Spectral Continuous Wavelet Transform for the Simultaneous Spectrophotometric Analysis of a Combined Pharmaceutical Formulation

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Continuous wavelet transform (CWT) combined with zero crossing technique was proposed for the simultaneous spectrophotometric determination of telmisartan (TMS) and hydrochlorothiazide (HCT) in their binary mixtures without using a chemical pretreatment. This new hybrid analytical approach is based on the application of the CWT method to the absorption spectra of the analytes and their samples. In the signal analysis, Gaussian (GAUS3) with order 3 and BiorSplines (BIOR1.2) with 1.2 order were found to be suitable for the quantitative spectral resolution of TMS and HCT in samples. These hybrid approaches were named as GAUS3-CWT and BIOR1.2-CWT. The validation of the CWT signal processing methods was carried out by using various binary mixtures of the analytes. The amounts of TMS and HCT in tablets were successfully determined by using the proposed GAUS3-CWT and BIOR1.2-CWT tools.

Keywords: continuous wavelet analysis, binary mixture, trimethoprim, sulphamethoxazole, tablets

In the spectrophotometric studies, various graphical and numerical spectral methods have been applied to the quality control of several combined commercial preparations containing a constant sample matrix. The derivative spectrophotometry can be applied for the binary mixture analysis but this technique has several major disadvantages, e.g. the signal/noise ratio diminishes and for the higher order derivative the main band and the noise peak may interfere with each other. As a result, new spectral approaches for the analysis of the multi-component mixtures should be developed.

During the last decades the wavelet transform became an efficient tool to solve problems in several areas of science and engineering [1-2]. Very recently, this method has been successfully applied to analytical chemistry [3-12]. The advantage of continuous wavelet transform (CWT) over the derivative method is that CWT provides a set of wavelet families which give us a rich spectral resolution of a given overlapping absorption spectra.

One of the open problems of the continuous wavelet transform (CWT) or the discrete wavelet transform (DWT) in quantitative drug analysis is to find, for a given specified mixture, the optimal wavelet family giving the acceptable recovery results. The existence of various wavelet families and the complexity of the spectra create difficulties in handling properly this problem. The common encountered case is that several families provide comparable recoveries for a given complex data system. As a result, we have to analyze the values of other quantities, e.g. mean recovery, the standard deviation and the relative standard deviation in order to decide which wavelet family gives the better recovery results.

As it is known, TMS and HCT combination has been used in anti-hypertension pharmaceutical formulations. The angiotensin II type 1-receptor antagonist telmisartan and the diuretic hydrochlorothiazide are two antihypertensive agents that have a well-recognized clinical efficacy. Their combination was shown in randomized, controlled trials to be more effective than each agent alone in lowering blood pressure, due to a dual and synergistic mechanism. The quantitative analysis of TMS and HCT in their binary combination was investigated recently by several authors [13-16].

The main aim of this study is to develop a new CWT spectral resolution of the mixture TMS and HCT compounds. In our knowledge this techniques was not applied in the literature for the above mentioned compounds. In finding the optimal signal processing tools several wavelet families were tested and GAUS3-CWT and BIOR 1.2 were found to be appropriate for the spectral quantitative resolution of TMS and HCT compounds in their mixtures. The validity of CWT approaches is performed by analyzing various synthetic mixtures TMS and HCT compounds. The results indicate that the proposed GAUS3-CWT and BIOR1.2-CWT approaches can be used for the routine analysis of the commercial tablets containing TMS and HCT drugs.

Wavelets

The wavelet function is orthogonal to all functions which are obtained by shifting the wavelet function to right or left by an integer number. Also, the wavelet function is orthogonal to all functions which are obtained by dilating the mother by a factor of 2^j and shifting by multiples of 2^j units. It was shown in the literature that the wavelets families have the property to efficiently represent functions possessing localized features.

Wavelet families together with their combinations with other chemometric techniques were used for the quantitative analysis of complex mixtures.

