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Novel spectrophotometric determination of chloramphenicol and dexamethasone in the presence of non labeled interfering substances using univariate methods and multivariate regression model updating

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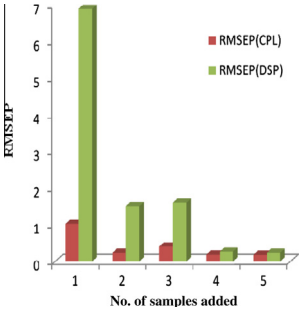
HIGHLIGHTS

- CPL is co-formulated with DSP in eye preparations.
- No spectrophotometric method was reported for their determination.
- High spectral interference is attributed to non labeled substances in eye drops.
- Overlapped spectral resolution is achieved by univariate and multivariate methods.
- Novel approach based on derivative transformation via multiplying by decoding spectrum.

GRAPHICAL ABSTRACT

The influence of the number of new samples added to the calibration set on RMSEP of multivariate calibration models: $X_{upd} = \begin{bmatrix} X \\ X_{new} \end{bmatrix}$ $Y_{upd} = \begin{bmatrix} Y \\ Y_{new} \end{bmatrix}$.



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ABSTRACT

Smart and novel spectrophotometric and chemometric methods have been developed and validated for the simultaneous determination of a binary mixture of chloramphenicol (CPL) and dexamethasone sodium phosphate (DSP) in presence of interfering substances without prior separation. The first method depends upon derivative subtraction coupled with constant multiplication. The second one is ratio difference method at optimum wavelengths which were selected after applying derivative transformation method via multiplying by a decoding spectrum in order to cancel the contribution of non labeled interfering substances. The third method relies on partial least squares with regression model updating. They are so simple that they do not require any preliminary separation steps. Accuracy, precision and linearity ranges of these methods were determined. Moreover, specificity was assessed by analyzing synthetic mixtures of both drugs. The proposed methods were successfully applied for analysis of both drugs in their pharmaceutical formulation. The obtained results have been statistically compared to that of an official spectrophotometric method to give a conclusion that there is no significant difference between the proposed methods and the official ones with respect to accuracy and precision.

Introduction

Chloramphenicol (CPL) (Fig. 1(a)) is a broad spectrum antibiotic used in bacterial infection. It is chemically2,2-dichloro-[1,3-dihy-

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droxy-1-(4-nitrophenyl)propan-2-yl]acetamide [1]. Dexamethasone sodium phosphate (DSP) (Fig. 1(b)) is a highly selective glucocorticoid which is widely used in ocular inflammatory diseases. Its chemical name is 9-fluoro-11b,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt [1]. CPL is co-formulated with DSP in several anti-infective eye preparations for treatment of acute and sub-acute conjunctivitis caused by susceptible strains of aerobic gram positive and negative bacteria [2].

By reviewing the reported methods, CPL was determined by spectrophotometry [3], high performance liquid chromatography (HPLC) [4] and gas chromatography (GC) [5]. Similarly, several methods were reported for determination of DSP by HPLC [6,7] and GC [8]. Few methods were also given for the simultaneous determination of CPL and DSP along with other drugs such as ciprofloxacin and ofloxacin [9–12]. The simultaneous determination of CPL and DSP has been accomplished using HPLC method [13,14]. Two spectrophotometric methods were reported for the determination of CPL and DSP in presence of Tetryzoline HCL and benzalkonium chloride [15,16]. Additionally; stability indicating method with degradation studies was reported [17].

Accordingly, no spectrophotometric method was reported for the simultaneous determination of the co-formulated drugs. This was suggested to be attributed to the high spectral interference from interfering substances either additives or preservatives. The labeled interfering substances; benzalkonium chloride (detergent preservative) while non labeled ones; thiomersal (oxidative preservative) and/or hydroxypropylmethylcellulose (lubricant) which were reported to be components of the studied ophthalmic eye drops [13]. Therefore, our aim was to achieve accurate determination of the two drugs by resolution of the overlapped spectral bands by both univariate and multivariate methods, without preliminary separation steps. Univariate approach was followed with the intent of finding a specific wavelength or two wavelengths for each of the two cited drugs where the interfering substances have no contribution. As for multivariate approach, regression model updating was followed in order to recalibrate the developed model with new samples to incorporate new variables. The developed methods have been validated according to ICH guidelines [18] to determine their suitability for the intended use.

