Novel Spectrophotometric Methods for Simultaneous Determination of Cefixime trihydrate and Sodium benzoate in Powder for Oral Suspension Dosage form

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Abstract

Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally to treat infection due to susceptible gram-positive and gram-negative bacteria. Up till now, no spectrophotometric methods have been published for the determination of cefixime trihydrate and sodium benzoate in their pharmaceutical formulation. Novel, specific, precise, simple, and accurate spectrophotometric methods are developed and validated for the simultaneous determination of cefixime trihydrate (CFX) and sodium benzoate (SDB) in powder for oral suspension (POS) dosage form. Firstly, CFX is directly determined using its extended spectra at 290 nm, where no interference from the co-formulated SDB has been detected. In method (I), CFX and SDB are determined by first derivative ratio spectrophotometric method (1DD) at 284 and 318 nm for CFX, while SDB is determined at 216 and 234 nm.

In method (II), simultaneous ratio subtraction method (SRSM) is established for resolving the overlap between CFX and SDB by dividing the spectrum of the binary mixture by the standard spectrum of 20 µg/mL CFX as divisor, then subtract the constant value determined in the plateau region at 240-325 nm, then multiply by the divisor to obtain zero order (D°) original spectrum of SDB at 227 nm, further zero order of CFX is determined at λmax 290 nm after multiplication the divisor by the obtained constant. Finally, in the third one, ratio difference spectrophotometric method (RDSM), laboratory prepared mixtures are divided by the absorption spectra of standard 40 µg/mL CFX for the determination of SDB and standard 30 µg/mL SDB for the determination of CFX. The ratio spectra are recorded at 231 nm and 290 nm for CFX, while at 223 nm and 250 nm for SDB. The obtained results for the proposed methods are statistically compared with those obtained by the official method for CFX besides the recently published HPLC one for their simultaneous determination using one-way analysis of variance (ANOVA) where no significant difference is observed between the proposed methods and the well-established ones which prove their validity for the analysis of this binary mixture.

Keywords: Cefixime Trihydrate; Sodium Benzoate; Zero order; First derivative ratio spectrophotometric method; Simultaneous ratio subtraction method; Ratio difference Spectrophotometric method

Abbreviations: CFX: Cefixime Trihydrate; SDB: Sodium Benzoate; SRSM: Simultaneous Ratio Subtraction Method; RDSM: Ratio Difference Spectrophotometric Method; ANOVA: Analysis of Variance

Introduction

Cefiximetrihydrate (CFX); is chemically known as (6R,7R)-7-[[Z]-2-(2-Aminothiazol-4-yl)-2-[(carboxymethoxy) imino] acetyl] amino]-3- ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid trihydrate (Figure 1a) [1,2]. Cefixime is a bactericidal drug and is stable to hydrolysis by many beta-an antibacterial. Like other cephalosporin, it possesses a mechanism of action like penicillins i.e. inhibition of transpeptidation process resulting in the formation of imperfect cell wall; osmotic drive from the outside isotonic environment of the host cell to the inside of the hypotonic bacterial cytoplasm and finally activation of the autolysin enzyme leading to the lysis of bacteria. Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food [3]. Cefixime is better absorbed from oral suspension than from tablets. Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally to treat infection due to susceptible gram-positive and gram-negative bacteria, including gonorrhoea and infections of the respiratory and urinary tracts [3].

Sodium benzoate (SDB); is chemically known as sodium benze carboxylate (Figure 1b) [1,2]. Sodium benzoate is used primarily as antimicrobial preservative in cosmetics, foods, and pharmaceuticals. It is used in concentration of 0.02-0.5%
in oral medicines, 0.5% in parenteral products, and 0.1-0.5% in cosmetics. The inhibitory concentration of sodium benzoate required in emulsion increases with oil content. It has also been used as a tablet lubricant at 2-5 %w/w concentrations, providing rapid disintegration times [4]. Cefixime is official in British Pharmacopoeia (BP), European Pharmacopoeia (EP) [1,2] and United States Pharmacopoeia (USP) [5], both of them includes HPLC method for estimation of CFX. Literature review revealed that various analytical methods have been described for the determination of cefixime including colorimetric and spectrophotometric [6-19], thin layer chromatography [20-23], capillary electrophoresis [24-26], HPLC [27-36] and electrochemical methods [37-40] in pure or in dosage forms.

