Discrete Wavelet Transform-Partial Least Squares Versus Derivative Ratio Spectrophotometry for Simultaneous Determination of Chlorpheniramine Maleate and Dexamethasone in the Presence of Parabens in Pharmaceutical Dosage Form

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Received: 5 January 2015 Revised accepted: 27 April 2015

Abstract

Purpose: To compare two methods, based on different approaches, for simultaneous determination of chlorpheniramine maleate (CHP) and dexamethasone (DX) in the presence of methyl and propyl paraben in phenadone syrup.

Methods: The first method used, based on univariate calibration approach, was first derivative of the ratio spectrophotometry (DD1). The second method, which is a multivariate calibration approach, was discrete wavelet transform followed by partial least squares method (DWT-PLS) which anticipated high predictive ability for the determination of both CHP and DX.

Results: DD1 method failed to determine DX due to the absence of adequate zero crossing point while DWT-PLS method was successfully applied for the analysis of raw materials and the dosage form. For DD1 method, recovery of chlorpheniramine maleate in the dosage form was 100.33 ± 0.91 % while for DWT-PLS method, recovery of chlorpheniramine maleate and dexamethasone was 100.24 ± 1.21 and 99.99 ± 1.08 %, respectively. The proposed methods were validated using standard addition technique and the results compared favorably with those obtained by a reference high performance liquid chromatography (HPLC) method.

Conclusion: The findings of this work show the superiority of DWT-PLS over DD1 method in solving such complex mixtures, and would thus be suitable for use in quality control (QC) laboratories and pharmaceutical industry.

Keywords: Quantitative analysis, Discrete wavelet transform, First derivative of ratio spectra, Chlorpheniramine maleate, Dexamethasone

INTRODUCTION

Although HPLC and other conventional spectrophotometric methods have been extensively applied to the simultaneous analysis of pharmaceutical mixtures, they have some well-known disadvantages in the analytical applications. However, the emerging of the new mathematical methods, namely the wavelet transforms (WT) [1-3] and the chemometric methods [4] developed the resolution of the overlapping peaks in the spectra of multi-
mixtures. WT is a recent signal processing technique [5]. Many applications of WT in chemistry appeared in the literature such as resolution of overlapped chromatographic peaks [6], signal denoising [7] and multivariate calibration [8,9].

Previously, derivative spectrophotometry was a comparative technique for the quantitation of multi-mixtures. But due to its various disadvantages, including fair resolution of mixture spectra with higher order, new methods (such as WT) have been proposed for the quantitative and routine analysis of the drugs in their samples. Hence the aim of this work is to highlight the algorithm, advantages and the merits of WT on increasing the predictive power of multivariate calibration methods. The second aim is to show the superiority of WT over the first derivative of ratio spectra method (DD1) in the quantitation of multi-mixtures.

The comparison is conducted on a pharmaceutical data set; chlorpheniramine maleate (CHP) and dexamethasone (DX) in presence of methyl paraben (MP) and propyl paraben (PP) as a case study. CHP is an antihistaminic drug while DX is a corticosteroid anti-inflammatory agent [10]. Simultaneous determination of the two analytes in their combined tablets were reported by HPLC methods [11, 12], spectrofluorimetric method [13] chemometric methods [14] and derivative spectrophotometric method [15].

EXPERIMENTAL

Instruments

A double beam UV–visible spectrophotometer (SHIMADZU, Japan) model UV-1601 PC with quartz cell of 1 cm pathlength, connected to IBM compatible computer. The software was UVPC personal spectroscopy software version 3.7. The spectral bandwidth was 2 nm and wavelength-scanning speed 2800 nm/min.

Software

All multivariate calibration methods were implemented in Matlab® 7.1.0.246 (R14) using wavelet toolbox and PLS toolbox software version 2.1. The t test, F test and ANOVA test were performed using Microsoft® Excel 2013. All calculations were performed using intel ©core™ i5-2400, 3.10 GHz, 4.00 GB of RAM under Microsoft Windows 7.

