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ScienceDirect
Microchemical Journal 87 (2007) 35–40
MICROCHEMICAL JOURNAL
www.elsevier.com/locate/microc

Development of a stability-indicating capillary electrophoresis method for norfloxacin and its inactive decarboxylated degradant

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Received 16 January 2007; received in revised form 15 April 2007; accepted 2 May 2007
Available online 22 May 2007

Abstract

A simple, accurate, precise, rapid and sensitive stability-indicating capillary electrophoresis (CE) method was optimized and validated for the simultaneous determination of norfloxacin and its inactive decarboxylated degradant in pharmaceuticals. The univariant method was used to optimize electrophoretic factors including injection time, separation voltage and column temperature. Electrolyte concentration and pH were optimized using the factorial design and response surface methods. The optimum conditions obtained were: 10 mmol l^{-1} phosphate at pH 2.5, hydrodynamic injection time of 8 s at pressure 0.5 p.s.i., separation voltage 25 kV and column temperature 25 °C. The separation was carried out into a fused-silica capillary column (31.2 cm length × 50 μm i.d.) with detection at 301 and 285 nm for the intact drug and the degradant, respectively using a diode array detector. For both analytes, the method enjoys wide dynamic range (1–50 μg ml^{-1}) with good detectability (limits of detection 0.11 μg ml^{-1}). In addition, acceptable accuracy (recovery > 95%); and good repeatability and intermediate precision (RSD < 3.5%) were obtained.
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Keywords: Capillary electrophoresis; Pharmaceutical analysis; Stability-indicating method; Norfloxacin; Experimental design methods

1. Introduction

Norfloxacin is chemically known as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-ethyl-fluoro-1.4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid (Fig. 1). It is a member of antibacterial agents named as fluoroquinolone derivatives, which are derived from nalidixic acid [1]. Norfloxacin is the first choice drug for the treatment of diseases caused by *Campylobacter*, *E. coli*, *Salmonella*, *Shigella* and *V. cholera* [2]. The drug is also used for the treatment of gonorrhoea as well as infection of eyes and urinary tract [3].

Norfloxacin is a photosensitive and hygroscopic drug. It decomposes upon exposure to light into amino, ethylenediamine and formylpiprazine functionalized degradants (Fig. 1). Moreover, the hydrolysis of the drug throughout prolonged heating of its acid solution yields a decarboxylated degradant (Fig. 1) [4,5]. This degradant has a particular significance since the pharmacological activity of the drug depends on the carboxylic group [6]. On the other hand, this degradant was recorded as impurity in the bulk form and precipitate in the injection formulation [5].

The presence of degradants and impurities in pharmaceutical formulations may effect on their efficacy and safety. This can cause changing of chemical, pharmacological and toxicological properties of drugs. Drug stability is considered to be the secure way to ensure the delivery of therapeutic values to patients [7–9]. Therefore, the adoption of stability-indicating methods is always required to control the quality of pharmaceuticals during and after preparation in industries and dispensaries.

A literature survey of norfloxacin stability-indicating methods has enumerated many HPLC and few spectrophotometric methods; some of them are listed in the references [5,10–12]. The capillary electrophoresis (CE) technique has not been utilized for this purpose yet.

CE has many advantages over HPLC with respect to separation efficiency, consumption of reagents and samples,

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doi:10.1016/j.microc.2007.05.001

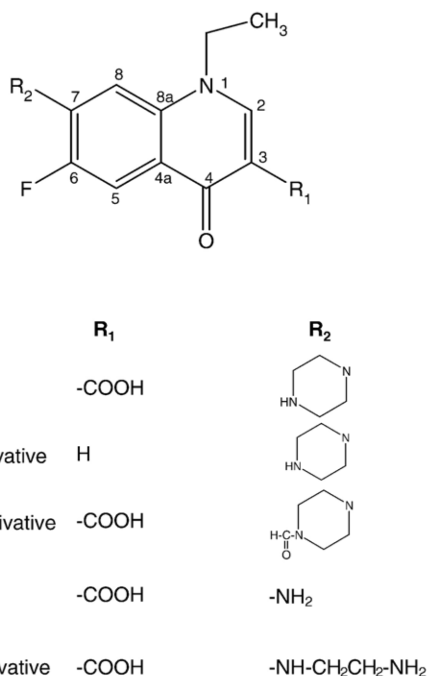

Fig. 1. Structures of norfloxacin and its possible degradant derivatives.

analysis time and simplicity in instrumentation [13]. Nevertheless, HPLC is still the dominant technique in pharmaceutical analysis; but the extensive utilization of CE will generate complementary and alternative methods. On the other hand, the main component and structurally related degradants and impurities in pharmaceutical formulations have similar chemical properties and thus make resolution difficult. However, the separation efficiency of CE makes this type of pharmaceutical analysis available [14].

