Simultaneous Infrared Spectrometric Determination of Lisinopril and Hydrochlorothiazide in Tablets by Chemometric Methods

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ABSTRACT

A new Fourier transform infrared (FTIR) spectrometric method was developed for assaying hydrochlorothiazide (Hctz) and lisinopril (Lnp) in binary solid pharmaceutical formulations. Initially, the mixture of hydrochlorothiazide and lisinopril in solid mixtures was analyzed using FT-IR spectrometry in mid-IR range. Simultaneous determination of Hctz and Lnp carried out with inverse least squares (ILS) multivariate calibration of infrared spectra of binary standards of the drugs. The spectral range of1508-1850 $cm^{-1}$was selected for the measurement in methanolic solutions. In this method the statistical parameters such as $R^2$for Hctz and Lnp were 0.9995, 0.9994 and relative standard deviation (RSD) for Hctz and Lnp were 0.71%, 0.63% (n=6), respectively. Detection limits of Lnp and Hctz were obtained 0.75 and 0.90 mg/mL, respectively. USP methods were also used for comparing with proposed method, as a reference method. The proposed method was successfully applied to the determination of these drugs in laboratory-prepared mixtures and in commercial tablets. This method has suitable accuracy, precision, repeatability; and is comparable with reference standard methods.

Keywords: Lisinopril determination, FT-IR spectrometry, Hydrochlorothiazide determination, Pharmaceutical tablets.

1. INTRODUCTION

Lisinopril is a relatively new oral angiotensin converting enzyme (ACE) inhibitor. Lnp like its first generation relative, captopril has been shown to be effective in the treatment of hypertension and congestive heart failure [1].

Lisinopril, [(s)-1-[N^2-(S)-1-Carboxy-3-phenylpropyl)-1-IYSYL]-L-proline dehydrate is a prod rug which is de-esterified in the hepatic system todiacid form[2]. Only few methods were reported for simultaneous determination of ACE Inhibitors[3-10]. The drug is official in the USP XXll[11]. The methods of analysis of the bulk drug and its tablets are high-performance liquid chromatography (HPLC) and FT-IR methods[12-14]. Recently, lisinopril has been marketed in combination with hydrochlorothiazide (Hctz) in tablets such as Zestoretic (by AstraZeneca Pharmaceuticals), Prinzide (by Merck & Co.) and generic Lnp/Hctz binary tablets (by IVAX pharmaceuticals INC.). Hctz, 6-chloro-3,4-di hydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide-1,1-dioxide, is a diuretic of benzothiadiazine class, extremely useful in the treatment of edema, hypertension and hypercalciuria. The tablet manufacturers claim that the combined oral, administration of Lnp with Hctz has been found to be more effective than either drug alone in the treatment of hypertension.

A literature review revealed that several methods have

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been described for the determination of Lnp in pure forms and in pharmaceutical preparations including spectrofluorimetry[15], flow injection[16], spectrophotometry[17-20], HPLC techniques [21-23] and capillary electrophoresis[24]. Hydrochlorothiazide is one of the oldest and widely used thiazide diuretics. The drug is official in both BP93[25] and USP XXII[11]. Its analysis was reported either alone or in binary mixtures with other drugs[26-28]. The analytical profile of hydrochlorothiazide including several references to analytical methods for the determination of hydrochlorothiazide has been reviewed[29]. These reports commonly use labor intensive, time consuming and difficult procedures which could not be ideal for routine analyses in quality control laboratories.

During the last years the quantitative analysis of HCT in its binary mixtures was studied[29-33]. The binary mixture of hydrochlorothiazide and lisinopril has been analyzed by a validated reverse phase HPLC Method[34].

