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EXTRACTIVE VISIBLE SPECTROPHOTOMETRIC METHOD FOR DETERMINATION OF OLMESARTAN MEDOXOMILAND VALSARTAN IN PHARMACEUTICAL FORMULATIONS

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***Abstract* - Simple, accurate, rapid and sensitive method has been developed for the estimation of olmesartan and Valsartan in bulk and pharmaceutical formulations. The method is based on the formation of ion association complex of the drug with eriochrome black-T in acidic buffer of pH 3.5 followed by extraction into chloroform. The linearity range ofolmesartan and Valsartan witheriochrome black-T was found to be 50 – 250 µg/mL. The developed method was found to be precise and accurate from the statistical validation of the analytical data. The proposed method has been successfully applied for analysis of dosage formulations.**

Keywords- olmesartan Valsartan, Eriochrome black-T and Spectrophotometric method

I. INTRODUCTION

Olmesartan Medoxomil is the member of angiotensin receptor blocker approved by the Food and Drug Administration (FDA) for the treatment of hypertension 1, 2, 3. Chemically it is (5-methyl-2-oxo-2H-1, 3-dioxol-4-yl) methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1, 2, 3, 4-tetrazol-5-yl) phenyl] phenyl} methyl)-1H-imidazole-5-carboxylate (Figure 1). Key structural elements of Olmesartan Medoxomil include a hydroxy alkyl substituent at the imidazole 4-position and a hydrolysable ester at the imidazole 5- position. Inter and Intramolecular hydrogen bonding involving these groups may contribute to the potentiation of antagonistic activity. After the oral administration, Olmesartan Medoxomil is de-esterifies in the intestinal tract to produce the active metabolite Olmesartan and this active Olmesartan acts by blocking the binding of angiotensin II to the AT1 receptors in vascular muscle; it is therefore independent of angiotensin II synthesis pathways, unlike ACE inhibitors 4. By blocking binding rather than synthesis of angiotensin II, olmesartan inhibits the negative regulatory feedback on rennin secretion. As a result of this blockage, olmesartan reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance. Olmesartan Medoxomil is a white to light yellowish-white powder or crystalline powder with a formula of C29H30N6O6 (MW 558.59). It is practically insoluble in water and sparingly soluble in methanol. UV method is commonly employed method for routine analysis since it is economical and easy to perform. Literature reports reveal that olmesartan Medoxomil can be estimated by RPLC-HPLC, RP-HPLC, LC-MSand HPLC methods individually or in combination with other drugs. Parambi and coworkers developed a UV Spectrophotometric method for the estimation of olmesartan Medoxomil in pharmaceutical dosage form.

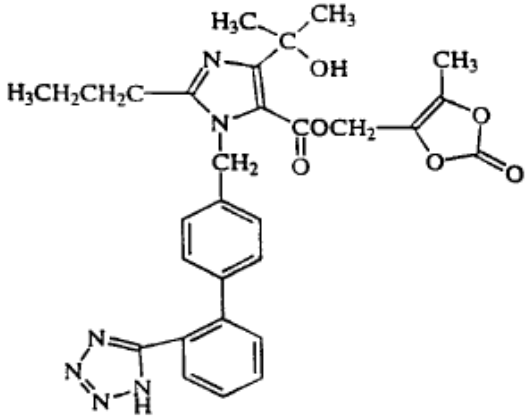

Figure 1: Olmesartan Medoxomil

Valsartan chemically is N-[p-(o-1H-Tetrazol-5-ylphenyl) benzyl]-N-valeryl-L-valine1(Figure 1).It is an angiotensin II receptor antagonist, effective in the treatment of hypertension. It is also effective when used alone or in combination with other drugs for the treatment of high blood pressure. It is not official in any of the pharmacopoeia. The pharmacokinetic properties of valsartan have been investigated in healthy volunteers after oral administration of the sample. High

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performance liquid chromatographic (HPLC) determination of valsartan in biological fluids was studied and also a chiral HPLC method was developed .

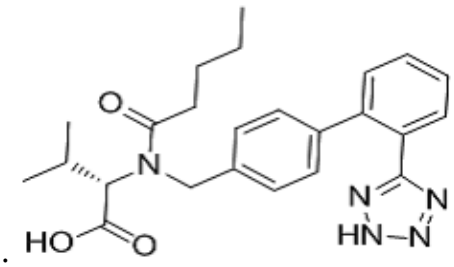

Fig. 2: Structure of valsartan

Literature survey revealed a few analytical methods for quantitative determination of olmesartan and valsartan in biological fluids and pharmaceutical formulations. The main aim of the present study is to develop a relatively simple, sensitive, validated and inexpensive extractive visible Spectrophotometric method for the estimation of olmesartan and valsartan in pure and in pharmaceutical formulations. Since most of the previous methods involve tedious sample preparation, critical reaction conditions and expensive instruments, so the authors have made an humble attempt to develop a simple method which does not involve any heating to produce the color and also cost effective. The proposed method has been extended for the routine quality control analysis of pharmaceutical formulations of olmesartan and valsartan.

