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Two smart spectrophotometric methods for the simultaneous estimation of Simvastatin and Ezetimibe in combined dosage form

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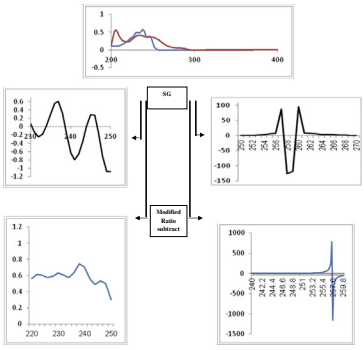
HIGHLIGHTS

- The minimum sample preparation, low cost and the ease of using Excel software are the main advantages of these methods.
- Regarding simplicity, modified ratio subtraction showed minimal data manipulation.
- In modified ratio subtraction, simply ΔP is calculated at any two wavelengths in the ratio spectrum.
- The derivative obtained using Savitsky–Golay function corrects for any interference.
- Application of this function would eventually produce high degree of purity of analytical peaks.

GRAPHICAL ABSTRACT



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ABSTRACT

Two simple, accurate, precise, sensitive and economic spectrophotometric methods were developed for the simultaneous determination of Simvastatin and Ezetimibe in fixed dose combination products without prior separation. The first method depends on a new chemometrics-assisted ratio spectra derivative method using moving window polynomial least square fitting method (Savitzky-Golay filters). The second method is based on a simple modification for the ratio subtraction method. The suggested methods were validated according to USP guidelines and can be applied for routine quality control testing.

Contents

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Introduction

Chemically, Simvastatin (SIM) is butanoic acid, 2, 2-dimethyl-, 1, 2, 3, 7, 8, 8a-hexahydro-3,7-dimethyl-8-[2(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenylester. SIM is a lactone that inhibits the enzyme HMG Co Enzyme A, which is responsible for the conversion of Hydroxy Methyl Glutaryl to cholesterol, thus used in the treatment of hyperlipidemia [1]. Ezetimibe (EZ) is (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxylpropyl)]-4-(4-hydroxy phenyl)-2-azetidinone. Having azetidinone ring structure, EZ inhibits the absorption of cholesterol and reduces the blood cholesterol level. It also decreases the excessive accumulation of cholesterol in blood vessels [1].

This distinct mechanism of action results in a synergistic cholesterol lowering effect when used together with statins that inhibits cholesterol synthesis by liver [2].

Several methods have been reported for the determination of both SIM and EZ. By the literature survey, HPLC [3–6], TLC [7] and UV spectrophotometric methods have been reported for the simultaneous estimation of SIM and EZ in combined dosage form [8–13].

The present work deals with simultaneous determination of SIM and EZ by two new different spectrophotometric techniques. The first method is a chemometrics-assisted ratio spectra derivative method using moving window polynomial least square fitting method (Savitzky-Golay filters) (SG). The derivative deduced by the direct-difference method amplifies noise. This disadvantage can be overcome by using the Savitzky-Golay filter [14–16] which gives smoothed derivative spectrum better than that obtained by the simple difference method. As it is based on polynomial fitting, one can directly perform derivation on the polynomial and then obtain the weighting expression for the central point in the moving window to give the derivative spectrum. The second method is a modified ratio subtraction method. It has the advantages of minimal data processing and wider range of application [17].

Theoretical background

Ratio derivative method using Savitzky-Golay filter

SG filters use best least squares fit polynomials to approximate data and derivatives. They can be computed very rapidly it can provide smoothed derivatives of many orders. The central idea of SG filters is to use best least squares polynomial fits to approximate data; then use those polynomials to estimate data or derivatives.

As it is based on polynomial fitting, one can directly perform derivation on the polynomial and then obtain the weighting expression for the central point in the moving window to give the derivative spectrum.

Employing the derivative function according to the SG method for each measuring value of y_i, a new value of y'_i is computed by a weighted average. The general form of this polynomial is:

$$y'_j = \sum_{i=-m}^{i=m} \frac{c_j y_{j+i}}{N}$$

The coefficients c_j can be determined by deciding the order of the model, deciding on the window size and selecting the appropriate number from the SG tables and dividing by the normalization constant [18–21].

Modified ratio subtraction method

Upon dividing the absorption spectrum of a compound by a spectrum of the same compound, a straight line of constant amplitude (parallel to the baseline) will result. While upon dividing the absorption spectrum of a compound by the absorption spectrum of another compound, a new spectrum (ratio spectrum) will result, mathematically it can be explained as follows:

In the ratio spectrum of a lab mixture of X and Y divided by a divisor Y'

$$P_1 = P_1X + K \quad (1)$$

$$P_2 = P_2X + K \quad (2)$$

where P_1 and P_2 are the amplitudes of the mixture spectrum at $\lambda 1$ and $\lambda 2$, respectively.

P_1X and P_2X are the amplitudes of X at $\lambda 1$ and $\lambda 2$, respectively. K is the constant resulting from Y/Y′

$$\Delta P_{1-2} = P_1 - P_2 = (P_1X + K) - (P_2X + K) = P_1X - P_2X \quad (3)$$

So the component Y will be completely cancelled and the difference will represent the X component only. Component X in a binary mixture can be determined from a calibration curve that relates the difference in amplitudes (ΔP_{1-2}) in the ratio spectrum at $\lambda 1$ and $\lambda 2$ using a certain concentration of Y as a divisor to the corresponding concentration of X.