The Lisinopril-hydrochlorothiazide mixture is not yet official in any pharmacopoeia. To our knowledge, no spectrometric methods have been described for the simultaneous determination of both drugs in tablets. Therefore, it is desirable to develop a simple and fast procedure that could be applied in quality control laboratories for the determination of both drugs in the presence of each other. In spectrometric analysis, calibration techniques like chemometrics has been regarded as an important tool while monitoring quality and quantity of drugs in pharmaceutical formulations or biological systems, as it provides the advantage of not requiring any separation procedure in analysis of two or more drugs having spectral overlapping[35,36]. In this report, a FT-IR-based method is introduced for the quantification of both drugs in their binary solid dosages. The utility of developed method to determination the content of both drugs in commercial tablets is also demonstrated.

EXPERIMENTAL

Apparatus and reagents

A vector 22 FT-IR spectrometer from Bruker (Ettlingen, Germany) equipped with a DTGS mid-range detector, a KBrGe/Sb2S3-coated beam splitter and a Global source was employed for spectral measurements; spectra were obtained by accumulating 20 scans at a resolution of 4 cm^{-1}. Version 4 of Opus software, developed by Bruker, was employed to control the instrument, for data acquisition and also for preliminary processing the analytical results.

Omnic 1.2 and Quant IR 1.2 software packages (Nicolet) were used for acquisition of the spectra, statistical treatment of data and performing the ILS method. Transmission flow cell was assembled using two zinc selenide (ZnSe) windows and a 0.5 mm Teflon spacer in cell body (cell pathlength=0.5 mm).

Table 1. Concentration data for binary standard solutions used as calibration set

sample	Concentration mg mL^{-1}	
	Lnp	**Hctz**
1	0.00	0.00
2	2.00	0.00
3	6.00	0.00
4	9.00	0.00
5	0.00	3.00
6	2.00	3.00
7	6.00	3.00
8	9.00	3.00
9	0.00	7.00
10	2.00	7.00
11	6.00	7.00
12	9.00	7.00
13	0.00	10.00
14	2.00	10.00
15	6.00	10.00
16	9.00	10.00

Table 2. Concentration data for binary standard solutions used as validation(prediction) set

sample	Concentration mg mL^{-1}	
	Lnp	Hctz
1	15.00	25.00
2	16.00	13.00
3	18.00	23.00
4	20.00	12.50
5	20.00	20.00
6	30.00	30.00

Reagents and samples

Authentic lisinopril and hydrochlorothiazide were used as supplied. The purity of both drugs as assessed by the USP XXII methods was 98.5% and 99.1% for lisinopril male ate and hydrochlorothiazide, respectively. All solvents and reagents were of analytical grade and used without further purification. An orthogonal design with a training set of standards containing Lnp and Hctz at four concentration levels covering a total of 16 solutions, based on the model 4^2 standard was taken. In Table 1, the compositions of these binary mixtures used in the calibration matrix design are summarized.

Six more binary standard solutions were prepared for evaluation of this calibration matrix design by mixing different weights of two calibration samples. The composition of these two validation set is also shown in Table 2. Each sample in calibration set was prepared by dissolution of accurately weighted different amounts of Lnp and Hctz in methanol.

RESULTS AND DISCUSSION

Spectral region and ILS calibration

Sample solutions were introduced to the transmission cell and the spectra were recorded at a nominal resolution of 4 cm^{-1} with 20 scans. IR spectra of solid samples were collected from their KBr disk.