Sodium benzoate is official in BP, EP [1,2] and United States Pharmacopoeia (USP) [5], which includes direct titration for the estimation of SDB. Thus, a variety of methods have been developed for its determination including spectrophotometric [41,42], thin layer chromatography [43] and HPLC [44-53]. Recently, an HPLC method [54] has been published for simultaneous determination of both CFX and SDB together in pure or dosage forms. The combination of these two drugs is not official in any pharmacopoeia. According to the best of our knowledge, no spectrophotometric method has been published for determination of both CFX and SDB together in pure or dosage forms. The present work aims to develop novel spectrophotometric methods, for the first time, for the determination of CFX and SDB in pure and in their dosage form with high sensitivity and low cost. The developed methods have advantages over the published ones regarding simplicity and no need for expensive or sophisticated apparatus. Besides, they are suitable as routine methods in quality control analysis laboratories. They are validated according to ICH guidelines.

**Materials and Methods**

**Apparatus**

UV- 1800 double beam UV-Visible spectrophotometer (Shimadzu-Japan) with highest resolution in which the spectral bandwidth is 1nm for the spectral range 190-1100 nm, is used for all absorbance measurements, matched with 1 cm quartz cells. Data analysis is performed by software (UV-Probe 2.5.2).

**Pure samples**

Pure samples of cefixime trihydrate and sodium benzoate are kindly supplied by EPCI Pharmaceutical Company part of HIKMA group, Beni-Suef, Egypt with claimed purity of 99.97% and 99.90%, respectively, according to quality control certificates of analysis.

**Pharmaceutical dosage form**

SUPRAX® 100 mg/5mL POS (60mL) (Batch No. 2000) and SUPRAX®100 mg/5mL POS (30 mL) (Batch No. 2002) are manufactured by EPCI Pharmaceutical Company part of HIKMA group, Beni-Suef, Egypt. Each 5mL is claimed to contain 100 mg of cefixime and 2.5 mg of sodium benzoate.

**Chemicals**

Methanol of HPLC-grade is used as a solvent. It is obtained from (Scharlau, Spain).

**Preparation of standard and samples Solution**

**Stock Solutions of Cefixime and Sodium Benzoate (1000 μg /mL):** Accurately weigh 100mg of each of CFX & SDB, transfer into 100 mL volumetric flask, add 70 mL of the solvent and sonicate to dissolve and complete to the mark with the same solvent and mix well.

**Working Standard Solutions of Cefixime and Sodium Benzoate (100μg /mL):** Accurately transfer 10 mL of CFX & SDB from their stock solutions in two 100 mL volumetric flasks, add 70 mL of the solvent and sonicate to dissolve and complete to the mark with the same solvent and mix well.

**Laboratory Prepared Mixture:** Prepare mixtures of CFX & SDB containing different ratios from their working standard solutions (100 μg /mL) into a series of 10 mL volumetric flasks. Make up to the mark with the same solvent. Concentrations of CFX & SDB are calculated from the corresponding regression equations describing the linearity for each method.

**Dosage Form Preparations (SUPRAX® 100 mg/5mL POS (60mL)&(30mL):** To reconstitute, suspend SUPRAX®100 mg/5mL POS (60mL)&(30mL) with 40 mL and 20 mL water, respectively. Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well. Transfer 2 mL from the prepared flask into 1000mL volumetric flask and complete to the mark with diluents to obtain concentrations of CFX & SDB (40 & 1μg /mL), respectively.

