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التوثيق الالكتروني والميكروفيلم

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Electrochemical and Thermal Studies on Some Fluoroquinolones

A Thesis Submitted By

Manal Abdel-Hamid Ragheb El-Shall

B. Sc. Chemistry
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M. Sc. (Analytical Chemistry)
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To
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بسم الله الرحمن الرحيم

"فأما الزبد فيذهب جفاء وأما ما ينفع الناس فيمكث في الأرض كذلك يضرب الله الأمثال"

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ABSTRACT

Name: Manal Abdel-Hamid Ragheb El-Shall

Title of Thesis: Electrochemical and Thermal Studies on Some Fluoroquinolones

- This work has been carried out to investigate the electrochemical micro determination of lomefloxacin (LFX), sparfloxacin (SFX), gatifloxacin (GFX) ,and moxifloxacin (MFX) through oxidation reaction at carbon paste electrode in acetate buffer of pH 5, and reduction reaction at hanging mercury dropping electrode HMDE in Britton-Robinson Buffer. Pd(II)-4-quinolone complexes were prepared and identified through the modification of the direct HMDE method.
- These three methods were applied for determination of the investigated drugs in raw materials, pharmaceutical preparations, and biological fluids.
- Solid state study of the cited drugs through thermal analysis techniques TG and DTA, was carried out. The kinetic and activation parameters were calculated and the order of stability was found to be LFX > SFX > GFX > MFX. The DSC method was found to be suitable for the determination of the investigated drugs. Some thermal parameters were also calculated using Arrhinus and Ozawa methods.

Keywords: lomefloxacin, sparfloxacin, gatifloxacin, moxifloxacin, carbon paste electrode, hanging mercury dropping electrode, Pd(II)-4-Quinolone complexes, TG, DTA, DSC.

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The authoress

Manal Abdel-Hamid ElShall

List of Publications

1- Part 1:

"Adsorptive electrochemical behavior of some Fluoroquinolones at carbon paste electrode", Analytical Siences, Vol 21, (2005), 1249.

2- Part 2 & 3:

"***Validated Polarographic Methods for Determination of Certain Antibacterial Drugs***", Analytical Siences, Vol 23, (2007), 1053.

3- Part 4:

مـــؤتمر الهيئـــة القوميـــة للرقابـــة والبحـــوث الدوائيـــة مـــارس ٢٠٠٤

"Thermal stability of some selected fluoroquinolines"

ANALYTICAL SCIENCES OCTOBER 2005, VOL. 21

Notes

Electrochemical Adsorptive Behavior of Some Fluoroquinolones at Carbon Paste Electrode

M. A. El RIES,*† A. A. WASSEL,* N. T. Abdel GHANI, and M. A. El-SHALL***

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Cyclic voltammetry and differential pulse voltammetry were used to explore the adsorption behavior of three antibacterial agents at a carbon paste electrode. The drugs were accumulated on a carbon paste electrode, and a well-defined oxidation peak was obtained in acetate buffer (pH 5.0). The adsorptive stripping response was evaluated as a function of some variables such as the scan rate, pH and accumulation time. A simple, precise, inexpensive and sensitive voltammetric method has been developed for the determination of the cited drugs (Lomefloxacin (LFX), Sparfloxacin hydrochloride (SFX), and Gatifloxacin (GFX)). A linear calibration was obtained from 2×10^{-7} M to 4×10^{-5} M for LFX, 2×10^{-7} M to 6×10^{-5} M for SFX, and GFX. The limits of detection (LOD) were 4.2×10^{-7}, 7×10^{-7} and 6.6×10^{-7} M, while the limits of quantification (LOQ) were 1.4×10^{-6}, 2.3×10^{-6} and 2.2×10^{-6} M for LFX, SFX, and GFX, respectively. The R. S. D. of five measurements at the 1×10^{-6} M level were 0.4, 0.5 and 0.3 for LFX, SFX and GFX, respectively. The method was applied to the determination of LFX, SFX and GFX in dilute urine samples and dosage forms, and compared with the HPLC method.

(Received October 18, 2004; Accepted March 7, 2005)

Introduction

Quinolones have been found to possess an antibiotic property. Fluorinated 4-quinolone derivatives have a broad-spectrum antibacterial activity against many gram-positive and gram-negative bacteria through inhibition of their DNA gyrase.[1-3] Lomefloxacin (LFX) [1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid], Separefloxacin (SFX) [rel-5-amino-1-cyclopropyl-7-{(3*R*, 5*S*),3,5-dimethyl-piperazinyl}-6,8-difluoro-1,4-dihydro-4-oxo-3-quinholinecarboxylic acid], and Gatifloxacin (GFX) [1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid] are new additions to the class of fluoroquinolones that are widely used in the treating of respiratory trace and urinary trace infections.[4] The structures of the cited drugs are shown in Table 1.