Preparation of standard solution (1mg/mL): 100 mg of each drug was accurately weighed and transferred to separate 100 mL volumetric flasks. To dissolve the drug in methanol was added to each flask and the volume was made up to the mark with methanol.

Preparation of reagents: Eriochrome black-T solution (0. 1%): 100 mg of eriochrome black-T was dissolved in 100 mL of distilled water and washed with chloroform to remove chloroform soluble impurities.

Acetate buffer (pH 3.5): 0.4 gm of anhydrous sodium acetate in 84 mL of distilled water and sufficient amount of glacial acetic acid to adjust pH to 3.5 (about 15 mL) and the volume was made up to 100 mL with distilled water.

ASSAY

Twenty tablets of each drug were weighed accurately, finely powdered and powder equivalent to 100 mg of each drug was transferred to 100 mL volumetric flask extracted with 10 mL of methanol and made up to volume with distilled water. The sample solution of each drug was filtered through what Mann filter paper and from the filtrate required aliquots of the each drug solution was transferred to two 60 mL separating funnel and the same procedure was followed. The concentration of unknown was calculated from the regression equation

Selection of wavelength

In order to select the wavelength of maximum absorbance, olmesartan and valsartan solutions were scanned in the range from 400-600 nm against the respective reagent blank to record the absorption spectra. The resulting spectra's were shown in Fig 2a and 2b and the absorption curve showed characteristic absorption maxima at 510 nm for both the drugs.

Procedure for calibration curve

Aliquots of standard solution of olmesartan and valsartan ranging from 50 – 250 µg/mL were delivered in to a series of 60 mL separating funnels. To each separating funnel 2.5 mL of pH 3.5 buffer (for both the drugs) and 1.0 mL of 0.1% eriochrome solution for olmesartan and 3.0 mL for valsartan was added and the total volume of aqueous phase in each funnel was adjusted to 10 mL Then 10 mL of chloroform was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated chloroform layer was measured at 510 nm for both the drugs against the reagent blank prepared similarly. Calibration curves were constructed by plotting the absorbance against the concentration of the respective drug. The optimum conditions are presented in Table-1.

II. METHOD VALIDATION

Aliquots of standard stock solutions of olmesartan and valsartan were taken in to 60 mL separating funnel and required amount of buffer and reagent was added to each separating funnel and 10 mL of chloroform was added to extract the colored complex. The absorbance of colored complex was measured at 510 nm and calibration curves were constructed in the range 50 -250 µg/mL for both the drug Fig 3a and 3b.

Precision

The intraday and interday precision was carried out for three different concentrations of telmisartan and irbesartan by measuring the corresponding absorbance six times on the same day and for three different days. The results are reported in terms of % relative standard deviation (%RSD) and presented in Table 1.

Table-1: Optical characteristics of the proposed method. Parameters

	Telmisartan	**Irbesartan**
λmax (nm)	510	510
Beer's law limit (µg/ml)	50 - 250	50 - 250
Sandel sensitivity (mcg/cm2/0.001 A.U)	0.1282	0.047058
Molar absorptivity	4.014×10^4	2.090×10^5

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mL/mol-1 cm-1		
Slope (a)	0.02687	0.04296
Intercept (b)	0.00273	0.00463
Correlation coefficient (r2)	0.9981	0.9931
Confidence limit with 0.05level	0.3652	0.3198
Confidence limit with 0.01level	0.5403	0.2283
%RSD	0.4368	0.4738

Specificity
Commonly used excipients were spiked into pre weighed quantity of the drugs. The absorbance was measured after appropriate dilutions and the quantities were determined. No interference of placebo was observed with absorbance hence the method is specific for these drugs.

Stability
No changes in the assay values were observed after 24 hrs indicating stability of the drugs in the solvent and the color obtained was stable up to 45 min after extraction. However a decrease in absorbance was measured thereafter.

Recovery studies
To study the accuracy of the proposed method, recovery studies were carried by standard addition method at three different levels. A known amount of drug was added to pre analyzed tablet powder and percentage recoveries were calculated.

