



Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Successive ratio subtraction coupled with constant multiplication spectrophotometric method for determination of hydroquinone in complex mixture with its degradation products, tretinoin and methyl paraben



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ARTICLE INFO

Article history:

Received 15 August 2015

Received in revised form 28 November 2015

Accepted 17 December 2015

Available online 19 December 2015

Keywords:

Stability study

Hydroquinone

Tretinoin

Benzoquinone

Spectrophotometric successive ratio subtraction method coupled with constant multiplication

ABSTRACT

A sensitive and selective stability-indicating successive ratio subtraction coupled with constant multiplication (SRS-CM) spectrophotometric method was studied and developed for the spectrum resolution of five component mixture without prior separation. The components were hydroquinone in combination with tretinoin, the polymer formed from hydroquinone alkali degradation, 1,4 benzoquinone and the preservative methyl paraben. The proposed method was used for their determination in their pure form and in pharmaceutical formulation. The zero order absorption spectra of hydroquinone, tretinoin, 1,4 benzoquinone and methyl paraben were determined at 293, 357.5, 245 and 255.2 nm, respectively. The calibration curves were linear over the concentration ranges of 4.00–46.00, 1.00–7.00, 0.60–5.20, and 1.00–7.00 $\mu\text{g mL}^{-1}$ for hydroquinone, tretinoin, 1,4 benzoquinone and methyl paraben, respectively. The pharmaceutical formulation was subjected to mild alkali condition and measured by this method resulting in the polymerization of hydroquinone and the formation of toxic 1,4 benzoquinone. The proposed method was validated according to ICH guidelines. The results obtained were statistically analyzed and compared with those obtained by applying the reported method.

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1. Introduction

The drug combination of hydroquinone (HQ), tretinoin (TRT) and fluocinolonone acetonide (FLA) is used as external cream for treatment of melasma. Their actions are blocking the synthesis of melanin, accelerating the cell turnover and anti-inflammation [1]. Stability-indicating HPLC and TLC-densitometric methods were developed for determination of hydroquinone in combination with tretinoin and fluocinolonone acetonide [2]. Two HPLC methods were reported for determination of HQ in combination with TRT and FLA [3–4]. HPTLC chromatographic method was reported as stability indicating determination of single HQ in pharmaceutical formulations [5]. Hydroquinone and TRT were determined spectrophotometrically using the ratio difference method and with momentasone furoate using the simultaneous equation method [6–7].

The scientific novelty of this work was using the SRS-CM spectrophotometric method for resolving the UV spectrum of five component mixture. The proposed method was stability indicating for determination of HQ with TRT and the preservative methyl paraben (MET) without

prior separation in bulk powder and in pharmaceutical formulation. No published work was found in the literature dealing with the spectrophotometric determination of HQ, TRT and MET with HQ degradation products; the polymer formed from its alkali degradation (HQ polymer) and 1,4-benzoquinone (BQ). This method was simple without sophisticated apparatus than the published HPLC and TLC methods for determination of the selected compounds [2–4]. The proposed method could determine the BQ in the pharmaceutical formulation when subjected to mild alkali condition. The compound BQ is very toxic and if it is present in the pharmaceutical formulation, it will be absorbed through the skin [8]. The chemical structures of the studied compounds were shown in Fig. 1.

The ratio subtraction method was developed first by El-Bardicy et al. [9] for canceling the extended spectrum and determining the other component in binary mixtures. Successive spectrophotometric resolution techniques were developed such as successive derivative subtraction, successive derivative of ratio spectra, mean centering of ratio spectra [10] and successive spectrum subtraction coupled with constant multiplication [11]. The ratio subtraction method was developed to successive ratio subtraction [12], extended ratio subtraction [13] and SRS-CM spectrophotometric method which enabled the UV spectra resolution of multi-component mixture [14]. To apply the SRS-CM spectrophotometric method each component spectrum must be extended than the other.

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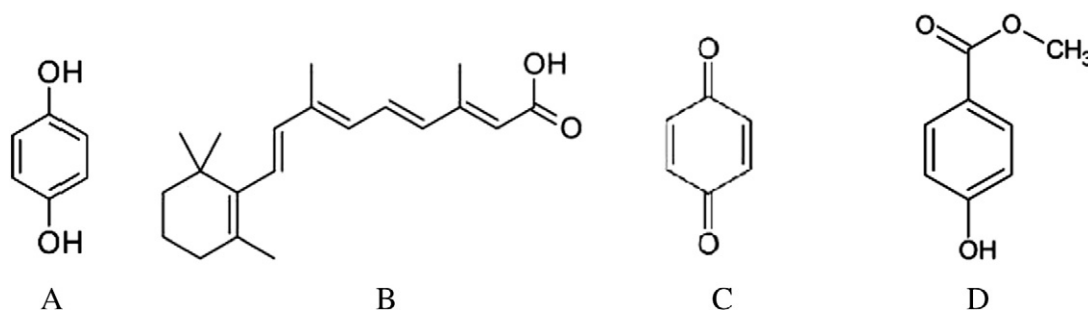


Fig. 1. The chemical structure of (A) hydroquinone, (B) tretinoin, (C) 1,4 benzoquinone and (D) methyl paraben.

