Summary

This thesis consists of four parts in addition to 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: DETERMINATION OF EZETIMIBE, ATORVASTATIN CALCIUM AND/OR SIMVASTATIN IN THEIR BINARY MIXTURES AND IN DIFFERENT PHARMACEUTICAL FORMULATIONS

This part includes five sections.

Section (A): Introduction and literature Review

This section includes an introduction about the pharmacological action of Ezetimibe (EZ), Atorvastatin Calcium (ATR) and Simvastatin (SIM), their chemical structure, physical properties and summary of the methods reported for their analysis in their formulations and in their binary mixture.

Section (B): Determination of Ezetimibe and Atorvastatin Calcium by Dual Wavelength Spectrophotometric Method

In this section, Dual wavelength method has been applied for determination of EZ and ATR in their binary mixture using methanol as a solvent. EZ concentrations were determined by measuring the absorbance difference at 228.6 nm and 262.8 nm. While ATR concentrations were determined by measuring the absorbance difference at 226.6 nm and 244 nm. The developed method has been applied for determination of the studied drugs in different laboratory prepared mixtures. The results obtained by applying the proposed method for determination of pure EZ and ATR and on dosage form were statistically compared to those obtained by a reported RP-HPLC method and no significance difference was found regarding both accuracy and precision.

Section (C): Determination of Ezetimibe and Atorvastatin Calcium by Mean Centering of Ratio Spectra Spectrophotometric Method

In this method, the mean centered ratio spectra amplitudes at 215 and 260 nm were used for quantitation of both EZ and ATR. The suggested method has been applied for determination of EZ and ATR in their pure form and in their pharmaceutical preparations. Statistical comparison with the reported RP-HPLC Method showed no significant difference.

Section (D): Determination of Ezetimibe in combination with Atorvastatin calcium or Simvastatin by Multivariate Calibration Method

Multivariate calibration models, such as PCR and PLS have been successfully applied for determination of EZ and ATR, the developed PLS model was updated for determination of EZ and SIM in their combined dosage forms.

To validate the predictive ability of the developed models, they were applied to predict the concentrations of EZ and ATR in an external validation set. Statistical analysis of the results obtained by the developed models were compared with those of the reported RP-HPLC methods, no significant difference was found, within probability of 95 % regarding both accuracy and precision.

Section (E): Determination of Ezetimibe in combination with Atorvastatin Calcium or Simvastatin by TLC-Densitometric Method

The developed TLC-Densitometric method depended on chromatographic separation of EZ, ATR and SIM using ethyl acetate: hexane: glacial acetic acid (5.5: 4.5: 0.1, by volume) as a mobile phase. The separated bands were scanned at 254 nm in the range of 0.4-4, 0.4-3.1 and 5-2.3µg band^{-1} for EZ, ATR and SIM, respectively. The Proposed TLC-Densitometric method was applied successfully for determination of EZ, ATR and SIM in their pharmaceutical formulations

Part II: DETERMINATION OF CHLORZOXAZONE IN BINARY MIXTURES WITH KETOPROFEN OR IBUPROFEN IN PRESENCE OF 2-AMINO-4-CHLOROPHENOL

This part includes five sections.

Section (A): Introduction and literature Review

This section includes an introduction about the pharmacological action of Chlorzoxazone (CLZ), Ketoprofen (KT) and Ibuprofen (IBU), their chemical structure, physical properties and summary of the methods developed for their analysis in their formulations and in their binary mixture. At the end of this section MS and IR spectra of the prepared CLZ-Deg have been illustrated for the identification of the prepared degradation product.

Section B: Determination of Chlorzoxazone in Binary Mixtures with Ketoprofen or Ibuprofen in Presence of 2-Amino-4chlorophenol by Derivative and Ratio Derivative Spectrophotometric Methods

In this section, the first derivative of ratio spectra (^{1}DD) and first derivative spectrophotometric methods (^{1}D) have been applied to improve selectivity for determination of CLZ, KT and IBU in presence of CLZ degradation product (ACP) using methanol as a solvent. CLZ and KT (mixture 1) were determined by dividing the absorption spectra of different concentration of them, in the range of 4 – 23 and 4-26 μg mL^{-1} by standard spectrum of 10 μg mL^{-1} of ACP. The amplitudes at 264.4 nm and 274.6 nm were measured for CLZ and KT, respectively. On the other hand ACP in this mixture was determined by dividing the absorption spectra of its different concentrations, in the range of 1 – 10 μg mL^{-1} by the standard spectrum of 8 μg mL^{-1} of KT and the amplitudes at 316.6 nm was measured.

For CLZ/ IBU/ ACP mixture to determine CLZ and IBU ^{1}DD spectra were obtained using the standard spectrum of 10 μg mL^{-1} of ACP as a divisor. The amplitudes at 264.4 nm and 228 nm were measured for CLZ and IBU,

respectively. ACP in this mixture was determined by performing ^{1}D method, measuring the amplitudes at 310 nm. The results obtained by applying the proposed methods were statistically compared with those obtained by applying the reported RP-HPLC methods and there was no significant difference regarding accuracy and precision.

