Summary

This thesis consisted of three parts in addition to references and an Arabic summary. Each part included; an introduction, literature review, experimental work for the studied components, results, discussion and ended with a conclusion.

PART I: STABILITY INDICATING METHODS FOR DETERMINATION OF OLMESARTAN MEDOXOMIL, HYDROCHLOROTHIAZIDE, AND THEIR DEGRADATION PRODUCTS

This part included three sections.

SECTION A: Introduction and Literature Review

This section included an introduction about the pharmacological action of olmesartan medoxomil (OLM), hydrochlorothiazide (HCZ), and their degradtion products; olmesartan (OL), and salamide (SAL). It also included their chemical structure, physical properties, and summary of the methods published for the analysis of the cited drugs in their formulations and in their binary mixture. Additionally, stability of OLM was illustrated in this section, as well as separation and structure elucidation of OL.

SECTION B: Chemometric Assisted Spectrophotometric Methods for Determination of Olmesartan Medoxomil, Hydrochlorothiazide and Their Degradation Products

In this section, multivariate calibration methods; PLS and PCR had been applied for determination of OLM, HCZ, OL, and SAL in their quaternary mixture using ethanol as a solvent. The used spectral range was 210-343. Training set of 15 mixtures containing different ratios of the mentioned components was used for the construction of these two models. The specificity of the proposed models was checked using laboratory prepared mixtures (external validation set of ten mixtures). Satisfactory results were obtained on applying the proposed methods for the analysis of OLM and HCZ in Erastapex plus®, Angiosartan plus®, and Medosartan® tablets.

SECTION C: Thin Layer Chromatographic Method for Determination of Olmesartan Medoxomil, Hydrochlorothiazide and Their Degradation Products

In this section, TLC-densitometric method had been developed for estimation of OLM, HCZ, OL, and SAL in their quaternary mixture. The chromatographic separation was obtained using ethyl acetate: chloroform: methanol: formic acid: tri-ethylamine solution (6: 4: 0.4: 0.4: 0.1, by volume) as a mobile phase. The separated bands were scanned at 254 nm. The suitability of the proposed chromatographic

methods was ensured by the determination of system suitability testing parameters of the separated drugs. The developed method compared favorably with the reported method.

PART II: QUANTITATIVE DETERMINATION OF FOSINOPRIL SODIUM, HYDROCHLOROTHIAZIDE, AND HYDROCHLOROTHIAZIDE SYNTHETIC PRECURSOR

This part included four sections.

SECTION A: Introduction and Literature Review

This section included an introduction about the pharmacological action of fosinopril sodium (FOS), hydrochlorothiazide (HCZ), and hydrochlorothiazide starting material; Chlorothiazide (CZ), their chemical structure, physical properties, and summary of the methods reported for the analysis of the cited drugs in their formulations and in their binary mixture.

SECTION B: Different Spectrophotometric Methods for Determination of Fosinopril Sodium, Hydrochlorothiazide, and Hydrochlorothiazide Synthetic Precursor

In this section, different spectrophotometric methods had been applied including; ratio difference and mean center of ratio spectra methods using methanol as a solvent. The first method depended on measuring the amplitude difference between (204.6 and 231.2 nm) and (290 and 302.6 nm) for determination of FOS and CZ, respectively. While the difference between 275 and 293.6 nm was selected for estimation of HCZ. The second method was mean centering of ratio spectra spectrophotometric method, in this method FOS, HCZ and CZ can be determined using the mean centered second ratio spectra amplitudes at 215.6 and 215.8 nm (peak to peak), 223.8 and 224 nm (peak to peak) and 243.4 nm, respectively. The results obtained by applying the proposed methods were statistically compared with those obtained by applying the reported HPLC method and there was no significant difference regarding accuracy and precision.

SECTION C: Thin Layer Chromatographic Method for Determination of Fosinopril Sodium, Hydrochlorothiazide, and Hydrochlorothiazide Synthetic Precursor

This section was concerned with the development of sensitive, rapid, and specific TLC-densitometric for determination of the ternary mixture of FOS, HCZ, and CZ in the bulk powder and laboratory prepared mixtures. The three studied components were well separated using ethyl acetate: chloroform: methanol: formic acid (6: 4: 0.5: 0.05, by volume) as a developing system followed by densitometric measurement of the separated bands at 215 nm. This developed chromatographic method had been

applied for determination of the cited drugs in their commercial pharmaceutical formulations. Statistical comparison of the results obtained by the proposed methods and the published HPLC method showed no significant difference.