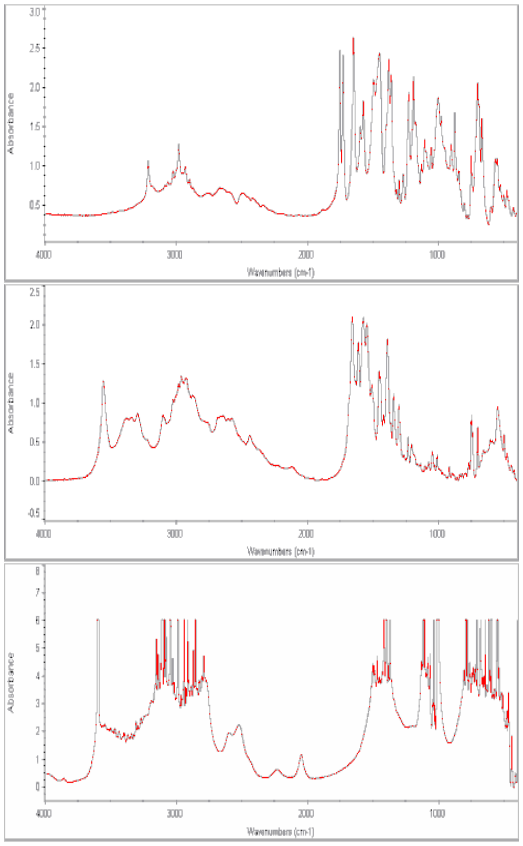

Figure 1: The IR absorption spectra of Hctz (top), Lnp (middle) and Methanol (bottom) in pure form

Figure 1 shows the absorbance spectra of Hctz and Lnp and methanol in mid-IR. These spectra show that methanol has adequate transparency for spectrometric measurements in wave number 1500-1850 cm^{-1}. Therefore, methanol was selected as best choice for the dissolution of both drugs due to its relative spectral transparency in selected spectral range, good solubilities of Lnp and Hctz in it and negligible spectral interferences of drug excipients.

Figures 1 and 2 show the spectrua of two binary standard solutions of Lnp, Hctz and their mixture containing different amount of these components in the spectral region of 1508-1850cm^{-1}. As can be seen, the resulting difference spectra shows that the relative changes in absorbance appear to be linearly spaced in this wave number range for these binary solutions.

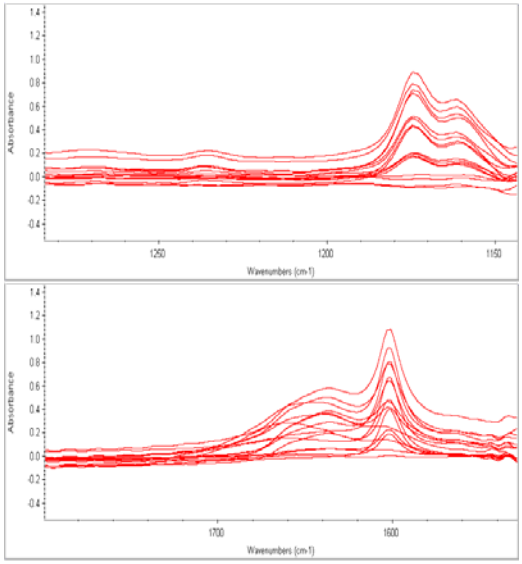

Figure 2: IR absorption spectra of standard solutions containing different amount of Lnp (2, 6, 9mgmL^{-1}) (top), Hctz (3, 7, 10 mgmL^{-1}) (bottom)

Multivariate calibrations are useful tools to be used in spectral analysis in order to overcome the spectral overlapping and to improve the precision and predictive abilities[31]. With the aim of simultaneous determination of Lnp and Hctz in commercial tablets formulations, the ILS multivariate model was applied with the absorbance spectral data obtained for both calibration and validation set standards The problem of overlapping spectra of Lnp and Hctz has also been circumvented by making use of their derivative spectra.

To select the best spectral region for simultaneous determination of these tablets, The FT-IR derivative spectra of training set were also collected in the spectral region of1508-1850 cm^{-1}.Figure 3 shows the display for the calibration spectral data in wave number range 1508-1850 cm^{-1}containing spectra of Lnp (top), Hctz (middle) and their binary mixture (bottom) in methanolic solution. This derivative spectra plot can be very useful for identification of active (useful) versus inactive spectral regions.