Section C: Determination of Chlorzoxazone in Binary Mixtures with Ketoprofen or Ibuprofen in Presence of 2-Amino-4-chlorphenol by Multivariate Calibration Methods With Application of Model Updating

Multivariate calibration models, such as PCR and PLS have been applied as stability indicating methods for determination of CLZ, KT in presence of CLZ degradation product, and the developed PLS model has been updated to determine of CLZ and IBU in their dosage forms. Training set of 17 mixtures containing different ratios of CLZ, KT and ACP was used for construction of the two models. Satisfactory results were obtained on applying the proposed methods for the analysis of CLZ/ KT and CLZ/ IBU in Flexofan® , Markfast®, Myofen® and Profenazone® capsules,

Section D: Determination of Chlorzoxazone in Binary Mixtures with Ketoprofen or Ibuprofen in Presence of 2-Amino-4-chlorphenol by TLC-Densitometric Method

This section is concerned with the development of sensitive, economic and specific stability indicating TLC-Densitometric method for determination of CLZ/ KT and CLZ/ IBU in their bulk powder and pharmaceutical formulations as well as in the presence of the degradation product of CLZ. The four studied components were well separated using acetone: chloroform: methanol: ammonia (7.5: 2.5: 0.5: 0.4, by volume) as a developing system and the sparated bands were scanned at 215 nm.

Linear relationships were obtained in the concentration ranges of 1-10, 0.5-3.7, 0.2-2.9 and 0.4-2.5 μg band^{-1} for CLZ, KT,, IBU and ACP , respectively.

The developed TLC-Densitometric method has been applied for determination of the studied drugs in their commercial capsules.

Section E: Determination of Chlorzoxazone in Binary Mixtures with Ketoprofen or Ibuprofen in Presence of 2-Amino-4-chlorphenol by RP-HPLC Method

In this section, an accurate and selective RP-HPLC method has been investigated and validated for quantitative analysis of CLZ, KT and IBU in their binary mixture and in the presence of CLZ degradation product. In this method, an isocratic elution of the four components was performed at ambient temperature on C_{18} column with a mobile phase consisting of acetonitrile: water: trifluroracetic acid (60: 40: 1, by volume pH 7.5 adjusted with sodium hydroxide) at flow rate of 1.5 mL/min. and the detection was performed at 225 nm.

Statistical comparison of the results obtained by the proposed method and the reported RP-HPLC method showed no significant difference. The proposed RP-HPLC method has the advantage over the reported RP-HPLC methods of being able to separate and determine the four studied components in short analysis time using one mobile phase and detection wavelength.

Part III: STABILITY INDICATING ANALYTICAL METHODS FOR DETERMINATION OF CHLORPROPAMIDE

This part includes five sections.

Section (A): Introduction and literature Review

This section includes an introduction about the pharmacological action of Chlorpropamide (CLP), its chemical structure, physical properties and summary of the published methods developed for its analysis in pure form and in its tablets. Moreover it contains schematic diagram of the degradation pathway of CLP and structural illucidation of the prepared degradate.

Section B: Stability Indicating Isoabsorptive Point Spectrophotometric Method for Determination of Chlorpropamide

In this section, isoabsorptive spectrophotometry (ISO) and second derivative (^{2}D) methods have been applied for determination of CLP and CLP degradation product in their binary mixture using 0.1 N HCl as a solvent. The absorbance value at the isoabsorptive point (λ 236.6 nm) was used for calculating the total mixture concentration, on the other hand CLP degradation product concentration could be selectively determined using ^{2}D amplitudes at 242.8 nm, by subtraction CLP content in the mixture could be determined.

The developed methods have been applied for determination of the studied components in different laboratory prepared mixtures also applied for determination of CLP in Pamidin® tablets. The results obtained by applying the proposed method for determination of CLP were statistically compared to those obtained by applying the reported RP-HPLC and no significant difference were found regarding both accuracy and precision.

Section C: Stability Indicating Q-Analysis Spectrophotometric Method for Determination of Chlorpropamide

In this section, Q-analysis spectrophotometric method was developed for determination of CLP in the presence of its degradation product. The developed Q-analysis method for determination of CLP was based on using two wavelengths, one at the isoabsorptive point (236.6 nm) and the other being the λ max of CLP (232.8 nm).

The proposed method was validated with different laboratory prepared mixtures and it was successfully applied for determination of CLP in Pamidin® tablets and the standard addition technique has been applied to verify its validity.

Section D: Stability Indicating Mean Centering of Ratio Spectra Spectrophotometric Method for Determination of Chlorpropamide

In this method, CLP was determined by measuring the amplitudes of the mean centered ratio spectra at 203.6 and 227.6 nm (peak to peak) for CLP using the standard spectrum of 27 μg mL^{-1} of CLP degradation product as a divisor. While the amplitudes at 203.6 and229.6 nm (peak to peak) was used for determination of CLP degradation product using 29 μg mL^{-1} of CLP as a divisor. The proposed method was used for quantitation of CLP in Pamidin ® tablets and the results of the standard addition technique confirmed that tablets additive did not interfere.

Section E: Stability Indicating TLC-Densitometrc Method for Determination of Chlorpropamide

This method depended on TLC-Densitometric separation of the binary mixture of CLP and CLP degradation product using chloroform: ethyl acetate: triethylamine: glacial acetic acid (7:3:0.3:0.1, by volume) as a developing system. The separated bands were scanned at 230 nm in the range of 0.5 – 3.2 μg $band^{-1}$, 0.2– 2.4 μg $band^{-1}$, and for CLP and CLP degradation product, respectively. Statistical comparison of the results obtained by the proposed TLC-Densitometric method and those obtained by the reported RP-HPLC one. The of t and F values are less than the tabulated values indicating no significant difference between them.

Part V: Appendix

This part includes a brief idea about the instruments, solvents and chemicals used throughout the whole work. In addition to the detailed preparation of the solutions used in each part and also methods for preparation of CLZ and CLP degradation products.

This thesis refers to 187 references, contains 80 tables, 70 figures and ends with an Arabic summary.