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Novel spectrophotometric determination of flumethasone pivalate and clioquinol in their binary mixture and pharmaceutical formulation

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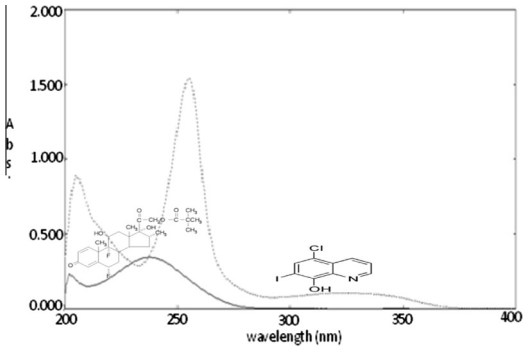
HIGHLIGHTS

- Three smart methods for flumethasone pivalate and clioquinol binary mixture analysis.
- Two spectrophotometric methods are recently developed and one is well established.
- The methods can determine the minor component which has low absorption.
- There was no interference with dosage form additives.
- Validation was done according to ICH recommendations.

GRAPHICAL ABSTRACT



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ABSTRACT

This work is concerned with development and validation of three simple, specific, accurate and precise spectrophotometric methods for determination of flumethasone pivalate (FP) and clioquinol (CL) in their binary mixture and ear drops. Method A is a ratio subtraction spectrophotometric one (RSM). Method B is a ratio difference spectrophotometric one (RDSM), while method C is a mean center spectrophotometric one (MCR). The calibration curves are linear over the concentration range of 3–45 μg/mL for FP, and 2–25 μg/mL for CL. The specificity of the developed methods was assessed by analyzing different laboratory prepared mixtures of the FP and CL. The three methods were validated as per ICH guidelines; accuracy, precision and repeatability are found to be within the acceptable limits.

Introduction

Flumethasone pivalate (FP) is a corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders, it produces dramatic suppression of skin diseases in which inflammation is a prominent feature [1].

Clioquinol (CL) is a halogenated hydroxyquinoline with antibacterial and antifungal activity [1].

The two drugs are co formulated in ear drops for the treatment of otitis externa [1], their chemical structures are shown in Fig. 1.

FP was determined by several methods in raw material and pharmaceutical formulations including spectrophotometry [2], colorimetry [3], electrochemical [4,5] and HPLC [6] methods.

CL was determined by spectrophotometric [7], fluorimetric [8], electrochemical [9], gas chromatographic [10] and HPLC [9,11,12] methods.

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From this literature review, no reported method was found for determination of both drugs in combination, so the aim of this work was development of spectrophotometric methods for simultaneous determination of the studied drugs in their binary mixture without preliminary separation.

Three recently developed spectrophotometric methods were applied. They are considered simple, accurate, precise, cost effective and do not require any sophisticated apparatus or computer programs.

Theory of the applied spectrophotometric methods

Ratio subtraction method (RSM)

Ratio subtraction method (RSM) [13] can determine the concentration of both components in their binary mixture using simple steps. For a mixture of two drugs X and Y, you can determine X by dividing the spectrum of the mixture ($X + Y$) by a known concentration of Y as a divisor (Y'). The division will give a new curve that represents $\frac{X}{Y'}$ + *constant t*. Measure the value of this constant $\frac{Y}{Y'}$ in the plateau region. If we subtract this constant value, then multiply the obtained curve after subtraction by Y' (the divisor), therefore we can obtain the zero order absorption spectrum (D^0) of X (original spectrum of X).

The concentration of X is calculated using the regression equation representing the linear relationship between the absorbance at its λ_{max} versus the corresponding concentration of X.

Ratio difference spectrophotometric method (RDSM)

For ratio difference spectrophotometric method [14], you can determine X by dividing the spectrum of the mixture by a known concentration of Y as a divisor (Y'). The division will give a new curve that represents $\frac{X+Y}{Y'}$ i.e. $\frac{X}{Y'} + \frac{Y}{Y'}$.

Where $\frac{Y}{Y'}$ is a constant. By selecting 2 wavelengths $\lambda 1$ and $\lambda 2$ on the obtained ratio spectrum and subtracting the amplitudes at these two points, the constant $\frac{Y}{Y'}$ will be cancelled along with any other instrumental error or any interference from the sample matrix. Similarly, the concentration of Y in the mixture can be determined by the same steps using a known concentration of X as a divisor (X').

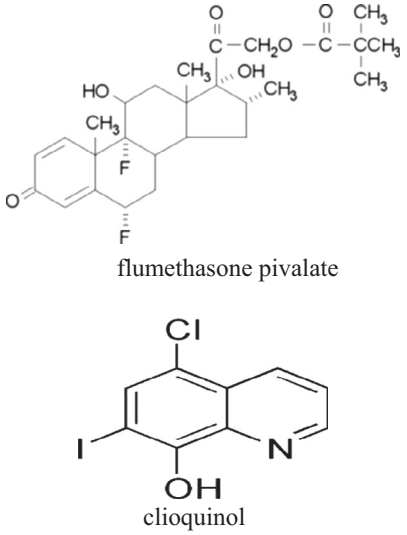

Fig. 1. The chemical structures of flumethasone pivalate and clioquinol.

Mean centering of ratio spectra spectrophotometric method (MCR)

This is a well-established spectrophotometric method in which both binary and ternary mixtures could be determined without previous separation. In this method the ratio spectra are obtained after which the constant is removed by mean centering of the ratio spectra [15–17].

Experimentals

Apparatus

Double beam UV–visible spectrophotometer (SHIMADZU, Japan) model UV-1601 PC with quartz cell of 1 cm path length, connected to IBM compatible computer. The software was UVPC personal spectroscopy software version 3.7. The spectral bandwidth was 2 nm and wavelength-scanning speed 2800 nm/min.

Software

Matlab® version 6.5.

Samples

Pure samples

Both FP and CL were kindly supplied by Amoun pharmaceutical company. According to the manufacturers, their purity was found to be 99.65% and 99.73% for FP and CL, respectively.

Market samples

Viotic® ear drops batch No. 124225. Each 1 mL claimed to contain 0.2 mg of FP and 10 mg of CL, manufactured by Amoun pharmaceutical company and obtained from local market.

Solvents

Methanol HPLC grade (E. Merck, Germany).

Procedure

Stock and working standard solutions

FP and CL stock standard solutions were prepared in the concentration of 1 mg/mL in methanol. Their working solutions were prepared in the concentration of 0.1 mg/mL by diluting 10 mLs of their respective stock standard solutions to 100 mL in methanol.

Spectral characteristic of FP and CL

The zero-order absorption spectrum of 10 μg/mL of each of FP and CL was recorded using methanol as a blank over the range of 200–400 nm.

Construction of calibration curves

Aliquots equivalent to 3.0–45.0 μg of FP and 2.0–25.0 μg of CL were accurately transferred from their working standard solutions (0.1 mg/mL) into two separate sets of 10-mL volumetric flasks then completed to volume with methanol. The spectra of the prepared standard solutions were scanned from 200–400 nm and stored in the computer.

For ratio subtraction spectrophotometric method (RSM). A calibration curve was constructed relating the absorbance of the zero order spectra of FP at 234 nm versus its corresponding concentrations, the regression equation was computed.