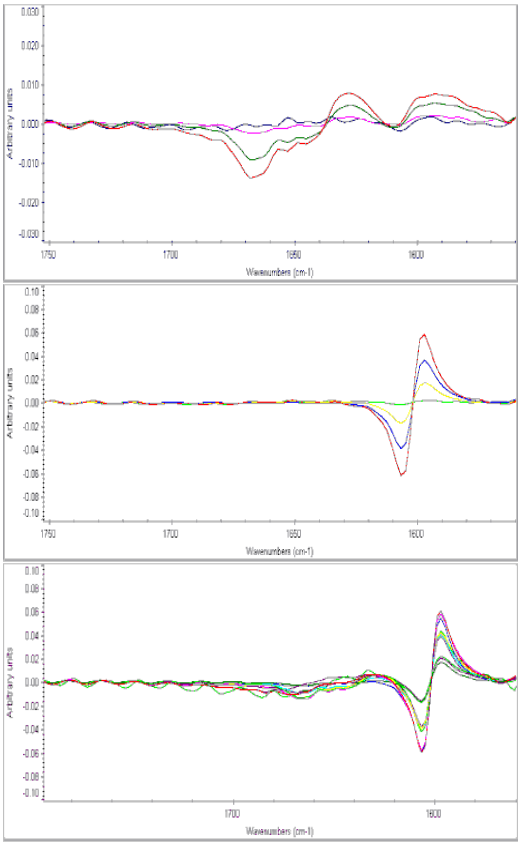

Figure 3: IR derivative spectra of standard solutions containing different amount of Lnp (2, 6, 9 mgmL^{-1}) (top), Hctz (3, 7, 10 mgmL^{-1}) (middle) and their nine binary solutions (over mentioned concentrations) (bottom) in the spectral region of 1508-1850 cm^{-1}

The selected spectral region used for the model should be restricted to those regions showing the highest spectral response. As suggested by this derivative spectra plot, wave number range of 1508-1850 cm^{-1} was selected as most convenient Spectral range.

Two sets of absorption spectra were obtained at this one spectral region for all of the calibration binary standard samples (Table 1). Baseline correction was applied for all these two sets of spectra. For each set of spectra, by using derivative spectra, ILS algorithm as calibration model was constructed. The viability of these model were tested by comparing the optimal number of factor, Statistical parameters such as correlation coefficient (R), standard error of estimation (SEE),

standard error of prediction (SEP), and standard error of cross validation (SECV) obtained for each component of binary standard samples in each model. For each component of binary calibration standards, the cross validation method was used [40]. SECV was calculated each time a new factor was added giving rise to different ILS models. One reasonable choice for the optimum number of factors would be that number which yields the minimum SECV. Each sample of calibration set was predicted at each of these spectra range and then SEE and the R for each component of the sample in each model were also calculated [38]. SEP which is an indication of the average error in the analysis of validation binary samples was calculated using expression.

$$SEP = \sqrt{\frac{\sum_{i=1}^{n}(C_i - CP_i)^2}{n}}$$

C_i is the actual concentration of each component in the sample i and CP_i represents the predicted concentration of that component in the sample. The optimal number of factor, SECV, SEE, SEP and R^2 values obtained for Lnp and Hctz. Three chemometric methods, including inverse least squares calibration of derivative spectra, partial least squares(PLS) calibration of derivative spectra and partial least square calibration of absorbance (zero order) spectra were applied for treatment of IR spectral data of standard sets. Statistical comparison of results obtained in analyzing samples of calibration and validation sets at three of chemometric methods in calibration step of 1508-1850 $cm^{-1}$are reported in Table 3.

Table 3. Statistical comparison of results obtained in analyzing samples of calibration and validation sets at three of chemometric methods in calibration step of 1508-1850 cm^{-1}

Statistical parameter	R^2		SEE ($mgmL^{-1}$)		SECV ($mgmL^{-1}$)		SEP ($mgmL^{-1}$)	
	Hctz	Lnp	Hctz	Lnp	Hctz	Lnp	Hctz	Lnp
ILS derivative spectra	0.9995	0.9994	0.30	0.25	0.59	0.45	0.92	0.80
PLS absorbance spectra	0.9991	0.9982	0.39	0.46	0.80	0.85	1.02	0.35
PLS derivative spectra	0.9975	0.9961	0.63	0.63	0.83	0.90	1.49	0.84

Evaluation of selected model

Plots of the actual concentrations versus predicted by selected ILS spectra model for each component of the 16 calibration binary standard mixtures revealed better correlations (Table 1). The square correlation coefficient of these regression lines (R^2) were 0.9994 for Lnp and 0.9995 for Hctz. PLS- based methods showed weaker calibrations in comparison with ILS calibration.

