# DEVELOPING NEW ANALYTICAL METHODS FOR DETERMINATION OF SOME CHEMICALS IN DRUG FORMULATIONS AND LAB WASTEWATER WITH PROPOSAL FOR TREATMENT

Thesis presented by

## **Ashgan Youssef Hashem**

B.SC. (Geophysics), Faculty of Science, Suez canal University, 1999

A Thesis Submitted In Partial Fulfillment

Of

The Requirement of the Master Degree

In

**Environmental Science** 

Department of Environmental Basic Science Institute of Environmental Studies and Research Ain Shams University

# DEVELOPING NEW ANALYTICAL METHODS FOR DETERMINATION OF SOME CHEMICALS IN DRUG FORMULATIONS AND LAB WASTEWATER WITH PROPOSAL FOR TREATMENT

Thesis presented by

## **Ashgan Youssef Hashem**

B.SC. (Geophysics), Faculty of Science, Suez canal University, 1999

A Thesis Submitted In Partial Fulfillment

**Of** 

The Requirement of the Master Degree

In

Environmental Science
Department of Environmental Basic Science

### Under the supervision of:

### Prof. Dr. Mostafa M. H. Khalil

Prof. of Inorganic Chemistry, Faculty Of Science AinShams University

### Dr. Taha A. Azim M. A. Razek

Ass.Professor of Environmental Analytical Chemistry Institute of Environmental Studies and Research AinShams University

### Dr. Mohamed Sultan Mohamed

Researcher, National Organization of Drug Control And Research

### Acknowledgement

First and above all, I thank Allah (subhana wa taala) for endowing me with health, patience, and knowledge to fulfill this thesis.

I would like to pay special thankfulness, warmth and appreciation to the persons below who made my research successful and assisted me at every point to cherish my goal:

Prof. Dr. Mostafa M. H. Khalil, professor of inorganic chemistry, Faculty of Science, Ain Shams University, for his vital support and assistance. His encouragement made it possible to achieve the goal.

Dr. Taha Abd El Azim, Assistant professor of Environmental chemistry, Institute of Environmental Studies and Research, Ain Shams University, for his extreme patience, assistance and guidance.

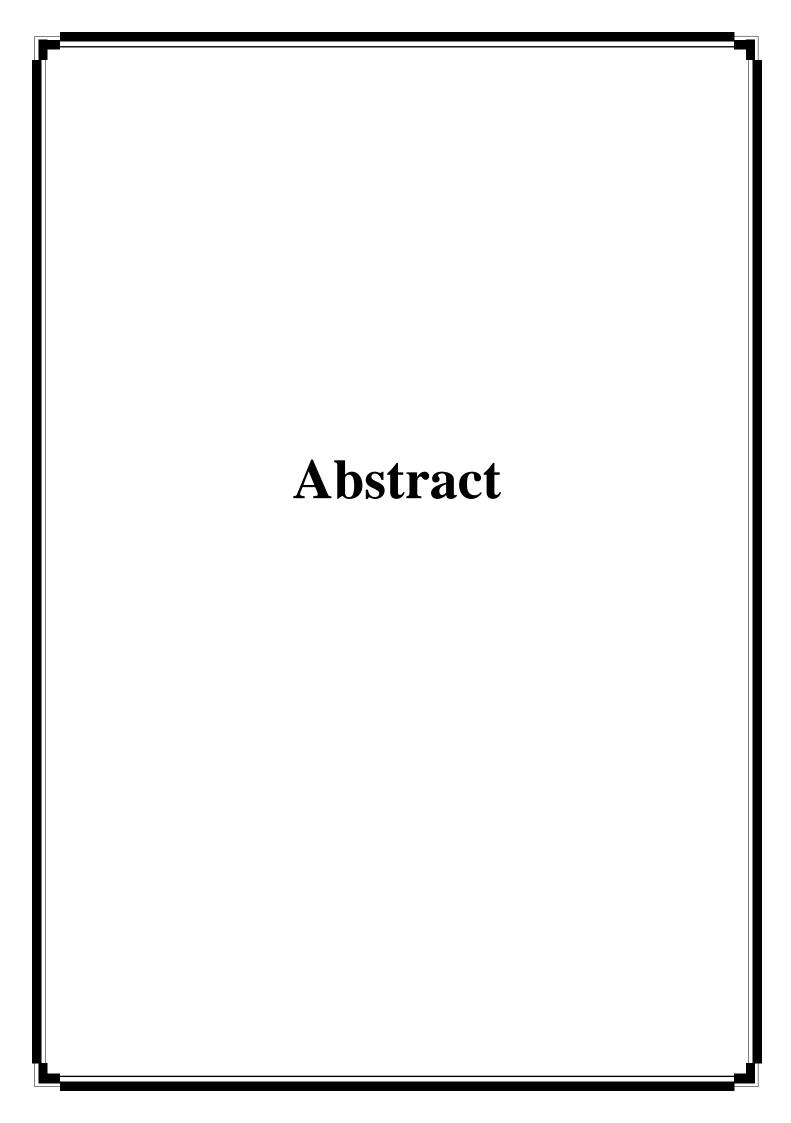
Dr. Enas Abdel Hakim Amer, Researcher, National Organization for Drug Control and Research, whose help and sympathetic attitude at every point during my research helped me to work in time.

