ANALYTICAL STUDY OF SOME DRUGS AFFECTING NERVOUS SYSTEM

Presented by

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ABSTRACT

The thesis comprises four parts:

PART I: GENERAL INTRODUCTION

This part includes a brief idea about classification and mechanism of action of drugs affecting central nervous system.

PART II : STABILITY INDICATING METHODS FOR DETERMINATION OF TIAPRIDE IN PURE FORM, PHARMACEUTICAL PREPARATION AND HUMAN PLASMA.

This part includes a general introduction about the chemistry and mode of action of Tiapride, followed by presentation of the reported methods used for its quantitative analysis. Experimental, results and discussion are also given.

This part contains four sections:

Section (A): Second Derivative Spectrophotometric Method.

D_2 spectrophotometric method at 253.4 nm is suggested for determination of Tiapride without interference from its degradation products using acid hydrolysis. The sensitivity range is1.5-9 $\mu g.ml^{-1}$ with mean percentage recovery 99.96 ±1.381%.

The selectivity of the suggested method was checked by using different laboratory prepared mixtures. It was successfully applied to the analysis of Tiapride in pharmaceutical preparation and its validity was further assessed by applying the standard addition technique.

Section (B): First Derivative of Ratio Spectra Method.

This method is based on the simultaneous use of the first derivative of the ratio spectra (^{1}DD) with measurements at 245 nm using the spectrum of 8µg ml^{-1} of the first degradate (I) as a divisor over a concentration range 1.5-9µg.ml^{-1} with mean percentage recovery 99.64 ±1.082%.

The suggested method is selectively determined Tiapride in laboratory prepared mixtures. It was successfully applied to pharmaceutical preparation containing Tiapride, where acceptable results were obtained.

Application of standard addition technique assessed the validity of this method.

Section (C): Spectrofluorimetric Method.

Tiapride is determined by measuring its native fluorescence in presence of its degradation products at λ_{em}= 339 nm upon excitation with λ_{ex}=230 nm over a concentration range 0.2-3 µg.ml^{-1} with mean percentage recovery 99.66 ±1.460%.

The suggested method is highly sensitive, so it can be applied for Tiapride determination in spiked human plasma with mean percentage recovery 99.69 ± 1.380%. Also it was applied for determination of Tiapride in laboratory prepared mixtures and in its pharmaceutical formulation without interference from other dosage form additives.

Section (D): Reversed Phase- High Performance Liquid Chromatographic Method.

In this section, a RP- HPLC method is applied which utilizes methanol: deionized water: triethylamine (535:465:0.8 v/v/v) as a mobile phase and Sulpiride as an internal standard, maintaining the flow rate at 1 ml min^{-1} and UV detection of the effluent at 214 nm . Two peaks were obtained for the drug at t_1=5.88 min and its degradate at t_2=1.50 min. The sensitivity range is 2-30µg. ml^{-1} with mean percentage recovery 99.66 ±0.910%.

The validity of this method as stability indicating method was checked by using laboratory prepared mixtures. Applying the standard addition technique assessed its validity.

Part III: STABILITY INDICATING METHODS FOR DETERMINATION OF ZALEPLON IN PHARMACEUTICAL PREPARATIONS AND IN PRESENCE OF ITS ACID DEGRADATE.

This part includes a general introduction about the chemistry and mode of action of Zaleplon , followed by presentation of the reported methods used for its quantitative analysis. Experimental, results and discussion are also given.

This part comprises five sections:

Section (A): Second Derivative Spectrophotometric Method.

In this section, the second derivative D_2 spectrophotometric method is applied, which allows determination of Zaleplon in presence of its degradation product using alkaline hydrolysis at 235.2 nm in the range of 1-10µg.ml^{-1} with mean percentage recovery of 100.24± 0.860%.

Selectivity of this method was checked by analyzing different laboratory prepared mixtures.

Results obtained by applying this method to the analysis of pharmaceutical preparations containing Zaleplon were statistically compared to those obtained by applying the company method and no significant difference were found between the results of the two methods regarding accuracy and precision.

Section (B): First Derivative of Ratio Spectra Spectrophotometric Method.

This method is based on the use of the first derivative of the ratio spectra (^{1}D) with measurement at 241.8 nm for determination of Zaleplon using the spectrum of the degradate as a divisor where the degradate shows no interference. The sensitivity range is1-10µg.ml^{-1} and the percentage recovery is 99.90 ±1.071%.