Let us consider a wavelet family $\psi(\lambda)$ [1-2]. By scaling and shifting the wavelet function $\psi(\lambda)$ we obtain a set of functions denoted by $\psi_{a,b}(\lambda)$ as

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$$\Psi_{a,b(\lambda)} = \frac{1}{\sqrt{|a|}} \Psi\left(\frac{\lambda - b}{a}\right) \quad a \neq 0, \qquad a, b \in R, \qquad (1)$$

where a denotes the scale parameter, b represents the translation parameter and R denotes the domain of real numbers. For a given signal f (λ) we define CWT as

$$CWT\{f(\lambda); a,b\} = \int_{-\infty}^{\infty} f(\lambda) \psi^{*}_{a,b}(\lambda)\, d\lambda = \left\langle f(\lambda), \psi_{a,b} \right\rangle \quad (2)$$

where the superscript * denotes the complex conjugate and $\langle f(\lambda), \psi_{a,b} \rangle$ is the inner product of function f(λ) onto the wavelet function $\psi_{a,b}(\lambda)$. In this paper we used six wavelet families abbreviated as BIOR1.2 and GAUS3.

Experimental part

Instruments and softwares

A Shimadzu UV-160 double beam UV–visible spectrophotometer connected to a computer loaded with Shimadzu UVPC software was used for the registration of the absorption spectra of the drugs and their samples. The mathematical treatments of the absorption data was performed in a computer by using the Microsoft EXCEL and Wavelet Toolbox in MATLAB 7.0 software.

Standard solutions

Stock solution for each of the pure compounds (TMS and HCT) was separately prepared dissolving 50mg of TMS and HCT in 100-calibrated flask ml within methanol. Calibration solutions of TMS and HCT in 2.0-23.0 μg/mL and 1.0-15 μg/mL, respectively were separately prepared from the above stock solutions. For the validation of the proposed CWT signal processing methods, an independent set containing the different mixtures of TMS and HCT in the concentration range of 2.0-23.0 μg/mL and 1.0-15 μg/mL, respectively was prepared by using the prepared stock solutions.

Commercial tablet formulations

The quantitative analyses of the commercial tablet formulations, MICARDIS PLUS® Tablet (I) (produced by Boehringer Ingelhiem Ind. Pharm.) and PRITOR PLUS® Tablet (II) (produced by Glaxo Smith Kline Ind.Pharm.) containing of 80 mg TMS and 12.5 mg HCT per tablet were carried out by using the proposed GAUS3-CWT and BIOR 1.2 –CWT methods.

Results and discussiond

Figure 1 indicates the absorption spectra of TMS and HCT in the concentration range of 2.0-23.0 μg/mL and 1.0-15 μg/mL in methanol. As it can be seen from this figure, their absorption spectra overlap in the spectral region of 200-350 nm. As we know well there are many difficulties in the spectral analysis of multi-component mixtures. We could not obtain desirable analysis results due to the overlapping spectra, interference of main compound with its degradation product's peaks and noise peaks, high and low concentration levels of compounds in samples etc. In the presence of the above drawbacks, it is clear that the classical derivative spectrophotometry (CDS) will not give better spectral resolution of complex mixtures. For these reasons, we need new, modern and robust signal processing methods in analytical chemistry or in the area of spectrophotometric quantitative analysis. New CWT methods are the candidates to eliminate the disadvantages of the CDS to reach rapid, precise and accurate analysis results. In our case, various wavelet families were tested the absorption signals of TMS and HCT and then CWT-GAUS3 and CWT- BIOR1.2 were found as suitable signal processing methods for the determination of two drugs in tablets. The details of the application of the proposed CWT methods are explained below.

Continuous wavelet transform

The UV spectra of TMS and HCT in the concentration ranges between 2.0-23.0 μg/mL and 1.0-15 μg/mL in methanol were plotted with intervals of Δλ=0.1 nm in the spectral region of 200-350 nm (fig. 1). The same spectral procedure was applied to samples containing TMS and HCT to obtain UV spectra. For the calibration graphs, validation set and samples, spectral data vectors corresponding to 1024 data points in the selected spectral region of 238-340.3 nm were transferred into wavelet domain. The applications of several wavelet families at different scale parameters (a) to the absorbance data vectors were tested to be located the optimal wavelet signal processing tools and GAUS3 (a=64) and CWT-BIOR1.2 (a=150) providing the highest recovery results were found to be the optimal ones.