All my colleagues in National Organization for Drug Control and Research especially TLC and GIT laboratories.

I would like to acknowledge with gratitude, the support and love of my family- my parents and my brothers Mohammed and Ali- they were always supporting me and encouraging me with their best wishes.

Thank you

Ashgan Youssef



### **Abstract**

Name of candidate: Ashgan Youssef Hashem

**Title of the thesis:** Developing New Analytical Methods for Determination of Some Chemicals in Drug Formulations and Lab wastewater with Proposal for Treatment

Recent advances in analytical methods have been mirrored by our increased ability to detect and quantify organic contaminants at trace levels, or in highly complex matrix as in wastewater. Pharmaceutical compounds are generally present in parts –per- trillion or parts- per- billion levels.

Questions regarding persistence and long term adverse effects of pharmaceuticals in the environment have been raised. There are low drug concentrations in the environment that have undesirable ecological and potentially human health effects.

New, simple, rapid, accurate and sensitive methods have been suggested for determining three commonly used antidepressant drugs. They are namely; tianeptine sodium (TIA), duloxetine hydrochloride (DUL) and fluoxetine hydrochloride (FLU), respectively,in their bulk powder and pharmaceutical preparations. They are measured as well as in combination in lab wastewater.

High performance liquid chromatography (HPLC) is the most powerful and versatile instrumental technique used for detection and quantitation of TIA, DUL and FLUby using  $C_8$  column, mobile phase: (sodium acetate: acetonitrile) (60:40, v/v)pH 3.85 with a flow rate: 2 ml/min at wavelength: 231 nm. The retention timeswere( $t_R$ = 3.016 min) for TIA, ( $t_R$ = 3.714 min) for DUL, and ( $t_R$ = 4.823 min) for FLU, respectively.

The first derivative ratio spectra was based on determination of one drug in the presence of the other to eliminate interference. The amplitude in the first derivative of the corresponding ratio spectra at 327.8nm, 252.4nm, were selected to determine TIA, and FLU, respectively, using DUL on (10  $\mu$ g/ml) as divisor, and DUL showed amplitude at 255.8nm, 238.4 nm using TIA (6  $\mu$ g/ml) or FLU (40  $\mu$ g/ml) as devisor.

Degradation of the drugs occurred by using the advanced oxidation process presented in the presence of titanium dioxide as a photocatalyst in the presence of UV irradiation led to destruction of the pollutants to simpler molecules.

**Key words:**Drugs, Duloxetine, Tianeptine, Fluoxetine, derivative ratio, Titanium dioxide, photocatalsis, wastewater, treatment.

