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Development and validation of multivariate calibration methods for simultaneous estimation of Paracetamol, Enalapril maleate and hydrochlorothiazide in pharmaceutical dosage form

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ABSTRACT

Three multivariate calibration spectrophotometric methods were developed for simultaneous estimation of Paracetamol (PARA), Enalapril maleate (ENM) and Hydrochlorothiazide (HCTZ) in tablet dosage form; namely multilinear regression calibration (MLRC), trilinear regression calibration method (TLRC) and classical least square (CLS) method. The selectivity of the proposed methods were studied by analyzing the laboratory prepared ternary mixture and successfully applied in their combined dosage form. The proposed methods were validated as per ICH guidelines and good accuracy; precision and specificity were confirmed within the concentration range of 5–35 μg mL^{-1}, 5–40 μg mL^{-1} and 5–40 μg mL^{-1} of PARA, HCTZ and ENM, respectively. The results were statistically compared with reported HPLC method. Thus, the proposed methods can be effectively useful for the routine quality control analysis of these drugs in commercial tablet dosage form.

1. Introduction

Paracetamol (PARA) is chemically N-(4-hydroxy) acetanilide and it is commonly used for analgesic, antipyretic and anti-inflammatory activity [1,2]. Hydrochlorothiazide (HCTZ) is chemically 6-chloro-3, 4 dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide and it is a potent diuretic by inhibiting reabsorption of chloride and other ions [3,4]. Enalapril maleate (ENM) is chemically (S)-1-(N-(1-(Ethoxycarbonyl)-3-phenylpropyl)-L-alanyl)-Lproline (Z)-2-butene dioate an angiotensin-converting enzyme (ACE) inhibitor, use in management of hypertension [5]. Structures of PARA, HCTZ and ENM respectively were shown in Fig. 1.

The combinations of these drugs are frequently prescribed for treatment of blood pressure, fluid retention and heart failure. Furthermore, it is used to increase the pain threshold [6,7]. Several studies suggested that use of NSAIDS is associated with cardiovascular risk i.e. increase in blood pressure [8,9]. However, most of the hypertensive patients who are suffering from osteoarthritis requiring chronic pain relief, particularly in case of increased risk of hypertensive and atherosclerotic complications [10,11]. Though, Paracetamol belongs to NSAIDS hence, it can also be associated with risk of increase in blood pressure but there is no agreement on this issue [12]. Therefore, Paracetamol appears to be one of the best options for hypertensive patients requiring analgesia.

Present study involves with simultaneous estimation of marketed formulation and laboratory prepared mixture of Paracetamol, Hydrochlorothiazide and Enalpril maleate. The tablet contains variable amount of ingredients due to their recommended therapeutic dose; 325 mg Paracetamol, 25 mg Hydrochlorothiazide and 10 mg Enalpril maleate. The variable amount and different chemical properties of drugs in same formulation make the process tedious for the routine analysis [13]. Furthermore, the resolution of the mixtures containing two or more different analytes without prior chemical separation is major problems of the conventional analytical techniques. Hence, there is need for development of new methods for simultaneous estimation of multicomponent systems which have overlapping spectra.

The multivariate techniques such as classical least-squares, Tri-linear regression equation and Multi linear regression equation have been extensively used due to some advantages, i.e. rapid data processing related to the concentrations and absorbance values of compounds which have spectral interference [14]. Furthermore, minimize the errors of calibration model by measuring the absorbance of the zero order spectra at various points within the selected wavelength range. It gives satisfactory resolution for multicomponent systems and eliminates the interference problems. Multivariate calibration spectrophotometric methods were found to increase the selectivity and sensitivity by applying the mathematical algorithms methodology [15]. Hence, these methods are a power full technique for the quantitative analysis of these tablet formulations and laboratory prepared mixture.