**Construction of Calibration Curves**

Different aliquots equivalent to 10-50μg /mL and 1-30 μg /mL of CFX and SDB, respectively, are separately withdrawn from their respective working standards into separate series of 10 mL volumetric flasks, and the volumes are made up to the mark with the diluent. Zero order absorption spectra of CFX and SDB are scanned in the range of 200-400 nm (Figure 2) and

![Figure 1: Chemical structures of (a) Cefixime trihydrate and (b) Sodium Benzoate.](Image 88x443 to 245x593)
Simultaneous Ratio Subtraction Method (SRSRM)

Lotfy and Hegazy introduced (SRSRM) [53] for the analysis of a mixture of two drugs X and Y having overlapping spectra. Ratio subtraction method plays an important role in solving overlapped spectra between two drugs. The stored spectra of binary mixtures of CFX and SDB are divided by the absorption spectrum of CFX (20 μg/mL), then subtract the constant value at the plateau region 240-325 nm, then the zero-order absorption spectrum of SDB is obtained at 227 nm by multiplying the obtained curve after subtraction by 20 μg/mL of CFX as divisor. Calibration curves relating the absorbance of zero order spectra of SDB at 227.0 nm versus their corresponding concentrations are constructed and the regression equations are computed. For obtaining the second component (CFX), another extension of the already developed method has been established as a new approach in which CFX is determined by multiplication of 20 μg/mL of CFX divisor by the previously obtained constant, thus, the zero-order absorption spectrum of CFX is obtained at λ_{max} equals 290 nm. Calibration curves relating the absorbances of zero order spectra of CFX against their corresponding concentrations are constructed and the regression equations are computed.

Results and Discussion

The fundamental aim of this work is to introduce novel, simple, sensitive, accurate and precise spectrophotometric methods for the determination of binary mixture of the two drugs CFX and SDB in their pure form and pharmaceutical formulation and resolving overlapped spectra in zero order in the region 200 – 250 nm, which couldn’t be resolved neither by first nor the second derivative techniques as shown in (Figure 4), so other methods are applied to overcome the overlapping as ‘DD, SRSRM and RDSM. For convenience, each one will be discussed separately.

Methods Development and Optimization

Selection of the solvents, divisor and wavelengths is the key factors to the adjustment and development of the method, so different solvents were tried such as water, 0.01 M HCl, 0.01 M NaOH and methanol. The use of methanol as a solvent led to the development of the most resolved spectra with minimum noise and maximum sensitivity. Also, selection of the divisor at concentrations of 20 and 40 μg/mL of CFX and 30 μg/mL of SDB in the SRSM, ‘DD and RDSM which showed good selectivity and recovery. Different wavelengths were chosen to determine CFX and SDB, respectively. That of 284 nm for CFX 234 nm for SDB proved to be appropriate in the ‘DD; similarly, the difference
between the amplitudes at two wavelengths 231,290 nm for CFX and 223, 250 nm for SDB are most suitable in the RDSM. Finally, 227 and 290 nm for CFX and SDB, respectively gave good selectivity in the SRSM concerning laboratory prepared mixtures.

**First Derivative of Ratio Spectra Spectrophotometric Method**

Figure 4 shows the overlapped spectra between the binary mixture of CFX and SDB. It couldn't be resolved neither by first nor the second derivative techniques. However, the proposed method proved its capability for solving their overlapped spectra as shown in Figures 5&6, where the stored spectra of the pure standard CFX are divided by the standard spectrum of 30 µg/mL of SDB and their first derivatives are obtained using Δλ = 10 and scaling factor = 10 and peak amplitudes are measured at 284 nm versus the corresponding concentrations of CFX and the calibration graphs are constructed. Also, the stored spectra of pure standard SDB are divided by the standard spectrum of 40 µg/mL of CFX and the peak amplitudes are measured at 234 nm against the corresponding concentrations of SDB and the calibration graphs are constructed.

**Figure 4:** UV spectra of 20 μg/mL of each of CFX(—) and SDB (- - - -): (a) zero order spectra $D_0$, (b) 1st derivative spectra $D_1$, (c) 2nd derivative spectra $D_2$.

