Appendix 5 - Research Paper 1

RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF AMLODIPINE BESYLATE AND INDAPAMIDE IN COMBINED TABLET FORMULATION

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ABSTRACT

RP-HPLC method was developed and validated for simultaneous estimation of Indapamide (IND) and Amlodipine besylate (AML) in combined tablet dosage form and it can be used by analytical laboratories for routine analysis. The method was carried out on isocratic reverse phase mode. Column was Kromasil C18 having internal diameter 250mm x 4.6 mm and particle size 5 µm. It was kept at 40°C. Separation was achieved by UV detector at 240 nm with mobile phase having a mixture of ACN: 0.02M Na2HPO4 pH 7.0 adjusted with Orthophosphoric acid (70:30 v:v), at a flow rate of 1.0 ml/min. Linearity were observed in the concentration range of 37.5-112.5 µg/ml and 125-375 µg/ml for IND (r² > 0.9997) and AML (r² > 0.9999) respectively. Mean assay was found to be 98.44% for IND and 99.33% for AML.

Keywords: Indapamide(IND), Amlodipine besylate(AML), Reverse phase high performance liquid chromatography method.
Spectrophotometric Methods Development and Validation for Olmesartan Medoxomil and Indapamide in Combined Pharmaceutical Formulation

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Abstract: Two UV methods were developed for combined formulation of indapamide and olmesartan medoxomil. First method is simultaneous equation method. In this method the absorbance at 240 nm and 256 nm were used for IND and OLM respectively. Second method is first order derivative spectrophotometric method. In second method the absorbance at 225.4 nm (Zero crossing point of IND) and 256.6 nm (Zero crossing point of OLM) were used for estimation of OLM and IND respectively. In both methods linearity was taken in the concentration series of 1-30 μg/ml for IND and 10-70 μg/ml for OLM. The developed methods were validated as per ICH guidelines.

INTRODUCTION
Olmesartan medoxomil (OLM) and Indapamide (IND) in combination is used in Hypertension. Olmesartan medoxomil (Figure 1) is official in BP 2013 and Indapamide (Figure 2) is official in BP, JP, EP and JP. [1,4] Olmesartan medoxomil is orally active angiotensin II receptor antagonist used as an anti-hypertensive agent. [3] It is a prodrug which is hydrolyzed in body to form active olmesartan during absorption. Indapamide is an orally administered diuretic and anti-hypertensive drug. It contains both a polar sulfamoyl chlorobenzamide and non polar methyl-indole chemical moiety. [6] Presently normal prescribed medicines for hypertension are angiotensin receptor blockers and diuretics. Single drug is not sufficient to achieve target blood pressure levels and henceforth, a combination tablet formulation is beneficial in terms of its ease and patient fulfillment. The present drug combination has promising anti-hypertensive effect. The clinical and pharmacological analysis of this drug requires effective analytical procedures for quality control laboratories. Only Q- absorption spectrophotometric method is available for this combined dosage form. [7] The present research work aims to develop simple economical UV methods for simultaneous estimation of olmesartan medoxomil (OLM) and indapamide (IND) in its combined tablet formulation.

MATERIALS AND METHODS
OLM was procured as gift sample from Cadila Healthcare Limited, Ankleshwar, India and IND was procured from Torrent research centre, Ahmedabad, India. Marketed formulation OLMY-D 20 (20:1.5) and OLMY-D 40 (40:1.5) purchased from local Pharmacy. Methanol and other AR chemicals were used for analysis.

Instrumentation
Shimadzu 2450 double beam UV-visible spectrophotometer with two matched quartz cells with 1 cm light path and Digital analytical balance (CD2250, Sartorius) were used for analysis.

