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Original Article

Fourth-order derivative spectrophotometric method for simultaneous determination of pseudoephedrine and naproxen in pharmaceutical dosage forms

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Abstract

Combination dosage forms of naproxen sodium and pseudoephedrine hydrochloride are used for symptomatic treatment of cold and sinus disorders. In this study, fourth-order derivative spectrophotometric method was used for simultaneous determination of naproxen sodium and pseudoephedrine hydrochloride. The method was linear over the range of 2-28 μg/ml for pseudoephedrine hydrochloride and 4-200 μg/ml for naproxen sodium. The within-day and between-day coefficient of variation values were less than 5.8% and 2.5% for pseudoephedrine hydrochloride and naproxen sodium, respectively. The application of the proposed method for simultaneous determination of naproxen and pseudoephedrine in dosage forms was demonstrated without any special pretreatment.

Keywords: Pseudoephedrine hydrochloride; Naproxen sodium; Derivative spectrophotometry

INTRODUCTION

Naproxen, (+)-(S)-2-(6-methoxynaphthalen-2-yl) propionic acid (Fig. 1), is a non-steroidal anti-inflammatory drug with antipyretic, analgesic and anti-inflammatory activity (1). Pseudoephedrine, (S, S)-2-mehtylamino-1-phenylpropan-1-ol (Fig. 1), with sympatho-mimetic effect is used for the treatment of nasal congestion in cold or allergic rhinitis (1). A mixture of naproxen and pseudoephedrine could be used for the symptomatic treatment of cold, sinus and flu symptoms. A survey of the literature reveals that various high-performance liquid chromatography (HPLC) methods are available for determination of pseudoephedrine alone or in combination with other drugs in pharmaceutical dosage form.

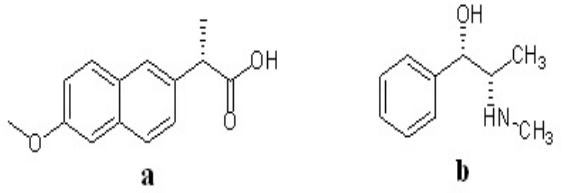

Fig. 1. Chemical structure of a; naproxen and b; pseudoephedrine.

A survey of the literature reveals that various high-performance liquid chromatography (HPLC) methods are available for determination of pseudoephedrine alone or in combination with other drugs in pharmaceutical dosage form. Simultaneous determination of pseudoephedrine and cetirizine has been reported by reversed phase HPLC in pharmaceutical dosage forms (2-4). There are also some reports on the HPLC determination of pseudoephedrine in the presence of codeine and triprolidine (5), paracetamol and chlorpheniramine (6) and ebastine (7). Trace amounts of ephedrine and pseudoephedrine was also detected in methamphetamine samples (8). The literature survey revealed some reports using HPLC and also derivative spectrophotometric methods for simultaneous determination of pseudoephedrine and desloratadine (9), acrivastine (10), and loratadine (11). Determination of naproxen alone or in combination with other drugs has been performed using HPLC assays. HPLC methods have also been used to determine naproxen in the presence of its degradation products (12-14). Identification of naproxen

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photo degradation products was reported by LC-ESI MS method (15). Determination of naproxen in the presence of diflunisal (16), sumatriptan (17), and esomeprazole (18) has also been reported.

Second derivative (19,20) and ratio spectra derivative spectrophotometric determination of pseudoephedrine in the presence of other drugs have been investigated. Improved spectrophotometric methods using chemometric techniques have been used for the simultaneous determination of fexofenadine and pseudoephedrine (24) and also pseudo-ephedrine and guaifenesin (25). Extractive spectrophotometric (26) and spectrofluorimetric (27) methods were also used for the determination of naproxen alone in pharmaceutical dosage forms. There are only two reported HPLC methods for simultaneous determination of naproxen and pseudoephedrine (28,29).

To the best of our knowledge, no spectrophotometric method has been reported for simultaneous determination of naproxen and pseudoephedrine. In continuation of our studies for the development of economical spectrophotometric methods and other studies (30-34), in this study a simple derivative spectrophotometric method based on zero-crossing measurements was used for simultaneous determination of naproxen sodium and pseudoephedrine hydrochloride.

