Analytical Studies on the Determination of Some Anti-infective Agents and Certain Drugs Acting on Cardiovascular System

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دراسات تحليلية لتعيين بعض مضادات العدوي و بعض العقاقير المؤثرة على القلب و الأوعيـــة الدمويـــة

رسالة مقدمة من

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بكالوريوس العلوم الصيدلية 2000

ماجستير العلوم الصيدلية 2004

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للحصول على درجة الدكتوراة

في العلوم الصيدلية

(كيمياء تحليلية)

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Preface

This thesis is the final work of my Ph.D. study at the Department of Analytical Chemistry, Faculty of Pharmacy, ***Zagazig University*** - Egypt and Chemistry Department, School of Humanities and Science, ***Virginia Commonwealth University*** – USA, as a member of the internal mission **(2005 – 2006)**. It serves as documentation of my work during the study, which has been made from **December, 2005** until **December, 2008**. This study has been funded (in its external part) by the Egyptian Cultural and Educational Bureau (Washington, D.C.). The study has been a part of my job as an assistant lecturer at the Analytical Chemistry Department, to which I have been affiliated since **January, 2001**.

Scope of this Thesis:

Throughout this thesis and as implied in the thesis title, we tried by and large to develop new and specific analytical procedures for a specific group of drugs, which share a definite pharmacological action. In general, this thesis will familiarize the reader with a number of techniques which were used to determine the studied drugs; per se or in pharmaceutical formulations. Those techniques can be categorized under two or three main classes; electroanalytical techniques [which can be sub classified into microfluidics and so the application of streaming potentials; and conductometry] and spectrophotometry.

The drugs investigated in each procedure and all their related information, [chemical structure, formula, molecular weight, therapeutic uses and physical properties], have been collected and listed in tables, which will be displayed within each part.

All the conditions of the proposed procedures as well as the experimental parameters were studied, discussed and then explained. In addition, the data given were statistically analyzed and then compared with the official or reference methods.

At least one commercial product for each drug either different dosage forms or products of different companies were subjected to the analytical procedures.

This Thesis Involves Two Main Parts: **Part I,** *which* concerns with the developed **Electroanalytical Techniques** and **Part II**, *which* discusses the **Spectrophotometric Methods** adopted for the determination of the studied drugs.

Part I can be subdivided into **Part I.1. Microfluidics** and **Part I.2. Conductometry**.

The following chapters are included under **Part I.1.**:

Chapter 1. In which, a general introduction which reviews the background information about microfluidics, their past, present and future together with the objectives of this project are mentioned.

Chapter 2. This chapter reviews microfabrication materials as well as the followed techniques, surface modification techniques, the phenomena involved and the diverse applications of microfluidics.

Chapter 3. A literature review on the drugs studied in this part; [Heparin and its analogs; Enoxaparin sodium, Chondroitin sulfate A and B] and their magnitude as biological molecules is revealed. The fabrication of a microfluidics platform for the determination of heparin is discussed.

Chapter 4. Herein, the implementation of electrochemical detection in plastic microfluidic channels built with the commodity thermoplastic Cyclic Olefin Copolymer (COC) and label-free detection of the studied bioprobes using *pulsed streaming potentials* in is discussed. This chapter can be divided into two subsections:

A. In which we discuss ***protamine sulfate*** as a bioreceptor for detection of Heparin.

B. This subsection will show how ***antithrombin III*** was used to tailor the surface of the microchannel to detect Heparin, Enoxaparin sodium and Chondroitin sulfates.

Part I.2. Conductometry.

In this part we discuss the conductometric determination of some pharmaceutically important carboxylic and hydrochloric acid derivatives in pharmaceutical formulations. This part includes the following chapters:

Chapter 5. A survey of literature of the drugs used in this part is viewed. Four drugs were investigated, mainly; flunarizine hydrochloride, ramipril, terbinafine hydrochloride and tranexamic acid.

Chapter 6. Conductometric determination of the studied drugs using ***sodium hydroxide*** and ***tetrabutylammonium hydroxide*** through acid - base reactions is covered in this chapter.

Chapter 7. In this chapter, **silver nitrate** was applied as a titrant for the precipitation of flunarizine and terbinafine hydrochlorides, locating the end point conductometrically.

Part II. Spectrophotometric Methods:

This part technically describes certain spectrophotometric methods that were applied for the determination of the studied drugs. The proposed procedures were described under the following chapters:

Chapter 8. Literature review of aciclovir, fluconazole and secnidazole is shown.

Chapter 9. Three ion – pairing reagents were applied for extractive spectrophotometric determination of flunarizine hydrochloride, ramipril and terbinafine hydrochloride:

A. The inorganic complex; ***molybdenum (V) thiocyanate***

B. The acid dyes; ***orange G*** and ***alizarin red S.***

Chapter 10. Application of **cobalt (II) – EDTA** complex as a novel reductant for **molybdophosphoric acid** used for the spectrophotometric assay of aciclovir, fluconazole, ramipril and secnidazole, was revealed.

PART I

ELECTROANALYTICAL TECHNIQUES

ELECTROANALYSIS

AN OVERVIEW

As the name entails, electroanalytical techniques are mainly concerned with the relationship between electrical quantities (such as current, potential, charge……) and chemical parameters.

Such interplay between electrical measurements and the field of chemical analysis is attracting more interest in many applications such as biomedical analysis, quality control purposes, and environmental analysis….etc.

In fact; the field of electrochemistry comprises an enormous assortment of diverse phenomena (like electrophoresis, corrosion); devices (sensors, batteries, fuel cells……); technologies (like electroplating of metals…..).[1, 2]

It is known that the contact between a solid surface and a solution creates a difference in potential between the interface and the region of the bulk solution close to the interface. This causes, of course, uneven distribution of ions of the solute close to the surface (if the solution is electrolyte). The positive ions will be adsorbed electrostatically on a negatively charged surface, forming what is known as "Electrical Double Layer". Pushing the liquid phase to flow would create a potential difference in the flow direction.

Electrokinetic phenomena associated with the movement of charged particles through a continuous medium or with the movement of a continuous medium over a charged surface include four principal parts; electrophoresis, electroosmosis, streaming potential, and sedimentation potential. These phenomena are related to one another through the zeta potential ζ of the electrical double layer which exists in the neighborhood of the charged surface.

In the course of ***Part.I.1.,*** we will be more interested in the application of pulsed streaming potentials as electrokinetic phenomenon for the study of some binding events within microfluidic platforms.

Commonly, electrochemical techniques can be classified into two main categories according to where they take place, mainly; bulk and interfacial. ***Bulk*** reactions refer to electrochemical techniques that occur in the entire solution; while ***interfacial*** ones are those which arise at the electrode – solution interface.[3]

A good example of bulk electrochemistry is conductometry which measures "conductance"; a property that involves the whole solution. The application of this phenomenon for the determination of some compounds of pharmaceutical interest will be covered through ***Part.I.2.***

PART I.1.

MICROFLUIDICS

Chapter 1

Microfluidics....

The Past ..... The Present