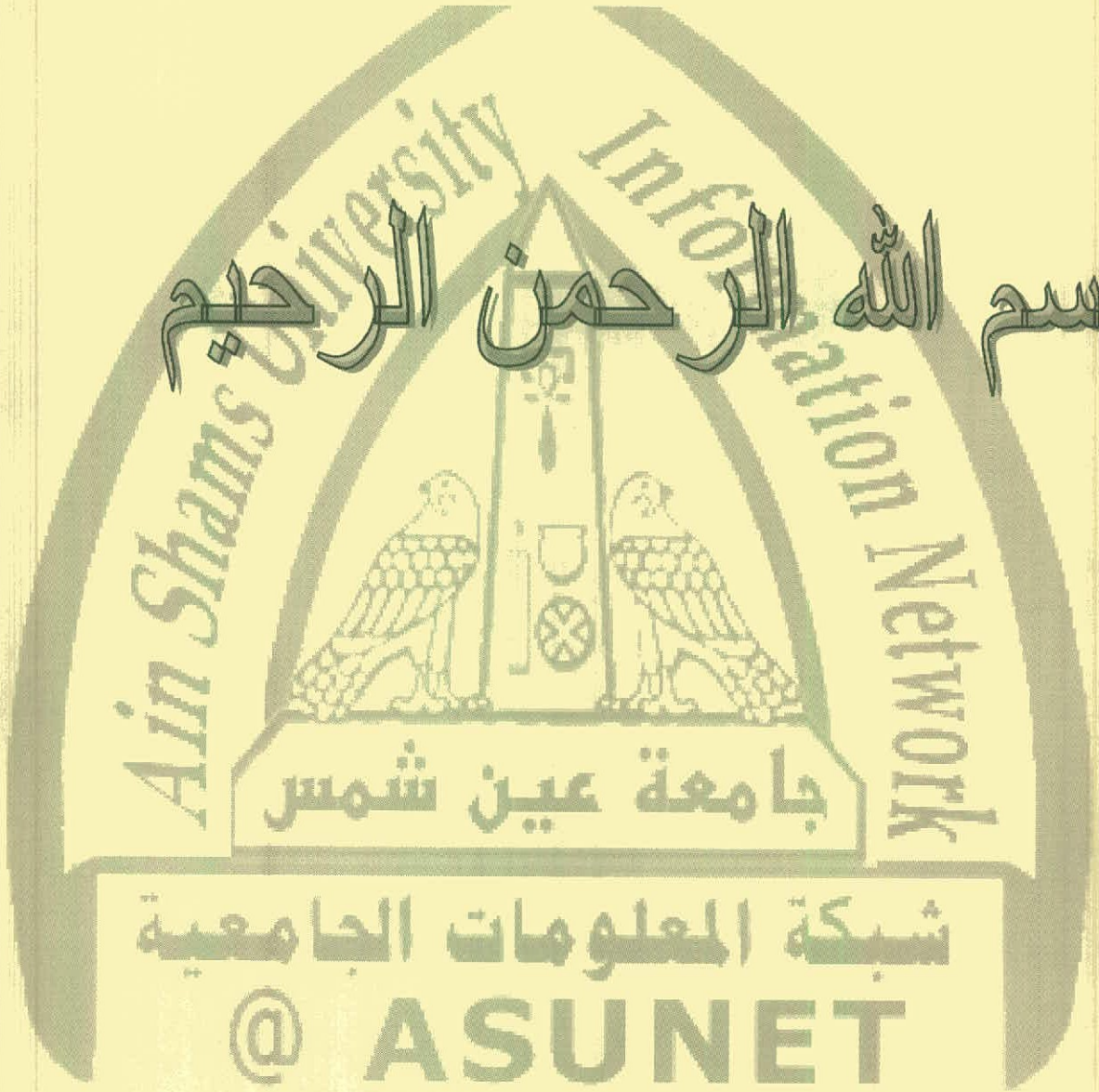
شبكة المعلومات الجامعية



بسم الله الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأفلام بعيدا عن الغبار

