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## Mean centering of double divisor ratio spectra, a novel spectrophotometric method for analysis of ternary mixtures



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### ABSTRACT

A novel spectrophotometric method was developed for determination of ternary mixtures without previous separation, showing significant advantages over conventional methods. The new method is based on mean centering of double divisor ratio spectra. The mathematical explanation of the procedure is illustrated. The method was evaluated by determination of model ternary mixture and by the determination of Amlodipine (AML), Aliskiren (ALI) and Hydrochlorothiazide (HCT) in laboratory prepared mixtures and in a commercial pharmaceutical preparation. For proper presentation of the advantages and applicability of the new method, a comparative study was established between the new mean centering of double divisor ratio spectra (MCDD) and two similar methods used for analysis of ternary mixtures, namely mean centering (MC) and double divisor of ratio spectra-derivative spectrophotometry (DDRS-DS). The method was also compared with a reported one for analysis of the pharmaceutical preparation. The method was validated according to the ICH guidelines and accuracy, precision, repeatability and robustness were found to be within the acceptable limits.

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### 1. Introduction

The use of molecular absorption spectroscopy for pharmaceutical analyses has the inherent constraint that most active drugs absorb in the UV region and exhibit strongly overlapped spectra that impede their simultaneous determination. Ternary mixtures suffer a higher degree of difficulty in spectrophotometric resolution than binary mixtures, due to the severe overlap usually noticed in their spectra. Many methods have been developed for resolution of the overlapped spectra of ternary mixtures using different spectrophotometric and chemometric techniques [1–8].

Signal processing techniques have an important role in spectrophotometric resolution of pharmaceutical mixtures, they are more reliable with respect to sensitivity and selectivity than normal spectrophotometry. Several signal processing techniques depend on manipulations of the ratio of overlapping spectra of ternary mixtures. Berzas et al. [9] introduced the derivative ratio zero crossing method for analysis of ternary mixtures, as an extension of the first derivative of ratio spectra method suggested by Salinas et al. [10] which was developed primarily for analysis of binary mixtures. Then Dinç and Onur [11] introduced the Double Divisor of Ratio Spectra-Derivative Spectrophotometry (DDRS-DS) method that was used for the analysis of ternary mixtures. The successive derivative of ratio spectra in two successive steps has been proposed by Afkhami and Bahram [12].

The fact that numerical differentiation degrades the signal to noise ratio (S/N) [13], suggested using other signal processing techniques as powerful alternatives for the analysis of pharmaceutical mixtures. Continuous wavelet transform was applied successfully in zero crossing and double divisor methods for analysis of ternary mixtures [14,15]. Fourier functions were also applied to double divisor method and used successfully for determination of ternary mixtures [16].

Afkhami and Bahram [17] also introduced mean centering as a signal processing resolution tool for analysis of binary and ternary mixtures which involved successive steps of division and mean centering.

In 1998, the Double Divisor Ratio Spectra-Derivative Spectrophotometry (DDRS-DS) method, introduced by Dinç and Onur [11], involved two simple steps for analysis of ternary mixtures. The spectrum of the component of interest was divided by the sum of the standard spectra of the other two components “a double divisor”, and then the ratio spectrum was derivatized, where the measurements were done at either maximum or minimum wavelengths. In 1999, Dinç [18] explained that the optimum wavelength for determination is the one at which a coincidence between the spectra of certain concentration of the component of interest and ternary mixture containing the same concentration of this component exists. In his work the coincident wavelengths were at either a maximum or a minimum, and in 2002 higher order derivatives were used to obtain the coincident points at a maximum or a minimum [19]. The method was also faced by the criticism that it cannot be popularized, because it can only be used for mixtures in which the ratio of the concentrations of two interfering compounds (used as double divisor) is known. In other words, the ratio of the concentrations of two interfering compounds should be

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the same in calibration, prediction and unknown samples. It is obvious that the ratio of the concentration of the analytes in real samples is always unknown [12]. This criticism will be refuted in this work.

Recently, Nejem et al. [20] suggested the use of double divisor in combination with mean centering to resolve five component mixtures. Their theory was based on three steps of division and mean centering. The main drawback of their method was that a spiking was required so that the concentrations of the two components of the double divisor will be equal to their concentrations in the real sample. This drawback again necessitates that the concentrations of the components of the double divisor should be known before analysis.

In this work, we introduced mean centering as a signal processing technique applied on double divisor ratio spectra for the resolution of ternary mixtures to overcome the previously mentioned drawbacks as it eliminates the derivative step, so S/N is enhanced at the working wavelength and can be used for analysis of mixtures having interfering components in concentration ratios different from those of the double divisor used.

For proper presentation of the method development and optimization, a synthetic ternary mixture of substances X, Y and Z was used. The method was then applied for quantitative determination of Amlodipine (AML), Aliskiren (ALI) and Hydrochlorothiazide (HCT) in laboratory prepared mixtures and in Amturnide® tablets. The results were compared with the known MC and DDRS-DS methods in laboratory prepared mixtures and with a reported method in the pharmaceutical preparation.

## 2. Mean Centering of Double Divisor Ratio Spectra (MCDD) Method

### 2.1. Theory

Mean centering, also known as “reduction by the mean” or “centering”, is a standard transformation of the data which is applied in multivariate analysis as a preprocessing operation. It involves the subtraction of the mean from each element of the matrix [21].

