"ANALYSIS of SOME AMINO GROUP CONTAINING PHARMACEUTICAL DRUGS"

PREFACE

This thesis is concerned with analytical study of some amino group containing pharmaceutical drugs belonging to different chemical classes namely Racecadotril (**RAC**) used as anti-diarrheal, Aspirin (**ASP**) used as analgesic and antipyretic ,Caffeine (**CAF**) used as stimulant , Orphenadrine Citrate (**OR**) used as skeletal muscle relaxant and Paracetamol (**PAR**) used as analgesic and antipyretic.

The aim of this work is to develop simple, sensitive and selective methods for determination of the cited drugs either in bulk powder or in pharmaceutical formulations.

Different analytical techniques are adopted in this thesis including Spectrophotometry, Spectrofluorimetry, chemometrics, Spectrodensitometry and RP-HPLC.

ABSTRACT

The thesis comprises four parts:

PART 1

INTRODUCTION AND LITRATURE REVIEW

This part includes a general introduction about the chemistry and mode of action of the drugs mentioned in the thesis, followed by presentation of the reported methods used for their quantitative analysis.

This part comprises three sections:

Section (1) : Racecadotril (**RAC**)

Section (2) : Mixture of Aspirin, Caffeine and Orphenadrine Citrate.

Section (3) : Mixture of Paracetamol and Orphenadrine Citrate in Presence of Para-aminophenol.

PART II

SPECTROPHOTOMETRIC AND SPECTROFLOURIMETRIC DETERMINATION OF RACECADOTRIL.

This part comprises two sections:

Section A

Spectrophotometric Determination of Racecadotril using Iron(III)phenanthroline Reagent.

In this work a spectrophotometric method depending on reduction of ferric-phenanthroline (ferriin) to ferrous-phenanthroline (ferroin) by **RAC** and the absorbance of the obtained ferroin chelate was measured at λ_{max} 510 nm**,** a linear relationship was obtained in the range of 2.5 – 25 µg $mL^{-1}$of **RAC .**The validity of the suggested procedure was assessed by applying the standard addition technique.

Section B

Spectrofluorimetric determination of Racecadotril.

This method is based on measuring the native fluorescence intensity of **RAC** at λ_{em} = 319 nm in acetonitrile solvent at room temperature using λ_{ex}= 252 nm**,** a linear relationship was obtained between **RAC** fluorescence intensity /100 and the concentration in the range of 50- 500 ng mL^{-1}.The validity of the suggested procedure was assessed by applying the standard addition technique.

Part III

DETERMINATION OF TERNARY MIXTURE OF ASPIRIN, CAFFEINE AND ORPHENADRINE CITRATE.

This part comprises six sections:

Section(A)

Determination of Mixture of Aspirin and Caffeine in presence of Orphenadrine Citrate by Derivative Spectrophotometric Method.

In this section, Aspirin could be determined in presence of Caffeine and Orphenadrine Citrate using the first derivative Spectrophotometry D_1 at λ_{max}236 nm. Beer's law was obeyed over concentration range 2 - 20 µg mL^{-1}.Caffeine could be determined in presence of Aspirin and Orphenadrine Citrate by first derivative D_1Spectrophotometry at λ_{max} 259.8 nm. Beer's law was obeyed over concentration range 2-12 µg mL^{-1}.The selectivity of the proposed method was checked using laboratory prepared mixtures and it was successfully applied for the analysis of the **ASP** and **CAF** in pharmaceutical formulation (Relatic®tablet) with no interference from **OR** and excipient.

Section B

Determination of Ternary Mixture of Aspirin, Caffeine and Orphenadrine Citrate by ^{1}DD First Derivative Ratio Spectrophotometric Method.