SECTION D: High Performance Liquid Chromatographic Method for Simultaneous Determination of Two Mixtures Containing Hydrochlorothiazide, Their Impurities, and Degradation Products

In this section, sensitive, selective, accurate, and rapid high performance liquid chromatographic method was developed for simultaneous determination of HCZ, OLM, FOS, OL, SAL, and CZ. Chromatographic separation was achieved in gradient elution mode using stationary phase of a Hidrosorb RP- C_{18} and mobile phase mixture consisted of; solvent (A) 0.05 M KH_2PO_4 solution pH 3 adjusted with O-phosphoric acid, solvent (B) acetonitrile and solvent (C) methanol. The temperature was adjusted to 35 °C and the pump pressure was 215 bars. The effluent was UV detected at 205 nm for FOS only and 225 nm for the rest of the cited components. The full chromatographic run time was 15 min. This method was used for quantitation of all the cited components in short analysis time and it compared favorably with the reported HPLC methods.

PART III: SIMULTANEOUS DETERMINATION OF BROMHEXINE HYDROCHLORIDE AND ITS MAIN IMPURITIES

This part included three sections.

SECTION A: Introduction and Literature Review

This section included an introduction about the pharmacological action of bromhexine hydrochloride (BHX) and its two main impurities; Impurity B (IMB) and impurity C (IMC), their chemical structure, physical properties, and summary of the published methods developed for the analysis of mentioned drug in pure form and in its pharmaceutical formulation.

SECTION B: Different Spectrophotometric Methods for Determination of Bromhexine Hydrochloride and Its Main Impurities

In this section, three different spectrophotometric methods were developed for determination of IMB, BHX, and IMC in their ternary synthetic mixture namely; direct spectrophotometry coupled with first derivative of ratio spectra spectrophotometric method (°D-^{1}DD), plateau amplitude coupled with ratio difference method (PA-RD), and area under the curve method (AUC). **In the first method** direct spectrophotometry coupled with first derivative of ratio spectra spectrophotometric method, for measuring IMB, its absorbance at 389 nm was measured while for determination of BHX and IMC,

their pure samples stored spectra were divided by the standard spectrum of 12.00 µg mL^{-1} of IMB. Then, ^{1}DD spectra for the obtained ratio spectra of BHX and IMC were carried out using $\Delta\lambda$ = 16 nm, scaling factor = 100. The peak amplitudes at 268 nm and 259 nm were measured for determination of BHX and IMC, respectively. **In the second method** plateau amplitude coupled with ratio difference method, the stored spectra of IMB, BHX, and IMC pure samples were divided by the standard spectrum of 12.00 µg mL^{-1} of IMB. Then for IMB determination, the amplitudes of the plateau at 380 nm were obtained and used for construction of its calibration curve. On the other hand, BHX and IMC were determined by measuring the ratio difference between (220.6 and 282.4 nm), and (210 and 229.8 nm) for BHX and IMC, respectively. **Finally the third method** area under the curve method, The stored spectra of IMC, BHX, and IMB were used for calculating the area under the curve using the ranges of 205-215 (λ_1-λ_2), 217-230 nm (λ_3-λ_4), and 235-250 nm (λ_5-λ_6). The absorptivity values (a) for each component at the selected area were calculated, a= (peak area at selected wavelength range divided by concentration of the analyte). Then, the concentrations of each component were obtained by applying Cramer's rule. The developed methods were successfully applied for analysis of BHX in its dosage form without interference from additives. Additionally, statistical analysis with the reported method showed no significant difference.

SECTION C: Different Liquid Chromatographic Methods for Determination of Bromhexine Hydrochloride and Its Main Impurities

TLC-densitometeric method was performed using pre-coated silica gel TLC aluminum plates (10×20 cm). Linear ascending development was allowed in glass tank saturated with a developing system mixture consisted of hexane: acetone: ammonia solution (9: 0.5: 0.08, by volume) at room temperature. UV scanning was done at 240 nm. Linearity was achieved in the ranges of (0.40-10.00), (0.20-2.00), and (0.20-2.00) µg/band of BHX, IMB, and IMC, respectively.

In the developed high performance liquid chromatographic method (HPLC), the chromatographic separation was performed on a Bridge C_{18} column (250 mm × 4.6 id, 5 µm particle size) and the developing system was methanol: water (pH adjusted to 2.5 using O-phosphoric acid) in the ratio of (90: 10, v/v). The effluent was UV detected at 240 nm. Linearity of this method was achieved in the ranges of (4.00–40.00), (0.20-10.00), and (0.50-10.00) µg mL^{-1} for BHX, IMB, and IMC, respectively. The developed chromatographic methods were successfully applied for analysis of BHX in its available dosage form without interference from additives. Additionally, statistical analysis with the reported method showed no significant difference.

This thesis referred to **411** references, contained **73** tables, **64** figures and ended with Arabic summary.