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Spectrophotometric resolution of the severely overlapped spectra of clotrimazole with dexamethasone in cream dosage form by mathematical manipulation steps

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ARTICLE INFO

ABSTRACT

Several spectrophotometric techniques were recently conducted for the determination of binary mixtures of clotrimazole (CLT) and dexamethasone acetate (DA) without any separation procedure. The methods were based on generation of ratio spectra of mixture then applying simple mathematic manipulation. The zero order absorption spectra of both drugs could be obtained by the constant center (CC) method. The concentration of both CLT and DA could be obtained by constant value via amplitude difference (CV-AD) method depending on ratio spectra, Ratio difference (RD) method where the difference between the amplitudes at two wavelengths (ΔP) on the ratio spectra could eliminate the contribution of the interfering substance and bring the concentration of the other, and the derivative ratio (DD^1) method where the derivative of the ratio spectra was able to determine the drug of interest without any interference of the other one. While the concentration of DA could be measured after graphical manipulation as concentration using the novel advanced concentration value method (ACV). Calibration graphs were linear in the range of 75–550 µg/mL for CLT and 2–20 µg/mL for DA. The methods applied to the binary mixture under study were successfully applied for the simultaneous determination of the two drugs in synthetic mixtures and in their combined form Mycuten-D cream. The results obtained were compared statistically to each other and to the official methods.

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1. Introduction

Clotrimazole (CLT) [1-[(2-Chlorophenyl)diphenyl methyl]-1H-imidazole] the antifungal agent leading to cell death of fungal cells by inhibiting ergosterol biosynthesis [1]. BP enclosed a titrimetric method for determining CLT [2] and an HPLC method in the USP [3]. The literature revealed also colorimetric methods [4–6], spectrophotometric methods [7,8] and HPLC methods [4,9–11] for quantitative estimation of CLT.

Dexamethasone acetate (DA) [16-methyl-11β, 17α, 21-trihydroxy-9α-fluoropregna-1,4 diene-3,20-dione 21-acetate], is a corticosteroid with anti-inflammatory effect [12]. USP described an HPLC method for determining DA [3], while in the BP it was determined by direct spectrophotometry [2]. The literature revealed also

determination of DA by HPLC [13–15], Chemometric-assisted spectrophotometric- assisted spectrophotometry [16], and capillary electrophoresis [17].

There was an established RP-HPLC method analyzing both DA and CLT together in mixtures [18], and several conventional and mathematically manipulated spectrophotometric methods dealing with CLT in low concentration range (1–12 µg/mL) [19]. Chemical structures illustrated in Fig. 1.

The aim of this work was to develop simple spectrophotometric methods which were able to resolve the severe spectral overlap of CLT and DA, the novel one namely advanced concentration value (ACV) while the other smart methods namely, constant center (CC), constant value via amplitude difference (CV-AD), ratio difference (RD) and derivative ratio (DD^1). The proposed spectrophotometric methods could be easily used accurately and precisely for simultaneous determination of the studied binary mixture with simple manipulation procedures. The proposed methods could be used in the analysis of their market formula named Mycuten-D® cream.
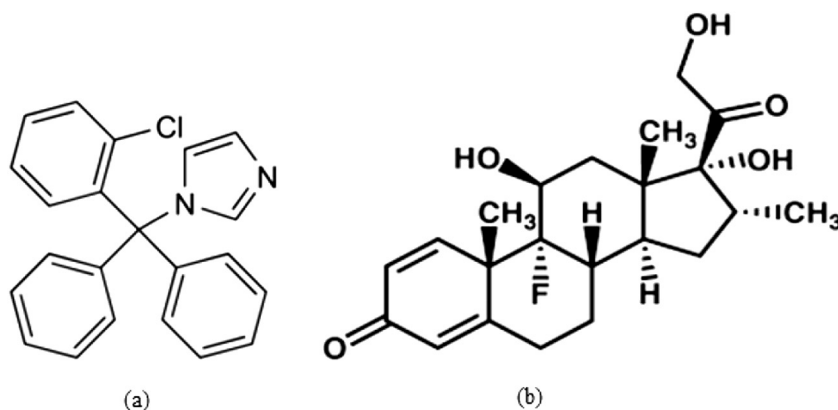
Fig. 1. The chemical structure of (a) CLT, (b) DA.