**Figure 5:** Ratio spectra (a) and first derivative of the ratio spectra (b) of (A) 10 µg/mL, (B) 20 µg/mL, (C) 30 µg/mL, (D) 40 µg/mL, (E) 50 µg/mL solution of cefixime trihydrate in methanol when 30 µg/mL solution of sodium benzoate in methanol used as a divisor (Δλ =10 nm).
Simultaneous Ratio Subtraction Method

This method is applied to solve the overlapping spectra between the constituents of the binary mixture CFX & SDB by dividing the spectrum of the mixture by a known concentration of CFX (20 µg/mL) as a divisor, subtract the constant value at the plateau region 240–325 nm then multiply the obtained spectrum by the divisor 20 µg/mL of CFX. Thus, the zero-order absorption spectrum of SDB is obtained at 227 nm as shown in Figure 7. Calibration curves relating the absorbances of zero order spectra of SDB at 227.0 nm versus their corresponding concentrations are constructed and the regression equations are computed. The original zero order spectrum of CFX is obtained at 290 nm after multiplication of the constant in the laboratory prepared mixture by the CFX (the divisor). (Figure 8). Calibration curves relating the absorbance of the zero order spectra of CFX versus their corresponding concentrations are constructed and the regression equations are, similarly, computed.

Figure 6: Ratio spectra (a) and first derivative of the ratio spectra (b) of (A) 1µg/mL, (B) 5µg/mL, (C) 10 µg/mL, (D) 20 µg/mL, (E) 30 µg/mL solution of sodium benzoate in methanol when 40 µg/mL solution of cefixime trihydrate in methanol used as a divisor (Δλ =10 nm).

Figure 7: (a) Ratio spectra of mixtures of CFX and SDM using 20 µg/mL of CFX as a divisor, (b) Ratio spectra after subtraction of constant, (c) new spectrum of SDM in Zero order.
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Figure 8: (a) Ratio spectra of mixtures of CFX and SDM using (b) 20 µg/mL of CFX as a divisor, (c) new spectrum of CFX in Zero order.

**Ratio Difference Spectrophotometric Method**

Two factors should be appropriately fulfilled during the application of RSDM, namely, the choice of the divisors and the two selected wavelengths; the selected divisor should be adjusted between the minimum noise and maximum sensitivity; the second is that each of the selected wavelengths has a contribution of the interfering substance. In the RSDM, the difference between the amplitudes at two points 223 - 250 nm are selected for determination of SDB using the absorption spectrum of CFX (40 µg/mL) as a divisor, (Figure 9). Similarly, the difference between the amplitudes at two points 231 & 290 nm are selected for the determination of CFX using the absorption spectrum of SDB (30 µg/mL) as a divisor, (Figure 10). Calibration curves are constructed by plotting the difference between the amplitudes at the two wavelengths 231, 290 nm for CFX and 223, 250 nm for SDB versus the corresponding concentrations and the regression equations are computed.

**Validation of the Analytical Method**

The method was validated, in accordance with ICH guidelines (ICH Q2R1), regarding linearity, precision, accuracy, selectivity, LOD and LOQ [56].
Linearity and Range

The linearity of the proposed methods is obtained in the concentration range (10.0-50.0 µg/mL) for CFX and (1.0 -30.0 µg/mL) for SDB. Calibration curves are composed by plotting the absorbance against the corresponding concentration. The obtained results of correlation coefficients, slope and intercept indicate the good linearity. Results are shown in Table1.

Precision

Repeatability: Expresses within-laboratories variations:
The intraday RSD % (n = 3), average of three concentrations (10, 20 and 30µg/mL) for each of CFX and SDB, respectively are repeated three times within the day. Good results are obtained as shown in Table 1.

Intermediate precision: The Interday RSD % (n = 3), average of three concentrations (10, 20 and 30µg/mL) for each of CFX and SDB, respectively are repeated three times in three successive days. Good results are obtained and presented in Table 1.

