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ORIGINAL ARTICLE

Double divisor mean centering of ratio spectra as a developed spectrophotometric method for the analysis of five-component mixture in drug analysis

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Abstract In this paper a simple method was developed for the simultaneous determination of five-component mixtures, without prior separation steps. The method is based on the combination of double divisor-ratio derivative method and mean centering of ratio spectra method. The mathematical explanation of the procedure is illustrated. The linear determination ranges were 0–30, 0–20, 0–20, 0–45 and 0–100 μg ml^{-1} for paracetamol, methylparaben, propylparaben, chloropheniramine maleate and pseudoephedrine hydrochloride in 0.1 M HCl, respectively. The proposed method was validated by using synthetic five-component mixtures and applied to the simultaneous determination of these drugs in Decamol Flu syrup. No published spectrophotometric method has been reported for simultaneous determination of the five components of this mixture. So the results of the double divisor mean centering of ratio method (DD-MCR) were statistically compared with those of a proposed classical least squares method (CLS).

1. Introduction

Paracetamol (PA) is an analgesic and antipyretic agent [1], which is associated with pseudoephedrine hydrochloride (PS), a direct- and indirect-acting sympathomimetic agent [2] and chloropheniramine maleate (CM), a potent antihistaminic [3], in addition to methylparaben (MP) and propylparaben, which are used as preservatives. This combination is used for symptomatic treatment of coughs and the common cold.

The UV absorption spectra of PA, MA, PP, CH, and PS display considerable overlap, where the application of the conventional spectrophotometry failed to resolve it. No spectrophotometric analytical method has been reported for the simultaneous determination of PA, MP, PP, CH, and PS in a multicomponent mixture.

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While official [4] and spectrophotometric methods [5–14] are available for the determination of each of these drugs alone or in mixture with other drugs, the most prominent method for simultaneous determination of PA, MP, PP, CH, and PS is the HPLC, GC–MS or LC–MS [15–21]. However, these reported methods suffered from time-consuming extraction procedure and long chromatographic analysis time. Additionally the United States pharmacopeia [22] suggested the reduction in the amount of toxic organic solvents used in HPLC assays that cause harm to human health and environment. Therefore, chemometric-assisted spectrophotometry as a simple, quick and low cost method may be a good alternative if it is combined with multivariate calibration methods for determination of a complex in pharmaceutical quality control laboratories.

Salinas et al. [23] proposed a ratio-derivative spectrophotometric method. Their method is based on the derivative of the ratio spectra for a binary mixture which divided by the spectra of a standard solution (one divisor). Berzas Nevada et al. [24] developed a derivative ratio spectrum-zero crossing for the simultaneous determination of three compounds in ternary mixtures (no divisor used). Dinc et al. [25–27] proposed a double divisor-ratio spectra derivative method for the simultaneous determination of ternary mixtures. Recently, Afkhami and Bahram proposed a new mean centering of ratio spectra method for the simultaneous determination of ternary mixtures [28–30]. Their method is based on the mean centering of the ratio spectra for a binary or ternary mixture which divided by the spectra of a standard solution (one divisor).

Unfortunately, the advantages of all these methods are at least partially offset because they are used only for the determination of binary or ternary mixtures.

In this paper a new and simple method was developed for the simultaneous determination of five-component mixtures, without prior separation steps. This method is based on the combination of double divisor-ratio spectra method and mean centering of ratio spectra method. This method eliminates derivative steps and therefore signal to noise ratio is enhanced [31]. The technique can be used for other systems, particularly for more than five component systems. It may be also used more than double divisor (three or four) for the five component mixtures.

No published method has been reported for simultaneous determination of PA, MP, PP, CH and PS. So the results of the double divisor mean centering of ratio spectra (DD-MCR) method were compared with those of a proposed classical least squares (CLS) method.

2. Theoretical background

2.1. Double divisor mean centering of ratio spectra method (DD-MCR)

If a mixture of five compounds (PA, MP, PP, CH and PS) is considered and if Beer's law is obeyed for all compounds over the whole wavelength range used, then

$$A_m = \alpha_{PA}C_{PA} + \alpha_{MP}C_{MP} + \alpha_{PP}C_{PP} + \alpha_{CH}C_{CH} + \alpha_{PS}C_{PS} \quad (1)$$

where A_m is the vector of the absorbance of the mixture, α_{PA}, α_{MP}, α_{PP}, α_{CH}, and α_{PS} are the absorptivity vectors of PA, MP, PP, CH and PS and C_{PA}, C_{MP}, C_{PP}, C_{CH}, and C_{PS} are the concentrations of PA, MP, PP, CH and PS, respectively. Absorptivity A: (1%, 1 cm) values were calculated by using the absorbance for zero-order spectra for each of the compounds in the five-component mixture.

