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Spectrophotometric methods for simultaneous determination of betamethasone valerate and fusidic acid in their binary mixture

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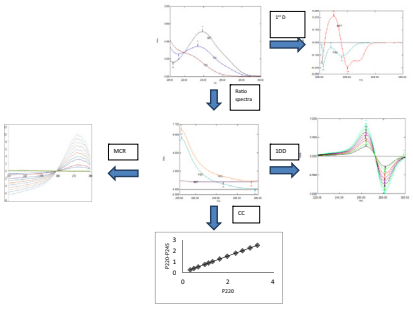
HIGHLIGHTS

- First spectrophotometric methods analyze betamethasone valerate and fusidic acid mixture.
- Five smart spectrophotometric methods are developed for the analysis of the binary mixture.
- Novel enrichment technique called spectrum addition is introduced and used.
- Spectrum addition technique overcomes the disadvantages of traditional spiking technique.
- All the proposed methods are validated and compared to BP official method of each drug.

GRAPHICAL ABSTRACT



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ABSTRACT

Five spectrophotometric methods were successfully developed and validated for the determination of betamethasone valerate and fusidic acid in their binary mixture. Those methods are isoabsorptive point method combined with the first derivative (ISO Point – D^1) and the recently developed and well established methods namely ratio difference (RD) and constant center coupled with spectrum subtraction (CC) methods, in addition to derivative ratio (^{1}DD) and mean centering of ratio spectra (MCR). New enrichment technique called spectrum addition technique was used instead of traditional spiking technique. The proposed spectrophotometric procedures do not require any separation steps. Accuracy, precision and linearity ranges of the proposed methods were determined and the specificity was assessed by analyzing synthetic mixtures of both drugs. They were applied to their pharmaceutical formulation and the results obtained were statistically compared to that of official methods. The statistical comparison showed that there is no significant difference between the proposed methods and the official ones regarding both accuracy and precision.

Introduction

Betamethasone valerate (BET), [(8S,9R,10S,11S,13S,14S,16S,17R)-9-fluoro-11-hydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a] phenanthren-17-yl] pentanoate (Fig. 1a), is a corticosteroid commonly used in topical preparation as the formation of the valerate ester with the hydrophilic 17-hydroxyl group of betamethasone increases the lipophilicity of betamethasone making it more suitable for topical application [1]. Fusidic acid (FSD), (3α,4α,8α,9β,11α,13α,14β,16β,17Z)-16-(acetyloxy)-3,11-dihydroxy-29-nordammara-17(20),24-dien-21-oic acid hemihydrate (Fig. 1b), is a

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bacteriostatic antimicrobial widely used topically as well as systematically [1]. Both drugs have been co-formulated and widely used to control and treat many dermal inflammations caused by bacterial infections.

Many methods have been reported for the determination of BET including spectrophotometric methods [2,3], densitometric method [4], HPLC assay [5–8], and polarographic method [9]. Several analytical procedures have been also reported for determination of FSD, including spectrophotometric methods [10–12], densitometric method [13] and HPLC [14–18].

Although some of the previously cited methods were used for the determination of BEC or FSD in mixtures with another drugs but only two methods have been reported for the analysis of a mixture containing both beclomethasone valerate and fusidic acid together which were HPLC complicated methods for the analysis of a mixture containing BET and FDS in addition to other drugs [19,20]. So this work is considered the first which represents analytical spectrophotometric methods for the analysis of a dosage form containing BET and FSD.

The main problem in the analysis of a mixture containing more than one component is the simultaneous determination of each component without prior separation as in most cases overlap between the spectra of more than one component occurs. The scientists in the spectrophotometry field were always interested in finding solution for that problem by manipulating the spectra. Many methods were developed due to their efforts such as derivative spectrophotometry [21–23], derivative ratio [24,25], isosbestic points [26,27], ratio subtraction [26] and others. With time due to the limitations of those traditional methods, new innovative techniques were recently developed to make the spectrophotometric analysis more suitable for resolving more mixtures, to get higher degree of accuracy and precision as well as to save time and effort like extended ratio subtraction [28,29], ratio difference methods [28], constant center [29,30], constant center coupled with spectrum subtraction [31] amplitude center method [32], absorbance subtraction and amplitude modulation [33].