Reagents and chemicals

Reference chlorpheniramine maleate (CHP), dexamethasone (DX), methyl paraben (MP) and propyl paraben (PP) certified to contain 99.59 %, 99.73 %, 98.50 % and 101.65 % respectively by the manufacturer method were kindly provided by The Arab Pharmaceuticals and Chemical Industries Company, Cairo, Egypt. Phenadone syrup is kindly supplied by the manufacturer (The Arab Drug Co.) and it is labeled to contain 0.4 mg mL\(^{-1}\) CHP, 0.1 mg mL\(^{-1}\) DX, 1 mg mL\(^{-1}\) MP and 0.2 mg mL\(^{-1}\) PP, batch no. 630351. Methanol and 0.1 N HCl used were of spectroscopic grade.

Standard stock and working solutions

Stock standard solutions of CHP, DX, MP and PP were prepared separately by dissolving 100 mg of CHP, 50 mg DX, 50 mg MP and 100 mg PP in 100 mL methanolic HCl (1mL methanol: 4 mL 0.1 N HCl). Corresponding working solutions were prepared by transferring accurately 25 mL from each stock standard solutions separately in 250 mL measuring flasks and volume was completed with methanolic HCl. Solutions (xc) and (xd) \(\{0.125 \text{ mg mL}^{-1}\}\) were also prepared by methanolic HCl.

Calibration procedures

**DD1 spectrophotometric method**

**Determination of the analytical wavelengths**

The absorption spectra of the solutions of standard drug CHP, DX, and PP (10 \(\mu\)g mL\(^{-1}\)) were recorded between 200-300 nm. The first derivatives of the ratio-spectra of CHP/MP, DX/MP were recorded (standard divisor, MP 12 \(\mu\)g mL\(^{-1}\) was used) smoothed at scaling factor 10 and \(\Delta \lambda = 4\) nm, then the selected zero-crossing wavelengths were determined and found to be 261.6 nm for CHP and 248.1 nm for DX.

**Construction of calibration curves**

Accurately measured portions of each of CHP and DX solutions equivalent to 10 - 30 and 5 - 14 \(\mu\)g mL\(^{-1}\), respectively, were transferred separately to a series of 25-mL measuring flask and volume was completed to the mark with methanolic HCl. The values of DD1 of CHP/MP and DX/MP (standard divisor was 12 \(\mu\)g mL\(^{-1}\) MP) with variable concentrations of standard solutions of CHP (10-30 \(\mu\)g mL\(^{-1}\)) and DX (5 - 14 \(\mu\)g mL\(^{-1}\)) at the above selected zero-crossing wavelengths were recorded. The calibration graph for each drug was constructed by plotting...
these values against the corresponding concentrations. The regression equations were computed for CHP and DX.

**Discrete wavelet transform-PLS method (DWT-PLS)**

**Construction of a training set**

A training set composed of 17 mixtures was prepared by diluting different volumes of each of CHP, DX, MP and PP working solutions into a series of 25-mL measuring flasks, each flask was spiked with 250 µg of CHP and 125 µg of DX, in addition to mixture no. 18 that contains spiked concentrations of CHP and DX, 10 µg mL\(^{-1}\) of MP and 2 µg mL\(^{-1}\) of PP, all flasks were diluted to volume with methanolic HCl. The absorption spectra of all 18 mixtures were recorded between 200-300 nm. Reject the regions from 200-215 nm and above 290 nm. Mean centering of the data was performed. The data points of the spectra were collected at every 1 nm.

**Assay of laboratory-prepared mixtures**

Different synthetic mixtures containing various concentrations of CHP, DX, MP and PP were prepared by transferring accurate volumes of the four components and diluted to the volume with methanolic HCl. These synthetic mixtures were used to check the performance of the developed models.