في درجة حرارة من ١٥-٢٥ مئوية ورطوبة نسبية من ٢٠-٤٠%

To be Kept away from Dust in Dry Cool place of 15-25- c and relative humidity 20-40%

بعض الوثائـــــــق الاصليـــــة تالفـــة

بالرسالة صفحات لم ترد بالاصل

Development and Adaptation of New Analytical Procedures for The Analysis of Some Pharmaceutical Combinations

A Thesis Presented By
Fawzy A. EL Barbary
(B.Pharm.Science)

In The Partial Fulfillment of The Requirements for The Degree

Master of Pharmaceutical Sciences
(Pharmaceutical Chemistry)

Department of Pharmaceutical Chemistry
Faculty of Pharmacy
University of Tanta
Tanta
Egypt
2002

TABLE OF CONTENTS

Aknowledgement iii
Scope of the investigation iv
Approval sheet v
List of abbreviations vi
List of figures vii
List of tables ix

Part (I): HPLC determination of the selective-serotonin re-uptake inhibitor, Fluoxetine
* Introduction and literature review 2
* Experimental 5
* Results and Discussion 10

Part(II): HPLC determination of chlorpheniramine maleate and tincture ipeca in cough preparations
* Introduction and Literature Review 27
* Experimental 32
* Results and Discussion 39

Part (III): HPLC determination of caffeine, ergotamine, propyphenazone, camylofin and mecloxamine in spasmomigraine tablet.
* Introduction and Literature Review 57
* Experimental (System1) 63
* Results and Discussion (system1) 69
* Experimental (System2) 87
* Results and Discussion (System2). 91

References 105

Summary (*English*) 115

Summary (*Arabic*)

Acknowledgement

I wish to express my sincere thanks and gratitude to **Professor Mohammed A. El-Dawy**; professor of pharmaceutical chemistry, department of pharmaceutical chemistry, faculty of pharmacy, Tanta university who suggested the subject, for his continuos guidance, encouragement and patience through the course of this research, the preparation of the manuscript, and the publication of the findings in renowned international peer reviewed periodicals.

I'm much obliged and deeply indebted to **Professor Mokhtar M. Mabrouk**; professor of pharmaceutical analytical chemistry and vice dean of graduate studies and research, faculty of pharmacy, Tanta University for his stimulating directions and sincere encouragement during various stages of the development of this research project.

The help and cooperation extended by Kahira Pharmaceutical & Chemical Industries Company, Cairo, Egypt during the development of this research project is highly appreciated.

My cordial thanks to my colleagues in the department of pharmaceutical chemistry, faculty of pharmacy, Tanta university for their help and cooperation.

Scope of the Investigation

The national pharmaceutical industry is currently facing lots of challenges that are imposed by globalization. Certain components of these changes address some technical requirements, particularly in the area of quality assurance, bioavailability and bioequivalency testing of the generic dosage forms.

These challenges call for compliance with current good laboratory practices (cGLPs) as stipulated by leading regulatory competent authorities at national (e.g. FDA), regional (EMEA), and international (e.g. ICH/WHO) levels.

The national industry faces these hurdles upon re-registration of the generic dosage forms for export to Arab, African and global markets, because these dosage forms, when first registered in Egypt- over a decade ago- were not commensurate with the current global requirements

Accordingly, the objective of this research project is to develop and adapt quality assurance methodology that is compliant with the cGLPs so as to enable Egyptian pharmaceutical industry to compete in a quality – driven global market.

This thesis was prepared under the supervision of: -

1-Prof. Dr. **Mohammed A. El-Dawy**; *Professor of Pharmaceutical Chemistry, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tanta university.*

2-Prof. Dr. **Mokhtar M. Mabrouk;** *Professor of Pharmaceutical Analytical Chemistry and Vice Dean of Graduate Studies and Research, Faculty of Pharmacy, Tanta University.*

The thesis has been approved by the examination committee on Aug. 12, 2002 by: -

Signature

1- ***Prof. Dr. Abd El-Kader Sayed Ahmed***
Professor of Analytical chemistry,
Department of analytical Chemistry,
Faculty of Pharmacy, Cairo University.

