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# Zero order and signal processing spectrophotometric techniques applied for resolving interference of metronidazole with ciprofloxacin in their pharmaceutical dosage form

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ABSTRACT

Four rapid, simple, accurate and precise spectrophotometric methods were used for the determination of ciprofloxacin in the presence of metronidazole as interference. The methods under study are area under the curve, simultaneous equation in addition to smart signal processing techniques of manipulating ratio spectra namely Savitsky–Golay filters and continuous wavelet transform. All the methods were validated according to the ICH guidelines where accuracy, precision and repeatability were found to be within the acceptable limits. The selectivity of the proposed methods was tested using laboratory prepared mixtures and assessed by applying the standard addition technique. So, they can therefore be used for the routine analysis of ciprofloxacin in quality-control laboratories.



## 1. Introduction

Ciprofloxacin, [1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(piperazinyl)-quinolone-3-carboxylic acid] Fig. 1(a) is a widely used second generation fluoroquinolone, useful for the treatment of a number of bacterial infections. Its broad spectrum activity includes Gram-positive, Gram-negative bacteria and many microorganisms [1]. Metronidazole, [2-methyl-5nitroimidazole-1-ethanol] Fig. 1(b), is a nitroimidazole antibiotic, medication [1] used mainly for anaerobic bacteria and protozoa while ciprofloxacin has low activity against anaerobic pathogens. Hence, a combination between ciprofloxacin HCl (CIP) and metronidazole (MET) is beneficial for mixed aerobic and anaerobic infections treatment [2].

Several methods have been reported for the estimation of CIP in pharmaceutical and biological samples. These methods include spectrophotometry [3–7], spectrofluorimetry [8–10], HPLC with UV detection [11–13], HPLC with fluorescence detection [14,15], liquid chromatography/mass spectroscopy [16], capillary electrophoresis [17,18] and HPTLC [19]. Also, few methods have been reported for determination of CIP and metronidazole mixture [7,20,21]. However, the aim of the present work is to determine CIP in the presence of MET as interference by different aspects of spectrophotometric methods namely area under the curve [22], simultaneous equation [23,24] in addition to smart signal processing techniques of manipulating ratio spectra namely Savitsky–Golay filters [25–28] and continuous wavelet transform [29–32].

## 2. Experimental

### 2.1. Materials and reagents

A. Pure CIP (99.25%) and MET (99.65%) was kindly supplied by Minapharm Pharmaceutical Company, Cairo, Egypt.
B. Ciprodiazole tablets nominally containing CIP (500 mg) and MET (500 mg) batch number EJE3135 were manufactured and supplied by MINAPHARM pharmaceuticals (Cairo, Egypt).
C. Methanol; El-NASR Pharmaceutical Chemicals Co., Egypt.

### 2.2. Instruments

SHIMADZU dual beam UV–visible spectrophotometer (Kyoto/Japan), model UV-1800 PC connected to a compatible IBM and an HP1020 laser jet printer. The bundled software, UV-Probe personal spectroscopy software version 2.43 (SHIMADZU) was used. The spectral band was 2 nm and scanning speed is 2800 nm/min with 1 nm interval.

### 2.3. Software

All signal processing methods (CWT, SG) were implemented in Matlab 8.2.0.701 (R2013b). The calculations used for Savitsky–Golay

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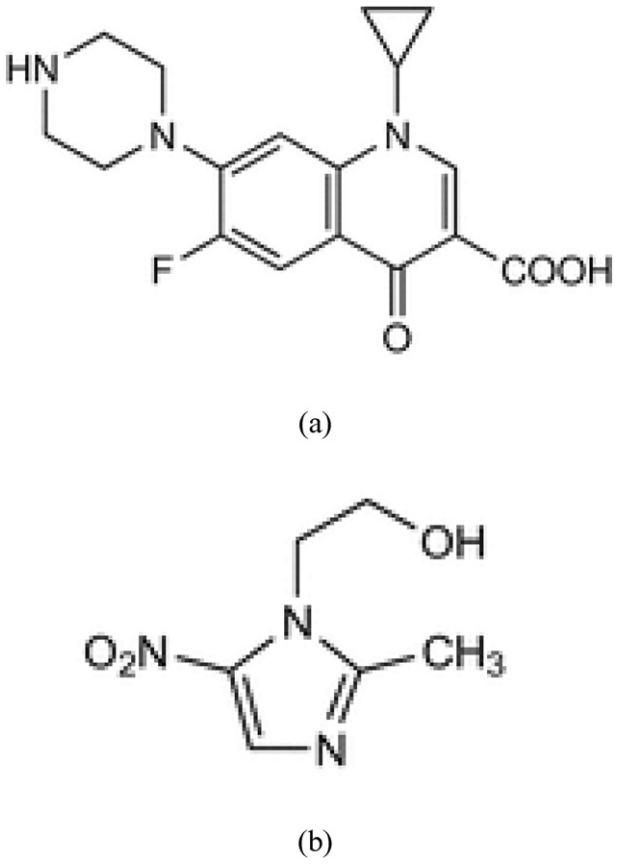


**Fig. 1.** Chemical structure of (a) ciprofloxacin and (b) metronidazole.

filters were done with our own written code in Matlab. The *t*-test and *F*-test were performed using Microsoft Excel. One way ANOVA test was performed using Graph Pad Prism version 5 (Graph Pad, San Diego, CA).