In the optimization of CE methods, many electrophoretic factors control the analysis in different levels. On the other hand, many CE responses are also obtained. Therefore, to reach the maximum efficiency of CE methods, all electrophoretic factors must be optimized and multiresponse must be considered. The common practice used in the optimization process is the univariant method. This method involves a large number of independent experiments irrespective possible interactions between factors [15]. Chemometric optimization methods including the experimental design are well suited to study the main and interaction effects; and consequently determine the optimum conditions in a minimum number of experiments [16].

This study presents a simple, accurate, precise, rapid and sensitive CE stability-indicating method for norfloxacin. The method was optimized and validated for the simultaneous determination of the intact drug and its inactive decarboxylated degradant in pharmaceutical formulations. Many CE aspects including separation, sensitivity, rapidity and repeatability were developed.

In CE analysis, electrolyte composition depends upon the nature of analytes and relevantly affecting the efficiency of the methods. For other electrophoretic factors, the effect is always irrelevant and straightforward [17]. A previous article reviewed the use of chemometrics for the optimization of CE methods [18]. The majority of the addressed studies considered electrolyte composition for optimization by chemometrics. Moreover, in chemometric optimization, to avoid complex matrices, it is advisable to minimize the number of factors as possible [16]. For these reasons, electrolyte concentration and pH were optimized using the experimental design-based methods. Injection time, separation voltage and column temperature were optimized using the univariant method.

2. Experimental

2.1. Chemicals and pharmaceutical samples

Chemicals and reagents used in this study were of analytical grade quality; and water was distilled deionized. Norfloxacin and excipients (microcrystalline cellulose, magnesium stearate, lactose, maize starch and talc) were supplied from EIPI, Inc. (Cairo, Egypt). Acetic acid, boric acid, sodium acetate and sodium tetraborate decahydrate as well as TLC silica gel GF_{254} plates were supplied from Sigma-Aldrich (Taufkirchen, Germany). Acetone, methanol, phosphoric acid and sodium phosphate were supplied from Sigma (St. Louis, MO, USA). Hydrochloric acid, potassium hydroxide and sodium hydroxide were supplied from Merck (Darmstadt, Germany).

Noroxin® tablets (400 mg norfloxacin) were prepared by Merck Sharp and Dohme B.V. (Haarlem, Netherlands). Noracin® tablets (400 mg norfloxacin) were prepared by JPM, Inc. (Naor, Jordan).

2.2. Preparation of standard solutions and pharmaceutical samples

1000 μg ml^{-1} norfloxacin was prepared as a stock solution by dissolving the standard material with stirring in water. The solution was stored protected from light at 4 °C and it was stable for two weeks. Mixed standard solutions containing norfloxacin and the degradant were prepared in different concentrations ranging from 0.1 to 500 μg ml^{-1} for calibration purpose.

The degradant drug was prepared using a previous method [5]. 250 mg norfloxacin was refluxed with 70 ml of 2 mmol l^{-1} hydrochloric acid at 150 °C for 48 h protected from light. Then, the solution was cooled and adjusted to pH 7.5 by 2 mmol l^{-1} sodium hydroxide. After that the solution was evaporated under vacuum to dryness. The residue was extracted three times by absolute ethanol and filtered in a 250 ml volumetric flask.

A pharmaceutical sample including 10 μg ml^{-1} norfloxacin, 1 μg ml^{-1} the degradant and excipients (as mentioned in section 2.1) in a total concentration of 1 μg ml^{-1} were synthesized at our laboratories.

Ready prepared tablets formulation (Noroxin® and Noracin®) were weighed and powdered. Quantities equivalent to 10 mg norfloxacin were dissolved in 70 ml of water with stirring for 30 min. Solutions were filtered in a 100 ml volumetric flask and filled to the mark. Solutions were stored protected from light at 4 °C.

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