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Successive spectrophotometric resolution as a novel technique for the analysis of ternary mixtures of pharmaceuticals

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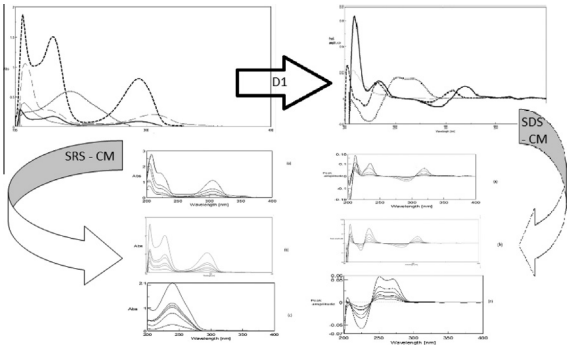
HIGHLIGHTS

- Successive spectrophotometric resolution for severely overlapped spectra.
- Each component could be obtained alone as its D^0 by CM only, or RS & SRS–CM.
- Each component could be obtained alone as its D^1 by CM only or by DS & SDS–CM.
- They were applied for the analysis of their pharmaceutical formulation.
- Validated according to the ICH guidelines & compared to the official methods.

GRAPHICAL ABSTRACT



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ABSTRACT

A novel spectrophotometric technique was developed for the simultaneous determination of ternary mixtures, without prior separation steps. This technique was called successive spectrophotometric resolution technique. The technique was based on either the successive ratio subtraction or successive derivative subtraction. The mathematical explanation of the procedure was illustrated. In order to evaluate the applicability of the methods a model data as well as an experimental data were tested. The results from experimental data related to the simultaneous spectrophotometric determination of lidocaine hydrochloride (LH), calcium dobesilate (CD) and dexamethasone acetate (DA); in the presence of hydroquinone (HQ), the degradation product of calcium dobesilate were discussed. The proposed drugs were determined at their maxima 202 nm, 305 nm, 239 nm and 225 nm for LH, CD, DA and HQ respectively; by successive ratio subtraction coupled with constant multiplication method to obtain the zero order absorption spectra, while by applying successive derivative subtraction they were determined at their first derivative spectra at 210 nm for LH, 320 nm or $P_{292-320}$ for CD, 256 nm or $P_{225-252}$ for DA and $P_{220-233}$ for HQ respectively. The calibration curves were linear over the concentration range of 2–20 μg/mL for both LH and DA, 6–50 μg/mL for CD, and 3–40 μg/mL for HQ. The proposed methods were checked using laboratory-prepared mixtures and were successfully applied for the analysis of pharmaceutical formulation containing the cited drugs with no interference from other dosage form additives. The proposed methods were validated according to the ICH guidelines. The obtained results were statistically compared with those of the official BP methods for LH, DA, and CD, and with the official USP method for HQ; using student *t*-test, *F*-test, and one way ANOVA, showing no significant difference with respect to accuracy and precision.

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Introduction

Anti-haemorrhoidal (Antihaemorrhoidalia) medicines are mainly used in symptomatic therapy, and only partially as causal therapy of anorectic region disease. They are used locally, mostly as a combination of active compounds. Dosage forms that are used are suppositories and ointments. Usual compounds used in this therapy are anesthetics, anti-inflammatory drugs, antibiotics, vasoconstrictors, haemostatics, anticoagulants and antihistaminic [1]. Lidocaine hydrochloride (LH) [acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl),monohydrochloride] is a local anesthetic drug reversibly inhibits nerve impulse transmission. It binds to the receptors in sodium channels and decreases their activity functioning as a cell membrane stabilizer. It has a good superficial activity, penetrates in depth through the mucous membranes and reduces the sensation of pain.

Dexamethasone acetate (DA) [16-methyl-11β, 17α, 21-trihydroxy-9α-fluoropregna-1,4 diene-3,20-dione 21-acetate] inhibits the inflammatory process, through the anti-inflammatory function, in the early stage. The function of glucocorticoids is not specific because it decreases the inflammatory action effects no matter what the cause of the reaction was [1].

Calcium dobesilate (CD) [calcium 2,5-dihydroxybenzenesulfonate] as a cyclohexadienolic bisulphate derivative also known as hydroquinone sulfonic acid, decreases the micro vascular permeability by inhibiting the histamine and bradykinin concentration. In that way it reduces edema, inflammation and bleeding from hemorrhoids. It has a protective effect on blood vessels. Recent studies showed CD as an antioxidant improving endothelial function [2,3].

