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Simultaneous determination of Fluticasone propionate and Azelastine hydrochloride in the presence of pharmaceutical dosage form additives

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ABSTRACT

Fluticasone propionate (FLU) and Azelastine hydrochloride (AZE) are co-formulated with phenylethyl alcohol (PEA) and Benzalkonium chloride (BENZ) (as preservatives) in pharmaceutical dosage form for treatment of seasonal allergies. Different spectrophotometric methods were used for the simultaneous determination of cited drugs in the dosage form. Direct spectrophotometric method was used for determining of AZE, while Derivative of double divisor of ratio spectra (DD-RS), Ratio subtraction coupled with ratio difference method (RS-RD) and Mean centering of the ratio spectra (MCR) are used for the determination of FLU. The linearity of the proposed methods was investigated in the range of 5.00–40.00 and 5.00–80.00 μg/mL for FLU and AZE, respectively. The specificity of the developed methods was investigated by analyzing laboratory prepared mixtures containing different ratios of cited drugs in addition to PEA and their pharmaceutical dosage form. The validity of the proposed methods was assessed using the standard addition technique. The obtained results were statistically compared with those obtained by official or the reported method for FLU or AZE, respectively showing no significant difference with respect to accuracy and precision at $p = 0.05$.

1. Introduction

Fluticasone propionate (FLU), 6a,9-Difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11b-hydroxy-16a-methyl-3-oxoandrosta-1,4-dien-17a-yl propanoate Fig. 1**a** [1] is a corticosteroid with mainly glucocorticoid activity. FLU is stated to exert a topical effect on the lungs without significant systemic effects at usual doses, due to its low systemic bioavailability. It is used by powder or aerosol inhalation for the prophylaxis of asthma and chronic obstructive pulmonary disease. Fluticasone propionate is administered by nasal spray in the prophylaxis and treatment of allergic rhinitis [2].

Azelastine hydrochloride (AZE), 4-(4-Chlorobenzyl)-2-[(4RS)-1-methylhexahydro-1H-azepin-4-yl] phthalazin-1(2H)-one hydrochloride Fig. 1**b** [1] is an antihistamine that, in addition to its histamine H_1-receptor-blocking activity, appears to inhibit the release of inflammatory mediators from mast cells. It is used topically in the symptomatic relief of allergic conditions including rhinitis and conjunctivitis. It is also used in the treatment of non-allergic (vasomotor) rhinitis [2].

Phenylethyl alcohol (PEA) Fig. 1**c** was used in many nasal spray formulations due to its antimicrobial, preservative properties in addition to its rose like odor. Also benzalkonium chloride used as a preservative.

Literature survey revealed that FLU and AZE are official drugs in British Pharmacopoeia [1] also FLU is an official drug in USP [3], There are several analytical methods that have been reported for the determination of FLU alone or in combinations including, spectrophotometry [4–8], HPLC [1,3,7–13], TLC [14,15] and capillary electrophoresis [16–18]. Besides, several methods have been reported for the determination of AZE alone or in combinations including, nonaqueous titration [1], Spectrophotometry [19–21] HPLC [22–25], TLC [26,27] and ion selective electrode methods [28]. Stability indicating methods were also reported for AZE using HPLC and spectrophotometric methods [29] or ion selective electrode [30].

Spectrophotometric method was developed for the determination of the binary mixture (FLU and AZE) without PEA [31]. Only one HPLC method for the cited mixture (FLU, AZE and the preservatives) was reported [32].

Therefore the aim of this work was to develop different simple, accurate, and precise spectrophotometric methods for the simultaneous determination of FLU and AZE in the presence of phenylethyl alcohol in bulk powder and in pharmaceutical dosage without the need of sophisticated instruments.

2. Experimental

2.1. Materials and reagents

2.1.1. Pure samples

Fluticasone propionate was kindly supplied by GlaxoSmithKline, Cairo, Egypt, its purity was found to be 100.00 ± 0.651 according to the official method [3]. Azelastine hydrochloride was kindly supplied

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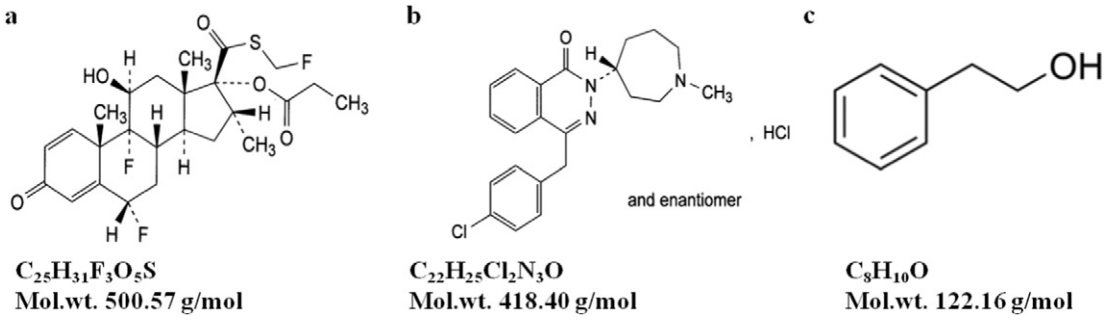

Fig. 1. Structural formula of (**a**) Fluticasone propionate (**b**) Azelastine hydrochloride (**c**) Phenylethyl alcohol.

by European Egyptian Pharm Co., Cairo, Egypt, its purity was found to be 100.23 ± 0.954 according to the reported method [29].