Preparation of Standard Solutions
1 mg/ml of OLM and IND were prepared by weighing 100 mg of OLM and IND separately and transferred in two different 100 ml volumetric flasks and volume was adjusted with methanol. Further stock solution 100 μg/ml of OLM and IND solution was prepared by diluting 10 ml of above solution with methanol in 100 ml volumetric flask. From this stock solution, 1, 2, 3, 4, 5, 6 and 7 ml of stock solutions (100 μg/ml) of OLM is transferred in 10 ml of volumetric flask to obtain 10, 20, 30, 40, 50, 60 and 70 μg/ml concentrations. Similarly standard solutions of IND were prepared by taking 0.1, 0.3, 0.5, 1, 1.5, 2 and 3 ml of stock solutions (100 μg/ml) of IND in 10 ml of volumetric flasks to get the final concentrations of 1, 3, 5, 10, 15, 20 and 30 μg/ml.

Method A: Simultaneous Equation Method
Each standard solution was scanned in spectrophotometer at 200 to 400 nm against methanol as a reagent blank. The zero order spectra of each solution were taken. Maximum wavelength of 240 nm and 256 nm were selected for this method. The overlay UV spectrum of OLM and IND was given in Figure 1. The linearity was determined in the series of 20-60 μg/ml and 1-5 μg/ml for OLM and IND respectively (n=6). Simultaneous equations were derived and concentration of each drug were determined.

Method B: First Derivative Spectrophotometric Method
The first order spectra of each above solution were taken. Overlay first order derivative spectra of OLM and IND is given in Figure 2. The zero crossing points were found to be 225.4 nm and 256.6 nm for IND and OLM respectively. Absorbance of each solution was taken at 225.4 nm and 256.6 nm. The linearity was found to be 20-60 and 3-20μg/ml for OLM and IND respectively. The graph of absorbance versus respective concentration was plotted for OLM (at 225.4 nm) and IND (at 256.6 nm) and regression line equations for OLM and IND were calculated as below:
SIMULTANEOUS ESTIMATION OF AMLODIPINE BESYLATE AND INDAPAMIDE BY DUAL WAVELENGTH SPECTROPHOTOMETRIC METHOD FOR COMBINED PHARMACEUTICAL DOSAGE FORM


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ABSTRACT

A simple, accurate, precise, rapid, economical UV spectrophotometry method, dual wavelength spectrophotometry, has been developed and validated for estimation of Indapamide (IND) and Amlodipine besylate (AML) in combined tablet dosage form and can be used in routine analysis. In this method, the absorbance at 360 nm and 256 nm of AML were same and no interference of IND at 360 nm was observed. So, absorbance difference at 256-360 is used for estimation of IND and absorbance at 360 nm used for AML. The method was found to be linear in the concentration range of 3-18 μg/mL for IND (r=0.99962) and 10-50 μg/mL for AML (r=0.99969). Mean assay was found to be 99.32% and 101.34% for IND and AML respectively. In first order derivative spectrophotometry, the absorbance at 237.4 nm (ZCP of AML) and 241 nm (ZCP of IND) were used for estimation of IND and AML respectively. The method was found to be linear in the concentration range of 1.5-9 μg/mL for IND (r=0.99983) and 5-30 μg/mL for AML (r=0.99966). Mean assay was found to be 99.72% and 100.28% for IND and AML respectively.

Keywords: Indapamide (IND), amlodipine besylate (AML), Dual wavelength spectrophotometry.

INTRODUCTION

Amlodipine besylate (AML), chemically 3-ethyl 5-methyl (4RS)-2-[(2 aminoethoxy) methyl]-4-(2-chlorophenyl) 6-methyl-1, 4 dihydro pyridine-3, 5-dicarboxylate benzenesulphonate, is a calcium channel blocker, used in the treatment of hypertension. It is official in IP, BP and USP, IP, BP and USP describe HPLC method for its estimation. Literature survey reveals UV spectrophotometry, RP-HPLC, spectrophotometric method for simultaneous determination of AML with other drug and RP-HPLC method for simultaneous determination of AML with other drug in pharmaceutical dosage forms as well as in biological fluids. Indapamide (IND), chemically 4-chloro-N-[(2RS)-2-methyl-2, 3-dihydro-1Hindol-1-yl]-3-sulphamoylbenzamide, is a thiazide diuretic for the treatment of hypertension. Indapamide is official in IP, BP and USP, IP, BP and USP describe HPLC method for its estimation. Literature survey reveals LC-MS, spectrophotometric and HPLC methods for simultaneous estimation of INDA in whole human blood. RP-HPLC method for simultaneous estimation of INDA and LC-ESI-MS method for the determination of INDA in human plasma. This combination is not official in any pharmacopoeia, hence official and reported methods of analysis are not available for this combination. However, there is no work was reported for the simultaneous estimation of these drugs by UV spectrophotometry using dual wavelength spectrophotometry, first order derivative spectrophotometry. Hence, in the present communication we propose fast, simple and accurate UV spectrophotometric method, without tedious extraction procedure. It was developed for the simultaneous estimation of both drugs in tablet dosage form by multi-component mode of analysis.