**Application to a pharmaceutical preparation (phenadone syrup)**

Five mL of phenadone syrup equivalent to 2 mg of CHP, 0.5 mg of DX, 5 mg of MP and 1 mg of PP was diluted to 100 mL with methanolic HCl, further dilution was made by taking 5 mL of the above solution in 25-mL measuring flask, 250 µg of CHP and 125 µg of DX were spiked and volume was completed by methanolic HCl. The general calibration was followed and the concentration of CHP and DX was calculated.

**RESULTS**

CHP is co formulated with DX in phenadone syrup and MP and PP are present as preservatives. Figure 1 shows the chemical structure of CHP and DX. The severe overlap between the absorption spectra of CHP, DX, MP and PP is anticipated in Figure 2.

**DD\(^1\) spectrophotometric method**

The ratio-spectrum is obtained by dividing the absorption spectrum of the mixture by standard spectrum of one of the components followed by calculation of the first derivative of the ratio-spectrum and DD\(^1\) values of other components were measured at suitably selected zero-crossing points. The concentrations are then determined from their respective calibration curves. Figure 3 shows the first derivatives of ratio-spectra of the standard solutions CHP/MP and DX/MP using 12 µg mL\(^{-1}\) of MP as a divisor. The arrows indicate the zero-crossing wavelengths selected for determination of CHP and DX. The calibration graphs for each drug were achieved by plotting the values of the first derivative of the ratio-spectra at the selected wavelengths against the corresponding variable concentrations of CHP and DX.

For determination of CHP and DX in laboratory prepared mixtures, fixed amount of both drugs should be added to each experiment to increase their absorbance to the linear limit then subtract these concentrations before calculating the claimed concentrations of the two drugs. Replicate determination of six synthetic quaternary mixtures of CHP, DX, MP and PP were performed to test specificity of the method. The results for DX determination were not satisfactory as seen in Table 1. For CHP, The results were satisfactory as anticipated in Table 1. Assay validation sheet of the proposed DD\(^1\) zero-crossing method for CHP determination was presented in Table 2.

![Chemical structure of Chlorpheniramine maleate (CHP)](image)

![Chemical structure of Dexamethasone (DX)](image)

**Figure 1:** Chemical structures of Chlorpheniramine maleate and Dexamethasone
Figure 2: Absorption spectra for CHP ( ), DX (-----), MP ( …… ) and PP ( . ) each 10 µg mL⁻¹

Figure 3: First derivative of the ratio spectra of CHP ( __ ) and DX (-----) each 14 µg mL⁻¹ using MP (12 µg mL⁻¹) as a divisor

Table 1: Determination of CHP and DX in laboratory prepared mixtures by the proposed DD¹ method

| Mix. no. | Mix. composition (µg mL⁻¹) | Recovery % |
|----------|---------------------------|------------|
| 1        | 14 6 10 2                 | 101.13 89.34 |
| 2        | 22 10 6 1.2               | 99.71 95.35 |
| 3        | 22 6 2 0.4                | 100.25 91.86 |
| 4        | 14 14 4 0.8               | 100.85 99.29 |
| 5        | 30 8 10 2                 | 99.05 92.77 |
| 6        | 18 14 6 1.2               | 100.49 99.32 |
| Mean     |                           | 100.25 94.66 |
| R.S.D. * % |                       | 0.764 4.083 |

*Relative standard deviation

DWT-PLS method

After DWT, the signal will be described by the wavelet transform coefficients so it is an important step to suppress the small coefficients by thresholding. Figure 4 shows the absolute values of wavelet coefficient vector sorted by magnitude. It is clear that small number of the coefficients (25 coefficients) whose absolute value is greater than 0.045; most of them are small enough to be suppressed. Thus by removing these coefficients, signal denoising and compression can be done in the wavelet domain.