Considering the literature LH was investigated in rectal medical gel [4] and human plasma using high-performance liquid chromatography (HLPC) [5,6], while its official methods are HPLC [7], or potentiometric titration [8] and LC–MS [9]. DA was determined by HPLC according to the USP [7], or direct spectrophotometry as the BP official method [8], or by HPLC in cream [10], injection solutions [11] and equine serum [12]. DA was also determined in tablets using chemometrics- assisted spectrophotometry [13], in addition to capillary electrophoresis [14]. CD was determined by HPLC [7] or potentiometric titration [8] as their official methods. CD was directly determined in plasma, using a flow-injection biamperometric method [15] and HPLC method after ion-pair extraction [16]. For the simultaneous determination of LH, DA, CD, and HQ qualitatively and quantitatively an isocratic reversed phase high performance liquid chromatographic method was described [17], and recently novel mathematical spectrophotometric techniques [18].

The chemical structures of the drugs [8] were shown in Fig. 1.

The aim of this work was to develop stability indicating spectrophotometric method for resolving the ternary mixture of LH, DA and CD drugs in the presence of HQ – the degradation product of CD and its precursor [19] – with spectral interfering problems without preliminary separation. LH had exceptional stability and was extremely resistant towards hydrolysis at room temperature, even in strong acidic or basic medium [20]. Dexamethasone acetate exhibited very slow degradation in aqueous solution at pH 6.0 which was consistent with previously reported stability results [21]. The paper dealt with the use of smart original mathematical techniques and how this could be adapted to resolve spectral overlap of LH, DA and CD in presence of HQ the degradation product of CD, in their mixtures without preliminary separation. Consequently, conducted a comparative study between them to prove their effectiveness compared to the official BP or USP methods. The proposed methods were very simple, accurate, precise, applicable for multi component preparations and did not require any sophisticated apparatus or computer programs.

Theoretical background

Resolving the overlapped spectra of multi component mixtures (ternary or more) without prior separation of the constituent analytes was rather a difficult task. In the last few years, the development of methods for the resolution of such mixtures has grown dramatically, probably as a result of the increasing affordability of mathematical techniques.

Successive spectrophotometric resolution technique (SSRT)

Successive spectrophotometric resolution technique based on the use of smart original mathematical techniques utilizing the constants present either in the ratio spectra or obtained by using derivative spectra, and how this could be adapted to resolve spectral overlap of the spectra of multicomponent dosage forms whether ternary or more, or as mixtures with their degradation products without prior separation.

Bardicy et al. [22] introduced ratio subtraction (RS) method and it was used for the determination of binary mixtures [23] where the spectrum of one component is extended than the other. Recently, ratio subtraction method is used as a resolution method [18,24] and a new approach, derivative resolution could be applied successfully as resolution techniques for solving the spectra of multi component dosage forms whether ternary or more, or as mixtures with their degradation products. In those resolution techniques the interference of one or more components in the mixtures was eliminated by applying stepwise elimination.

Successive ratio subtraction coupled with the constant multiplication method

If we had a mixture of *X*, *Y* and *Z*, where *Z* was more extended than *Y* and consequently *Y* was more extended than *X* so we could eliminate them one by one using successive ratio subtractions. Then *X* was determined.

So the determination of *X* could be done by successive ratio subtraction dividing the spectrum of the mixture by a certain concentration of *Z* as a divisor (*Z*′). The division would give a new spectrum that was represented as follows:

$$(X + Y + Z)/Z' = (X/Z') + (Y/Z') + (Z/Z') \quad (1)$$

$$(X + Y + Z)/Z' = (X + Y)/Z' + \text{constant} \quad (2)$$

The constant could be determined directly from the $(X + Y + Z)/Z'$ spectrum by the straight line that was parallel to the wavelength axis in the region where *Z* was extended.

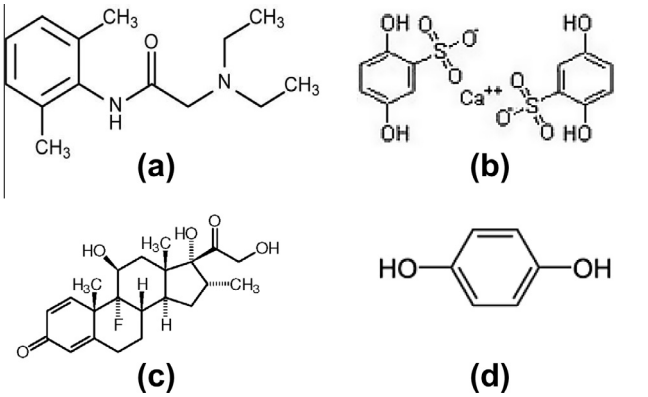

Fig. 1. The chemical structures of the proposed drugs (a) lidocaine hydrochloride [LH] (M.W = 288.8), (b) calcium dobesilate [CD] (M.W = 436.4), (c) dexamethasone acetate [DA] (M.W = 434.5), and (d) hydroquinone [HQ] (M.W = 110.1).