To evaluate the precision of the selected model, the concentration of each component of sample number 6 of the calibration set was predicted (n=6) by performing the selected model and calculating relative standard deviation (R.S.D.). The R.S.D. were found to be 0.63 for Lnp and 0.71 for Hctz. Detection limits of Lnp and Hctz were obtained 0.75 and 0.90 $mgmL^{-1}$ respectively. This method has suitable accuracy, precision, repeatability and is comparable with reference standard methods.

Statistical results of proposed method in for an independent set of standard samples are shown in Table 4.

Table 4. Estimated concentrations of FTIR-ILS method in calibration step for independent standard samples

sample	Actual content (mg mL^{-1})		Predicted content (mg mL^{-1})	
	Lnp	**Hctz**	**Lnp**	**Hctz**
1	20.00	25.00	20.90	24.23
2	25.00	25.00	26.03	24.53
3	28.00	25.00	29.06	24.45
4	30.00	25.00	31.04	24.61
5	20.00	30.00	21.14	29.16
6	20.00	33.00	21.16	32.36
7	20.00	35.00	21.20	34.06

Table 5. Determination of Lnp and Hctz in a commercial binary formulation. laboratory formulated Tablet Zestoretic (Averages of 4 measurements)

Amounts(mg)	Tablet Zestoretic	
	Lnp	**Hctz**
Claimed	20.00	25.00
Proposed method*	21.09	24.32
Reference method*	20.06	24.13

Real Samples Analysis

The proposed method was applied for the determination of Lnp and Hctz in a commercial tablet, Zestoretic. HPLC was also performed as reference method. As can be shown in Table 5, the results of both methods show good correlations.

CONCLUSIONS

The proposed system of Fourier transform infrared (FTIR) spectrometry combined with ILS regression shows considerable appropriation for the simultaneous determination of Lnp and Hctz in commercial available formulations such as Zestoretic Tablet (Table 5). Undiluted and minute amounts of samples without any treatment are employed and spectra are recorded rapidly. The relative errors in simultaneous determination of these two tablets can be similar and possibly better than those obtained by conventional methods, e.g. classical, potentiometric and extraction methods which are capable of determining a single component at a time.

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القياس الكمي من هيدروكلوروثيازيد وليزينوبريل متضمناً في المستحضرات العقارية باستخدام أسلوب كمومتريكس

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ملخص

لقد تم تطوير طريقة بمطياف تحليل الأشعة تحت الحمراء ذي تقنية معالجة فورير الرياضية. وقد تم تنفيذ تحليل الهيدروكلوروثيازايد والليزينوبريل سوياً بمعالجة نواتج التحليل بالأشعة تحت الحمراء لمواد مرجعية للدوائين بوساطة التحليل الرياضي لمتعددات التغير بمبدأ المخلفات الأقل المعكوس في هذا التحليل. تبين أن معامل الانحدار للهيدروكلوروثيازايد هو (9995) ولليزينوبريل (9994) والانحراف المعياري للهيدوكلوروثيازايد هو (71) ولليزينوبريل (63) ولأربع عينات. واستخدمت طريقة من دستور الأدوية الأميريكي للمقارنة مع هذه الطريقة كطريقة معيارية. ونجحت الطريقة المقترحة بتحليل الأدوية المذكورة في خلطات دوائية معدة في المختبر وفي المستحضرات التجارية. و قد وجد للطريقة الجديدة صحة نتائج ودقة وتكرارية مقبولة ومقاربة للطرق المعيارية.

الكلمات الدالة: القياس ليزينوبريل، القياس الطيفي، هيدروكلوروثيازيد، المستحضرات العقارية.

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