In this section, Aspirin could be determined in presence of Caffeine and Orphenadrine Citrate using the first derivative of the ratio spectra (^{1}DD) with measurements at 242 nm using the spectrum of caffeine 10 µg

mL^{-1} as a divisor. Linear relationship was obtained over the concentration range of 2-20 µg mL^{-1} of **ASP** .Orphenadrine Citrate could be determined in presence of Caffeine and Aspirin using the first derivative of the ratio spectra (^{1}DD) with measurements at 228 nm using the spectrum of caffeine 10 µg mL^{-1} as a divisor, linear relationship was obtained over the concentration range of 5 – 40 µg mL^{-1} of **OR** .Caffeine could be determined in presence of Aspirin and Orphenadrine Citrate using the first derivative of the ratio spectra (^{1}DD) with measurements at 285.7 nm using the spectrum of Aspirin 20 µg mL^{-1} as a divisor. Linear relationship was obtained over the concentration range of 2-12 µg mL^{-1} of **CAF** .The selectivity of the proposed method was checked using laboratory prepared mixtures and it was successfully applied to the analysis of the pharmaceutical preparation (Relatic®tablet) with no interference from other dosage form additives.

Section C

Determination of Ternary Mixture of Aspirin, Caffeine and Orphenadrine Citrate by Multivariate Spectrophotometric Technique (PLS) and (PCR).

Two chemometric techniques, namely Principle Component Regression (PCR) and Partial Least Squares (PLS) have been successfully applied for simultaneous determination of Aspirin (**ASP**), Caffeine (**CAF**) and Orphenadrine citrate (**OR**) in pure forms and in pharmaceutical formulation(Relatic®tablet). Training set of 15 mixtures containing different ratios of the three drugs is used for construction of the two models.

Section(D)

Determination of mixture of Aspirin and Orphenadrine Citrate in presence of Caffeine by Spectrflourimetric method.

This method is based on measuring the native fluorescence intensity of **ASP** (λ_{em}= 408 nm , λ_{ex}= 220 nm) and of **OR** (λ_{em}= 295 nm , λ_{ex}= 220 nm) in deionized water solvent at room temperature**,** a linear relationship was obtained between fluorescence intensity /100 and the concentration in the range of 100- 800 ng mL^{-1} for **ASP** and in the range of 100 – 1000 ng $mL^{-1}$for **OR** .The selectivity of the proposed method was checked using laboratory prepared mixtures and it was successfully applied for the analysis of **ASP** and **OR** in the pharmaceutical formulation (Relatic®tablet) with no interference from **CAF** and additives.

Section(E)

Determination of Ternary Mixture of Aspirin, Caffeine and Orphenadrine Citrate by TLC Spectrodensitometric Method.

In this section, the three drugs are separated on a silica gel plate using ethyl acetate: acetone: methanol: triethylamine (6:3:1:0.2, by volume) as mobile phase and scanning at 220 nm, linear relationship was obtained between the peak area for each drug and the corresponding concentration in the ranges of 0.4-2 μg $band^{-1}$ for **ASP**, 0.4-2 μg $band^{-1}$ for **CAF** and 0.3-3 μg $band^{-1}$ for **OR** .Applying this method for the analysis of laboratory prepared mixtures assessed the selectivity of the suggested method.

Section (F)

Determination of Ternary Mixture of Aspirin, Caffeine and Orphenadrine Citrate by RP-HPLC.

In this section, the three drugs are separated on a reversed-phase C18 column using 0.01 M KH_2PO_4-methanol-acetonitrile-isopropyl alcohol (420: 20: 30: 30, by volume) [pH was adjusted to 7.9 with orthophosphoric acid or ammonia solution] as mobile phase at a flow rate of 0.6 $mL.min^{-1}$ and UV detection at 225 nm, linear relationship was obtained between the peak area for each drug and the corresponding concentration in the ranges of 4 – 250 μg mL^{-1} for **ASP**, 2– 150 μg mL^{-1} for **CAF** and 5 – 250 μg mL^{-1} for **OR**. Applying this method to the analysis of laboratory prepared mixtures assessed the selectivity of the suggested method.

Part IV

DETERMINATION OF MIXTURE OF PARACETAMOL AND ORPHENADRINE CITRATE IN PRESENCE OF PARA-AMINOPHENOL (DEGRADATION PRODUCT OF PARACETAMOL).