Phenylethyl alcohol and benzalkonium chloride were kindly supplied from Sigmatech Company, Cairo, Egypt their purity was found to be 99% and 95% for PEA and BENZ, respectively.

2.1.2. Pharmaceutical formulation

2.1.2.1. Dymista® nasal spray suspension. Labeled to contain 137.00 μg Azelastine hydrochloride and 50.00 μg Fluticasone propionate per each spray, batch No. FC3419 is manufactured by Meda pharma GmbH & Co. KG, Hamburg, Germany and obtained from the Danish market.

2.1.3. Reagent

Methanol of spectroscopy grade was purchased from Sigma-Aldrich, (St. Louis, MO, USA).

2.1.4. Standard stock and working solutions

- Standard stock solution of FLU, AZE, PEA and BENZ: 1.00 mg/mL in methanol.
- Working standard solution of FLU and BENZ: 0.10 mg/mL in methanol.
- Working standard solution of AZE and PEA: 0.20 mg/mL in methanol.

2.1.5. Laboratory prepared mixtures containing different ratios of FLU, AZE and PEA

Aliquots of FLU, AZE and PEA were transferred from their working standard solutions (0.10 mg/mL, 0.20 mg/mL and 0.20 mg/mL, respectively) into a series of 10-mL volumetric flasks, completed to the volume with methanol to prepare mixtures containing different ratios of FLU, AZE and PEA.

2.1.6. Dosage form solutions

Two sprays were delivered in 10.00 mL volumetric flasks containing 5.00 ml methanol then the volume was completed to the mark with methanol, then the flask was sonicated for 15 min then the solution was filtered through syringe filter 0.20 μm.

2.2. Instruments and software

Spectrophotometric measurements were carried out on Shimadzu dual beam UV–visible spectrophotometer (Kyoto, Japan), model 1650 PC connected to an HP compatible computer, with UV-PC personal spectroscopy software version 3.70 and a HP1020 laser jet printer. The absorption spectra were carried out using 1.00 cm quartz cells. Scans were carried out in the range from 200 to 400 nm at 0.1 nm intervals. For MCR computations, Matlab®_version 7, release 14 was used along with PLS-toolbox. Filtration of the pharmaceutical dosage form was done by using syringe filter 0.20 μm Sigma-Aldrich, (St. Louis, MO, USA).

3. Procedures

3.1. Spectral characteristics of FLU, AZE, PEA and BENZ

The zero-order absorption spectra (D^0) of FLU, AZE, PEA and BENZ (10.00 μg/mL, 30.00 μg/mL, 80.00 μg/mL and 10.00 μg/mL, respectively) were recorded against methanol as a blank over the range of 200–400 nm.

3.2. Construction of calibration curves

Aliquots equivalent to 50.00–400.00 μg FLU and 50.00–800.00 μg AZE are accurately transferred from their working standard solutions (0.10 mg/mL and 0.20 mg/mL, respectively) into three separate series of 10-mL volumetric flasks then completed to volume with methanol. The spectra of the prepared standard solutions were scanned from 200 to 400 nm and stored.

3.2.1. Direct spectrophotometric (D^0) method for AZE

The absorbance values of AZE at its λ_{max} (290.0 nm) were plotted against their corresponding concentrations (5.00–80.00 μg/mL) and the regression parameters were computed.

3.2.2. First derivative of double divisor of ratio spectra (^{1}DD-RS) method for FLU

The zero order spectra of FLU were divided by the stored spectrum of standard mixture solution of AZE and PEA (80.00 μg/mL of each), then the first derivative of the ratio spectra were obtained at $\Delta\lambda = 4$ nm and scaling factor = 100. The values of peak amplitude of the obtained derivative ratio spectra were recorded at 253.4 nm, plotted against the corresponding concentration. The regression equation and correlation coefficient were computed.

3.2.3. Ratio subtraction coupled with ratio difference method (RS-RD) for FLU

The zero order spectra of FLU were divided by the stored spectrum of standard solution of PEA (100.00 μg/mL). The amplitude difference of the ratio spectra (FLU/PEA) at 229.0 and 249.0 nm ($\Delta P_{229.0-249.0}$) was plotted against the corresponding concentration and the regression equation was computed.

3.2.4. Mean centering of the ratio spectra method (MCR) for FLU

For determination of FLU, the stored scanned spectra of FLU, AZE and PEA were exported to MATLAB® for subsequent calculation. The spectra of FLU with wavelength range of 240–270 nm were divided by the spectrum of 40.00 μg/mL AZE to obtain the first ratio spectra which were then mean centered and divided by the mean centered ratio of (α_{PEA}/α_{AZE}) to get the second ratio spectra which were then mean centered.

The calibration curve of FLU was constructed by plotting the mean centered values of the second ratio spectra at 252.0 nm versus the