If Eq. (1) is divided by $\alpha_{MP}C^{\circ}_{MP} + \alpha_{PP}C^{\circ}_{PP}$ ($C^{\circ}_{MP} = C^{\circ}_{PP} = 1\ \mu g\ ml^{-1}$) corresponding to the spectrum of a standard solution of C_{MP} and C_{PP} the first ratio spectrum is obtained [25,28]:

$$x = \frac{A_m}{\alpha_{MP} + \alpha_{PP}} = \frac{\alpha_{MP}C_{MP} + \alpha_{PP}C_{PP}}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{PA}C_{PA}}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{CH}C_{CH}}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{PS}C_{PS}}{\alpha_{MP} + \alpha_{PP}} \quad (2)$$

Here in our method, in the synthetic mixture, C_{MP} and C_{PP} are equal and in the real sample, standard addition method is used ($C_{MP} = C_{PP} + C_{PP,x}$)

$$x = \frac{A_m + \alpha_{PP}C_{PP,x}}{\alpha_{MP} + \alpha_{PP}} = \frac{\alpha_{MP}C_{MP} + \alpha_{PP}\lfloor C_{PP} + C_{PP,x} \rfloor}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{PA}C_{PA}}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{CH}C_{CH}}{\alpha_{MP} + \alpha_{PP}} + \frac{\alpha_{PS}C_{PS}}{\alpha_{MP} + \alpha_{PP}} \quad (3)$$

If Eq. (2), (3) are mean centered, therefore

$$\mathrm{mc}\,x = \mathrm{mc}\frac{\alpha_{PA}C_{PA}}{\alpha_{MP} + \alpha_{PP}} + \mathrm{mc}\frac{\alpha_{CH}C_{CH}}{\alpha_{MP} + \alpha_{PP}} + \mathrm{mc}\frac{\alpha_{PS}C_{PS}}{\alpha_{MP} + \alpha_{PP}} \quad (4)$$

By dividing Eq. (4) by $\mathrm{mc}\frac{\alpha_{CH}}{\alpha_{MP}+\alpha_{PP}}$, the second ratio spectrum is obtained

$$y = \frac{\mathrm{mc}\,x}{\mathrm{mc}\frac{\alpha_{CH}}{\alpha_{MP}+\alpha_{PP}}} = C_{CH} + (Z)\,C_{PA} + \frac{\mathrm{mc}\frac{\alpha_{PS}}{\alpha_{MP}+\alpha_{PP}}}{\mathrm{mc}\frac{\alpha_{CH}}{\alpha_{MP}+\alpha_{PP}}}\,C_{PS}$$

$$\mathrm{mc}\,y = \mathrm{mc}\,Z\,C_{PA0} + \mathrm{mc}\,\frac{\mathrm{mc}\frac{\alpha_{PS}}{\alpha_{MP}+\alpha_{PP}}}{\mathrm{mc}\frac{\alpha_{CH}}{\alpha_{MP}+\alpha_{PP}}} \quad (5)$$

Finally we obtain the third ratio spectrum

$$\mathrm{mc}\,\frac{\mathrm{mcy}}{\mathrm{mcZ}} = (\mathrm{constant})C_{PS} \quad (6)$$

Eq. (6) is the mathematical foundation of multicomponent analysis which permits the determination of the concentration of each compound without interference from the other components of the mixture.

In practice, the signal of third ratio spectrum of PS is dependent only on the concentration values C_{PS} and $\frac{A_m}{\alpha_{MP}+\alpha_{PP}}$ (also C_x in real sample), but is independent of the concentration values C_{PA}, C_{MP}, C_{PP}, and C_{CH} in the mixture. The double divisor concentration used in our developed method is shown in Table 1, therefore, the concentration C_{PS} in the mixture is proportional to the amount of mc $\frac{\mathrm{mcy}}{\mathrm{mcZ}}$ corresponding to a maximum or minimum point.

A calibration curve could be constructed by plotting mc $\frac{\mathrm{mcy}}{\mathrm{mcZ}}$ against different concentrations of PS. As explained here, this technique can be used for other systems, particularly for more than five component systems. By using the calibration curve, the concentration of PS is determined in the sample containing PA, MA, PP and CH. The concentrations of other components are determined by analogous procedures.

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