III. RESULTS AND DISCUSSION

The color product is due to ion pair formation of the drug with the dye in acidic medium. The optimum conditions were established by varying one parameter at a time and keeping other parameters fixed by observing the effect produced on the absorbance of the colored species. Investigations were carried out to establish most favorable conditions for the formation of colored product. The influence of buffer pH (pH ranging from 1.2-6.8) and different amounts of pH3.5 buffer on the reaction has been studied. It was observed that the absorbance started decreasing above 2.5 mL of pH 3.5 for both the drugs, so 2.5 mL of buffer was used for further study. The effect of changing the concentration of eriochrome black T over the range 0.5 mL to 4.0 mL was examined and it was observed that the absorbance started decreasing above 1.0 mL for olmesartan and 3.0 mL for valsartan. Hence 1.0 mL of 0.1% w/v eriochrome dye solution for olmesartan and 3.0 mL for valsartan was used for further studies. The optimum conditions such as λ max, volume of drug used, volume of reagent and buffer used were presented in Table-1. The optical characteristics and regression analysis are summarized in Table-3.To study accuracy, reproducibility, reliability and the interference from excipients used in the formulation, recovery experiment was carried out by standard addition method. From the total amount of drug found, the percentage recovery was calculated. The results of recovery analysis were presented in Table-2.
The analysis results of marketed formulation were in good agreement with the labeled claim. High percentage of recovery shows that this method is free from the interference of excipients used in formulation and can be used in routine quality control analysis of these drugs.
The proposed method for determination of olmesartan and valsartan by using eriochrome black –T was applied to commercial tablets together with the reference method. These determinations were carried out on the same batches of samples. The results obtained were compared statistically by student T-test and variance ratio F-test. The experimental values did not exceed the theoretical values in either test which indicates that there was no significant difference between the methods compared.

IV. CONCLUSION

The proposed method is simple, rapid, sensitive and can be successfully applied for estimation of these drugs in pharmaceutical dosage form. The proposed reagent is cheaper and easily available and the method does not need any heating for color development.

Fig 3a: Calibration curve of olmesartan with eriochrome Black-T.

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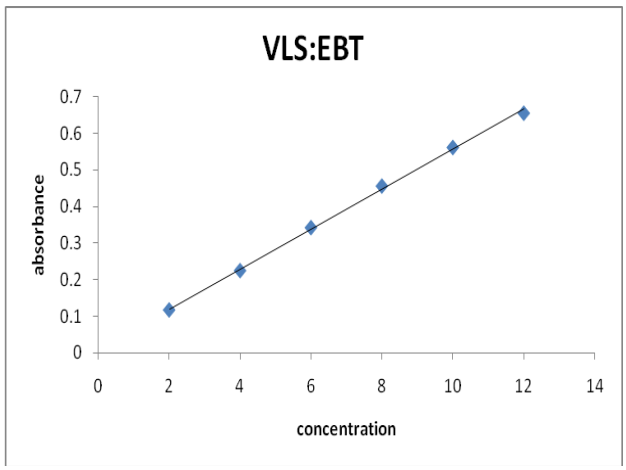
Fig. 3b Calibration curve of valsartan with eriochrome Black-T



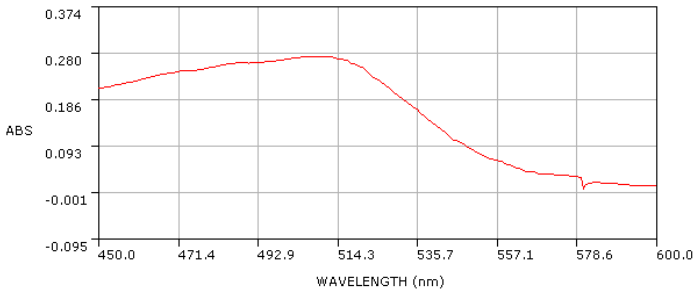


Fig.2a spectrum of olmesartan with eriochrome Black – T.

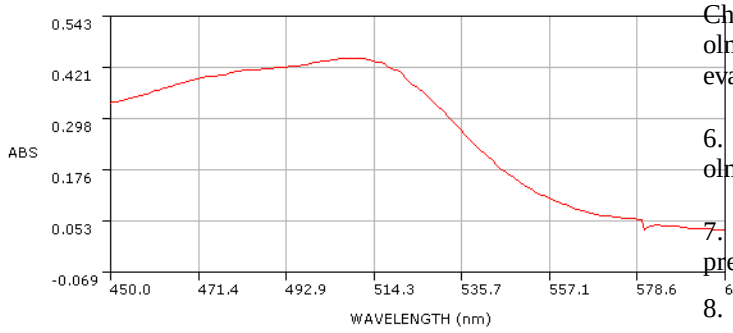


Fig. 2b Spectrum of valsartan with eriochrome Black –T.

Table-2: Assay and Recovery studies of proposed method

Name of the dosage form	Labeled Amount(mg)	Reference method	% Recovery by the proposed method
OLSAR	80	100.80 ±0.46	100±0.854 t = 0.51, F = 3.45
VALZAAR	40	100.88±0.48	99.62±0.704 t=1.68 T=2.15

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