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Ratio manipulating spectrophotometry versus chemometry as stability indicating methods for cefquinome sulfate determination

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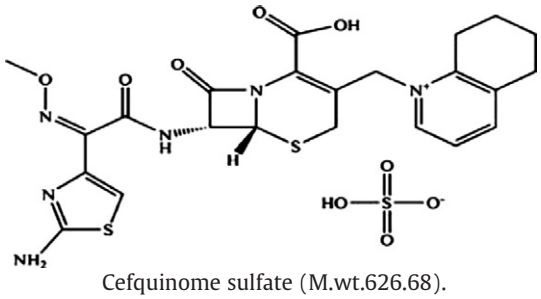
ABSTRACT

Spectral resolution of cefquinome sulfate (CFQ) in the presence of its degradation products was studied. Three selective, accurate and rapid spectrophotometric methods were performed for the determination of CFQ in the presence of either its hydrolytic, oxidative or photo-degradation products. The proposed ratio difference, derivative ratio and mean centering are ratio manipulating spectrophotometric methods that were satisfactorily applied for selective determination of CFQ within linear range of 5.0–40.0 μg mL^{-1}. Concentration Residuals Augmented Classical Least Squares was applied and evaluated for the determination of the cited drug in the presence of its all degradation products. Traditional Partial Least Squares regression was also applied and benchmarked against the proposed advanced multivariate calibration. Experimentally designed 25 synthetic mixtures of three factors at five levels were used to calibrate and validate the multivariate models. Advanced chemometrics succeeded in quantitative and qualitative analyses of CFQ along with its hydrolytic, oxidative and photo-degradation products. The proposed methods were applied successfully for different pharmaceutical formulations analyses. These developed methods were simple and cost-effective compared with the manufacturer's RP-HPLC method.

1. Introduction

Cefquinome sulfate is designed chemically as {6R-[6α, 7β (Z)]}-1-[(7-{[(2-amino-4-thiazolyl)-(methoxyimino) acetyl] amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-en-3-yl) methyl]-5, 6, 7, 8-tetrahydroquinolinium sulfate. It can be shown in the following structure



Cefquinome sulfate (M.wt.626.68).

Cefquinome sulfate is a fourth-generation cephalosporin with antibacterial property and used mainly in the treatment of coliform mastitis which is a disease caused by *Staphylococcus aureus* (Gram positive bacteria) [1]. Cefquinome sulfate is used only in veterinary applications. Chemically, its zwitterionic structure can facilitate rapid penetration across biological membranes, including porins of bacterial cell walls. Introducing aminothiazolyl methoxyimino moiety into the acyl side chain extends the activity against both Gram-negative and Gram-positive bacteria and makes cefquinome more resistant to β-lactamase inhibition. Moreover, this group enhances cefquinome bioavailability compared with older generations of cephalosporin [2].

Cephalosporins in general showed instability in solution [3] and in solid state [4]. Cefquinome sulfate showed low stability towards acid and alkaline hydrolysis, along with its susceptibility to photo-degradation and thermal decomposition [5,6]. Several methods have been suggested in the literature for determination of CFQ in biological fluids and most of them were chromatographic methods with the aid of SPE as a pre-treatment and purification step for biological samples [7–10]. The kinetic decomposition of CFQ was monitored by spectrophotometric method [6] in bulk powder and its pharmaceutical formulation. However upon reviewing the literature, no previous spectrophotometric method or multivariate calibration has been reported for determination of CFQ in the presence of all its susceptible degradation products.

The aim of this work was to develop spectrophotometric methods for the determination of CFQ in the presence of its hydrolytic, oxidative and photo-degradation products. Ability of simple ratio manipulating spectrophotometric methods like ratio difference (RD), derivative ratio (^{1}DD) and mean centering (MC) to be used as stability indicating

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was applied and compared with multivariate calibrations. Moreover, two chemometric models were challenged for both quantitative and qualitative analyses of the studied components.

2. Experimental

2.1. Instruments and software

- A dual beam Shimadzu (Kyoto/Japan) UV–vis spectrophotometer, model UV-1601 PC connected to IBM compatible with an Hp 600 inkjet printer. The bundle software, UV PC personal spectroscopy software version 3.7 (Shimadzu) was used to process absorption and derivative spectra, the spectral band width was 2 nm and scanning speed was 2800 nm/min.
- PH meter HANAA 8417 (Portugal).
- Thermostatically controlled hot plate (Memmert, Germany).
- MATLAB® (MATLAB 2004) for Windows™ version 7.0.1 MathWorks Inc. 2004 was used in calculating multivariate calibrations. The PLS procedure was taken from PLS Toolbox 2.1 Eigenvector Research, Inc. 2005 created by B.M. Wise and N.B. Gallagher for use with MATLAB®. CRACLS computation was performed by MATLAB® with previously designed codes [11].

