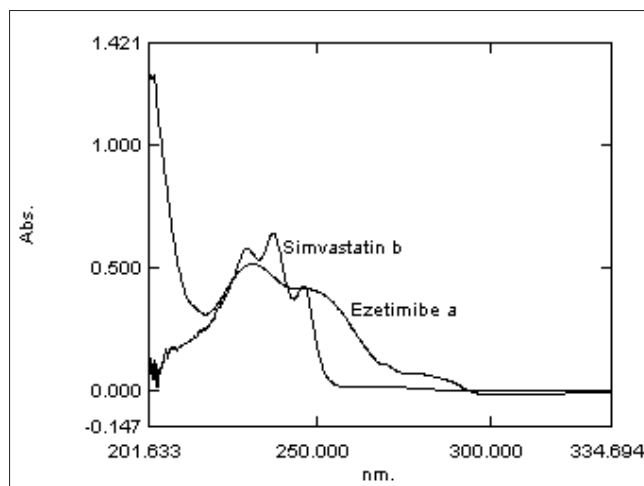


Fig. 1: Zero order spectra  
Zero order spectra of (a) ezetimibe (10  $\mu\text{g/ml}$ ) and (b) simvastatin (10  $\mu\text{g/ml}$ )

of 200-380 nm is presented in fig. 2. The optimum  $D_1$  values without interference for ezetimibe and simvastatin were 265.20 and 245.4 nm, respectively (fig. 2).

The linearity of the method was established from first-derivative spectra by measurement of the absorbance of standard solutions containing varying concentrations of each compound in the presence of constant concentration of the other one. The calibration curves were constructed by plotting the  $D_1$  value against ezetimibe or simvastatin concentration at the zero-crossing wavelength of simvastatin (265.20 nm) or ezetimibe (245.4 nm), respectively. The results obtained are summarized in Table 1. The linearity of the calibration curves and the adherence of the method to Beer's law are validated by the high value of the correlation coefficient and the value of intercept on ordinate which is close to zero.

The limit of detection that was found to be 0.39  $\mu\text{g/ml}$  and 0.12  $\mu\text{g/ml}$  for ezetimibe and simvastatin. The accuracy and precision were determined by using

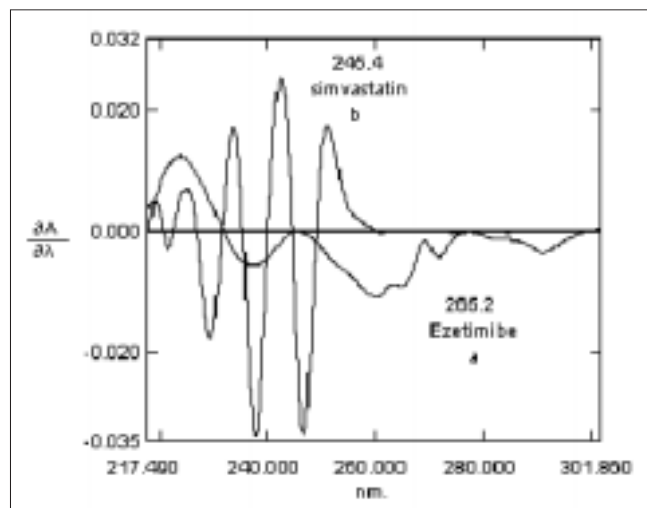


Fig. 2: First derivative spectra  
First derivative spectra of (a) ezetimibe (10  $\mu\text{g/ml}$ ) and (b) simvastatin (10  $\mu\text{g/ml}$ )

TABLE 1: STATISTICAL DATA OF CALIBRATION CURVES OF EZETIMIBE AND SIMVASTATIN USING FIRST-DERIVATIVE SPECTRA

Parameters	Ezetimibe	Simvastatin
Wavelength (nm)	265.20	245.4
Linearity ( $\mu\text{g/ml}$ )	1 - 40	1 - 40
Regression equation *	$Y = 0.0018x \pm 0.00001$	$Y = 0.0014x \pm 0.0003$
Correlation coefficient	0.9993	0.9923
Limit of detection ( $\mu\text{g/ml}$ )	0.39	0.12
Limit of quantification ( $\mu\text{g/ml}$ )	1.10	0.4