### 2.4. Standard solutions

A. CIP and MET standard stock solutions; 200 μg/mL in methanol.
B. CIP and MET standard working solutions; 50 μg/mL in methanol.

## 3. Methods

### 3.1. Area under the curve method

Aliquots from CIP and MET working solutions (50 μg/mL) equivalent to 10–100 μg and 40–140 μg, respectively, were accurately transferred into two separate sets of 10-mL volumetric flasks and completed to the mark with methanol. The zero order absorbance of each set was scanned in the range of 200–400 nm. Area under the curve for the wavelength ranges selected for determination of CIP in presence of MET are 273–283 nm and 307–317 nm, the absorptivity values of each of the two drugs were determined at the selected wavelength ranges. The absorptivity 'Y' values were determined as, Y = area under the curve of component (from 273 to 283 nm or 307 to 317 nm) divided by concentration of the component.

### 3.2. Simultaneous equation method

The zero order spectra obtained as mentioned in Section 3.1 and the absorptivity is calculated for CIP and MET at 280 nm and 311 nm.

### 3.3. Savitsky–Golay filters (SGF)

The zero order spectra obtained as mentioned in Section 3.1. The zero order absorption spectrum of each solution for CIP was recorded versus methanol as a blank, divided by the spectrum of MET (7 μg/mL). The first derivative of the obtained ratio spectra was employed according to the SGF method using Matlab software through the use of 7-point window size and a cubic model filter. Calibration curve was constructed by plotting the amplitude of the first derivative of the ratio spectra as calculated by SGF at 262 nm against their corresponding concentrations.

### 3.4. Continuous wavelet transform (CWT)

The ratio spectra obtained as before. *Sym 2* family was used [scale value (a) = 20]. The calibration curve was constructed by plotting the amplitude of the transformed signals at 257 nm against their corresponding concentrations.

### 3.5. Application to laboratory prepared mixtures

Accurate aliquots of CIP and MET were transferred from their working solutions into a series of 10 mL volumetric flasks to prepare mixtures containing different ratios of both. The volumes were completed with the solvent. The spectra of the prepared series from 200 to 400 nm were recorded and stored. The concentrations of CIP were calculated for each proposed method.

### 3.6. Application to pharmaceutical preparation

The content of 10 tablets was weighed, powdered and mixed. The appropriate weight of powder equivalent to 20 mg of the components was accurately transferred to 100 mL flask and the volume was made up to 75 mL with methanol. The solution was shaken vigorously for

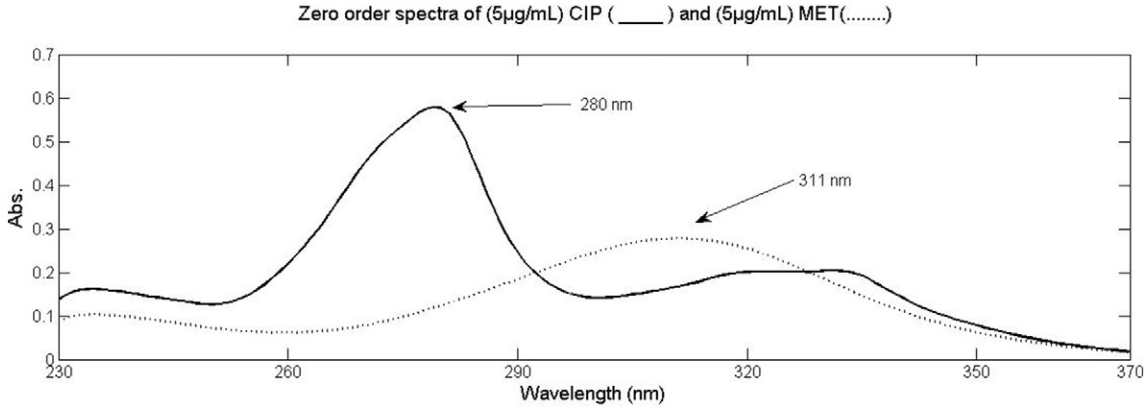


**Fig. 2.** Zero order spectra of (5 μg/mL) CIP (__) and (5 μg/mL) MET (.....).