Detection and Quantitation limits

These approaches are based on the Standard Deviation of the Response and the Slope. A specific calibration curve should be studied using samples containing an analyte in the range of LOD and LOQ. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation. LOD =3.3×σ /slope and LOQ =10×σ /slope, where σ = the standard deviation of the response (Table 1).

Table 1: Regression and validation parameters of the proposed methods for determination of CFX and SDM.

|          | SDM 227 nm | RDSM (250 - 223) nm | DD 234 nm | SRSM 290 nm | RDSM (290 - 231) nm | DD 284 nm |
|----------|------------|---------------------|-----------|-------------|---------------------|-----------|
| 1-30     | 1-30       | 1-30                | 10.50     | 10.50       | 10.50               |
| 0.0637   | 0.0407     | 0.0288              | 0.0415    | 1.652       | 1.117               |
| 0.0308   | 0.0203     | 0.0101              | 0.018     | 0.8488      | 0.463               |
| 0.9994   | 0.9994     | 0.9996              | 0.9998    | 0.9998      | 0.9998              |
| 0.09     | 0.156      | 0.23                | 0.24      | 0.01       | 0.01                |
| 99.50±1.47 | 99.71±1.36 | 99.99±1.46         | 100.03±1.42 | 100.10±1.62 | 100.10±1.48       |
| 0.71     | 0.71       | 0.53                | 1.22      | 1.29       | 1.17                |
| 2.16     | 2.16       | 1.66                | 3.7       | 3.93       | 3.54                |
| 0.121    | 0.159      | 0.295               | 0.14      | 0.031      | 0.003               |
| 0.151    | 0.245      | 0.378               | 0.413     | 0.035      | 0.017               |
| 99.97±0.60 | 102.02±0.28 | 102.02±0.28        | 100.85±0.42 | 100.51     | 99.97±0.60         |

*Limit of detection (3.3× σ /Slope) and limit of quantization (10×σ /Slope).

Accuracy and recovery

Accuracy of the proposed methods is calculated as the mean percentage recoveries of pure samples of the studied drugs. Accuracy is assessed using three different concentrations (10 & 20 & 30 µg/mL) for CFX and SDB, respectively within the linearity range (i.e. three concentrations and three replicates).

Table 2: Determination of CFX and SDM in their pharmaceutical formulation by the proposed methods and application of standard addition technique.

| Standard addition | Found µg/mL | Added µg/mL | Method | Drug | Pharmaceutical formulation |
|-------------------|-------------|-------------|--------|------|---------------------------|
| Recovery*         | Found µg/mL | Added µg/mL |        |      |                           |
| 100.7             | 2.01        | 2           | 102.02±0.28 | DD 284 nm | CFX SUPRAX®100 mg/5mL POS (60mL) |
| 101.33            | 4.05        | 4           |        |      |                           |
| 100.51            | 8.04        | 8           |        |      |                           |
| 100.85±0.42       | Mean ±RSD  | 99.97±0.60  | RDSM (290 - 231) nm | CFX, 100 mg(claimed) SDM,2.5 mg(claimed) |
| 98.52             | 1.97        | 2           |        |      |                           |
| 98.44             | 3.94        | 4           |        |      |                           |
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|        | SDM | CFX | Added(µg/mL) SDM | Added(µg/mL) CFXs | Ratio of CFX:SDM |
|--------|-----|-----|-----------------|------------------|-----------------|
| SRSM   |     |     |                 |                  |                 |
| 227 nm |     |     |                 |                  |                 |
| 99.54  | 101.41 | 101.82 | 101.78 | 101.52 | 100.75 | 30 | 30 | 1.01 |
| 98.32  | 98.67 | 99.27 | 100.09 | 100.55 | 99.45 | 10 | 20 | 2.01 |
| 99.58  | 99.23 | 100.55 | 101.09 | 101.33 | 100.29 | 15 | 45 | 3.01 |
| 99.82  | 98.39 | 101.83 | 98.89 | 98.54 | 101.7 | 20 | 15 | 3.04 |
| 100.46 | 98.57 | 100.97 | 101.3 | 98.87 | 101.38 | 3 | 10 | 10.03 |
| 98.61  | 98.48 | 100.13 | 100.34 | 99.34 | 98.83 | 5 | 40 | 8.01 |
| 98.63  | 99.16 | 100.12 | 100.58 | 101.92 | 99.67 | 10 | 50 | 5.01 |
| 99.28 ± 0.78 | 99.13 ± 1.06 | 100.66 ± 0.93 | 100.58 ± 0.94 | 100.30 ± 1.37 | 100.29 ± 1.04 | Mean ± RSD |