\* $Y = bx + a$ , where x is the concentration of drug in  $\mu\text{g/ml}$  Y is the amplitude at the specified wavelength, b is slope and a is intercept.

synthetic mixture of ezetimibe and simvastatin in the laboratory. The mean recoveries and SD are illustrated in Tables 2 and 3. Data of these tables showed a good accuracy and precision over the entire concentration range. The within-day and between-day variations showed co-efficient of variation (CV%) values less than 1% for both ezetimibe and simvastatin respectively in all four selected concentrations. The data indicate that the proposed derivative spectroscopic method is highly precise during one analysis and between different runs.

The percentage of recovery in each case was calculated. The results obtained from the recoveries of both drugs (Tables 2 and 3) showed excellent accuracy. The influence of excipients was studied by mixing two formulation containing 10  $\mu\text{g/ml}$  of ezetimibe and 10  $\mu\text{g/ml}$  of simvastatin. No interference was observed from the presence of excipient in the amounts, which are commonly present in tablet dosage forms. Study of stability of ezetimibe and simvastatin in the solutions during analysis showed that analytes were stable at least for 72 h in solutions.

TABLE 2: ACCURACY AND PRECISION OF DETERMINATION OF EZETIMIBE IN THE PRESENCE OF SIMVASTATIN

Added amount of ezetimibe ( $\mu\text{g/ml}$ )	Found ( $\mu\text{g/ml}$ ) SD	
	Within day*	Between day*
10	10.22 $\pm$ 0.15	10.01 $\pm$ 0.51
20	20.02 $\pm$ 0.21	19.89 $\pm$ 0.27
30	30.13 $\pm$ 0.10	29.91 $\pm$ 0.11
40	39.99 $\pm$ 0.17	40.11 $\pm$ 0.21

Accuracy and precision data of determination of ezetimibe in the presence of simvastatin (10  $\mu\text{g/ml}$ ) using first derivative spectroscopy. \*Mean of six determinations

TABLE 3: ACCURACY AND PRECISION OF DETERMINATION OF SIMVASTATIN IN THE PRESENCE OF EZETIMIBE

Added amount of simvastatin ( $\mu\text{g/ml}$ )	Found ( $\mu\text{g/ml}$ ) SD	
	Within day*	Between day*
10	10.11 $\pm$ 0.17	10.19 $\pm$ 0.45
20	20.02 $\pm$ 0.19	20.19 $\pm$ 0.22
30	29.89 $\pm$ 0.14	30.00 $\pm$ 0.28
40	39.98 $\pm$ 0.10	39.99 $\pm$ 0.05

Accuracy and precision data for determination of simvastatin in the presence of ezetimibe (10  $\mu\text{g/ml}$ ) by first derivative spectroscopy. \*Mean of six determinations

TABLE 4: RESULTS OF THE ANALYSIS OF COMMERCIAL PRODUCT

Formulation	Simvastatin	Ezetimibe
	% Found $\pm$ SD (n=4)*	% Found $\pm$ SD (n=4)*
Sample 1	99.8 $\pm$ 0.09	98.9 $\pm$ 0.21
Sample 2	99.5 $\pm$ 0.44	99.4 $\pm$ 0.37

\*Mean of four determinations. Both the sample from simvotin<sup>TM</sup> EZ 10, Ranbaxy, containing 10 mg of simvastatin and 10 mg of ezetimibe. SD is the standard deviation

The proposed method was successfully applied to analyze preparation containing ezetimibe and simvastatin. The results are summarized in Table 4. The results obtained are in good agreement with the labeled content.

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