Table 2: Assay parameters and method validation obtained by applying the proposed DD¹ method for CHP determination

| Parameter | DD¹ method | CHP |
|-----------|------------|-----|
| Range (µg mL⁻¹) | 10-30 | |
| Slope      | 0.0126     | |
| Intercept  | 0.0026     | |
| Mean       | 100.33     | |
| S.D.       | 0.709      | |
| Variance   | 0.503      | |
| Correl. Coef.(r) | 0.9999 | |
| LOD * (µg mL⁻¹) | 1.458 | |
| LOQ * (µg mL⁻¹) | 4.419 | |
| R.S.D. % ** a | 100.33 ± 0.709 | |
| R.S.D. % ** b | 100.45 ± 1.735 | |

*Limit of detection (LOD) and limit of quantification (LOQ) were determined by calculation **RSD%, RSD% the intra-day, inter-day respectively (n = 4) relative standard deviation

The denoising and compression effectiveness mainly depends on the wavelet filter and resolution level. In this work root mean square error (RMSE) method was used as the criterion for simultaneous denoising and compression. The optimal filter is defined as that for which the RMSE is a minimum. The RMSE method is applied to a single spectrum so the mean spectrum of the calibration set was used for this purpose. Table 3 shows the composition of the training set.

Figure 4: Plot of the absolute values of coefficient vector sorted by magnitude obtained by applying DWT to the simulated signal.

Different wavelet bases at different resolution level were tested on the mean spectrum like Daubechies wavelet family, Symlet family and Coiflet family at different levels (Tables 4 and 5) using compression ratio 5 (i.e. using 20 % of the total coefficients). It can be seen that RMSE
Table 3: Determination of CHP and DX in calibration set by the proposed DWT-PLS method

| Mix. no. | Mix. composition (µg mL⁻¹) | Recovery % DWT-PLS method |
|----------|-----------------------------|---------------------------|
|          | CHP | DX | MP | PP | CH | PP |
| 1        | 22  | 6  | 2  | 0.4| 99.2|99.74|
| 2        | 14  | 14 | 4  | 0.8| 101.22|100.28|
| 3        | 30  | 8  | 10 | 2  | 99.09|102.89|
| 4        | 18  | 14 | 6  | 1.2| 99.12|100.40|
| 5        | 30  | 10 | 2  | 0.4| 101.12|99.52|
| 6        | 22  | 8  | 2  | 0.4| 101.35|101.12|
| 7        | 18  | 8  | 8  | 1.6| 101.14|100.35|
| 8        | 18  | 12 | 10 | 2  | 101.96|99.52|
| 9        | 26  | 14 | 8  | 1.6| 99.75|100.17|
| 10       | 30  | 12 | 6  | 1.2| 101.56|99.55|
| 11       | 26  | 10 | 10 | 2  | 98.24|99.46|
| 12       | 22  | 14 | 10 | 2  | 101.19|99.26|
| 13       | 30  | 14 | 2  | 0.4| 99.76|100.23|
| 14       | 30  | 6  | 8  | 1.6| 99.85|97.39|
| 15       | 14  | 12 | 2  | 0.4| 98.09|99.53|
| 16       | 26  | 6  | 6  | 1.2| 99.84|100.36|
| 17       | 14  | 10 | 8  | 1.6| 101.78|99.62|
| 18       | 10  | 5  | 10 | 2  | 99.97|99.98|
| Mean     | 100.24| 99.99|
| R.S.D. * % | 1.207| 1.080|

*Relative standard deviation

Table 4: Root mean square error (RMSE) between experimental UV spectrum of 4 components of phenadone syrup and reconstructed signal by DWT with different filters and resolution level \( J = 4 \) (CR = 5)

| Filter  | RMSE  | Filter  | RMSE  | Filter  | RMSE  |
|---------|-------|---------|-------|---------|-------|
| Daub2   | 0.0186| Sym2    | 0.0186| Coif1   | 0.0202|
| Daub4   | 0.0146| Sym4    | 0.0233| Coif2   | 0.0191|
| Daub6   | 0.0186| Sym6    | 0.0239| Coif3   | 0.0267|
| Daub8   | 0.0203| Sym8    | 0.0236| Coif4   | 0.0244|
| Daub10  | 0.0315| Sym10   | 0.0239| Coif5   | 0.0361|
| Daub12  | 0.0396| Sym12   | 0.0317|         |       |
| Daub14  | 0.0661| Sym14   | 0.0270|         |       |