It is a very simple method without complex mathematical equations compared to the combination of the double divisor-ratio derivative method and mean centering of the ratio spectra method in five component mixture separation. Each spectrum could be eliminated one by one from the more extended to the lowest. This method was coupled with constant multiplication for determination of the eliminated extended compound.

2. Experimental

2.1. Instruments

The UV–Visible spectrophotometer was double beam model UV-1601 PC with quartz cell of 1 cm path length (Shimadzu, Japan). The software was UVPC personal spectroscopy software version 3.7. The spectral bandwidth was 2 nm and wavelength-scanning speed 2800 nm min⁻¹.

The pH meter was Jenway 3510 (Essex, UK).

2.2. Materials and chemicals

2.2.1. Pure form

Hydroquinone, TRT, FLA and MET were kindly supplied by T3A pharmaceutical company, Cairo Egypt; their purity was 99.76 %, 100.54 %, 100.24 % and 100.36 %, respectively, according to the reported method [2]. 1,4 benzoquinone 98.00 % was supplied by Sigma-Aldrich.

2.2.2. Pharmaceutical formulation

Melanofree® cream was labeled to contain HQ 4%, TRT 0.05% and FLA 0.01% as active ingredients. The preservatives were MET 0.1% and propyl paraben (PRP) 0.01%. Sodium metabisulfite 0.5%, butylated hydroxyl toluene 0.2% and butylated hydroxyl anisole 0.02% were found besides the bases for oil in water cream. It was manufactured by T3A Pharmaceutical Company, Cairo, Egypt. Batch No. 130054.

2.2.3. Chemicals and solvents

All chemicals used were of analytical grade, and the solvents were spectroscopic grade. Sodium carbonate and hydrochloric acid 37% were supplied from Adwic and acetonitrile was supplied from S D Fine-Chem Limited. The water was prepared by double distillation.

A solvent mixture of acetonitrile:water 70:30, v/v was prepared as solvent A with pH ranges from 3 to 5 adjusted by 0.005 M HCl. Another solvent mixture containing acetonitrile:0.01 M aqueous sodium carbonate 70:30, v/v was prepared as solvent B.

2.3. Preparation of HQ polymer

A 100 mg of HQ was dissolved in 100 mL of 0.02 M aqueous sodium carbonate solution and left in the dark in air for ten days. The solution became dark brown and its pH was about 7.5. The solution was evaporated on boiling water bath. The residue formed was used as a divisor.

2.4. Degradation of HQ under mild alkali condition

A stock solution of HQ was prepared by dissolving an amount of 40 mg in 100 mL of solvent A. A dilution was done by withdrawing 1 mL of the stock solution and adding 2 mL of solvent B and left for 5 min. Then the volume was completed to 10.0 mL by solvent A. Further dilution was done by withdrawing 1 mL of the previous dilution and completed to 10 mL by solvent A.

2.5. Standard solutions

All standard solutions must be freshly prepared and protected from light.

Stock standard solutions of HQ (1.0 mg mL⁻¹), TRT (100.0 µg mL⁻¹), HQ polymer (1.0 mg mL⁻¹), BQ (100.0 µg mL⁻¹) and MET (100.0 µg mL⁻¹) were prepared in solvent A. Working standard solutions of HQ (100.0 µg mL⁻¹), HQ polymer (100.0 µg mL⁻¹) and BQ (10.0 µg mL⁻¹) were prepared in solvent A.

2.6. Laboratory prepared mixtures

Different aliquots of HQ, TRT, HQ polymer, BQ and MET were accurately transferred into a series of 10-mL volumetric flasks to prepare different mixtures. The volume was completed by solvent A to prepare mixtures of different ratios of the cited compounds.

3. Procedure

3.1. Spectral characteristics

Into five separate 10-mL volumetric flasks, aliquots containing 400.0 µg of HQ, 60.0 µg of TRT, 40.0 µg of HQ polymer, 30.0 µg of BQ and 60.0 µg of MET were separately transferred from their corresponding standard solutions. Then the volume was completed to the mark with solvent A. The D⁰ spectra of all the prepared solutions and laboratory prepared mixtures were scanned from 200 to 700 nm using the solvent mixture as a blank. The D⁰ spectra were stored in the computer.

3.2. Construction of calibration curves

Aliquots of standard solutions (equivalent to 40.0–460.0 µg of HQ, 10.0–70.0 µg of TRT, 100.0–700.0 µg of HQ polymer, 6.0–52.0 µg of BQ and 8.0–70.0 µg of MET) were separately transferred into a series of 10-mL volumetric flasks. The volume was diluted to the mark with solvent A. Calibration curves were constructed relating a linear relationship between the D⁰ of HQ, TRT, BQ, and MET at 293, 357.5, 245 and 255.2 nm, respectively, versus the corresponding concentrations. The regression equations were then computed.

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