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Novel spectroscopic methods for determination of Cromolyn sodium and Oxymetazoline hydrochloride in binary mixture

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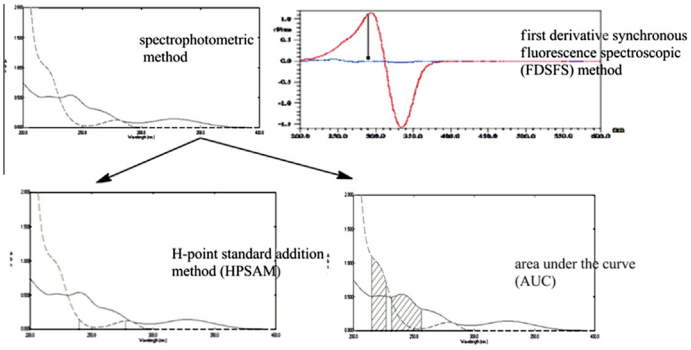
HIGHLIGHTS

- New spectroscopic determination of Cromolyn sodium and Oxymetazoline HCl.
- H-point standard addition method and area under the curve done for this mixture.
- First derivative synchronous spectrofluorimetry developed for this combination.
- These methods are sensitive and resolve binary mixture with overlapping spectra.
- The good recovery and accuracy make them applicable in QC laboratories.

GRAPHICAL ABSTRACT



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ABSTRACT

New accurate, sensitive and selective spectrophotometric and spectrofluorimetric methods were developed and subsequently validated for determination of Cromolyn sodium (CS) and Oxymetazoline HCl (OXY) in binary mixture. These methods include 'H-point standard addition method (HPSAM) and area under the curve (AUC)' spectrophotometric method and first derivative synchronous fluorescence spectroscopic (FDSFS) method.

For spectrophotometric methods, absorbances were recorded at 241.5 nm and 274.9 nm for HPSAM and the wavelength was selected in ranges 232.0–254.0 nm and 216.0–229.0 nm for AUC method, where the concentration was obtained by applying Cramer's rule. For FDSFS method, the first-derivative synchronous fluorescence signal was measured at 290.0 nm, using $\Delta\lambda = 145.0$ nm.

The suggested methods were validated according to International Conference of Harmonization (ICH) guidelines and the results revealed that they were precise and reproducible. All the obtained results were statistically compared with those of the reported method and there was no significant difference.

Introduction

CS, 5,5′-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4H-1-benzopyran-2-carboxylate] (Fig. 1a), is a mast-cell stabilizer which prevents the release of inflammatory chemicals, as histamine, from mast cells and blocks early and late asthmatic responses induced by allergen inhalation and exercise. It also blocks the increase in bronchial hyper-reactivity induced by chronic allergen exposure [1,2]. It can be formulated as a single ingredient or in multi ingredient dosage forms as Nazocrom® nasal spray with OXY.

Determination of CS in pharmaceutical formulations and biological fluids has been reported by several methods including spectroscopy [3,4], radioimmunoassay [5], thin layer chromatography

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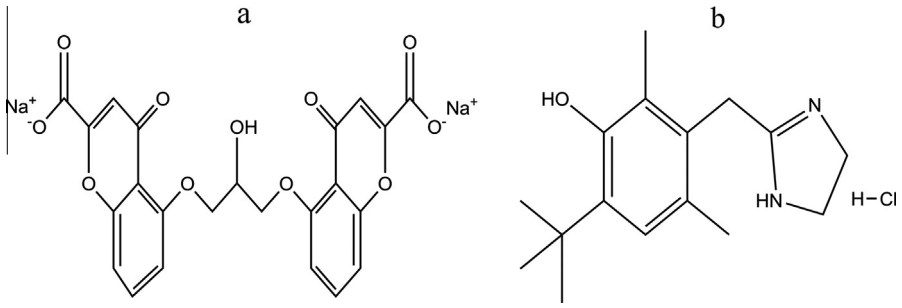

Fig. 1. Structure of Cromolyn sodium (a) and Oxymetazoline HCl (b).

(TLC) [6,7], HPLC using UV [8–11], fluorescence [12] and tandem mass [13–15] detectors, capillary electrophoresis [16] and electrochemical methods [17–19].

OXY, 3-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethyl ethyl)-2,4-dimethyl-phenol hydrochloride, (Fig. 1b), belongs to non-selective adrenergic drugs acting as a nasal decongestant [20]. It is used as a vasoconstrictor to treat epistaxis and eye redness due to minor irritation [21].

Several analytical techniques have been used for the determination of OXY as high-performance liquid chromatography [22,23], liquid chromatographic mass spectrometry [24], chemiluminescence [25], potentiometry [26] and spectrophotometry [27,28].