Various methods have been adopted for estimation of Paracetamol and its combinations in pharmaceuticals dosage form and biological fluids, which includes fluorimetry [16], colorimetry [17], UV-

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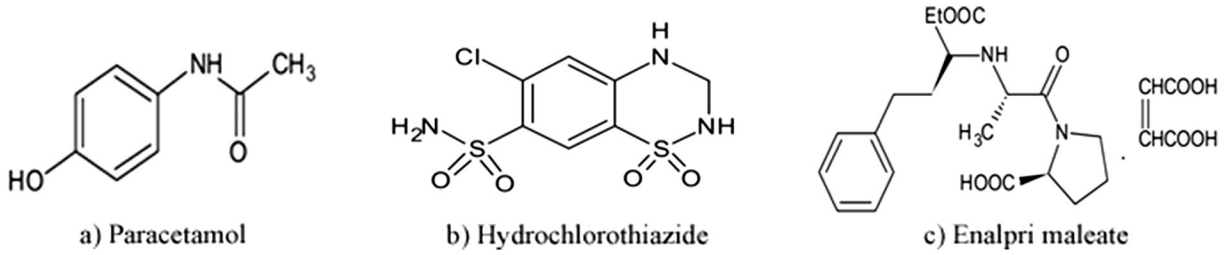

Fig. 1. Structure formulae of a) Paracetamol, b) Hydrochlorothiazide and c) Enalpril maleate.

spectrophotometry [18], quantitative thin-layer chromatography (TLC) [19], high-performance liquid chromatography (HPLC) [20–22], gas chromatography (GC) [23] and chemometric methods [24,14]. Likewise, for estimation of hydrochlorothiazide in pharmaceutical formulations, spectrophotometric [25,26], HPLC [27–28], HPTLC [29] and chemometric method [30–32] have been reported. Additionally, for Enalpril maleate various methods such as UV-HPLC [33,34], LC-MS-MS [35], UV [36,37] and chemometric method [32] have been reported. Beside this very few methods of derivative spectroscopy [38] and chromatography [39,40] were reported for the simultaneous estimation of these drugs in combined dosage forms. These methods have ability to give more resolved and precise results. In spite of that these methods required long time for preparation of samples, relied on tedious liquid–liquid extraction process, complex gradient elution and derivatization of the spectra. Although no multivariate calibration methods have been reported for simultaneous estimation of these three drugs. Therefore, there is need to develop new, fast and less expensive method for the determination of PARA, HCTZ and ENM and improve the outcome of analysis in multicomponent systems.

In the present study, multivariate calibration methods were developed for simultaneous estimation of these three drugs in tablet dosage form. The proposed methods were validated as per ICH guidelines [41–42] and compared with reported HPLC [39] methods.

2. Theoretical background

2.1. Tri-linear regression-calibration (TLRC)

If the absorbance values of a mixture of three analytes (X, Y and Z) are measured at a three wavelength set (λi = 1, 2 and 3) [14]. The following equations (Eq.) can be written for a three-component analysis as:

$$\begin{aligned} \boldsymbol{A_{mix1}} &= \boldsymbol{b_{X1}C_X} + \boldsymbol{b_{Y1}C_Y} + \boldsymbol{b_{Z1}C_Z} + \boldsymbol{a_{XYZ1}} \\ \boldsymbol{A_{mix2}} &= \boldsymbol{b_{X2}C_X} + \boldsymbol{b_{Y2}C_Y} + \boldsymbol{b_{Z2}C_Z} + \boldsymbol{a_{XYZ2}} \\ \boldsymbol{A_{mix3}} &= \boldsymbol{b_{Z3}C_X} + \boldsymbol{b_{Y3}C_Y} + \boldsymbol{b_{Z3}C_Z} + \boldsymbol{a_{XYZ3}} \end{aligned} \quad (1)$$

where, A_{mix1}, A_{mix2} and A_{mix3} represent the absorbance of the mixtures X, Y and Z analytes at the three-wavelength set. $b_{X\,(1,2\text{ and }3)}$, $b_{Y(1,2\text{ and }3)}$ and $b_{Z(1,2\text{ and }3)}$ are the slopes of linear regression equations of X, Y and Z, respectively; and $a_{XYZ(1,2\text{ and }3)}$ are the sums of intercepts of linear regression equations at the three wavelengths ($a_{XYZ1} = a_{X1} + a_{Y1} + a_{Z1}$, $a_{XYZ2} = a_{X2} + a_{Y2} + a_{Z2}$ and $a_{XYZ3} = a_{X3} + a_{Y3} + a_{Z3}$).

