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RP-HPLC Analysis of Trandolapril in Pharmaceutical Dosage Forms

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A rapid and sensitive reverse phase HPLC method is applied for the qualitative and quantitative assay of trandolapril in pharmaceutical dosage forms. Trandolapril was chromatographed on a reverse phase C_{18} column with a mobile phase consisting of methanol:phosphate buffer (pH 7.8) in the ratio of 90:10 v/v. The mobile phase was pumped at a flow rate of 1 mL/min. Mizolastine was used as an internal standard and the eluents were monitored at 220 nm. The retention time of the drug was 2.634 min. With this method, linearity is observed between area under curve (AUC, expressed in mV.min) and concentration of trandolapril in the injected solution, in the range of 5-150 μg/mL. The method was found to be applicable for analysis of drug in tablets. The results of the analysis were validated statistically.

Key Words: Trandolapril, Mizolastine, RP-HPLC.

INTRODUCTION

Trandolapril is (2S, 3aR, 7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenyl propyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid. It has been shown to be an orally active, highly specific angiotensin converting enzyme (ACE) inhibitor drug[1-3]. A few methods of analysis of trandolapril have been reported using different techniques such as high performance liquid chromatography (HPLC)[4-7], high performance thin layer chromatography[8], liquid chromatography-mass spectrophotometry[9,10]. Most of these methods are considered tedious. The HPLC methods using the most commonly available columns and detector like UV are preferred. The present study describes the determination of trandolapril in pharmaceutical dosage forms by using RP-C_{18} column with UV detectors. Owing to the widespread use of HPLC in routine analysis, it is important that well validated HPLC methods are to be developed for estimating trandolapril. The aim of this study is development of a simple, precise, rapid & accurate reverse phase HPLC method for the estimation of trandolapril in different pharmaceutical dosage forms.

EXPERIMENTAL

Trandolapril was gifted by Lupin Laboratories Ltd, Mumbai, India. Methanol and water was of HPLC grade (Merck). All other reagents were of AR grade. An isocratic HPLC (Waters India, USA) with a single Waters 510 Pump, Waters 486 tunable absorbance detector and RP-C_{18} column (Bondapak C18, 250 × 4.6 mm, packed with 5 μm particle size) was used. The HPLC system was equipped with Millennium software.

Chromatographic conditions: The composition of the mobile phase is methanol and phosphate buffer at pH 7.8 in the ratio of 90:10 v/v. The mobile phase was filtered before use through a 0.45 μm membrane filter and degassed for 0.5 h.

The components of the mobile phase were pumped from the solvent reservoir to the column at a flow rate of 1 mL/min that produced column back pressure 140-150 kg/cm^2. Ambient column temperature was maintained. The eluents were monitored at 220 nm.

Drug and internal standard solution: A pure sample of trandolapril was used as reference standard in the study. About 50 mg of trandolapril was weighed accurately and transferred into a 50 mL volumetric flask and dissolved in 25 mL of the mobile phase. The volume was made up with a further quantity of the mobile phase to get 1 mg/mL solution. Following this, the solution was sonicated for 0.5 h to ensure complete solubility of the drug. Subsequent dilutions of this solution ranging from 5 to 150 μg/mL were made in 10 mL volumetric flasks after addition of 0.3 mL mizolastine solution (30 μg/mL) as an internal standard to each dilution. 20 μL of the solution was injected each time into the stream of mobile system at a flow rate of 1 mL/min. Each of the dilutions was injected 6 times into the column and the corresponding chromatograms were obtained. From these chromatograms, the area under the peaks of the drug and the internal standard were noted. Using these values, the mean ratio of peak area of the drug to that of the internal standard for each dilution was calculated. The regression of the drug concentration over these ratios was computed. This regression equation was used to estimate the amount of trandolapril in the pharmaceutical dosage forms. Solutions containing 10, 70 and 150 μg/mL of trandolapril were subjected to the proposed HPLC analysis to check the intra-day and inter-day variation of the method. The recovery studies were carried out by adding known amounts of trandolapril to the preanalyzed samples and then analyzing them by the proposed HPLC method.