MATERIALS AND METHODS

Materials

Naproxen sodium was from Sigma-Aldrich Company. Pseudoephedrine hydrochloride was from Malladi Drugs & Pharmaceuticals Limited, Chennai, India and kindly provided by Dr. Abidi Pharmaceutical Laboratory, Tehran, Iran. Methanol, ethanol, acetonitrile, hydrochloric acid and sodium hydroxide were of analytical grade and purchased from Merck (Darmstadt, Germany). Naprocold® tablets containing 220 mg naproxen sodium and 30 mg pseudoephedrine hydrochloride were from Iran Daru Co. (Tehran, Iran) which prepared from a local pharmacy.

Instrumentation

The spectrophotometric spectra were recorded using a Shimadzu 160A spectrophotometer (Kyoto, Japan) along the wavelength range of 200-350 nm in a 1 cm quartz cell. Zero order and first- to fourth-order derivative spectra were obtained at different $\Delta\lambda$ values over the wavelength range of 200-350 nm.

Standard solutions

Stock solutions of naproxen sodium at 2200 µg/ml and pseudoephedrine hydrochloride at 30 µg/ml were prepared in ethanol. Working standard solutions were prepared by appropriate dilution of these solutions with ethanol.

Derivative spectrophotometric method

Fourth-order derivative spectra of the standard solutions were obtained using the wavelength interval of $\Delta\lambda$ = 12.0. Zero-crossing value of pseudoephedrine hydro-chloride at 316 nm and zero-crossing value of naproxen sodium at 221 nm were selected as the working wavelengths.

Linearity

To evaluate the linearity of the proposed method, two series of calibration solutions were prepared in ethanol. The first series contained different concentrations of pseudoephedrine hydrochloride at 2, 4, 8, 12, 16, 20, 24 and 28 µg/ml at a fix concentration of naproxen sodium (88 µg/ml). The second series contained different concentrations of naproxen sodium at 4, 10, 20, 40, 80, 120, 160, and 200 µg/ml at a fix concentration of pseudoephedrine hydrochloride (12 µg/ml). Six binary mixtures were prepared and the fourth derivative values of the solutions at specified wavelengths were obtained to construct the calibration curves.

Accuracy and precision

Three sets of pseudoephedrine hydro-chloride solutions at three different concentration levels (4, 16, and 28 µg/ml) and fixed concentration of naproxen sodium (88 µg/ml) were analyzed and the concentrations were calculated using the corresponding calibration curve. The same procedure was performed using another series of solutions containing naproxen sodium at 4, 80, and 200 µg/ml and fixed concentration of pseudoephedrine hydrochloride at 12 µg/ml. This procedure was repeated three times in one day and for three consecutive days.

Application of the method in dosage form

Ten Naprocold® tablets were weighed and finely powdered. A portion of the powder equivalent to one tablet was transferred into a 50-ml volumetric flask and sonicated for 15 min with 30 ml of ethanol. The volumetric flask was brought to volume with ethanol, filtered and treated according to the standard method after ten times dilution. Tablets were analyzed using the proposed spectrophotometric method and also by using a previously published HPLC method (29).

RESULTS

Derivative spectrophotometric method

As shown in Fig. 2, large overlap of zero order spectra of pseudoephedrine hydrochloride and naproxen sodium prevents simultaneous determination of these compounds. First- to fourth-order derivative spectra of naproxen sodium and pseudoephedrine hydrochloride standard solutions were examined in order to select suitable spectrum to be used for simultaneous determination of these drugs.

Different solvents were also used to find out appropriate wavelengths in derivative spectrum for simultaneous determination of these drugs. In this regard, methanol, acetonitrile, methanol and 0.1 M hydrochloric acid (50:50), methanol and 0.1 M sodium hydroxide (50:50), and ethanol were used. Higher efficiency and better results were observed by using fourth-order derivative spectra with $\Delta\lambda$ = 12.0 and ethanol as the solvent (Fig. 3). A maximum fourth derivative value at 316 nm was obtained for naproxen sodium, where pseudoephedrine hydrochloride exhibits no absorbance.