|         | CONTENTS   | page |
|---------|--|------|
| ABST    | RACT   | i    |
| LIST    | OF FIGURES   | iii  |
| LIST    | OF TABLES  | vi   |
| LIST    | OF ABBREVIATION  | viii |
| CHAI    | PTER 1. INTRODUCTION AND LITERATURE REVIEW                                       | 1    |
| 1.1.    | Classification of antidepressants  | 3    |
| 1.2.    | Action mechanisms of antidepressants   | 6    |
| 1.3.    | Analytical methods used for determination of the antidepressant                  | 6    |
|         | drugs in environmental matrices  |      |
| 1.4.    | Wastewater Treatment   | 10   |
| 1.5.    | What is Titanium Dioxide?  | 13   |
| 1.6.    | Mechanism of TiO <sub>2</sub> photocatalysis                                     | 14   |
| 1.7.    | Characteristics and Analytical methods used for determination of the             | 17   |
|         | investigated compounds   |      |
| 1.7.1.  | Tianeptine   | 17   |
| 1.7.2.  | Duloxetine   | 19   |
| 1.7.3.  | Fluoxetine   | 22   |
| Aim o   | f the Work   | 25   |
| CHAI    | PTER 2. MATERIALS AND METHODS  | 26   |
| 2.1. G  | eneral consideration   | 26   |
| 2.2. A  | pparatus   | 26   |
| 2.3. Sa | amples   | 27   |
| 2.3.1.  | Pure samples   | 27   |
| 2.3.2.  | Market samples   | 27   |
| 2.4. C  | hemicals and reagents  | 28   |
| 2.5. Pi | reparations  | 28   |
| 2.5.1.  | standard stock solutions   | 28   |
| 2.5.2.  | mobile phase   | 28   |
|         | laboratory prepared mixture for HPLC   | 28   |
|         | standard stock solutions of the devisors   | 29   |
|         | laboratory prepared mixture for first derivative ratio                           | 29   |
|         | 1. Duloxetine and Tianeptine   | 29   |
|         | 2. Duloxetine and Fluoxetine   | 29   |
|         | 3. Tianeptine and Duloxetine   | 29   |
|         | 4. Fluoxetine and Duloxetine   | 30   |
|         | djusting chromatographic conditions  | 30   |
|         | etermination of Duloxetine, Tianeptine and Fluoxetine in bulk powder HPLC method | 30   |
| _       | Determination of Duloxetine, Tianeptine and Fluoxetine in their                  | 31   |
|         | aceutical formulations using HPLC method.  |      |
| -       | Determination the wavelength of the measurements for first derivative            | 31   |
| ratio:  | Ç  |      |
| 2.9.1.  | For Duloxetine in the presence of Tianeptine                                     | 31   |
|         | For Duloxetine in the presence of Fluoxetine                                     | 32   |
|         | For Tianeptine in the presence of Duloxetine                                     | 32   |
|         | For Fluoxetine in the presence of Duloxetine                                     | 32   |
|         | Determination of mixtures in bulk powder using first derivative of the           | 33   |
|         | pectra method.   |      |
|         | General procedure  | 33   |

| (A) For DUL  | _  |
|--|----|
|  | 34 |
| (B) For TIA  | 34 |
| (C) For FLU  | 34 |
| 2.11.2. First derivative ratio method                  | 3: |
| (A) DUL/TIA  | 33 |
| (B) DUL/ FLU   | 33 |
| (C) TIA/DUL  | 3: |
| (D) FLU/ DUL   | 30 |
| 2.12. Photodegrdation                                  | 30 |
| <b>CHAPTER 3: RESULTS AND DISCUSSION</b>               | 33 |
| 3.1.HPLC method  | 33 |
| (A) For DUL  | 4. |
| (B) For TIA  | 4  |
| (C) For FLU  | 4  |
| Validation of the method                               | 5  |
| 3.2. First derivative ratio method                     | 5  |
| (A) DUL/TIA  | 5  |
| (B) DUL/FLU  | 6  |
| (C)TIA/DUL   | 6  |
| (D) FLU/DUL  | 6. |
| Validation of the method                               | 7  |
| 4. Application to environmental analysis               | 7  |
| 5.Photodegradation of the drugs using TiO <sub>2</sub> | 7  |
| CONCLUSION   | 8  |
| SUMMARY  | 8  |
| REFERENCES   | 8  |
| ARABIC SUMMARY   | 9  |
| ARABIC ABSTRACT  |    |