The mean centering of double divisor ratio spectra (MCDD) method is based on the mean centering of ratio spectra obtained by using a double divisor (sum of two standard spectra).

To explain the mean centering expression and its ability to remove a constant value, i.e., the mean centering of a constant is zero, let us consider a three dimensional vector [22].

$$z = \begin{bmatrix} 5 \\ 1 \\ 3 \end{bmatrix}$$

We center or mean center (MC) this column by subtracting the mean of the three numbers:

$$z' = \begin{bmatrix} 3 \\ 3 \\ 3 \end{bmatrix}$$

$$MC(z) = z - z' = \begin{bmatrix} 5 \\ 1 \\ 3 \end{bmatrix} - \begin{bmatrix} 3 \\ 3 \\ 3 \end{bmatrix} = \begin{bmatrix} +2 \\ -2 \\ 0 \end{bmatrix}$$

If a new vector  $x$  (representing constant data) is added to  $z$

$$x = \begin{bmatrix} 5 \\ 5 \\ 5 \end{bmatrix}$$

$$y = z + x(\text{constant}) = \begin{bmatrix} 10 \\ 6 \\ 8 \end{bmatrix}$$

by mean centering of  $y$ ,

$$y' = \begin{bmatrix} 8 \\ 8 \\ 8 \end{bmatrix}$$

$$MC(y) = y - y' = \begin{bmatrix} 10 \\ 6 \\ 8 \end{bmatrix} - \begin{bmatrix} 8 \\ 8 \\ 8 \end{bmatrix} = \begin{bmatrix} +2 \\ -2 \\ 0 \end{bmatrix}$$

The equal values of  $MC(z)$  and  $MC(y)$ , indicate that MC could remove the constant data  $x$  without affecting the data of  $z$ .

If a mixture of three compounds (X, Y and Z) is considered and Beer's law is obeyed for all components and the path length is 1 cm, the absorption spectrum of the ternary mixture can be written in the form of the equation [11]:

$$A_{m, \lambda_i} = \alpha_{X, \lambda_i} C_X + \alpha_{Y, \lambda_i} C_Y + \alpha_{Z, \lambda_i} C_Z \quad (1)$$

Here  $A_{m, \lambda_i}$  is the absorbance of the mixture at wavelength  $\lambda_i$ ,  $\alpha_{X, \lambda_i}$ ,  $\alpha_{Y, \lambda_i}$  and  $\alpha_{Z, \lambda_i}$  are the absorptivities at  $\lambda_i$  for X, Y and Z, respectively and  $C_X$ ,  $C_Y$  and  $C_Z$  are the concentration of X, Y and Z, respectively.

A similar equation for two compounds in the same ternary mixture as in a standard binary mixture can be written as:

$$A_{m, \lambda_i} = \alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0 \quad (2)$$

Here  $C_X^0$  and  $C_Y^0$  are the concentrations of X and Y in the double divisor.

If Eq. (1) is divided by Eq. (2), the ratio spectrum is obtained:

$$\frac{A_{m, \lambda_i}}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0} = \frac{\alpha_{X, \lambda_i} C_X + \alpha_{Y, \lambda_i} C_Y}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0} + \frac{\alpha_{Z, \lambda_i} C_Z}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0}$$

The ratio  $\frac{\alpha_{X, \lambda_i} C_X + \alpha_{Y, \lambda_i} C_Y}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0}$  is equal to a constant ( $k$ ) with respect to  $\lambda_i$ , in a certain region or point of wavelength (where the interference of X and Y is eliminated):

$$\frac{A_{m, \lambda_i}}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0} = k + \frac{\alpha_{Z, \lambda_i} C_Z}{\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0}$$

However, if the standard concentrations of  $C_X^0$  and  $C_Y^0$  in Eq. (2) are equal or very close to each other ( $C_X^0 = C_Y^0$ ) or ( $C_X^0 \approx C_Y^0$ ), we could write:

$$\alpha_{X, \lambda_i} C_X^0 + \alpha_{Y, \lambda_i} C_Y^0 = C_X^0 [\alpha_{X, \lambda_i} + \alpha_{Y, \lambda_i}]$$

$$\frac{A_{m, \lambda_i}}{[\alpha_{X, \lambda_i} + \alpha_{Y, \lambda_i}] C_X^0} = k + \frac{\alpha_{Z, \lambda_i} C_Z}{[\alpha_{X, \lambda_i} + \alpha_{Y, \lambda_i}] C_X^0} \quad (3)$$

If Eq. (3) is mean centered, and since the mean centering of a constant is zero, Eq. (4) would be obtained:

$$MC \left[ \frac{A_{m, \lambda_i}}{[\alpha_{X, \lambda_i} + \alpha_{Y, \lambda_i}] C_X^0} \right] = MC \left[ \frac{\alpha_{Z, \lambda_i} C_Z}{[\alpha_{X, \lambda_i} + \alpha_{Y, \lambda_i}] C_X^0} \right] \quad (4)$$

Eq. (4) is the mathematical basis of MCDD which permits the determination of the concentration of each component (Z in this equation) without interference from the other components of the ternary mixture (X and Y).

From Eq. (4), the mean centered signal of the ratio spectrum of the ternary mixture is dependent only on the concentration values  $C_X^0$  (or  $C_Y^0$ ), but is independent of the concentration values  $C_X$  and  $C_Y$  in the ternary mixture. Eq. (4) shows that there is a linear relation between the mean centered amplitude at a certain wavelength and the concentration of Z in the solution.

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