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Research Article

NEW FLUORIMETRIC METHOD DEVELOPMENT FOR LISINOPRIL BY CONDENSATION REACTION

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ABSTRACT

Simple, new flourimetric method is developed for Lisinopril by the condensation with 1-Naphthylamine to form the fluorescent complex which is measurable in the linearity range of 3- 16 µg/ml in methanol. The developed method was validated according to ICH guidelines for parameters like accuracy, precision, specificity, ruggedness, robustness and percentage recovery. The Relative Standard Deviation was 0.44; recovery was 99-100%. Tablet formulations were used as sample for estimation and the results were found to be well within the specified limit. The developed method can be applied successfully in estimation of Lisinopril in routine in-processes of manufacturing.

Key words: Lisinopril, 1-Naphthylamine, Condensation, Fluorometry.

INTRODUCTION

Lisinopril is ACE inhibotor widely used as antinypertenive either in single or in combination with other drugs and which is official in IP, BP, and USP[1]. The reported methods for estimation of Lisinopril include spectrophotometric, Capillary electrophoresis, spectro-fluorometry, immunoflourescence, Potentiometry and HPLC[2-13]. The Potentiometric and HPLC methods are official in pharmacopoeias[14-16]. The literature survey reveals that there is no fluoremetric method available for estimation of Lisinopril.

Objectives

There is need of simple, rapid, easily accessible method of estimation for Lisinopril. The objective of present study is to develop new fluoremetric method of estimation for Lisinopril in pure or in the dosage form.

The developed fluoremetric method of estimation is based upon the condensation reaction between the free amino group of 1-Naphthylamine which reacts with ketonic functional group of Lisinopril forming fluorescent condensation product (Figure-1and Table 1).

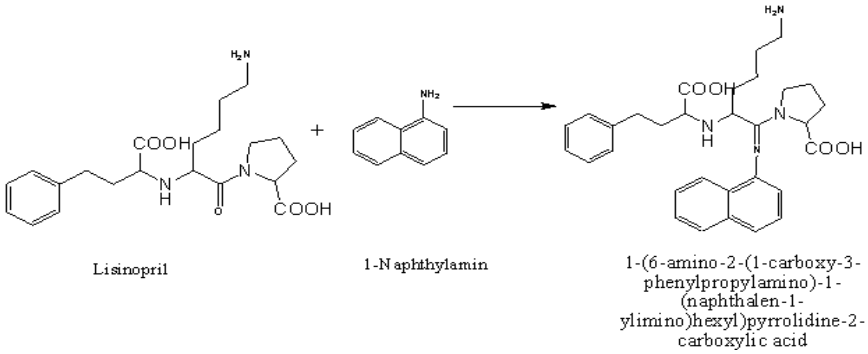

Fig. 1: Condensation reaction between Lisinopril and 1-Naphthylamine

Table 1: Characterization of Lisinopril 1-Naphthylamine derivative

Parameter		**Observation**
Appearance		Blue colored dye
Molecular Formula		C31H38N4O4
Molecular weight		530.29 gm/mol
Melting point		46 ^{0}C
Solvent		Methanol
IR:KBr:cm-1		
Group and mode of vibration Frequency	**Observed**	**Expected range**
-NH stretch	3365	3500-3100
-NH2 stretch	3470	3600-3200
C=N stretch	1670	1649.19
-COOH stretch	1386.86	1300-1000
-C-O-H Bend	1462.09	1440-1220
-C=C stretch Aromatic	2928.04, 3061.13	2800-3100
Aromatic Bend	771.55, 700.18	900-690

The reaction proceeds in methanolic media at 50^{o}C for 5 min. The reagent 1-naphthylamine shows limit of highest measurable concentration of 0.1µg/ml whereas the limit of detection of complex is 2.5µg/ml.

MATERIALS AND METHODS

Fluorimetric determination was carried out using Elico Fluorimeter, model CL-53. The fluorescence intensity of test and reference solutions was recorded in 3 ml borosilicate cells. The Relative Intensity was measured with filters of excitation wavelength of 366 nm and emission wavelength of 475 nm.

Standard drug, marketed formulations and reagents used

Lisinopril standard drug was procured from Unimark Pharmaceuticals Vapi. All reagents and solvents used were of Analytical Grade. Three commercial brands of Lisinopril, Listril 5 mg, Lipril 10 and Lisoril 5 mg were used as samples for estimation.

Procedure for estimation: Lisinopril standard drug of 100 mg is weighed accurately and transferred to 100 ml volumetric flask, 50 ml of methanol was added, shaken well to dissolve then 32.4 mg of 1-Naphthylamin was added and shaken to mix. The mixture was heated at 50°C for 5 min on water bath to complete the condensation reaction. Dilution containing 17 µg/ml of concentration was used to set 100% intensity and readings were recorded against methanol as blank. Sample readings were recorded using commercial brands of Lisinopril. Standard dilutions in the range of 4-14µg/ml prepared for linearity measurement.