2.2. Materials and reagents

2.2.1. Pure standard

Cefquinome sulfate (CFQ) was kindly provided by Intervet Schering-Plough, Animal Health. Its purity was 100.32% according to the manufacturer's RP-HPLC method, using C18 stainless steel (4.6 mm × 250 m × 4 mm) column, mobile phase mixture of 90 mL acetonitrile, 12 mL phosphoric acid and 3.45 g of sodium perchlorate mono-hydrate in 1 L water, pH 3.6 adjusted with diethylamide, and UV detection at 270 nm.

2.2.2. Pharmaceutical dosage formulations

Cobactan™ 2.5% suspension (Intervet Schering-Plough, Animal Health) batch no. A445A02, labeled to contain 25 mg cefquinome/mL and cobactan™ LC (Intervet International Germany) batch no. B009801, syringe content is 8 g ointment labeled to contain 75 mg cefquinome.

2.2.3. Degradation product samples

2.2.3.1. Preparation of acid degradation products. Fifty mg of CFQ was weighted and dissolved in 25 mL of 0.05 N sulfuric acid and refluxed for 2 h. The solution was cooled and neutralized with 0.1 N sodium hydroxide solution to pH 7. The solution was evaporated, dissolved in methanol, filtered into 50 mL volumetric flask and completed to the volume with methanol.

2.2.3.2. Preparation of alkali degradation products. They can be prepared as described above using 0.1 N sodium hydroxide and neutralized with 0.05 N sulfuric acid.

2.2.3.3. Preparation of photo-degradation products. Fifty mg of CFQ was dissolved in 50 mL distilled water and subjected to a UV source at 254 nm for 1 h.

2.2.3.3. Preparation of oxidative degradation products. These were prepared by adding 50.0 mg of CFQ to 4 mL of hydrogen peroxide 10%. This solution was diluted with water to 50 mL and refluxed for 1 h.

Complete degradation of CFQ samples were confirmed by RP-TLC using disodium hydrogen phosphate dehydrate (2.0 g %w/v), adjusted to pH 3.5 by phosphoric acid–acetone (15:10, v/v) as a developing system. The spots were detected under UV lamp at 254 nm.

2.2.4. Chemicals and reagents

All chemicals used in this work were of analytical grade, and also the solvents were of spectroscopic grade. Sodium hydroxide, sulfuric acid 98%, hydrogen peroxide 10% (Adwic), methanol, disodium hydrogen phosphate dehydrate, phosphoric acid, acetone (E. Merck, Darmstadt, Germany) and double distilled water were used.

2.3. Solutions

2.3.1. Stock standard solutions (1.0 mg mL^{-1})

Stock standard solutions of cefquinome sulfate and its degradation products were prepared by the procedures described above.

2.3.2. Working solutions

For ratio manipulating spectrophotometric methods working solutions of CFQ (100.0 μg mL^{-1}) and its degradation products equivalent to 100.0 μg mL^{-1} of CFQ were prepared from their corresponding stock solutions by suitable dilutions with methanol.

While working solutions of CFQ (400 μg mL^{-1}) and its degradation products equivalent to 200 μg mL^{-1} of CFQ were prepared for multivariate calibrations.

2.3.3. Laboratory prepared mixture solutions

Solutions containing different ratios of CFQ with either its hydrolytic or oxidative degradation products in methanol were prepared from their respective working solutions and diluted with methanol.

2.3.4. Pharmaceutical solutions

Amounts of suspension and ointment formulations equivalent to 10 mg of CFQ were accurately transferred into two separate 100-mL beakers. About 60 mL methanol was added to each and the solutions were sonicated for 30 min to enhance the extraction of the drug. The solution was filtered into 100-mL volumetric flasks and the residue was washed three times each using 10 mL methanol. The volumes were diluted to the mark with methanol. Transfer accurately 2 mL of this prepared solution (100 μg mL^{-1}) to a 10-mL volumetric flask and complete to the mark with methanol to obtain a solution with a final concentration of 20 μg mL^{-1} of CFQ.

2.4. Procedure

2.4.1. Spectral characteristics of cefquinome sulfate and its degradation products

The zero order absorption spectra (^0D) of CFQ (20.0 μg mL^{-1}) were recorded along with 20.0 μg mL^{-1} of its acid and alkali hydrolytic, oxidative and photo-degradation products. The spectra were recorded against methanol as a blank over the range 200–400 nm.

2.4.2. Ratio manipulating spectrophotometric methods (RD, ^1DD and MC)

Aliquots equivalent to 50.0–400.0 μg of CFQ were accurately transferred from its working standard solution (100.0 μg mL^{-1}) into a set of 10-mL volumetric flasks and the volumes were diluted to the mark with methanol. Absorption spectrum of each solution was recorded against methanol as a blank and then divided by either its hydrolytic or oxidative degradation products' spectra having a concentration equivalent to 10 μg mL^{-1}.

2.4.2.1. Construction of calibration curves for ratio difference. Difference between peak amplitudes at 271 nm and 295 nm of obtained ratio spectra using hydrolytic degradation spectrum as a divisor was plotted against the corresponding CFQ concentrations. Likewise, the difference between peak amplitudes at 260 nm and 288 nm of ratio spectra using oxidative degradation spectrum as a divisor was plotted against