Theoretical background

Derivative subtraction coupled with the constant multiplication method (DS-CM)

This method [19] has recently been introduced to solve mixtures of severely overlapped spectra. If we have a binary mixture of *X* and *Y* where the zero order absorption spectra are severely overlapping which hinders the constant measurement and consequently the application of well established ratio subtraction method [20]; but the first derivative spectrum of *Y* is more extended than *X*, so they could be estimated using derivative subtraction via zero contribution of the less extended one.

Consider a mixture of two compounds *X* and *Y*, the absorbance of the binary mixture at each wavelength could be written as:

$$A_m = a_X C_X + a_Y C_Y \tag{1}$$

A_m is the vector of the absorbance of the mixture, a_X, a_Y are the absorptivity vectors of *X* and *Y* while C_X, and C_Y are the concentrations of *X* and *Y*, respectively.

Taking the first derivative of Eq. (1), the following equation is obtained:

$$(d/d\lambda)[A_m] = (d/d\lambda)[a_X C_X] + (d/d\lambda)[a_Y C_Y] \tag{2}$$

Dividing Eq. (2) by first derivative of spectrum *Y′* as a divisor $(d/d\lambda)[a_Y C_{Y'}]$, the following equation is obtained:

$$(d/d\lambda)[a_X C_X]/(d/d\lambda)[a_Y C_{Y'}] + \text{constant} \tag{3}$$

The constant value can be determined directly from the $(d/d\lambda)[A_m]$ spectrum by the straight line parallel to the wavelength axis in the region where *Y* is extended. Constant multiplication method [21,22] has been established as a new approach in which *Y* can be determined by multiplying $(d/d\lambda)[a_Y C_{Y'}]$ divisor by the previously obtained constant, thus, the D^1 spectrum of *Y* is obtained again. This can be formulated as follows:

$$(d/d\lambda)[a_Y C_Y]/(d/d\lambda)[a_Y C_{Y'}] * (d/d\lambda)[a_Y C_{Y'}] \tag{4}$$

The concentration of *Y* is calculated using the regression equation representing the linear relationship between the amplitudes $P_{\text{maxima–minima}}$ of first derivative spectra versus the corresponding concentrations of *Y*.

Subtracting the measured value of the constant from the ratio spectrum Eq. (4), and then multiplying the new spectrum by $(d/d\lambda)[a_Y C_{Y'}]$, the first derivative spectrum of *X* is obtained. This can be formulated in the following equations:

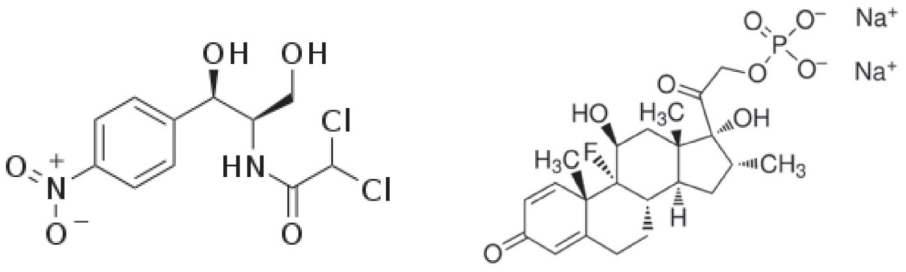
$$(d/d\lambda)[a_X C_X]/(d/d\lambda)[a_Y C_{Y'}] + \text{constant} - \text{constant} \tag{5}$$

$$(d/d\lambda)[a_X C_X]/(d/d\lambda)[a_Y C_{Y'}] \tag{6}$$

$$(d/d\lambda)[a_X C_X]/(d/d\lambda)[a_Y C_{Y'}] * (d/d\lambda)[a_Y C_{Y'}] \tag{7}$$

$$(d/d\lambda)[a_X C_X] \tag{8}$$

The concentration of *X* is calculated by using the regression equation representing the linear relationship between the peak to peak amplitudes ($P_{\text{maxima–minima}}$) of first derivative spectra versus the corresponding concentrations of *X*.



(a) $C_{11}H_{12}C_{l2}N_2O_5$ 323.1 (b) $C_{22}H_{28}FNa_2O_8P$ 516.4

Fig. 1. Chemical structure of chloramphenicol (a) and dexamethasone sodium phosphate (b).