This part comprises five sections:

Section A

Determination of Binary Mixture of Paracetamol and Orphenadrine Citrate in Presence of Para-aminophenol By ^{1}DD First Derivative Ratio Spectrophotometric Method.

In this method, **PAR and OR** could be determined in presence of each other and in presence of **PAP** using the first derivative of the ratio spectra (**^{1}DD**) with measurements at 214 nm for **PAR** and 223.5 nm for **OR** using the spectrum of 5 μg mL^{-1} **PAP** as a divisor, linear relationship between the peak amplitude at 214 nm for **PAR** and 223.5 nm for **OR** and their concentrations were obtained in the ranges of 2-10 μg mL^{-1} for **PAR** and 5 – 40 μg mL^{-1} for **OR**. The selectivity of the proposed method was checked by analysis of laboratory prepared mixtures and it was successfully applied to the analysis of the pharmaceutical preparation containing the above drugs with no interference from other dosage form additives.

Section B

Determination of Ternary Mixture of Paracetamol, Orphenadrine Citrate and Para -aminophenol By Multivariate Spectrophotometric Technique (PLS) and (PCR).

Two chemometric techniques namely, Principle Component Regression (PCR) and Partial Least Squares (PLS) have been successfully applied for simultaneous determination of Paracetamol (**PAR**), Para-aminophenol (**PAP**) and Orphenadrine citrate (**OR**) in pure forms and in pharmaceutical preparation(Orphamol®tablet) .Training set of 15 mixtures containing different ratios of the two drugs and degradate is used for construction of the two models .

Section C

Determination of Binary Mixture of Paracetamol and Orphenadrine Citrate in Presence of Para-aminophenol By Spectrflourimetric Method.

This method is based on measuring the native fluorescence intensity of **PAR** (λ_{em}= 663 nm, λ_{ex}= 220 nm) and of **OR** (λ_{em}= 567 nm , λ_{ex}= 220 nm) in deionized water solvent at room temperature **,** a linear relationship was obtained between fluorescence intensity /100 and the concentration in the range of 100- 2500 ng mL^{-1} for **PAR** and in the ranges of 100 – 1000 ng mL^{-1} for **OR**. The selectivity of the proposed method was checked using laboratory prepared mixtures and it was successfully applied for the analysis of **PAR** and **OR** in the pharmaceutical preparation with no interference from **PAP** and additives.

Section D

Determination of Ternary Mixture of Paracetamol, Orphenadrine Citrate and Para-aminophenol by TLC Spectrodensitometric Method.

In this section, the two drugs and degradate of Paracetamol are separated on a silica gel plate using ethyl acetate: acetone: methanol: glacial Acetic acid (5: 4: 1:0.1, by volume) as mobile phase and scanned at 220 nm, linear relationship was obtained between the peak area for each drug and the corresponding concentration in the ranges of 0.2-1.4 μg $band^{-1}$ for **PAR**, 0.2-1.4 μg $band^{-1}$ for **PAP** and 0.3-3 μg $band^{-1}$ for **OR**. Applying this method for the analysis of laboratory prepared mixtures

assessed the selectivity of the suggested method. Also applying the standard addition technique assessed its validity.

Section F

Determination of Binary Mixture of Paracetamol and Orphenadrine Citrate in presence of Para-aminophenol by Microemulsion High Performance Liquid Chromatography (MELC).

In this section, the two drugs in presence of degradate are separated on a reversed-phase C18 column using Microemulsion (formulated by mixing 15 gram of Berj35 with 5 mL ethyl acetate and 30 mL butanol in beaker with stirring and gentle heating then complete to 1 liter with phosphate buffer (pH=3))as mobile phase at a flow rate of 1 $mL.min^{-1}$ and UV detection at 225 nm, linear relationship was obtained between the peak area for each drug and the corresponding concentration in the ranges of 5 – 200 $\mu g\ mL^{-1}$ for **PAR** and 5 – 250 $\mu g\ mL^{-1}$ for **OR**. Applying this method to the analysis of laboratory prepared mixtures assessed the selectivity of the suggested method.

This thesis refers to 204 references, contains 60 tables, 98 figures and ends with an Arabic summary.