Table 5: Root mean square error (RMSE) between experimental UV spectrum of 4 components of Phenadone syrup and reconstructed signal by WT with wavelet filter Daubechies4 and different resolution levels (CR = 5)

| Resolution level (J) | RMSE  |
|----------------------|-------|
| 2                    | 0.0121|
| 3                    | 0.0075|
| 4                    | 0.0146|
| 5                    | 0.0107|
| 6                    | 0.0186|

reaches minimum when resolution level is 3 using db4 as wavelet basis. The DWT was then applied to the training and validation set and the coefficients determined by RMSE method were kept for PLS-1 calibration for each component separately. The concentrations of CHP and DX, in their quaternary mixtures with the parabens, were calculated with three latent variables chosen by Haaland's and Thomas method [16]. Actual concentration and recoveries of CHP and DX in training set and validation set are listed in Tables 3 and 6 respectively.

The validation of the developed WT-PLS model was assessed using several diagnostic tools (Table 7). These tools were grouped into two categories: model diagnostic tools that are used to determine the quality of the model, and sample diagnostic tools which are used to study the relationship between the samples and to identify unusual samples. The predicted concentrations of the validation samples were plotted against the true concentration values. This was used to determine whether the model accounted for the concentration variation in the validation set. All plots had a slope of nearly one and an intercept close to zero (Table 7). Root mean square error of prediction (RMSEP) was another diagnostic tool for examining the errors in the predicted concentrations, it indicates both the precision and accuracy [17]. The results in
Table 6: Determination of CHP and DX in validation set by the proposed DWT-PLS method

| Mix. no. | Mix. Composition (µg mL⁻¹) | Recovery % | DWT-PLS |
|----------|----------------------------|------------|---------|
|          | CHP | DX | MP | PP | CHP | DX |         |         |
| 1        | 14  | 8  | 6  | 1.2| 99.54 | 99.49 |         |         |
| 2        | 22  | 12 | 8  | 1.6| 101.80 | 99.98 |         |         |
| 3        | 26  | 12 | 4  | 0.8| 99.09 | 101.62 |         |         |
| 4        | 26  | 8  | 2  | 0.4| 99.88 | 98.04 |         |         |
| 5        | 18  | 6  | 4  | 0.8| 98.55 | 100.86 |         |         |
| 6        | 18  | 10 | 2  | 0.2| 99.32 | 99.56 |         |         |
| 7        | 14  | 6  | 10 | 2  | 99.72 | 99.36 |         |         |
| 8        | 22  | 10 | 6  | 1.2| 99.99 | 100.75 |         |         |
| Mean     |     |    |    |    | 99.74 | 99.96 |         |         |
| R.S.D. * %|    |    |    |    | 0.955 | 1.111 |         |         |

*Relative standard deviation

Table 7: Summary of results obtained by applying the diagnostic tools for model validation of the DWT-PLS method

| Validation parameter | DWT-PLS |         |         |
|----------------------|---------|---------|---------|
|                      | CHP     | DX      |         |
| a) Predicted vs. known concentration plot | 1.0036 | 1.0191 |         |
| 1- Slope             | 0.1163  | 0.1673  |         |
| 2- Intercept         | 0.9991  | 0.9993  |         |
| 3- Correlation coefficient |       |         |         |
| b) Residual vs. actual concentration plot (± error in prediction) | 0.396  | 0.1944  |         |
| c) RMSEP *           | 0.1790  | 0.1420  |         |

*Root mean square error of prediction

Table 7 indicate the high predictive abilities of the suggested model.

The results obtained for the analysis of the analytes in the pure powdered from by the suggested methods were statistically compared with those obtained by applying one of reported method [11] (HPLC analysis using C18 column and 0.005 M heptane sulphonic acid sodium salt in bi-distilled water: acetonitrile (70:30 v/v), pH 5). The results obtained were compared for the mean and the standard deviation using the t-test and F-test respectively. There were no significant differences between the results as shown in Table 8. In addition, the results found were in good agreement with the data indicated in the formulations given by the manufacturer.

