Beni-Suef University
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جامعة بني سويف

كلية الصيدلة

Master Thesis Summary

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"Analytical study of some drugs affecting respiratory system"

The thesis includes a general introduction about the respiratory system and the drugs affecting it. In addition it contains three parts concerning the determination of diphenhydramine hydrochloride/ menthol mixture by gas chromatography (GC); UV-spectrophotometry and colorimetry as well as doxycycline hyclate/ ambroxol hydrochloride mixture by direct ; first derivative, first derivative of ratio spectrophotometry and spectrodensitometry. Oxeladine citrate was determined in presence of its oxidative degradate α,α -diethylbenzeneacetic acid and the two preservatives methylparaben and propylparaben by second derivative spectrophotometry and multivariate manipulation of the spectrophotometric data. All these techniques where applied to the drugs in pure forms and in pharmaceutical dosage forms.

This thesis is concerned with analytical study of some drugs affecting the respiratory system representing different chemical classes namely diphenhydramine hydrochloride, menthol, doxycycline hydrochloride in the hyclate form, ambroxol hydrochloride and oxeladine citrate.

The aim of this work was the development of analytical methods which would be feasible, simple, rapid, sensitive and selective for determination of diphenhydramine hydrochloride /menthol mixture, doxycycline hydrochloride /ambroxol hydrochloride mixture and oxeladine citrate in presence of its oxidative degradate α,α -diethylbenzeneacetic acid and the two preservatives methylparaben and propylparaben in pure forms and the the adaptation of these methods to the available pharmaceutical dosage forms.

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Different analytical techniques were applied in this thesis including; direct spectrophotometry, first and second derivative spectrophotometry , first derivative of the ratio spectra, colorimetry, spectrodensitometry, gas chromatography and chemometric manipulation of the spectrophotometric data.

The aim was achieved by studying the conditions of degradation for some of these drugs and isolation of the corresponding degradation products, followed by the elucidation of their structures. The isolated degradates were subsequently used for the development of stability indicating analytical methods.

This thesis is composed of four parts:

Part I: GENERAL INTRODUCTION

This part includes a brief idea about classification pharmacology and mechanisms of actions of drugs affecting the respiratory system.

PART II: SIMULTANEOUS DETERMINATION OF DIPHENHYDRAMINE HYDROCHLORIDE AND MENTHOL IN PURE FORM AND PHARMACEUTICAL PREPARATION.

This part includes a general introduction about the chemistry and the mode of actions of diphenhydramine hydrochloride and menthol followed by representation of the reported methods for their quantitative analysis. Experimental results and discussion are also given.

This part contains three sections:

Section (A): Simultaneous Determination Of Diphenhydramine Hydrochloride And Menthol By Gas Chromatographic Method.

In this section a GC method was applied which utilizes Nitrogen as a carrier gas at a flow rate of 25 cm^3/min adjusting the column temperature programming to be (from 70 to 225◦C at a rate of 10◦C / min using a flame ionization detector adjusted at 250◦C. Two peaks were

obtained for diphenhydramine hydrochloride (R_t=15.51min) and menthol (R_t=6.2min). The sensitivity ranges were 10-60 and 10-40 µg/mL for the two drugs, respectively, with mean percentage recoveries of 99.25±0.664% and 100.45±0.634% respectively.

The selectivity of the method was checked by using different laboratory prepared mixtures. It was successfully applied to the dosage form and the accuracy was checked by application of standard addition technique.

Section (B): Determination Of Diphenhydramine Hydrochloride In Presence Of Menthol By The Direct Spectrophotometric Method.

This method depends on the direct measurement of the absorbance of diphenhydramine hydrochloride at 258 nm as menthol has no absorbance in the UV-visible region . The sensitivity range was 5-20 µg/mL with mean percentage recovery of 101.03±0.466%.

The selectivity of the method was checked by using different laboratory prepared mixtures. It was successfully applied to the dosage form and the accuracy was checked by application of standard addition technique.

Section (C): Determination Of Menthol In Presence Of Diphenhydramine Hydrochloride By Colorimetric Method.

In this section a colorimetric method was applied with the use of a solution of 1% vanillin in concentrated sulfuric acid to give a blue color measured at 619nm. The sensitivity range was 5-30 µg/mL with mean percentage recovery of 100.26±0.859%.

The selectivity of the method was checked by using different laboratory prepared mixtures. It was successfully applied to the dosage form and the accuracy was checked by application of standard addition technique.

PART III: SIMULTANEOUS DETERMINATION OF DOXYCYCLINE HYCLATE AND AMBROXOL HYDROCHLORIDE IN PURE FORM AND PHARMACEUTICAL PREPARATION.

This part includes a general introduction about the chemistry and the mode of actions of doxycycline hyclate and ambroxol hydrochloride followed by presentation of the reported methods for their qualitative analysis. Experimental results and discussion were also given.