*Average of three determinations

**Selectivity**

The selectivity of the laboratory prepared mixture containing both drugs in different ratios is determined within the linearity range. The proposed methods are assessed by analysis of laboratory prepared mixtures containing different ratios of CFX and SDB which gave good accuracy and recovery for CFX and SDB as shown in Table 3.

**Statistical analysis**

The results obtained for analysis of CFX and SDB by the proposed methods are statistically compared with those obtained by official [5] and the HPLC methods [55] for the simultaneous determination of both drugs in a mixture. The results showed no significant differences among the proposed spectrophotometric methods and the reference methods as presented in Table 4. In order to compare the ability of the proposed methods for the simultaneous determination of CFX and SDB, their results versus those obtained by applying the official [5] and the reported [54] methods are subjected to statistical analysis using one way ANOVA test. Results of ANOVA analysis showed that no significant differences among the proposed spectrophotometric methods and compared ones as presented in Table 5.
Table 4: Statistical comparison among the results obtained by applying the proposed methods and those obtained by the official and the reported methods for the analysis of the pure form of CFX and SDB in their dosage form.

| Parameter | Cefixime (CFX) | Sodium Benzoate (SDM) | Mean | Variance | t-test * | F-value * |
|-----------|-----------------|-----------------------|------|----------|----------|-----------|
| SRSM 290 nm | 103.46 | 99.97 | 102.01 | 0.677 | 0.29 | 0.05 | -0.02 | 0.014 | 0.05 | -0.02 | 0.014 |
| RDSM (290 - 231) nm | 0.677 | 0.599 | 0.29 | 0.458 | 0.084 | 0.168 | 0.037 | 0.109 | 0.015 |
| DD 284 nm | 0.458 | 0.58 | 0.084 | 6 | 6 | 6 | 6 | N | 103.46 | 102.83 | 102.01 | 102.01 | 102.01 |

The values in parenthesis are corresponding to the theoretical values of t and F (p = 0.05).

Table 5: One way ANOVA testing for the different proposed and the reported methods for the analysis of the pure form of CFX and SDB in their dosage form.

| Source of Variation | Degree of Freedom | Sum of Squares | Mean square | F-value* |
|---------------------|-------------------|----------------|-------------|----------|
| CFX | Between columns | 3 | 0.138 | 0.416 | 3.238 |
| | Within columns | 16 | 13.788 | 0.861 | |
| | Total | 19 | 14.205 | | |

| Source of Variation | Degree of Freedom | Sum of Squares | Mean square | F-value* |
|---------------------|-------------------|----------------|-------------|----------|
| SDB | Between columns | 3 | 1 | 3.02 | 3.238 |
| | Within columns | 16 | 13.01 | 0.813 | |
| | Total | 19 | 16.03 | | |

* There was no significant difference between the methods using one-way ANOVA at p < 0.05.

Conclusion

Novel, simple, precise and accurate spectrophotometric methods are performed for the simultaneous determination of binary mixture of CFX and SDB in pure and dosage form. Distinct features of the proposed methods are that being of low cost, rapid and neither require sophisticated instruments nor special software; also, could be easily applied for the routine analysis of the drugs either in their pure bulk powders and in dosage form in quality control laboratories.

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