One-way ANOVA was applied for the purpose of comparison of developed methods. Table 9 shows that there was no significant difference between them for the determination of CHP in presence of DX, MP and PP.

Application to pharmaceutical preparation

The proposed methods were successfully applied for the determination of CHP in Phenadone syrup in presence of parabens while DX was determined only by DWT-PLS method. The results are shown in Table 10. Each value indicated is the mean of 4 determination of the same commercial batch. The validity of the proposed methods was further assessed by applying the standard addition technique. Results obtained are shown in Table 10.

Table 8: Statistical comparison for the results obtained by the proposed methods and reported HPLC method [11] for the analysis of CHP and DX in pure powder form

| Item     | DD¹ method | DWT-PLS method | Reported HPLC method |
|----------|------------|----------------|----------------------|
|          | CHP | DX | CHP | DX | CHP | DX |
| Mean     | 100.33 | 99.99 | 99.93 | 99.96 |
| R.S.D.   | 0.909 | 1.207 | 1.080 | 1.920 | 1.746 |
| Variance | 0.826 | 1.457 | 1.166 | 3.686 | 3.049 |
| N        | 6 | 18 | 18 | 7 | 7 |
| F test   | 4.462 | 2.530 | 2.615 | 2.70 |
| (4.95)   | (2.70) | (2.70) |         |         |
| Student's t test   | 1.164 | 0.487 | 0.052 |         |
| (2.201) | (2.069) | (2.069) |         |         |

*Figures in parentheses are theoretical values for t- and F- at confidence level of 95 %

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Table 9: One-way ANOVA testing for the different proposed methods used for the determination of CHP

| Source of variation | DF | Sum of squares | Mean square | F-value |
|---------------------|----|----------------|-------------|---------|
| Between exp.        | 1  | 0.893          | 0.893       | 1.152   |
| Within exp.         | 12 | 9.305          | 0.775       |         |

There was no significance difference between the methods using one-way ANOVA (F-test), where $F_{tabulated} = 4.747$ at $p < 0.05$

Table 10: Applying standard addition technique for determination of CHP by the two proposed methods and DX by the DWT-PLS method in phenadone syrup (Batch No. 630351)

| Sample No. | Authentic added µg mL$^{-1}$ | DD$^1$ method Recovery % of CHP | DWT-PLS method Recovery % of CHP |
|------------|------------------------------|--------------------------------|---------------------------------|
|            | CHP                          | DX                             |                                 |
| 1          | 2                            | 1                              | 99.40                           | 98.50                           | 99.30 |
| 2          | 4                            | 2                              | 99.08                           | 100.15                          | 98.85 |
| 3          | 6                            | 3                              | 99.53                           | 101.55                          | 102.07 |
| Mean ± R.S.D. |                               |                                | 99.34 ± 0.237                   | 100.07 ± 1.527                  | 100.07 ± 1.742 |

Found of CHP and DX in phenadone syrup* (± R.S.D.) 100.33 ± 2.497 100.37 ± 0.696 101.15 ± 1.309

*The average of 4 experiments

DISCUSSION

In this work, quantitation of CHP and DX in this quaternary mixture was tried using first derivative of the ratio spectra (DD$^1$) and the smart DWT-PLS method. Derivative spectrophotometry has received increasing attention over the last few decades with regard to the assay of the drugs in dosage forms and biological fluids as a result of the development of microcomputer technology which allows the rapid generation of the derivative spectra and its application for the simultaneous determination of mixtures with closely overlapping absorption spectra [16,18,19].