The suggested method selectivity was checked by its application to the analysis of laboratory prepared mixtures. The method was successfully applied to determination of Zaleplon in different pharmaceutical preparations.

Section (C): Spectrodensitometric Method.

In this method, Zaleplon is determined after separation from its degradation product on silica gel plates using chloroform: acetone: ammonia solution (9:1:0.2 v/v/v) as a mobile phase and UV detection at 338 nm over a concentration range of 0.2-1 µg. $band^{-1}$, with mean percentage recovery 99.73 +1.350% .

Applying this method to the analysis of laboratory prepared mixtures assessed the selectivity of the suggested method. Also applying the standard addition technique assessed its validity.

Section (D): Reversed Phase- High Performance Liquid Chromatographic Method.

In this section an HPLC method is used for simultaneous determination of Zaleplon in presence of its degradation product. The stationary phase used is C8 column; the mobile phase consists of acetonitrile: water (35:65 v/v) with UV detection at 232 nm and flow rate of 1.5 ml min^{-1}. Two peaks were obtained for the drug at t_1= 4.06 min and its degradate at t_2=2.50 min. The calibration range is 2-20µg.ml^{-1} with mean percentage recovery 100.19 ±1.150%.

The suggested procedure was checked using laboratory prepared mixtures and was successfully applied for the analysis of Zaleplon in capsules. The method retained its validity when applying the standard addition technique.

Section (E): Spectrofluorimetric Stability Indicating Method for Determination of Zaleplon in Pharmaceutical Preparations and Human Serum.

This section includes studying of different factors affecting the native fluorescence of Zaleplon, including the solvents, different surface active agents,

different pH values and different excitation and emission wavelengths. Also the stability of Zaleplon fluorescence intensity by time is studied.

After optimization of this method, Zaleplon is determined at λ_{em}= 422nm and λ_{em}=536nm after excitation at 230nm with percentage recovery 99.97±1.210 % and 99.62 ± 0.991% respectively.

Zaleplon was determined in presence of its alkaline degradation product using λ_{em}= 422nm and λ_{ex}=230nm with mean percentage recovery 100.53 ±1.251%.

The high sensitivity of this method allows determination of Zaleplon in human serum using acetonitrile as a solvent and λ_{em} =536nm when using λ_{ex}= 230nm with mean percentage recovery 100.28 ± 1.691%**.**

Also this method was applied for the analysis of Zaleplon in its pharmaceutical preparations and applying the standard addition technique assessed its validity.

PART IV: APPLICATION OF BIVARIATE AND MULTIVARIATE SPECTROPHOTOMETRIC METHODS FOR DETERMINATION OF PARACETAMOL AND CAFFEINE IN THEIR BINARY MIXTURES AND IN PRESENCE OF CAFFEINE OXIDATIVE DEGRADATE.

This part includes a general introduction about the chemistry and mode of action of both Paracetamol and Caffeine, followed by presentation of the reported methods used for their quantitative analysis. Experimental, results and discussion are also given.

This part comprises two sections:

Section (A): Bivariate Calibration Spectrophotometric Method.

This method allows determination of Paracetamol and Caffeine in their binary mixtures. It is based on the resolution of the two components by the bivariate calibration depending on the simple mathematic algorithm which provided simplicity and rapidity.

It is depended on the quantitative evaluation of the absorbencies at 248.4 and 272 nm over a concentration range of 2-30 µg.ml^{-1} and 1.5-25 µg.ml^{-1} of Paracetamol and Caffeine, respectively.

This method was used for determination of both drugs in laboratory prepared mixtures and different pharmaceutical preparations where satisfactory results were obtained. Applying the standard addition technique assessed the validity of the method.

<u>Section (B):</u> Multivariate Spectral Analysis Method.

Two chemometric techniques, Principle component regression (PCR) and Partial least squares (PLS) are used for simultaneous determination of the two drugs in presence of Caffeine oxidative degradate. Training set consisting of 16 mixtures containing different ratios of Paracetamol, Caffeine and the degradate is used for construction of the two models.

The selectivity of the proposed method was checked using laboratory prepared mixtures (validation set consisting of 8 mixtures). Also it was successfully applied to the analysis of the two drugs in different pharmaceutical preparations.

The validity of this method was assessed by applying the standard addition technique.

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