CHEMOMETRIC DETERMINATION OF EPHEDRINE-HCL IMPURITY IN PSEUDOEPHEDRINE-HCL RAW MATERIAL USING FT-IR

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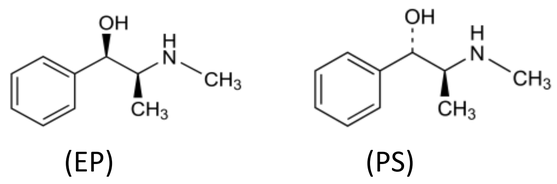
Abstract

Ephedrine-HCl and pseudoephedrine-HCl are both sympathomimetic agents that possess vasopressor effect. Ephedrine-HCl is mainly used as a bronchodilator in asthma preparations while pseudoephedrine-HCl is used as nasal decongestant. The British pharmacopoeia stated a limit of 1% of ephedrine-HCl impurity in pseudoephedrine-HCl pharmaceutical raw material [1]. Ephedrine-HCl and pseudoephedrine-HCl are diastereomers that possess the same UV spectral features. Hence, their simultaneous spectrophotometric determination is practically impossible. Chemometric multivariate methods, principal component regression (PCR) and partial least squares (PLS) were applied to the simultaneous determination of both isomers using Fourier transform infrared spectrometry (FT-IR). The training set was constructed using a full factorial calibration design at four levels. Both multivariate calibration models were developed using the correlation between the concentration and the absorbance data matrices in two spectral regions; the non-specific region (3260–2790 cm^{-1}) and the finger print region (1450–850 cm^{-1}). The two isomers possess very slight variations in the IR spectra at the selected regions that can be utilized by the chemometric models to generate the calibrations. The methods were validated by analyzing an independent validation set. The methods were found to be accurate and precise as indicated by the mean % recovery (100.19 – 100.67 %) and % relative standard deviation (0.75 – 1.03 %), respectively. The methods were successfully applied to the determination of trace ephedrine-HCl impurity in pseudoephedrine-HCl bulk raw material within the British pharmacopoeial limit without any prior separation step. The results were statistically compared to those obtained using the BP HPLC reference method.

Introduction

Ephedrine hydrochloride (EP) and its stereoisomer pseudoephedrine hydrochloride (PS) (Fig. 1) are both sympathomimetic agents [2]. The vasopressor effect of PS is one fourth that of EP and it may be used with caution in case of hypertensive patients. Some methods have been reported for the simultaneous determination of EP and PS. These methods include capillary electrophoresis with laser-induced fluorescence detection and high performance liquid chromatography. Diffuse reflectance infrared Fourier transform spectroscopy coupled with Partial-least-squares data analysis has been used for the determination of EP as a minor component in a mixture of EP and PS in solid state. EP and PS are official drugs in both the British Pharmacopeia (BP) [1] and the United States Pharmacopeia (USP) [3] as bulk pharmaceutical raw materials. Both BP [1] and USP [3] described potentiometric titration with sodium hydroxide for determination of EP and PS raw materials. The BP [1] described an HPLC method to test for the related compounds in PS and stated limits that should not exceed 1.0 % w/w for the individual impurity and 1.0 % w/w for other impurities.

The present work deals with the simultaneous FT-IR spectrometric determination of EP and its stereoisomer PS using multivariate regression algorithms; principal component regression (PCR) and partial least squares (PLS). The study is considered as an approach for the assessment of the isomeric purity of PS which is a crucial parameter in pharmaceutical quality control to determine the limit of EP in PS pharmaceutical grade raw materials.



(EP) (PS)

Fig. 1: Chemical structures of ephedrine (EP) and pseudoephedrine (PS).

Experimental

Stock standard solutions of EP (4.0 % w/v) and PS (4.0 % w/v) free bases were prepared in carbon tetrachloride after extraction of the free bases using diethylether. Suitable dilutions were made from both stock standard solutions using carbon tetrachloride to prepare the solutions of the training set containing different concentration ratios of EP and PS (Table 1). The training set solutions were used to develop the multivariate calibrations according to a 3-level full factorial design [4]. The number of experiments is given by $N = I^k$ where I is the number of concentration levels selected (= 3), and k the number of factors (Principle components) (=2). Hence 9 mixtures were prepared, each in three replicates, to construct the calibration model. Solutions of the validation set (Table 1) were prepared similarly using independently prepared stock standard solutions of both drugs and were used to validate the developed calibration. Solutions for testing the isomeric purity of PS were prepared as described for the preparation of the stock standard PS solution except that PS pharmaceutical grade raw material was used and the concentration of PS in the measured solutions were ranged from 1.00 % (w/v) to 2.00 % (w/v).

The IR absorption spectra of solutions of EP and PS in carbon tetrachloride were recorded over the wave number range of 4000-440 cm^{-1} using 64 accumulated scans with scan speed of 1 scan $4s^{-1}$ and a resolution of 4 cm^{-1}. The absorbance readings were measured at the IR regions of 1480-850 cm^{-1} and 3260-2790 cm^{-1} at 5 cm^{-1} interval and were used for the multivariate analysis. The PCR and PLS analyses were carried out using the chemometrics Toolbox 3.02 software for use with MATLAB 6.5 [5].