In 1990, Salinas et al [18] developed a spectrophotometric method based on the use of the first derivative of the ratio spectra for resolving binary mixture. The method was then extended by Berzas et al [20] to resolving ternary mixture with overlapped spectra. The ratio-spectra zero-crossing first derivative spectra method is based on the simultaneous use of the first derivative of the ratio-spectra mixtures, followed by measurements at the zero-crossing wavelengths of first derivative of the ratio-spectra of single components. As accurate choice of the standard divisors and working wavelengths are of paramount importance [16,18], in this method various divisor concentrations were tested and the zero-crossing wavelengths were determined. For all subsequent measurements standard spectrum of 12 µg mL$^{-1}$ of MP was chosen as a divisor to determine CHP and DX. This divisor represents the best compromise in terms of sensitivity, signal to noise ratio and reproducibility.

The influence of the wavelength interval ($\Delta \lambda$) for obtaining the first derivative was tested and a wavelength interval of 4 nm was suitable ($\Delta \lambda = 4$ nm). A linear correlation was obtained between DD$^1$ values at selected wavelengths and the corresponding concentration in the range of 10 – 30 µg mL$^{-1}$ for CHP and 5 - 14 µg mL$^{-1}$ for DX. The regression equations were computed and found as follows:

\[
\text{DD}_{\text{261.6}}^1\text{ (CHP) = 0.0126 C}_1 + 0.0026; r = 0.9999} \quad \ldots \quad (1)
\]

\[
\text{DD}_{\text{248.1}}^1\text{ (DX) = 0.0263 C}_2 + 0.0014; r = 0.9998} \quad \ldots \quad (2)
\]

where: $C_1$ is CHP concentrations, $C_2$ is DX concentrations, $r$: correlation coefficient.

On application of the DD$^1$ method for determination of DX in different laboratory
prepared mixtures, the percentages recovery were not accurate. This may be due to that, the selected wavelength for DX determination (248.1) lay on the slope of DX band which subject the subsequent analysis of DX to error. This error is indicated by the higher value of R.S.D. (> 4 %) and deviation of the mean R % from 100 % value as seen in Table 1. Different divisors were tried but no maxima appeared for DX in the mixture.

Wavelet transform (WT) is similar to the Short time Fourier transform (STFT) in that both techniques analyze an input signal in blocks by translation (movement) of a basis function. This basis function in FT is sine wave and it is called waveform in WT.

There are two approaches for WT, discrete wavelet transform (DWT) and continuous wavelet transform (CWT). DWT is easier to implement than continuous wavelet transform (CWT). The CWT is computed at every possible scale while in DWT, the scale is chosen based on powers of two so called dyadic scales. An efficient way to implement DWT is the Mallat algorithm [21]. In DWT, the original signal is converted to wavelet coefficients. Many of the wavelet coefficients are very small in amplitude (‘detailed coefficients’) and can be removed without major loss in the information content of the signal.

There are many methods to determine the threshold value below which the wavelet coefficients can be removed safely [21]. The threshold defined by RMSE of the reconstructed signal is the most commonly used method because it is a measure of the quality of compression. In order to obtain optimal filter and resolution level j for the spectrum, the RMSE between the original measured spectrum and reconstructed signal by different wavelet filters and different resolution level j were investigated. Once the optimal filter and resolution level were selected, all individual spectra were transformed using this filter. Thereafter, the optimal number of the wavelet coefficients was used to construct $X_w$ matrix, which contains the important information. $X_w$ was used for calibration in wavelet domain i.e. no reconstruction of the signal was done. The index of the retained coefficients is kept for use with future samples.

**CONCLUSION**

This findings show the superiority of DWT-PLS over DD¹ method in solving this complex mixture (particularly in estimation of DX concentration). DWT-PLS method is considered powerful alternatives for traditional derivative ratio spectrophotometry. The applied method combines rapidness and simplicity advantages of traditional spectrometric methods together with other important analytical merits, such as sensitivity and specificity. The developed method can be applied to the routine quality control analysis of CHP and DX in their combined oral liquid dosage form without prior separation or interference from impurities/excipients.

**ACKNOWLEDGEMENT**

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project no. RGP-VPP-322.

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