Estimation of commercial tablets: 20 tablets are weighed and ground to fine powder. The tablet powder equivalent to 100 mg of Lisinopril was weighed and transferred to 100 ml volumetric flask; 50 ml of methanol was added, filtered. The filtrate was mixed with 32.4 mg of 1-Naphthylamin, stirred well to mix. The mixture was heated at 50°C for 5 min on water bath. Dilution containing highest concentration of 17µg/ml was used to set 100% intensity and readings were recorded against methanol as blank.

RESULTS

The reagent 1-naphthylamine is not used as blank in estimation because it shows limit of highest measurable concentration of 0.1µg/ml whereas the limit of detection of complex is 2.5µg/ml. Therefore under the concentration range of estimation there is no interference of reagent.

The developed method was optimized for the factors affecting the condensation reaction (Figure 2).

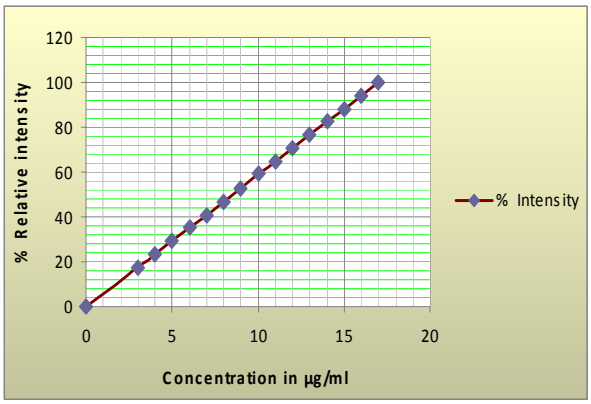

Fig. 2: Linear relationship between % relative intensities and concentration.

The method was validated, compared with standard method and statistically expressed. Statistical analysis of experiment shows the accuracy of 99–100%, relative standard deviation was 0.447214 and coefficient of correlation was 0.9999. Percentage recovery study was performed with constant quantity of sample spiked with the standard which on calculation showed 99 – 100 % recovery. Samples of marketed formulations were determined and statistically complied for specification. The factors which influence reaction such as temperature and heating time were studied and optimized for satisfactory range of stability and completion of reaction i.e. ±10°C and heating time 4 to10 min(Figure 3).

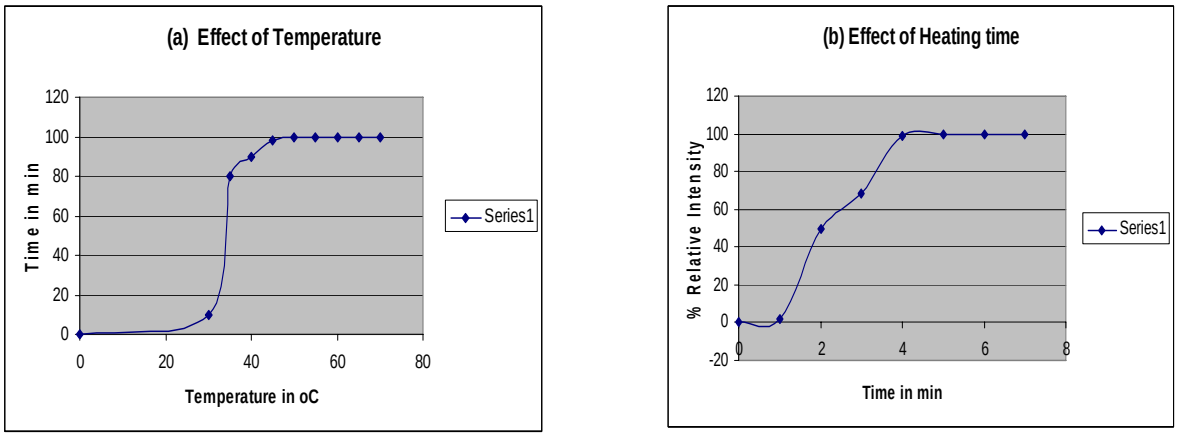

Fig 3: Effect of (a) Temperature and (b) Heating Time on % Relative Intensity.

DISCUSSION AND CONCLUSION

Fluorimetric method makes use of simple reagents, and enable to measure in low concentrations (3 µg to 16 µg) of drug with accuracy 99-100%. Developed method is simple, reliable, precise, accurate and specific which can be performed within short time and producing the data at appreciable sensitivity even in low concentration and method was compared with standard method[14] show within the limit of specification. With large set of data obtained by repeated experimentation it was found that t- value calculated was 0.02 (t_{tab} 2..85) at p=0.05 level of significance with 16 degrees of freedom indicating no significant difference (Table 2).

Table 2: Statistical Calculation of Validation parameters

Parameter	Calculated Value
Range and Linearity	3 - 16 g/ml
Relative Standard Deviation	0.447213595
Coefficient of Correlation	0.999978431
Accuracy	99 - 100 %
Slope[a]	5.89978
Intercept	- 0.142829

a. Equation of linearity for % Relative Intensity = Slope x Concentration + Intercept.

b. Method was compared statistically t-test value calculated was 0.023012 (t_{tab} 2.85) at 0.05 level of significance with 16degrees of freedom.

Thus developed method can be applied successfully in estimation of Lisinopril in routine in processes of manufacturing where large numbers of samples are required to be analyzed within short period of time.

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