Summary

This thesis consists of five parts in addition of references and an Arabic summary. Each part includes an introduction, literature review, descriptive experimental work for the studied drugs, results, discussion and ends with a conclusion.

Part I: Quantitative Determination of Orphenadrine Citrate in Presence of Its Degradation Product in Pure Form and Pharmaceutical Formulations

This part includes five sections.

Section (A): Introduction and literature Review

This section includes literature review about chemical structure, physical properties and pharmacology of Orphenadrine Citrate (ORPH), it also includes review of methods of analysis developed for determination of ORPH either alone or in presence of its degradation product in pure form and in pharmaceutical formulations.

Section (B): Determination of Orphenadrine Citrate in Presence of Its Degradation product by First Derivative of Ratio Spectra Method (DD^1).

In this section, the first derivative of ratio spectra spectrophotometric technique (DD^1) has been applied to improve selectivity for determination of ORPH in presence of its degradation product (ORPH Deg) using methanol as a solvent. ORPH was determined by dividing the absorption spectra of different concentration of it, in the range of $4 - 30$ μg mL^{-1} by the absorption of 15 μg mL^{-1} of ORPH Deg. The obtained ratio spectra were differentiated with respect to wavelength and the DD^1 values at 263 nm were recorded. The proposed method was successfully applied for determination of ORPH in Norflex tablets ® and Norflex® ampoules. The results obtained by applying the proposed method were statistically

compared to those obtained by applying the official HPLC method and there was no significant difference regarding accuracy and precision.

Section (C): Determination of Orphenadrine Citrate in presence of Its Degradation Product by Multivariate Calibration Methods.

Multivariate calibration models, such as PCR and PLS have been applied as stability indicating methods for determination of ORPH in presence of its degradation product. Training set of 17 mixtures containing different ratios of ORPH and ORPH Deg was used for construction of the two models. Satisfactory results were obtained on applying the proposed methods for the analysis of ORPH in Norflex tablets® and Norflex® ampoules.

Section D: Spectrophotometric Determination of Orphenadrine Citrate in Presence of Its Degradation Product using 7,7,8,8-tetracyanoquinodimethane (TCNQ) Reagent.

A simple and sensitive spectrophotometric method was suggested for the analysis of ORPH in the presence of ORPH Deg; the method is based on the reaction of ORPH with TCNQ to form a highly stable colored product, the formed color can be determined by measuring the amplitude at 745 nm and can be used for quantitative determination of ORPH in the concentration range of 5 – 50 µg mL^{-1}, on the other hand, ORPH Deg did not interact with TCNQ, due to lack of nitrogen atom. The method was successfully applied for determination of ORPH in Norflex tablets®.

Section E: Determination of Orphenadrine Citrate in Presence of Its Degradation product by HPTLC- Densitometric Method.

In this section HPTLC-Densitometric method was developed by separating ORPH from its degradation product successfully and efficiently using chloroform: ethyl acetate: ammonia (8: 2: 0.15, by volume) as a mobile phase. The separated bands of ORPH were scanned at 215 nm in the range of 0.5 – 3 µg $band^{-1}$. The proposed HPTLC-Densitometric

method was applied successfully for determination of ORPH in its pharmaceutical formulations.

Part II: Quantitative Determination of Naphazoline Hydrochloride and Chlorpheniramine Maleate in their Binary Mixture and in Presence of Naphazoline Hydrochloride Degradation Product.

This part includes five sections:

Section (A): Introduction and literature Review

This section includes literature review about chemical structure, physical properties and pharmacology of Naphazoline Hydrochloride (NAP) and Chlorpheniramine Maleate (CLO), it also includes review of methods of analysis developed for their determination in their single formulation, in binary mixture and in pharmaceutical formulations.

Section B: Determination of Naphazoline Hydrochloride and Chlorpheniramine Maleate in Presence of Naphazoline Hydrochloride Degradation product by Fourth Derivative (D^4) and Second Derivative Ratio (DD^2) Spectrophotometry.

This section includes two spectrophotometric methods for determination of NAP and CLO in their binary mixture in presence of Naphazoline Hydrochloride degradation product (NAP Deg). The developed spectrophotometric methods include fourth derivative (D^4) and second derivative ratio (DD^2) methods. The fourth derivative amplitudes at 302 nm were used for determination of NAP concentrations, while second derivative ratio amplitudes at 276.4 nm were used for determination of CLO concentrations. The suggested methods have been applied for determination of the cited drugs in Prisoline® Eye / Nose drops, Neozoline® eye / Nose drops and Nostamine® eye / Nose drops. The results obtained were statistically compared with that obtained by reported spectrophotometric one indicating no significant difference between them.

Section C: Simultaneous Determination of Naphazoline Hydrochloride and Chlorpheniramine Maleate in Presence of Naphazoline Hydrochloride Degradation product by Multivariate Calibration Methods.

In this section, PLS and PCR models have been successfully applied as selective stability indicating methods for determination of ternary mixture of NAP, CLO and NAP Deg.

To validate the predictive ability of the developed models, they were applied to predict the concentrations of NAP, CLO and NAP Deg in the validation set.