A comparative study was made between the obtained results to check the efficiency of the proposed methods in the estimation of the cited drugs.

1.1. Theoretical Background

1.1.1. Constant Center Method (CC) [20]

Considering a mixture X and Y, where the zero order absorption spectra of cited components were severely overlapped. Then using X as a divisor (X′), the constant X/X′ was calculated via amplitude difference and multiplied by the X′ spectrum in a step known as constant multiplication to get the zero order absorption spectrum of X.

$$X/X'^{*} \, X' = X \tag{1}$$

The concentration of X could be calculated using its corresponding regression equation representing the linear relationship between the absorbance values of the zero order curve of X at its λ_{max} versus the concentration. Similarly, the concentration of Y in the mixture could be determined by the same two steps [constant calculation via amplitude difference followed by constant multiplication].

1.1.2. Constant Value Via Amplitude Difference (CV-AD) [20]

Considering a mixture X and Y, where the zero order absorption spectra of cited components were severely overlapped. Then using X as a divisor (X′), the division would give a new curve that represents $(X + Y)/X' = (P_X) + ((P_Y)$, Where P_X was a constant.

By subtracting the amplitude at 2 selected wavelengths λ_1 and λ_2 on the obtained ratio spectrum of the mixture, the constant (P_X) is canceled eliminating the contribution due to X and the difference would represent component Y only; then;

$$P_1 - P_2 = (P_Y)_1 + \text{constant} - (P_Y)_2 + \text{constant})] \tag{2}$$

$$\Delta P = (P_Y)_1 - (P_Y)_2 \tag{3}$$

where; ΔP is the difference of ratio spectra amplitudes a λ_1 and λ_2, $(P_Y)_1$ and $(P_Y)_2$ is the amplitude of Y at λ_1 and λ_2.

Regression equation representing the linear relationship between the ΔP of different concentration of pure Y at λ_1 and λ_2 using a certain concentration of X′ as a divisor versus the corresponding ratio amplitude at one of the two selected wavelength λ_1:

$$\Delta P = \text{slope} \, (P_Y)_1 + \text{intercept} \tag{4}$$

Postulated $(P_Y)_1$ related to component Y only in the mixture of X + Y could be calculated by using the previously mentioned regression equation using the ΔP at the two selected wavelengths of the mixture ratio spectrum. The constant value (P_X) could be calculated by subtracting the P $_{recorded}$ of the mixture at (λ_1), and its P $_{postulated}$ at (λ_1) $C \cdot V = [P_{Recorded}] - [P_{Postulated}]$.

The concentration of X was calculated using the regression equation representing correlation between the amplitudes of the constant of ratio spectra and the corresponding concentrations.

Similarly, the concentration of Y in the mixture could be determined using Y as a divisor.

1.1.3. Ratio Difference (RD) [21]

Considering a mixture X and Y, where the zero order absorption spectra of cited components were severely overlapped. Then using X as a divisor where the amplitude difference $(P_1 - P_2)$ between two different wavelengths on the ratio spectra of a mixture was directly proportional to the concentration of Y without any interference of X. Similarly, X can be determined using Y as a divisor.

1.1.4. Derivative Ratio (DD[1]) [22]

Considering a mixture X and Y, where the zero order absorption spectra of cited components were severely overlapped. Then using X as a divisor where the amplitude of derivative of the ratio spectra of mixture was directly proportional to the concentration of Y without any interference of X. Similarly, X can be determined using Y as a divisor.

1.1.5. Advanced Concentration Value (ACV)

Novel approach depending upon graphical manipulation of the spectra, where the concentration value of the drug was recorded directly representing the actual concentration without substitution in the regression equation. It was conducted either using zero order absorption spectrum or derivative spectrum by dividing the zero order absorption spectrum of the mixture by zero order D° of the normalized spectrum of the more extended component, then the constant obtained from the plateau region parallel to the x-axis represents the concentration of the more extended component and was called concentration value method [19,23].

The advanced concentration value method was applied by using the same steps as the CV via amplitude difference using normalized spectrum of Y which representing the absorptivity all over the wavelengths where the measured constant value will be representing the concentration directly and the recovery percentage will calculated relative to the theoretical value.

$$a_Y \, C_Y/a_Y = C_Y \tag{5}$$