Eq. (2) can be formulated in matrix notation as:

$$\begin{pmatrix} A_{mix1} - a_{xyz1} \\ A_{mix2} - a_{xyz2} \\ A_{mix3} - a_{xyz3} \end{pmatrix} = \begin{pmatrix} bx1 & by1 & bz1 \\ bx2 & by2 & bz2 \\ bz3 & by3 & bz3 \end{pmatrix} \times \begin{pmatrix} Cx \\ Cy \\ Cz \end{pmatrix} \quad (2)$$

In simple manner

$$(\mathbf{A_{mix} - a_{XYZ}})_{3\times1} = \mathbf{K}_{3\times3} \cdot \mathbf{C}_{3\times1}$$

The matrix b, corresponding to the slope values of linear regression equations is called the matrix K:

$$K = \begin{pmatrix} bx1 & by1 & bz1 \\ bx2 & by2 & bz2 \\ bz3 & by3 & bz3 \end{pmatrix} \quad (3)$$

In this case, the concentration of the analytes, X, Y and Z in ternary mixture can be obtained by the matrix. $(A_{mix} - a_{XYZ})_{3\times1}$ is multiplied by the inverse $(K^{-1})_{3\times3}$of the matrix $K_{3\times3}$ and it can be written as:

$$\mathbf{C}_{3\times1} = [\left(\mathbf{K}^{-1}\right)_{3\times3} \times (\mathbf{A_{mix} - a_{xyz}})_{3\times1} \quad (4)$$

This procedure is the mathematical basis of the TLRC method for multi-component analysis. As given detail, this model can be applied easily to improve resolution of the three-component mixtures. The choice of selected wavelength set plays a significant role for the application of this numerical method to a multi-mixture analysis. For this reason, Kaiser's technique [15] was applied for the selection of the optimum wavelength set in order to provide the best sensitivity and selectivity in the application of the mathematical.

The sensitivity matrices K (square matrix) in Eq. (3) are formed by taking each three-pair of pre-selected wavelengths for ternary mixtures. The matrices K of the slope values obtained in the linear regression functions of the individual analytes X, Y and Z at three selected wavelengths are considered as the sensitivity parameter.

The sensitivity parameter is used for comparing different three-wavelength sets. The sensitivity of a multicomponent analysis is defined as the absolute value of the determinant of the sensitivity matrix K. The calculated maximum determinant value permits to decide the optimum wavelength set. The method is based on the nine linear regression functions with three linear regression lines for each compound at three selected wavelengths.

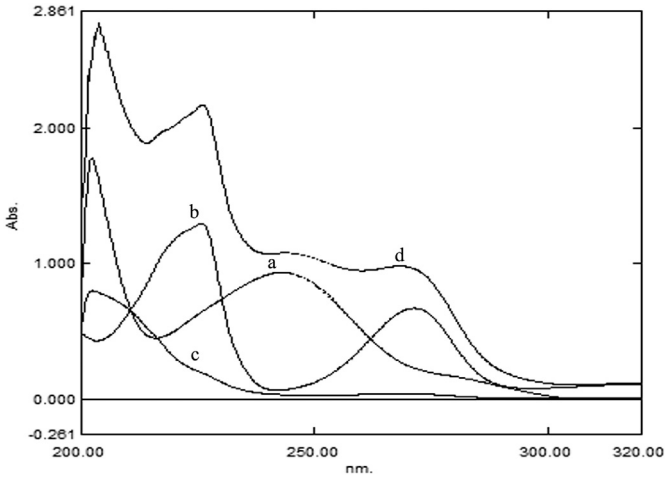

Fig. 2. Zero order overlain spectra of a) 15 μg mL^{-1} of Paracetamol, b) 15 μg mL^{-1} of Hydrochlorothiazide, c) 15 μg mL^{-1} of Enalpril maleate and d) Mixture in 0.1 M HC1.