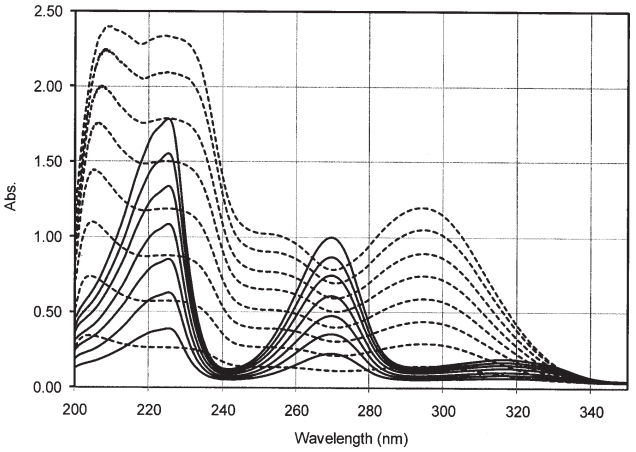

Fig. 1. GAUS2-CWT spectra 3, 5, 7, 9, 11, 13, 15 μg/mL HCT (—) and 2, 5, 8, 11, 14, 17, 20, 23 μg/mL TMS (- - -) in methanol

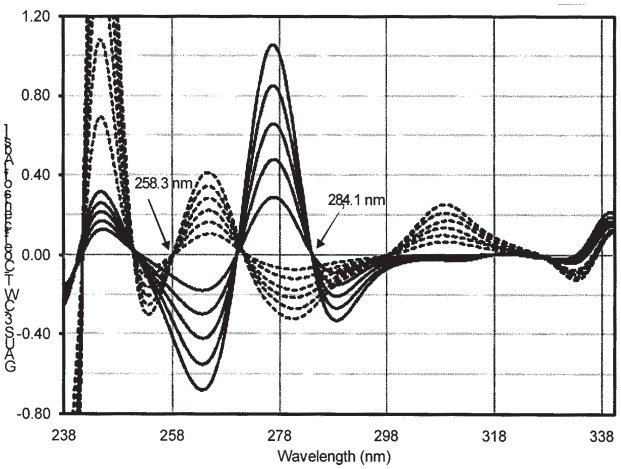

Fig. 2. Absorption spectra of 3, 5, 7, 9, 11, 13, 15 μg/mL HCT (—) and 2, 5, 8, 11, 14, 17, 20, 23 μg/mL TMS (- - -) by using scale parameter a = 64

GAUS3-CWT and BIOR1.2-CWT spectra of TMS and HCT in the linear concentration range of 2.0-23.0 μg/mL and 1.0-15 μg/mL, respectively, were obtained by fitting the wavelet coefficients ($C_{a,b}$) versus the wavelength in the range of 238-340.2 nm. The corresponding GAUS3-CWT and CWT- BIOR1.2 spectra were depicted in figure 2 and figure 3, respectively.

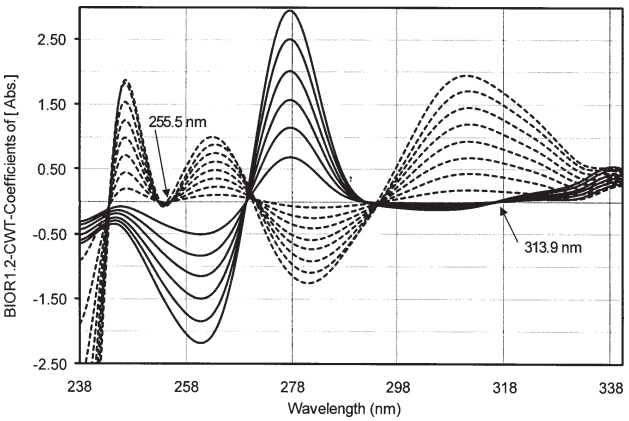

Fig. 3. BIOR1.2 CWT spectra of 3, 5, 7, 9, 11, 13, 15 µg/mL HCT (—) and 2, 5, 8, 11, 14, 17, 20, 23 µg/mL TMS (- - -) by using scale parameter a =1 150