The derivative value at this point was proportional to the naproxen sodium concentration, while the value of pseudoephedrine hydrochloride approaches near zero. The fourth derivative value at 221 nm was also dependent on the pseudoephedrine hydrochloride concentration and could be used for its determination. This absorbance value was not affected by different concentrations of naproxen sodium.

Linearity

As explained in experimental section, six series of calibration curves for each compound in the presence of fixed concentration of the other compound were constructed. The calibration curves were obtained by regression analysis and the statistical values are summarized in Table 1.

Accuracy and precision

Triplicate determinations of the mixtures were carried out to determine the precision and accuracy of the proposed method. The within-day and between-day coefficient of variation (CV) values showed acceptable repeatability of the proposed method for the simultaneous determination of naproxen and pseudoephedrine hydrochloride (Tables 2 and 3).

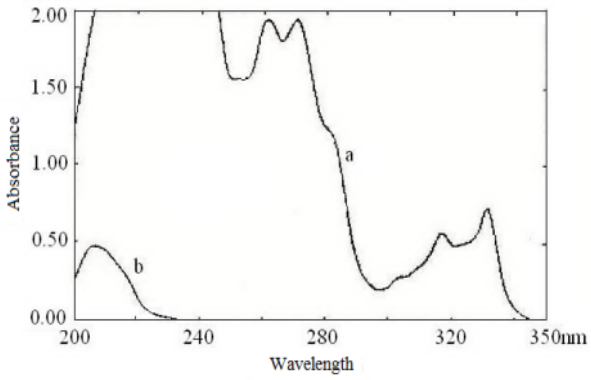

Fig. 2. Zero order spectra of a; naproxen sodium (88 μg/ml) and b; pseudoephedrine hydrochloride (12 μg/ml).

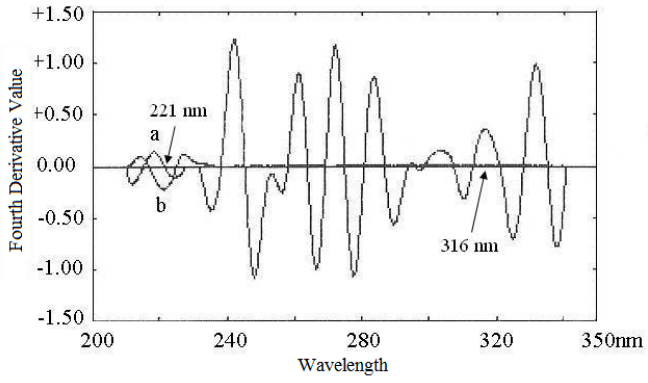

Fig. 3. Fourth-order derivative spectra ($\Delta\lambda$ = 12.0) of a; naproxen sodium (88 μg/ml) and b; pseudoephedrine hydrochloride (12 μg/ml).

Table 1. Statistical data of calibration curves of pseudoephedrine hydrochloride and naproxen sodium in mixtures with different concentrations using fourth-order (Δλ = 12.0) derivative spectra.

Parameters	Pseudoephedrine hydrochloride[a]	Naproxen sodium[b]
	$^4D_{221}$ (Δλ = 12.0)[c]	$^4D_{316}$ (Δλ = 12.0)[d]
Linearity range	2-28μg/ml	4-200 μg/ml
Regression equation	Y = 0.0044X+0.0247	Y = 0.0043X - 0.0004
Standard deviation of slope	4.08×10^{-5}	5.16×10^{-5}
Relative standard deviation of slope (%)	0.93	1.20
Standard deviation of intercept	0.0034	0.0003
Correlation coefficient	0.996	0.999

[a]In the presence of naproxen sodium (88 μg/ml)
[b]In the presence of pseudoephedrine hydrochloride (12 μg/ml)
[c]Fourth-order derivative value at 221 nm
[d]Fourth-order derivative value at 316 nm

Table 2. Accuracy and precision data for determination of pseudoephedrine hydrochloride (2-28 μg/ml) in the presence of naproxen sodium (88 μg/ml) by fourth-order (Δλ = 12.0) derivative spectrophotometry.

