Summary

The thesis represents an analytical study on some drugs acting on cardiovascular system; the selected drugs are Amlodipine besylate, Atorvastatin calcium, Valsartan and Hydrochlorothiazide. The aim of this thesis was to develop new simple, accurate and sensitive methods for analysis of these drugs in their mixtures or in presence of their degradation products. The methods were applied on dosage forms and compared with the reported methods.

This thesis includes seven parts:

PART I: General Introduction and Literature Review

In this part, introduction about cardiovascular system was introduced. Also the pharmacological properties, chemical structures and literature review on different methods of analysis for the studied drugs were discussed.

PART II: Simultaneous Determination of Amlodipine and Atorvastatin by Spectrophotometric Methods

This part includes four sections:

Section A: ***Simultaneous Determination of Amlodipine and Atorvastatin by Spectrophotometric Methods Manipulating Ratio Spectra***

In this section, four different methods were applied manipulating the ratio spectra for removal of the constant. The four methods are:

1) Derivative Ratio method
2) Mean Centering method
3) Ratio Difference method
4) Ratio Subtraction and zero order methods

Section B: ***Simultaneous Determination of Amlodipine and Atorvastatin by Spectrophotometric Methods Depending on Isoabsorptive Point***

In this section, two spectrophotometric methods which depend on the existence of an isoabsorptive point were described. The methods are:

1) Isoabsorptive Point and Zero order methods
2) Absorbance Ratio method

Section C: ***Simultaneous Determination of Amlodipine and Atorvastatin by H-Point Standard Addition Method***

This section depends on the principle of dual wavelength spectrophotometry and the standard addition method. For determination of Amlodipine, the two wavelengths chosen were 241 and 252.4 nm, while for Atorvastatin they were 278.0 and 305.6 nm.

Section D: ***Simultaneous Determination of Amlodipine and Atorvastatin by the Bivariate Method***

This section includes determination of Amlodipine and Atorvastatin using the bivariate method. The sensitivity matrices suggested that 238 and 266 nm were the optimal wavelengths for the determination of Amlodipine and Atorvastatin using the corresponding equations.

PART III: Stability Indicating Chemometric Methods for Simultaneous Determination of Amlodipine and Atorvastatin

This part includes three sections:

Section A: ***Preparation of Degradation Products***

In this section, the conditions required for the degradation of Amlodipine and Atorvastatin were studied, then the degradation products were isolated and their structures were confirmed using IR spectrophotometry and mass spectrometry.

Section B: ***Stability Indicating Partial Least Squares (PLS-1) and Genetic Algorithm Based Wavelength Selection-Partial Least Squares (GA-PLS) Methods for Simultaneous Determination of Amlodipine and Atorvastatin***

In this section, two chemometric techniques namely Partial Least Squares (PLS-1) and Genetic Algorithm based wavelength selection–Partial Least Squares (GA-PLS) multivariate methods were used for the determination of Amlodipine and Atorvastatin. Spectral data were subjected to pretreatment, followed by the construction of the models using a calibration set composed of 15 laboratory prepared mixtures containing different concentrations of Amlodipine and Atorvastatin. Further validation of the data was done using a validation set composed of 10 mixtures.

Section C: ***Stability Indicating Artificial Neural Network (ANN) Method for Simultaneous Determination of Amlodipine and Atorvastatin***

In this section the artificial neural network (ANN) method was used for the determination of Amlodipine and Atorvastatin. Raw spectral data and selected data by GA model were subjected to pretreatment, followed by the construction of the networks using a calibration set composed of 15 laboratory prepared mixtures and validation set composed of 10 mixtures containing different concentrations of Amlodipine and Atorvastatin.

PART IV: Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Spectrophotometric Methods

This part includes three sections:

Section A: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Derivative Ratio Spectra Zero Crossing Method***

The spectra of the mixtures were divided by the spectrum of one of the drugs then the first derivative of the ratio spectra were obtained to determine a second drug at the zero crossing point with the third one. It depends on measuring the peak amplitude of the first derivative of ratio spectra at 377.8 nm for determination of Amlodipine, at 283.0 nm for determination of Valsartan and at 267.4 nm for determination of Hydrochlorothiazide.