Table 1
LINEAR REGRESSION ANALYSIS AND ITS STATISTICAL RESULTS

	BIOR1.2-CWT (a=150)		GAUS3-CWT (a=64)	
	TMS	HCT	TMS	HCT
	313.9	255.5	284.1	258.3
Range	2 -23	2- 15	2 -23	2- 15
m	8.22×10^{-2}	-1.37×10^{-1}	-1.35×10^{-2}	-3.98×10^{-2}
n	1.03×10^{-2}	5.30×10^{-3}	-2.36×10^{-4}	9.30×10^{-3}
r	0.9998	0.9999	0.9990	0.9999
SE(m)	6.00×10^{-4}	9.47×10^{-4}	5.49×10^{-5}	2.02×10^{-4}
SE(n)	8.56×10^{-3}	9.33×10^{-3}	7.89×10^{-3}	1.99×10^{-3}
SE(r)	1.17×10^{-2}	1.00×10^{-2}	1.07×10^{-3}	2.14×10^{-3}
LOD	0.88	0.58	0.50	0.43
LOQ	2.95	1.93	1.65	1.42

m = Slope of the linear regression,
n = Intercet of the linear regression
r = Correlation coefficient of the linear regression,
SE(m) = Standard error of Slope of the linear regression
SE(m) = Standard error of Intercept of the linear regression
LOD = Limit of detection,
LOQ= Limit of quantitation

Table 2
RECOVERY DATA OBTAINED BY APPLICATION OF CWT METHODS TO THE BINARY SYNTHETIC MIXTURES

			BIOR1.2-CWT (a=150)				GAUS3-CWT (a=64)			
	Mixture		Found (µg/mL)		Recovery (%)		Found (µg/mL)		Recovery (%)	
	(µg/mL)		TMS	HCT	TMS	HCT	TMS	HCT	TMS	HCT
	TMS	HCT	313.9	255.5	313.9	313.9	284.1	284.1	284.1	284.1
1	2.0	3.5	2.03	3.53	101.5	100.8	1.95	3.68	97.4	105.2
2	5.0	3.5	4.86	3.51	97.2	100.2	5.07	3.68	101.5	105.0
3	8.0	3.5	7.78	3.51	97.2	100.3	8.19	3.72	102.3	106.2
4	11.0	3.5	10.72	3.43	97.4	98.1	11.00	3.62	100.0	103.4
5	14.0	3.5	13.77	3.42	98.4	97.6	14.01	3.58	100.0	102.3
6	17.0	3.5	16.67	3.41	98.0	97.5	17.00	3.58	100.0	102.2
7	20.0	3.5	20.08	3.40	100.4	97.1	20.22	3.65	101.1	104.4
8	23.0	3.5	22.97	3.40	99.9	97.0	23.22	3.56	101.0	101.7
9	22.5	1.0	22.53	0.98	100.1	97.5	22.91	1.04	101.8	104.2
10	22.5	3.0	22.53	2.94	100.2	97.9	22.41	3.08	99.6	102.6
11	22.5	5.0	22.27	4.97	99.0	99.5	22.40	5.21	99.6	104.2
12	22.5	7.0	22.07	7.10	98.1	101.4	22.74	7.08	101.1	101.1
13	22.5	9.0	22.11	9.03	98.3	100.4	22.60	9.09	100.5	101.0
14	22.5	11.0	22.00	10.95	97.8	99.5	22.59	11.03	100.4	100.3
15	22.5	13.0	21.98	12.94	97.7	99.5	22.83	13.06	101.5	100.5
16	22.5	15.0	21.75	16.12	96.7	107.5	23.06	15.10	102.5	100.7
17	22.5	3.5	22.41	3.49	99.6	99.7	22.91	3.55	101.7	101.4
				Mean	98.7	99.5			100.7	102.7
				SD	1.37	2.48			1.24	1.86
				RSD	1.39	2.49			1.24	1.81

In the case of GAUS3-CWT method, the concentrations of the TMS and HCT compounds are proportional to the CWT amplitudes at 313.9 nm and 255.5 as indicated in figure 2, respectively. At the above wavelength points, the linear regression analysis and its statistical results were shown in table 1. The concentrations of TMS and HCT in their samples were calculated by using the linear regression functions.