The investigated chemometric methods were successfully applied for the determination of NAP and CLO in Neozoline® eye / Nose drops and Nostamine® eye / Nose drops, with good percentage recovery and good agreement with the labeled amounts. The results obtained by applying the developed models showed no significant difference when compared to those obtained by applying the reported spectrophotometric one.

Section D: Simultaneous Determination of Naphazoline Hydrochloride and Chlorpheniramine Maleate in Presence of Naphazoline Hydrochloride Degradation product by TLC-Densitometry.

In this section HPTLC-Densitometric method was developed by separating the ternary mixture of NAP, CLO and NAP Deg successfully and efficiently using ethylacetate : methanol: ammonia (8: 2: 0.5, by volume) as a mobile phase. The separated bands were scanned at 254 nm in the range of 0.5 – 4.5 μg $band^{-1}$, 0.5– 4 μg $band^{-1}$, and 0.6 – 1.8 μg $band^{-1}$ for NAP, CLO and NAP Deg, respectively. The proposed HPTLC-Densitometric method was applied successfully for determination of both drugs in their pharmaceutical formulations.

Section E: Simultaneous Determination of Naphazoline Hydrochloride and Chlorpheniramine Maleate in Presence of Naphazoline Hydrochloride Degradation product by HPLC Method.

In this section, an accurate and selective HPLC method has been investigated and validated for quantitative analysis of NAP, CLO and NAP Deg in their ternary mixture. In this method, an isocratic elution of the three components was performed at ambient temperature on C_{18} column with a mobile phase consisting of 0.1 M KH_2PO_4 (pH= 7): methanol (55: 45 v/v). The mobile phase was delivered at a constant flow rate 1.5 mL min^{-1}, and the effluent was UV- detected at 265 nm.

By applying the suggested HPLC method, NAP, CLO and NAP Deg could be quantified in the range of 5- 37, 5- 50 and 5- 35 μg mL^{-1} for NAP, CLO and NAP Deg, respectively.

Statistical comparison of the results obtained by the proposed method and the reported spectrophotometric one, for the analysis of NAP and CLO was carried out. The values of calculated t and F are less than the tabulated ones, which reveals that there is no significant difference between the two methods with respect to accuracy and precision.

Part III: Simultaneous Determination of Naphazoline Hydrochloride, Chlorpheniramine Maleate and Methylene Blue in Their Ternary Mixture.

This part includes four sections:

Section (A): Introduction and literature Review

This section includes literature review about chemical structure, physical properties and pharmacology of Naphazoline Hydrochloride (NAP) and Chlorpheniramine Maleate (CLO) and Methylene Blue (MB). It also includes review of methods of analysis developed for determination of the cited drugs in their single formulation and in mixture with other drugs.

Section B: Determination of Naphazoline Hydrochloride, Chlorpheniramine Maleate and Methylene Blue by Second Derivative (D^2) and Second Derivative Ratio (DD^2) Spectrophotometry.

In this section, derivative spectrophotometric technique was used, for determination of NAP, CLO and MB in their ternary mixture and in presence of methylparaben that found as an additive in the pharmaceutical formulation. NAP and MB could be determined by D^2 method by measuring the peak amplitude at 299 nm and 337.4 nm for NAP and MB, respectively, while DD^2 was used to determine CLO by measuring the peak amplitude at 276.6 nm, using methanol as a blank. The proposed methods were successfully applied for determination of the suggested drugs in Prisoline Blue® Eye drops; satisfactory results were obtained for the three cited drugs and were in good agreement with the labeled amounts. The results obtained by the proposed methods for the analysis of pure NAP, MB and CLO were compared to the reported spectrophotometric methods, they showed no significant difference regarding accuracy and precision.

Section C: Simultaneous Determination of Naphazoline Hydrochloride, Chlorpheniramine Maleate and Methylene Blue in Their Ternary Mixture by a Multivariate Calibration Method.

In this section, PLS model has been successfully applied for determination of the ternary mixture of NAP, CLO and MB. Training set of 25 mixtures containing different ratios of NAP, CLO and MB was used for construction of the model; satisfactory results were obtained on applying the proposed methods for the analysis of the three cited drugs in their commercial formulation.

Section D: Simultaneous Determination of Naphazoline Hydrochloride, Chlorpheniramine Maleate and Methylene Blue in Their Ternary Mixture by TLC-Densitometry.

In this section HPTLC-Densitometric method was developed by separating the ternary mixture of NAP, CLO and MB successfully and efficiently using ethyl acetate: methanol: ammonia: Sodium lauryl sulphate (8.8: 1.2:

0.35: 0.15, v/v/v/w) as a mobile phase. The separated bands were scanned at 265 nm in the range of 0.5 – 4.5 μg band^{-1}, 0.5– 5 μg band^{-1}, and 0.1 – 1 μg band^{-1} for NAP, CLO and MB, respectively. The proposed HPTLC-Densitometric method was applied successfully for determination of the three cited drugs in their commercial formulation, in the presence of methylparaben. When results obtained by applying the proposed method for the analysis of pure NAP, CLO and MB were compared to those obtained by the reported spectrophotometric methods, no significant difference was observed.

Part IV: Appendix

This part includes a brief idea about the instruments, solvents and chemicals used in other parts, in addition to detailed preparation of the standard solutions used in each part through this work.

This thesis refers to 102 references, contains 58 tables, 77 figures and ends with an Arabic summary.