Section B: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Double Divisor Ratio Spectra Method***

The spectra of the mixtures were divided by the sum of spectra of two drugs and first derivative of these ratio spectra were calculated to determine the third drug concentration. The peak amplitudes at 373.2, 275.4 and 285.6 nm were used for determination of Amlodipine, Valsartan and Hydrochlorothiazide, respectively.

Section C: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Ratio Subtraction, Isoabsorptive Point and Zero Order Methods***

It depends on measuring the peak of the zero order spectra at 359.4 nm for determination of Amlodipine. Then after applying the ratio subtraction method Hydrochlorothiazide was measured at 316.4 nm. The total concentration of Hydrochlorothiazide and Valsartan could be

determined at the isoabsorptive point 256.8nm, and then Hydrochlorothiazide concentration was subtracted to get Valsartan concentration.

PART V: Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Chemometric Methods

Section A: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Principal Component Regression (PCR) and Partial Least Squares (PLS) Methods***

In this section the PCR and the PLS multivariate methods were used for the determination of Amlodipine, Valsartan and Hydrochlorothiazide. Spectral data was subjected to pretreatment, followed by the construction of the models using a calibration set composed of 15 laboratory prepared mixtures composed of different concentrations of the drugs. Further validation of the data was done using a validation set composed of 10 mixtures.

Section B: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Partial Least Squares (PLS-1) and Genetic Algorithm Based Wavelength Selection-Partial Least Squares (GA-PLS) Methods***

In this section PLS-1 and GA-PLS methods were used for the determination of Amlodipine, Valsartan and Hydrochlorothiazide. Spectral data was subjected to pretreatment, followed by the construction of the models using a calibration set composed of 15 mixtures composed of different concentrations of the drugs. In PLS the model was constructed using the whole spectra, while in GA-PLS model was constructed using the wavelengths selected by the GA procedure. Further validation of the data was done using a validation set composed of 10 mixtures.

Section C: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Artificial Neural Network (ANN) Method***

In this section ANN method was used for the determination of Amlodipine, Valsartan and Hydrochlorothiazide. Raw spectral data and selected data by GA were subjected to pretreatment, followed by the construction of the networks using a calibration set composed of 15 laboratory prepared mixtures and validation set composed of 10 mixtures composed of different concentrations of the three drugs.

PART VI: Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by Chromatographic Methods

Section A: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by HPLC with On-Line Wavelength Switching Method***

This section was concerned with application of HPLC for the determination of Amlodipine, Valsartan and Hydrochlorothiazide. Separation by HPLC was achieved using a Nucleosil C_{18} column and a mobile phase consisting of acetonitrile/methanol/isopropyl alcohol (55:41:4 by volume), pH was adjusted to 8 ± 0.1 with triethylamine at a flow rate of 1.2 mL/min. The detection wavelength was switched on-line between 238, 248 and 271 nm for Amlodipine, Valsartan and Hydrochlorothiazide, respectively.

Section B: ***Simultaneous Determination of Amlodipine, Valsartan and Hydrochlorothiazide by TLC-Densitometric Method***

In this section, densitometry technique was used for the determination of Amlodipine, Valsartan and Hydrochlorothiazide without previous separation using ethyl acetate/toluene/methanol/ammonia (50.5:23.5:23.5:2.5 by volume) as a developing solvent. Detection and quantification were performed densitometrically at 252 nm.

All the proposed methods were successfully applied for the determination of drugs under investigation in their laboratory prepared mixtures and pharmaceutical dosage forms. Statistical studies were done showing no significant difference in comparison with the reported methods.

PART VII: Appendices

This part includes instruments, reagents, samples and solutions.

This thesis contains 63 tables, 90 figures and 203 references.