2- ***Prof. Dr. Mohammed A. El- Dawy***
Professor of Pharmaceutical Chemistry
Department of Pharmaceutical Chemistry
Faculty of Pharmacy, Tanta university.

3- ***Prof. Dr. Salwa R. El- Shaboury***
Professor of Pharmaceutical Analytical chemistry,
Department of Pharmaceutical Analytical Chemistry,
Faculty of Pharmacy, Assiut University

4-***Prof. Dr. Mokhtar M. Mabrouk***
Professor of Pharmaceutical Analytical Chemistry,
Vice Dean of Graduate Studies and Research,
Faculty of Pharmacy, Tanta University.

List of Abbreviations

BP : British Pharmacopeia

CTD : Common Technical Document (of the ICH)

CV : Coefficient Of Variation

ECD : Electron-Caprture Detector

EMEA: European Medicines Evaluation Agency (of the EU)

EU : European Union

FDA : Food and Drug Administration (of the USA)

FID : Flame Ionization Detector

GC : Gas Chromatography

HPLC : High Performance Liquid Chromatography

ICH : International Conference on Harmonization (Japan, EU and USA)

IS : Internal Standard

LOD : Limit Of Detection

LOQ : Limit Of Quantitation

M : Molar

MP : Methyl Paraben

MS : Mass Spectroscopy

µ : Microgram

µL : Microlitre

mg : Milligram

ml : Millilitre

min : Minute

nm : Nanometer

NMR : Nuclear Magnetic Resonance

RSD : Relative Standard Deviation

SD : Standard Deviation

USP : United States Pharmacopeia

UV : Ultraviolet

VIS : Visible

WHO : World Health Organization

λ : Wavelength

List of Figures

Figure 1: HPLC chromatogram of 20 µg/L fluoxetine HCl and 8 µg/L pyridoxine HCl (IS).

Figure 2: Standard calibration curve of fluoxetine HCl by the proposed method using 8 µg/L pyridoxine HCl (IS).

Figure 3: HPLC chromatogram of plasma sample supplemented only with 8 µg/L pyridoxine (IS).

Figure 4: HPLC chromatogram of 80 µg/L fluoxetine HCl and 8 µg/L pyridoxine (IS) in presence of plasma.

Figure 5: Standard calibration curve of fluoxetine HCl in plasma by the proposed HPLC method using 8 µg/L pyridoxine (IS)

Figure 6: HPLC chromatogram of a volunteer's sample after 48 hours of one *Prozac* capsule administration using the proposed HPLC method.

Figure 7: Plasma levels of fluoxetine (µg/L) following an oral administration of one *Prozac* capsule in two healthy human volunteers.

Figure 8: HPLC chromatogram of 70 µg/ml chlorpheniramine maleate and 10 µg/ml propyl paraben (IS).

Figure 9: Standard calibration curve of chlorpheniramine maleate by the proposed method using 10 µg/ml propyl paraben (IS).

Figure 10: HPLC chromatogram of 20 µg/ml emetine HCl and 10 µg/ml propyl paraben (IS).

Figure 11: Standard calibration curve of emetine HCl by the proposed method using 10 µg/ml propyl paraben (IS).

Figure 12: HPLC chromatogram of emetine HCl and propyl paraben (IS) from the assay of tincture ipeca.

Figure 13: HPLC chromatogram of chlorpheniramine maleate, 10 µg/ml propyl paraben (IS) and emetine HCl from the assay of *Bronchistal* syrup.

Figure 14: HPLC chromatogram of 25 µg/ml ergotamine tartrate and 10 µg/ml methyl paraben (IS).

Figure 15: Standard calibration curve of ergotamine tartrate by the proposed method using 10 µg/ml methyl paraben (IS).

Figure 16: HPLC chromatogram of 80 µg/ml propyphenazone and 10 µg/ml methyl paraben (IS).

Figure 17: Standard calibration curve of propyphenazone by the proposed method using 10 µg/ml methyl paraben (IS).