Concentration added (μg/ml)	Concentration found (μg/ml)	Coefficient of variations (%)	Error (%)
Within-day (n = 3)			
4	3.93 ± 0.23	5.85	-1.75
16	15.83 ± 0.13	0.82	-1.06
28	28.10 ± 0.35	1.24	0.36
Between -day (n = 9)			
4	3.93 ± 0.20	5.09	-1.75
16	15.83 ± 0.23	1.45	-1.06
28	28.15 ± 0.28	0.99	0.54

Table 3. Accuracy and precision data for determination of naproxen sodium (4-200 μg/ml) in the presence of pseudoephedrine hydrochloride (12 μg/ml) by fourth-order (Δλ = 12.0) derivative spectrophotometry.

Concentration added (μg/ml)	Concentration found (μg/ml)	Coefficient of variations (%)	Error (%)
Within-day (n = 3)			
4	4.03 ± 0.06	1.49	0.75
80	79.86 ± 0.0.71	0.89	-0.18
200	201.56 ± 0.61	0.30	0.78
Between -day (n = 9)			
4	3.99 ± 0.10	2.51	-0.25
80	79.63 ± 0.67	0.84	-0.46
200	200.72 ± 1.61	0.80	0.36

Table 4. Comparison of the developed method with the reference method for the determination of Naprocold® tablets.

Compound	Label claimed (mg)	Found (mean ± SD*)		Statistical tests**
		Proposed method	HPLC method	
Pseudoephedrine HCl	30	29.81 ± 1.25	29.86 ± 0.19	t = 0.959, F = 0.043
Naproxen sodium	220	221.59 ± 2.09	222.44 ± 3.37	t = 0.669, F = 0.555

*Stnadard Deviation
**Theoretical values of t and F at $P = 0.05$ are 4.303 and 19.00 respectively.

Application of the method

The content of pseudoephedrine hydrochloride and naproxen sodium in Naprocold® tablets was analyzed by the proposed spectrophotometric method and also a previously reported HPLC method. Statistical analysis suggested no significant difference between these two methods (Table 4).

Relative recovery

The solutions of commercial tablets were spiked with standard solutions of naproxen sodium and pseudoephedrine hydrochloride to study the relative recovery. The mean recoveries of naproxen sodium and pseudoephedrine hydrochloride were found to be 100.72 ± 0.95% and 99.58 ± 0.97%, respectively.

DISCUSSION

Validating simple and time-saving methods for determination of active ingredients in pharmaceutical dosage forms is of our interest. Spectrophotometric methods are simple and accurate and could be suitable substitution for other time-consuming and high cost methods. One of the important limitations of spectrophotometric methods is the simultaneous determination of drugs with overlapped spectra. Derivative spectrophotometric methods are one of the best alternatives to overcome this problem and resolve the spectral overlap for simultaneous determination of drugs. Using different derivative orders, it would be possible to find out zero-crossing points for each component which could be used for simultaneous determination of drugs. The derivative value of one of the components at the zero-crossing point for the other component could be a function of its concentration. Zero-crossing technique could successfully be used for the determination of two or more components with peak overlapping in zero-order spectrum (30-34). As spectrophotometric method for simultaneous determination of naproxen and pseudoephedrine has not so far been reported, in the current study a derivative spectrophotometric method was developed. The proposed spectrophotometric method was validated and showed to be accurate and precise in the studied concentration range. There is no need for pretreatment processes which are relatively time-consuming. The simplicity and short analysis time is the advantage of this method over reported HPLC methods for simultaneous determination of these drugs in combination dosage forms.

CONCLUSION

The proposed spectrophotometric method was simple, accurate and reliable for simultaneous determination of naproxen sodium and pseudoephedrine hydrochloride. Fourth-order derivative spectrophotometric method was used for determination of these drugs. Acceptable within- and between-day accuracy (error less than 1.8% and 1% for pseudoephedrine hydrochloride and naproxen sodium, respectively) and precision (CV less than 6% and 2.5% for pseudoephedrine hydrochloride and naproxen sodium, respectively) were observed for the assay determining both drugs without any interference from excipients.

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