Results & Discussion

The FT-IR absorption spectra of EP and PS in carbon tetrachloride showed that the spectra of both compounds are similar except at the wave number intervals 1450-850 cm^{-1} and 3260-2790 cm^{-1} (Fig. 2). The composition of the solutions of the training set (Table 1) was orthogonally designed in order to obtain maximum information for each drug from the calibration procedure. The absorbance data matrix for the training set was obtained by selecting the absorbance readings within the wave number range 1480-850 cm^{-1} and 3260-2790 cm^{-1}. The multivariate calibrations were computed with the PCR and PLS algorithms using the correlation for the absorbance data matrix and the corresponding concentration data matrix of the training set. To validate the developed calibrations, an independent validation set of mixtures containing EP and PS in different concentrations (Table 1) was prepared and analyzed. The mean percentage recoveries indicated that the proposed PCR and PLS models applied to FT-IR spectra are accurate for the simultaneous determination of EP and PS in their mixtures. The RSD% values were less than 2 % indicating that the developed methods are of good precision.

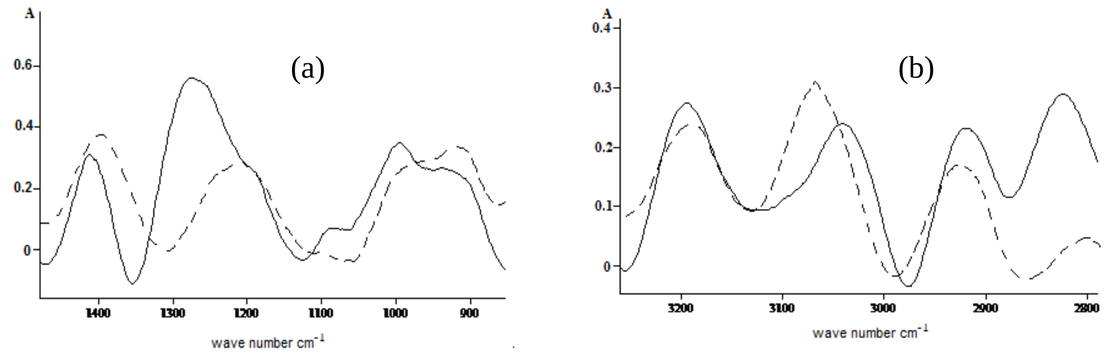


Fig. 2: IR absorption spectra of the bases of 1.0 % w/v EP (—) and 1.0 % w/v PS (– –) in Carbon tetrachloride at the fingerprint region (a) and the non specific region (b).

Table 1. Composition of the solutions of the training and the validation sets of EP and PS.

	Concentration % w/v					
	Training set			Validation set		
Sample Number	EP	PS	% of EP	EP	PS	% of EP
1,2,3	0.008	0.500	1.60	0.009	0.700	1.29
4,5,6	0.010	0.500	2.00	0.015	0.700	2.14
7,8,9	0.020	0.500	4.00	0.019	0.700	2.71
10,11,12	0.008	1.00	0.80	0.009	1.200	0.75
13,14,15	0.010	1.00	1.00	0.015	1.200	1.25
16,17,18	0.020	1.00	2.00	0.019	1.200	1.58
19,20,21	0.008	2.40	0.33	0.009	2.00	0.45
22,23,24	0.010	2.40	0.42	0.015	2.00	0.75
25,26,27	0.020	2.40	0.83	0.019	2.00	0.95

The Chemometric Toolbox 3.02 Software offers several indicator functions which could be used for determining the optimum number of factors to be used in the calibration. The studied indicator functions demonstrated that a rank of three factors is the optimum system rank for both the PCR and the PLS calibrations. The first two factors are suggested to be due to EP and PS as the main factors. The third factor is suggested to be due to base-line contribution from the instrument and the solvent. The constructed PCR and PLS models would span nearly all the data leaving only negligible residuals.

The proposed FT-IR multivariate methods were applied to the determination of the contents of PS and EP impurity in PS raw material. The results were in good agreement with those obtained using the reference British pharmacopeia method [1]. The results revealed that the investigated PS raw material contained EP in concentration below limit of the British pharmacopeia (1% w/w) and the content of PS in investigated samples comply with the BP specifications for PS. The results indicated that the tested PS is of high quality.

Conclusion

The proposed FT-IR multivariate regression methods are selective for the determination of ephedrine hydrochloride and its stereoisomer pseudoephedrine hydrochloride in their mixtures. The methods are sensitive to detect the presence of trace amount of one isomer in their mixtures. The proposed methods were proven to be applicable to determine EP as an impurity in bulk PS in concentrations within the limit described by the British pharmacopeia i.e. to test the isomeric purity of PS.

References

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