Figure 18: HPLC chromatogram of 70 µg/ml caffeine and 10 µg/ml methyl paraben (IS).

Figure 19: Standard calibration curve of caffeine by the proposed method using 10 µg/ml methyl paraben (IS).

Figure 20: HPLC chromatogram of ergotamine, caffeine, methyl paraben (IS) and propyphenazone from the assay of *spasmomigraine* tablet.

Figure 21: HPLC chromatogram of 30 µg/ml camylofin HCl and 10 µg/ml methyl paraben (IS).

Figure 22: Standard calibration curve of camylofin by the proposed method using 10 µg/ml methyl paraben (IS).

Figure 23: HPLC chromatogram of 50 µg/ml mecloxamine and 10 µg/ml methyl paraben (IS).

Figure 24: Standard calibration curve of mecloxamine by the proposed method using 10 µg/ml methyl paraben (IS).

Figure 25: HPLC chromatogram of camylofin, methyl paraben (IS) and mecloxamine from the assay of *spasmomigraine* tablet.

List of Tables

Table 1: Results of fluoxetine calibration curve in mobile phase using 8 µg/L pyridoxine (IS).

Table 2: Quantitative parameters for the determination of fluoxetine by the proposed HPLC method in the mobile phase and plasma.

Table 3: Results of recovery experiments of fluoxetine using 8 µg/ml pyridoxine (IS) by the USP method and the proposed HPLC method.

Table 4: Repeatability of different concentrations of fluoxetine using 8 µg/ml pyridoxine (IS) by the proposed HPLC method.

Table 5: Results of recovery experiments of fluoxetine in presence of interfering substances by the proposed HPLC method using 8 µg/ml pyridoxine (IS).

Table 6: Results of stability study of fluoxetine in solution over 24 hours.

Table 7: Results of fluoxetine analysis in its pharmaceutical preparations by the USP method and the proposed method.

Table 8: Results of fluoxetine calibration curve in spiked human plasma using 8 µg/L pyridoxine (IS).

Table 9: Results of recovery experiments of fluoxetine in presence of plasma by the modified USP method and the proposed HPLC method.

Table 10: Results of standard calibration curve of chlorpheniramine maleate using 10 µg/ml propyl paraben (IS).

Table 11: Quantitative parameters for the determination of chlorpheniramine maleate and emetine HCl by the proposed HPLC method.

Table 12: Results of recovery experiments of chlorpheniramine maleate using 10 µg/ml propyl paraben (IS) by the proposed method.

Table 13: Repeatability of different concentrations of chlorpheniramine maleate using the proposed HPLC method.

Table 14: Recovery experiments of chlorpheniramine and emetine in mixture with possible interfering materials using the proposed HPLC method.

Table 15: Results of stability study of chlorpheniramine maleate in solution over 24 hours.

Table 16: Determination of chlorpheniramine maleate in different dosage forms by the proposed HPLC method.

Table 17: Results of standard calibration curve of emetine HCl using 10µg/ml propyl paraben (IS).

Table 18: Results of recovery experiments of emetine HCl using 10 µg/ml propyl paraben (IS) by the proposed HPLC method.

Table 19: Repeatability of different concentrations of emetine using the proposed HPLC method.

Table 20: Results of stability study of emetine in solution over 24 hours.

Table 21: Determination of emetine content in each ml of ipeca liquid extract and tincture ipeca by the proposed HPLC method and the BP method.

Table 22: Results of analysis of chlorpheniramine and tincture ipeca (as emetine content) in dosage forms using the proposed HPLC method.

Table 23: Quantitative parameters for the determination of ergotamine, caffeine and propyphenazone with the proposed HPLC method.

Table 24: Recovery data of ergotamine using methyl paraben as IS by the proposed HPLC method

Table 25: Repeatability of different concentrations of ergotamine using methyl paraben as IS by the proposed HPLC method.

Table 26: Results of analysis of synthetic mixture of ergotamine, caffeine and propyphenazone in presence of interfering substances.