The aim of this work is to develop spectrophotometric methods for simultaneous determination of the binary mixture of betamethasone valerate and fusidic acid in their dosage form without prior separation in spite of the complete overlap between their UV spectra specially in high concentrations of FSD and to compare the results of the developed methods with that of reported or official ones. The proposed methods are very simple, accurate, precise and do not require any sophisticated apparatus. On the other hand a novel enrichment technique namely spectrum addition technique was developed and used instead of the traditional spiking technique. This technique gave better results as it decrease manual error as well as saving the effort and time.

Theoretical background

Spectrum addition (SA)

Spectrum addition technique is a novel enrichment technique and it is adopted in the dosage form where the spectrum of one of the components is extended and shows low absorbance at the extended part which hinders its analysis at the zero order spectrum and subsequently hinders the accurate determination of its constant at the ratio spectra using a suitable divisor of the same component at the extended region.

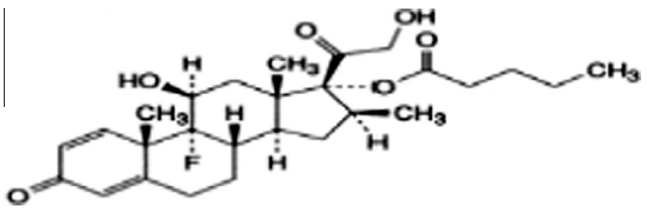

Fig. 1a. Chemical structure of betamethasone valerate.

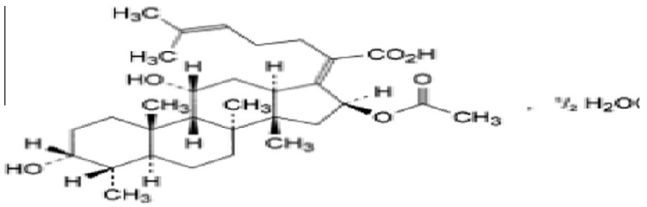

Fig. 1b. Chemical structure of fusidic acid.

Spectrum addition of pure standard solution of the extended component followed by spectrum subtraction where

(a) Zero order absorption spectrum of pure added standard solution + zero order absorption spectrum of unknown concentration of the extended component then get the ratio spectrum using a suitable divisor of the same component.
(b) Zero order absorption spectrum of pure added standard solution of the extended component then get the ratio spectrum using a suitable divisor of the same component.
(c) By difference between (a) and (b), the ratio spectrum of the unknown extended component (constant) could be achieved allowing accurate measurement of the constant.

This novel method can be applied for a binary mixture of X and Y where Y is extended, dividing the spectrum of the mixture by a certain concentration of Y as a divisor (Y′) after spectrum addition of a known concentration of Y, the division would give a new spectrum. This could be summarized in the following equations as follows:

$$[(X + Y_{mix}) + Y_{added}]/Y' = [X/Y' + (Y_{mix} + Y_{added})/Y'] \quad (1)$$

$$X/Y' + Y_{total}/Y' \quad (2)$$

$$X/Y' + Constant_{total} \quad (3)$$

The total constant after spectrum addition can be determined directly from the $(X + Y + Y_{added})/Y'$ spectrum by the straight line that was parallel to the wavelength axis in the region where Y was extended.

$$\therefore Y_{added}/Y' = Constant_{added} \quad (4)$$

The constant of the unknown Y in the mixture can be calculated from the difference between Eqs. (4) and (3) as follows:

$$Constant_{Unknown} = Constant_{total} - Constant_{added} \quad (5)$$

where $Constant_{Unkown}$ is the constant corresponding to unknown Y in the mixture, $Constant_{added}$ is the constant corresponding to the added spectrum of pure solution of Y, $Constant_{total}$ is the constant corresponding to total Y (unknown + added) using the same concentration of pure Y as a divisor.

Spectrum subtraction

This technique was used as a resolution technique for mixtures where one of its components is extended [31]. The obtained constant of the ratio spectrum of X and Y using Y′ as a divisor at the extended part could be multiplied by the divisor Y′ to get the original zero order spectrum of Y then subtracted the obtained spectrum of Y from the recorded spectrum of the binary mixture (X + Y) to get spectrum of X.