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Appendix 8 - Review Article

A Review of Analytical Methods for Determination of Olmesartan Medoxomil and Indapamide in Pharmaceutical Dosage Form

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Abstract: Olmesartan medoxomil is a new orally active angiotensin II type 1 receptor antagonist used as an anti-hypertensive agent. It is a prodrug and is rapidly de-esterified during absorption to form olmesartan, the active metabolite. Indapamide is an orally administered diuretic and anti-hypertensive drug. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a lipophilic methyl-indoline moiety. It differs chemically from thiazide in a way that it does not possess the thiazide ring system and contains only one sulfonamide group. Currently most commonly prescribed medicines for hypertension are angiotensin receptor blockers and diuretics. Monotherapy with oral anti-hypertensive agents is not sufficient to achieve target blood pressure levels and henceforth, a combination tablet formulation is beneficial in terms of its convenience and patient compliance. The present drug combination has promising antihypertensive effect. The clinical and pharmaceutical analysis of this drug requires effective analytical procedures for quality control and pharmacodynamic and pharmacokinetic studies as well as stability study. An extensive survey of the literature published in various analytical and pharmaceutical chemistry related journals has been conducted and the instrumental analytical methods which were developed and used for determination as single or combination with other drugs in bulk drugs, formulations and biological fluids have been reviewed. This review covers 50 analytical methods including spectrophotometric methods like spectrophotometry, chromatographic method including HPLC, HPTLC were reported.

INTRODUCTION

Olmesartan medoxomil (Figure 1) (a prodrug, which is hydrolyzed in body active olmesartan during absorption from the gastrointestinal tract) is chemically, 2,3-dihydroxy-2-buteny l-4-(1-hydroxy-1-methyl-ethyl)-2-propyl-1-[3-o-1H-tetrazol-5-ylphenyl] imidazole-5-carboxylate, cyclic 2,3 carbonate. Olmesartan medoxomil is an angiotensin II receptor blocker, which is used as an anti hypertensive agent. The literature survey reveals that olmesartan medoxomil was analyzed by the Liquid chromatography mass spectrometry (LC-MS) and reverse phase high performance liquid chromatography (RP-HPLC) methods. Indapamide (Figure 2) is an orally administered diuretic and anti-hypertensive drug. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a lipophilic methyl indoline moiety. It differs chemically from thiazide in a way that it does not possess the thiazide ring system and contains only one sulfonamide group. Indapamide is chemically 3-(aminosulfonyl)-4-chloro-N-(2,3-dihydroxy-2-methyl-1H-indol-1-yl) benzamide. Literature survey reveals bio-analytical methods by LC-MS for detection of indapamide in human serum and blood and few spectrophotometric methods and HPLC methods for the quantitative estimation of indapamide in bulk and pharmaceutical formulations. Currently most commonly prescribed medicines for hypertension are angiotensin receptor blockers and diuretics. Monotherapy with oral anti-hypertensive agents is not sufficient to achieve target blood pressure levels and henceforth, a combination tablet formulation is beneficial in terms of its convenience and patient compliance. The present drug combination has promising antihypertensive effect. This paper gives an overview of the analytical techniques that are available and now days have been used for determination of in pharmaceutical dosage forms and biological samples.

DISCUSSION

The presented review highlights on various analytical methods reported on Olmesartan Medoxomil and Indapamide in combination with other drug. HPLC-UV methods were found to be most widely used. Various chromatographic conditions are presented in under Table 1.