This part contains three sections:

Section (A): Simultaneous Determination Of Doxycycline Hyclate And Ambroxol Hydrochloride By The Spectrophotometric Method In The Presence Of The Oxidative Degradate Of Ambroxol (4-[(2- Amino -3,5- dirombenzyl) amino] cyclohexanone).

This section presents a spectrophotometric method which depends on the direct measurement of the absorbance of doxycycline hyclate at λ_{max} 359 .8 nanometer as both ambroxol and it's oxidative degradate have no absorbance in the wavelengths above 350 nm. The sensitivity range was 7-30 µg/mL with mean percentage recovery of 100. 92 ± 0.491%. As for ambroxol it was analyzed by measuring the D_1 amplitude value at 296.2 nm which is a zero crossing point for both the degradate and doxycycline. The sensitivity range was 7-30 µg/mL with mean percentage recovery of 98. 98±0.659 %.

The selectivity of the method was checked by using different laboratory prepared mixtures. It was successfully applied to the dosage form and its accuracy was checked by application of standard addition technique.

Section (B): Simultaneous Determination Of Doxycycline Hyclate And Ambroxol Hydrochloride By The First Derivative Of The Ratio Spectrophotometric Method.

This method depends on applying the first derivative of the ratio Spectra (^{1}DD) technique with measurement of the amplitude value of Doxycycline at 229 nm, using the spectrum of Ambroxol (7 µg/mL) as a divisor where it showed no interference the sensitivity range was (7 - 25 µg/mL) microgram per mille with mean percentage recovery of 98.80±0.408%. while for ambroxol analysis, the amplitude was measured at 292.6 and 327.2 nm, using the spectrum of Doxycycline (9 µg/mL) as a divisor. The sensitivity ranges were

(7-27µg/mL) for both wavelengths, with mean percentage recoveries of 98.63 ±0.304%and 99.61 ± 0.847 %) for the two wavelengths, respectively.

The selectivity of the methods was checked by using different laboratory prepared mixtures. The method was successfully applied to the dosage form and the accuracy was checked by application of standard addition technique.

Section (C): Determination Of Doxycycline Hyclate And Ambroxol Hydrochloride By The Spectrodensitometric Method.

In this section both drugs are separated on a silica gel plate using n-butanol: water :acetic acid (7:3:3 ,by volume) as a developing system and UV detection at 254nm over concentration range of (2 - 12 µg/band for both drugs with mean percentage recoveries of 100. 12±0.821% and 100.31±1.334% for doxycycline(R_f=0.63) and ambroxol (R_f=0.83), respectively.

The selectivity of the method was checked by using different laboratory prepared mixtures. The method was successfully applied to the dosage form and the accuracy was checked by application of standard addition technique.

PART IV: STABILITY INDICATING METHODS FOR THE DETERMINATION OF OXYGEN CITRATE IN PRESENCE OF ITS HYDROLYTIC DEGRADED AND EACH OF METHYLPARABEN AND PROPYLPARABEN IN PURE FORM AND PHARMACEUTICAL PREPARATIONS.

This part includes a general introduction about the chemistry and mode of action of oxeladine citrate, followed by presentation of the reporting methods for its qualitative analysis. Experimental results and discussions were also given. The hydrolytic degradation pathway of the drug was also presented, followed by the method of separation of the drug and its degradate.

This part contains 2 sections:

Section (A): Application Of Second Derivative Spectrophotometric Method As A Stability Indicating Method For The Determination Of Oxeladine Citrate In Presence Of Its Degradate And The Two Preservatives Methylparaben And Propylparaben. This section presents a D_2 spectrophotometric method which depends on the measurement of the peak amplitude of oxeladine citrate at 227.4nm, which is a zero crossing point for the degradate α, α diethylbenzene acetic acid. The interference of the two preservatives methylparaben and propylparaben present in the syrups was overcome by extracting the two preservatives from the syrups by ethyl acetate, in which oxeladine

citrate is insoluble. The sensitivity range was 10-40 µg/mL with mean percentage recovery of 100.12±0.363%.

The selectivity of the method was checked by using different laboratory prepared mixtures. It was successfully applied to the dosage form and its accuracy was checked by application of standard addition technique.

Section (B): Application Of The Multivariate Spectrophotometric Methods As Stability Indicating Methods For The Determination Of Oxeladine Citrate In Presence Of Is Degradate And The Two Preservatives MP And PP.

The chemometric techniques;Classical least squares (CLS), Principal component regression (PCR) and Partial least squares (PLS), have been successfully applied for the determination of oxeladine citrate in presence of its degradate and the two preservatives MP and BP. A training set of 12 mixtures containing different ratios of the four drugs is used.

The selectivity of the methods was checked using laboratory prepared mixtures (a validation set consisting of 8 mixtures). It was successfully applied for the determination of oxeladine citrate in its different syrup formulations. The validity of the methods was assessed by application of the standard addition technique.