# **List of Figures**

| No. | Title of figure  | Page |
|-----|--|------|
| 1   | Fate of pharmaceutical in the environment                                  | 2    |
| 2   | (a) Positions of valence(VB) and conduction (CB) bands                     | 13   |
|     | in semiconductors, (b) multifunction of titanium                           |      |
|     | dioxide.   |      |
| 3   | Simplified mechanism for the photo-activation of a semiconductor catalyst. | 15   |
| 4   | Figure 4. Some reactions that can occur on illumination of ${\rm TiO_2}$   | 17   |
| 5   | Chromatogram of TIA (t R= 3.016 min), DUL (tR=                             | 38   |
|     | 3.714 min), and FLU (tR= 4.823 min).                                       |      |
| 6   | Effect of the increasing of acetonitrile                                   | 40   |
| 7   | Peak resolution at increasing the molarity of buffer                       | 40   |
| 8   | Effect of pH   | 41   |
| 9   | Effect of using Zorbax SB- C <sub>18</sub> (250x4.6 mm i.d.), 5 μm         | 41   |
|     | column   |      |
| 10  | Effect of using Thermo BDS HypersilC <sub>18</sub> (250x4.6 mm             | 42   |
|     | i.d.), 5 µm column   |      |
| 11  | Effect of using Nucleosil 100-5- C <sub>18</sub> (150x4.6 mm i.d.),        | 42   |
|     | 5 μm column  |      |
| 12  | Calibration curve for determination of DUL over                            | 43   |
|     | concentration range of (1-100) µg/ml using HPLC                            |      |
|     | method.  |      |

| 13 | Calibration curve for determination of TIA over                    | 45 |
|----|--|----|
|    | concentration range of (5-200) µg/ml using HPLC                    |    |
|    | method.  |    |
| 14 | Calibration curve for determination of FLU over                    | 47 |
|    | concentration range of (5-100) µg/ml using HPLC                    |    |
|    | method.  |    |
| 15 | Zero order spectrum of DUL(14 $\mu$ g/ml) shows $\lambda_{max}$ at | 58 |
|    | 289nm, TIA (10 $\mu$ g/ml) shows $\lambda_{max}$ at 276.7nm        |    |
| 16 | Zero order spectrum of DUL(14 $\mu$ g/ml) shows $\lambda_{max}$ at | 59 |
|    | 289nm, FLU (10 $\mu$ g/ml) shows $\lambda_{max}$ at 264.3nm        |    |
| 17 | First derivative of the ratio spectra of different                 | 60 |
|    | concentrations of DUL/ TIA (6-300 µg/ml) at 255.8nm                |    |
|    | using TIA as devisor.  |    |
| 18 | Calibration curve for determination of DUL/TIA                     | 61 |
|    | mixture over the concentration range (6-300)µg/ml                  |    |
|    | using first derivative ratio at 255.8nm.                           |    |
| 19 | First derivative of the ratio spectra of different                 | 62 |
|    | concentrations of DUL/ FLU (5-300)µg/ml at 238.4nm                 |    |
|    | using FLU as devisor.  |    |
| 20 | Calibration curve for determination of DUL/FLU                     | 63 |
|    | mixture over the concentration range (5-300)µg/ml                  |    |
|    | usingfirst derivative ratio at 238.4nm.                            |    |
| 21 | First derivative of the ratio spectra of different                 | 64 |
|    | concentrations of TIA/ DUL (14-240)µg/ml at 327.8 nm               |    |
|    | using DUL as devisor.  |    |
| 22 | Calibration curve for determination of TIA/DLU                     | 65 |

|    | mixture over the concentration range (4-240)µg/ml        |    |
|----|--|----|
|    | using first derivative ratio at 327.8nm.                 |    |
| 23 | First derivative of the ratio spectra of different       | 66 |
|    | concentrations of FLU/ DUL (5-300)µg/ml at 252.4 nm      |    |
|    | using DUL as devisor                                     |    |
| 24 | Calibration curve for determination of FLU/DLU           | 67 |
|    | mixture over the concentration range (5-240)µg/ml        |    |
|    | using first derivative ratio at 252.4nm.                 |    |
| 25 | The effect of TiO <sub>2</sub> on the degradation of DUL | 78 |
| 26 | The relationship between the absorbance and the time     | 80 |
|    | for DUL.   |    |
| 27 | The absorbance of DUL before irradiation by using        | 80 |
|    | HPLC technique.  |    |
| 28 | The absorbance of DUL after irradiation by using HPLC    | 81 |
|    | technique.   |    |
| 29 | The absorbance of TIA before irradiation by using        | 81 |
|    | HPLC technique.  |    |
| 30 | The absorbance of TIA after irradiation by using HPLC    | 82 |
|    | technique.   |    |
| 31 | The absorbance of FLU before irradiation by using        | 82 |
|    | HPLC technique.  |    |
| 32 | The absorbance of FLU after irradiation by using HPLC    | 82 |
|    | technique.   |    |