The literature survey revealed that no methods have been reported for the analysis of the drug in combination with OXY. The aim of the present work is to develop new, simple, accurate and precise methods for routine analysis validated according to ICH guidelines.

The use of HPSAM, which is based on the principle of dual wavelength spectrophotometry and the standard addition method, allows direct correction of both proportional and constant errors produced by the matrix of the sample. It can remove the errors resulting from the presence of interferent and blank reagents, but it cannot remove the constant error resulting from other constituents in the system [29,30].

The selection of two wavelengths, at which the analytical signal of the interferent is constant and that of the drug is as different as possible, is necessary for applying this routine work. Two straight lines are achieved by plotting the analytical signal against the added analyte concentration.

These lines intersect in a point with the coordinates H ($-C_H$, A_H), where $-C_H$ is the unknown analyte concentration and A_H is the analytical signal due to the interfering substance [31].

The AUC method presents a simple way to determine the concentration of the component of interest depending on the area of its absorption spectrum. This method is extensively applied for determination of drugs in their binary mixtures, as it is sensitive, accurate and selective for resolving drug mixtures [32–35].

Synchronous fluorescence spectroscopy (SFS) is based on measurement of the synchronous fluorescence intensity of the drug. Because of its sharp and narrow spectrum, it has superior advantages over conventional fluorescence spectroscopy, as it results in simple spectra, low interference and high selectivity [36]. In terms of sensitivity, the combination of SFS and derivative spectroscopy is more valuable than conventional direct spectrofluorimetry [37,38].

HPSAM has the following theory [29]:

Consider an unknown sample containing an analyte X and an interferent Y. Determination of the concentration of X by HPSAM under these conditions requires selection of two wavelengths, λ_1 and λ_2, at which the interfering species, Y, should have the same absorbance. Then known amounts of X are successively added to the mixture and the resulting absorbances are measured at the two selected wavelengths and expressed by Eqs. (1) and (2)

$$A_{(\lambda 1)} = b_0 + b + M_{\lambda 1} C_i \quad (1)$$

$$A_{(\lambda 2)} = A_0 + A' + M_{\lambda 2} C_i \quad (2)$$

where $A_{(\lambda 1)}$ and $A_{(\lambda 2)}$ are the analytical signals measured at λ_1 and λ_2, respectively, b_0 and A_0 are the original analytical signals of X at λ_1 and λ_2 respectively, b and A' are the analytical signals of Y at λ_1 and λ_2, respectively, $M_{\lambda 1}$ and $M_{\lambda 2}$ are the slopes of the standard addition calibration lines at λ_1 and λ_2, respectively, C_i is the added concentration of analyte X. The two straight lines obtained intersect at the so-called H-point [$-C_H$, A_H].

At the H-point ($C_i = -C_H$), Eqs. (3) and (4) follow from Eqs. (1) and (2), since $A_{(\lambda 1)} = A_{(\lambda 2)}$.

$$b_0 + b + M_{\lambda 1}(-C_H) = A_0 + A' + M_{(\lambda 2)}(-C_H) \quad (3)$$

$$-C_H = [(A_0 - b_0) + (A' - b)]/(M_{\lambda 1} - M_{\lambda 2}) \quad (4)$$

From Eq. (4), the following conclusions can be drawn: (i) if component Y is the known interferent and the analytical signal corresponding to Y, b (at λ_1) and A' (at λ_2) do not change with the addition of analyte X, that is, $b = A' =$ constant, so:

$$-C_H = (A_0 - b_0)/(M_{\lambda 1} - M_{\lambda 2}) = -b_0/M_{\lambda 1} = -A_0/M_{\lambda 2} \quad (5)$$

If the value of $-C_H$ is included in Eq. (1), then

$$A_H = b_0 + b + M_{\lambda 1}(-C_H) \quad (6)$$

$$b_0 = M_{\lambda 1} C_H \quad (7)$$

$$\text{then } A_H = b \quad (8)$$

and similarly $A_H = A'$.

Hence, the A_H value is only related to the signal of the interfering species Y at the two selected wavelengths and C_H is independent of the concentration of interfering species.

According to the above discussion, at H-point C_H is independent of the concentration of interferent and so A_H is also independent of the analyte concentration.

For selection of appropriate wavelengths for applying HPSAM, the following principles were followed

- At the two selected wavelengths, the analyte signal must obey Beer–Lambert's law.
- The analyte signal obtained from a mixture containing the analyte and the interferent signal should be equal to the sum of the individual signals of the two species.
- In addition, the difference in the slopes of the two straight lines measured at two selected wavelengths, λ_1 and λ_2, must be as large as possible in order to get good accuracy and sensitivity.