Lomefloxacin is rapidly and almost completely absorbed following oral administration. The elimination halflife of Lomefloxacin is about 7 to 8 h. Lomefloxacin is extracted in the urine, mainly as an unchanged drug.[5] Sparfloxacin has been reported to be more active *in vitro* than other quinolones against some microorganisms, including staphylococci and mycobacteria,[6,7] and has a 16 h plasma halflife.[8] Gatifloxacin is an advanced-generation fluoroquinolones that offers several advantages over previous agents, including enhanced *in vitro* activity against clinically important pathogens and improved pharmacokinetics. These advantages result in enhanced pharmacodynamics, which may improve patient outcomes against certain bacterial pathogens, especially penicillin-resistant *streptococcus pneumonia*.[9]

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The mechanism of action of fluoroquinolones antibacterial involves the inhabitation of bacterial topoisomerase IV and DNA gyrase (both of which are type-II topoisomerases, enzymes required for DNA replication, transport, repair and recombination).[10] Two exhaustive reviews[11,12] are available that describe the current status of the analytical techniques for fluoroquinolones antibiotics. Few methods have been reported for the determination of LFX, SFX and GFX either pure or in dosage forms. For GFX, only three published papers[9,13,14] have described the complete methodology for a validation assay procedure, but no electrochemical method has been published for its determination. For SFX spectrophotometry, HPLC[15,16] and polarographic methods have been reported.[17] For LFX methods using various techniques have been reported including spectrophotometry,[18] HPLC[19] and polarography.[20]

The most sensitive electrochemical procedures for the demonstration of the trace concentrations of various pharmaceutical compounds have conventionally employed a two-step approach consisting of: (i) An initial preconcentration step, during which the analyte is allowed to accumulate at the electrode surface under carefully controlled conditions. (ii) A subsequent measurement in which the accumulated analyte is then stripped-off and determined by a voltammetric method. This preconcentration/measurement sequence forms the basis of all of the so-called stripping techniques that permit the determination of electroactive compounds at very low concentration.[21]

The application of microelectrodes to different analytical and kinetic studies offers several advantages compared to regular area electrodes.[22-26] They enhanced the mass transport and reduce the apparent electrochemical reversibility, allowing the determination of higher rate constants than regular-area electrodes.[26,27] Measurement in quite high resistive media, the monitoring of large concentration, working with very high scan

Validated Polarographic Methods for the Determination of Certain Antibacterial Drugs

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Two simple, precise, inexpensive and sensitive voltammetric methods for the determination of lomefloxacin (LFX), sparfloxacin hydrochloride (SFX), gatifloxacin (GFX), and moxifloxacin (MFX) were developed. The present methods were first used to explore the adsorption behavior of the four investigated antibacterial agents at a hanging mercury dropping electrode (HMDE), by a direct method and secondly by a modification *via* their complexation with $PdCl_2$. For the direct method, drugs were accumulated on HMDE, and a well-defined reduction peak was obtained in Britton-Robinson buffer of pH 7 for LFX and SFX, and pH 6 for GFX and MFX. The adsorptive stripping response was evaluated as a function of some variables such as the scan rate, pH, accumulation time and potential. For the modified method, the adsorptive behavior of Pd(II)-4-quinolone complexes at the HMDE developed a strippining voltammetry peak at a more negative potential than that of the free Pd(II) ions (−1.05 V). The limits of detection (LOD) were 2×10^{-8} M, while the limits of quantification (LOQ) were 6×10^{-8} M for the investigated drugs. The methods were applied to the determination of LFX, SFX, GFX, and MFX in biological samples and pharmaceutical preparations, and also compared with the official reference methods. Complete validation of the proposed methods was also done.

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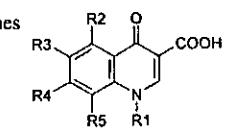
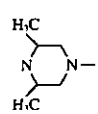
Quinolones have been found to possess an antibiotic property. Fluorinated 4-quinolone derivatives have a broad-spectrum antibacterial activity against many gram-positive and gram-negative bacteria through inhibition of their DNA gyrase.[1-3] Numerous structural modifications have been made in the quinoline nucleus to increase the antimicrobial activity, and to improve the pharmacokinetic performance. During the past 15 years, the 4-quinolone antibacterial has progressed from relative obscurity to a highly visible and intensely studied class of compounds. All of these newer agents have similar mechanisms of action, but numerous derivatives of the basic 4-quinolone structures have been synthesized in an effort to enhance the antimicrobial spectrum and pharmacological properties of these antimicrobials. A good guide to the work published for these compounds can be found in the review written by Belal *et al.*[4] Lomefloxacin (LFX) 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sparfloxacin (SFX) *rel*-5-amino-1-cyclopropyl-7-{(3*R*,5*S*)-3,5-dimethylpiperazinyl}-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, gatifloxacin (GFX) 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, moxifloxacin (MFX) 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4*aS*,7*aS*)octahydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-yl]-4-oxo-3-quinolinecarboxylic acid are new additions to the class of fluoroquinolones that are widely used in the treating of respiratory trace and urinary trace infections.[5] The structures of the investegated drugs are shown in Table 1.

LFX is rapidly and almost completely absorbed following oral administration and can be extracted in the urine, mainly as an unchanged drug.[6] SFX has been reported to be more active *in vitro* than other quinolones against some microorganisms, including staphylococci and mycobacteria.[7-9] GFX is an advanced generation of fluoroquinolones that offers several advantages over previous agents, including enhanced *in vitro* activity against clinically important pathogens and improved pharmacokinetics. MFX is readily adsorbed from the gastrointestinal trace with an absolute bioavailability of about 90%. It is widely distributed throughout the body tissues and is approximately 50% bound to plasma proteins. The elimination half-life[6,9] of LFX, SFX, MFX, and GFX is about 7 to 8, 16, and 12 h, respectively. These advantages result in enhanced pharmacodynamics, which may improve patient outcomes

Table 1 Selected fluoroquinolones



Name	R_1	R_2	R_3	R_4	R_5
Lomefloxacin (LFX)	$-C_2H_5$	H	F		F
Sparfloxacin (SFX)			F		F
Gatifloxacin (GFX)		H	F		OCH_3
Moxifloxacin (MFX)		H	F		OCH_3

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