In the similar manner, the calibration function for the related compounds were calculated by using the CWT amplitudes at 284.1 nm for TMS and 258.3 nm for HCT by

	BIOR1.5-CWR (a=150)				GAUS3-CWT (a=64)			
	(I)		(II)		(I)		(II)	
No.	TMS	HCT	TMS	HCT	TMS	HCT	TMS	HCT
1	82.72	12.95	80.88	12.27	80.42	12.05	77.77	12.08
2	83.85	12.76	79.99	12.32	79.83	12.06	77.92	12.17
3	83.18	13.21	82.33	12.40	78.63	12.82	79.96	12.27
4	84.22	13.32	82.20	12.39	79.29	12.76	80.28	12.38
5	82.55	12.73	83.61	12.34	79.81	12.78	81.27	12.65
6	83.77	12.78	82.51	12.40	78.97	12.77	80.26	12.93
7	82.64	12.43	82.23	12.39	78.17	12.35	79.77	12.59
8	83.23	12.58	83.35	12.73	79.16	12.76	81.16	12.15
9	82.84	12.85	82.52	12.21	78.75	12.78	80.44	12.43
10	82.90	12.84	82.87	12.52	78.57	12.76	80.35	12.04
Mean	83.19	12.85	82.25	12.40	79.16	12.59	79.92	12.37
SD	0.57	0.27	1.09	0.14	0.69	0.31	1.19	0.28
RSD	0.69	2.08	1.32	1.16	0.87	2.48	1.49	2.29
SE	0.18	0.08	0.34	0.05	0.22	0.10	0.38	0.09
CL(p=0.05)	0.36	0.17	0.67	0.09	0.43	0.19	0.74	0.18

Table 3
EXPERIMENTAL DETERMINATION RESULTS OBTAINED BY THE APPLICATION OF THE PROPOSED CWT METHODS

using BIOR1.5-CWT method (fig.3). For the working wavelength points, the results of the statistical linear regression analysis were presented in table 1. TMS and HCT in samples were determined by the linear regression lines obtained in the above step.

Validation of the signal processing methods

Calibration graphs in the concentration ranges between 2.0-23.0 μg/mL for TMS and 1.0-15 μg/mL for HCT were obtained by linear regression analysis based on the relationship between concentration and GAUS3-CWT and BIOR1.2-CWT amplitudes.

When it was considered the correlation coefficients (r), a good linearity for both compounds was observed as shown in table 1.

Good accuracy and precision for the results obtained by the proposed two signal processing tools were reported. For this purpose, the recovery studies were performed by applying the GAUS3-CWT and BIOR1.2-CWT methods to the analysis of the validation solutions of 17 independent mixtures by dilution of the stock solutions. The percentage recoveries and their relative standard deviations were indicated in table 2. Good accuracy and precision were observed for the results obtained by the application CWT methods.

Analysis of commercial tablets

In this study, GAUS3-CWT and BIOR1.2-CWT tools combined with zero crossing technique were successfully applied to the simultaneous quantitative analysis of TMS and HCT in two different commercial tablet formulations (MICARDIS PLUS® Tablet (I) and PRITOR PLUS® Tablet (II)). Experimental results obtained from the analysis of tablets were summarized in table 3. A good agreement was observed between the determined experimental results obtained from two wavelet families (CWT- GAUS3 and CWT- BIOR1.2). The proposed CWT methods were applied to tablet analysis without any separation step and no effect of tablet excipients was observed on the quantitative analysis of TMS and HCT in samples.

Conclusion

A given TMS-HCT combination can be considered as a complex mixture and several methods and techniques can be applied to the simultaneous determination of the given compounds. The new trends in the chemometric area are to develop new techniques and methods and to compare their results [16, 18]. On one side there are the classical methods and on another side there are the new one. The wavelet method by construction leads us to an optimal control problem, namely we have to answer the question which wavelet family gives better recovery results for a given mixture [16, 17].

In this paper it was reported that TMS and HCT in their mixture have the overlapping absorption spectra in the spectral region of 200 and 350 nm. The proposed methods can be applied to the routine quality control of the tablet containing TMS and HCT compounds.

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