Estimation of Trandolapril in the tablet dosage form: Two commercial brands of tablets (AAA and BBB) were chosen for testing suitability of the proposed method to estimate trandolapril in tablet formulations. 20 Tablets were weighed and powdered. An accurately

weighed portion of this powder equivalent to 50 mg of trandolapril was transferred to a 50 mL volumetric flask containing 25 mL of the mobile phase. The contents of the flask were allowed to stand for 0.5 h with intermittent sonication to ensure complete solubility of the drug and then filtered through 0.45 μm membrane filter. From the filtrate, different aliquots were taken in separate 10 mL volumetric flasks. These solutions were spiked with suitable volume of the internal standard solution, such that the concentration of each solution was 30 μg/mL. The contents of the flasks was made up to the volume with the mobile phase and mixed well. Each of these solutions (20 μL) was then injected 6 times into the column. The mean peak area ratio of the drug to the internal standard of 6 such determinations was calculated and the drug content in the tablets was quantified using the regression equation obtained for the pure sample.

RESULTS AND DISCUSSION

To achieve sharp peaks with good resolution, under isocratic conditions, mixtures of methanol and phosphate buffer in different combinations were tested as mobile phase on a C_{18} stationary phase. A binary mixture of methanol and phosphate buffer (pH 7.8) in 90:10 v/v proportions was proved to be the most suitable of all combinations, since the chromatographic peaks were well resolved and free from tailing with this system. Though the structure of mizolastine is not similar to trandolapril, it was chosen as an internal standard, because it showed better peak shape and peak location compared to other potential internal standards such as mirtazapine, bupropion hydrochloride, *etc.*, in this perspective. Under the above mentioned chromatographic conditions, the retention time obtained for trandolapril and the internal standard were 2.634 and 1.869 min, respectively.

Each of the samples was injected 6 times and almost same retention times were observed in all cases. The ratio of peak area of trandolapril to peak area of internal standard for different concentrations set up as above were calculated and the average values for 6 such determinations are shown in Table-1. The peak areas of both the drug and internal standard were reproducible as indicated by low coefficient of variation (Table-1). A good linear relationship ($r = 0.9994$) was observed between the concentration of trandolapril and the respective ratio of peak areas. The regression curve was constructed by linear regression, fitting into mathematical expression, $y = 0.0058x + 0.0016$ (where y is ratio of area under the curve of the drug to that of the internal standard and x is the corresponding concentration of trandolapril). When trandolapril solutions containing 10, 70 and 150 μg/mL were analyzed by the proposed method for finding out intra and inter-day variations, a low coefficient of variation was observed (Table-2). This

TABLE-1
CALIBRATION OF THE PROPOSED METHOD

Concentration of trandolapril (μg/mL)	Mean peak area ratio (n = 6)	Coefficient of variance (%)
5	0.032862684	0.25
10	0.061170427	0.51
20	0.107497647	0.39
30	0.180113664	0.63
40	0.245771284	0.27
50	0.299073675	0.58
60	0.346430280	1.07
70	0.409712835	0.98
80	0.457414334	0.08
90	0.514850326	0.51
100	0.575751771	0.73
150	0.882935611	0.28

Regression eqn. (from 5 to 150 μg/mL): y = 0.0058x + 0.0016, (r = 0.9994)

shows that the present HPLC method is highly precise. A recovery of 98.89% of trandolapril from the preanalyzed samples (Table-3) shows that the present method is highly accurate.

TABLE-2
PRECISION OF THE PROPOSED METHOD

Concentration of trandolapril (μg/mL)	Observed concentration of trandolapril (μg/mL)			
	Intra-day		Inter-day	
	Mean (n=6)	Coefficient of variation (%)	Mean (n=6)	Coefficient of variation (%)
10	10.08	0.49	10.13	0.58
70	70.21	0.83	70.28	0.91
150	150.31	0.31	150.52	0.27

The drug content in the tablets was quantified using the proposed analytical method. The mean amount of trandolapril in two different brands of tablet dosage form is shown in Table-4. The absence of additional peaks in the chromatogram indicates non-interference of the common excipients used in the tablets. The tablets were found to contain 99.02 to 100.5 % of the labeled amount of the drug. The low coefficient of variation indicates the reproducibility of the assay of trandolapril in tablets. It can be concluded that the proposed HPLC method is sufficiently sensitive and reproducible for the analysis of trandolapril in pharmaceutical dosage forms within a short analysis time. The method was duly validated by the required parameters.

TABLE-3
RECOVERY DATA OF TRANDOLAPRIL
(ACCORDING TO ICH GUIDELINES)

Amount of drug added (µg) to solutions of pure durg/tablet formulation	Recovery from drug solution		Recovery from tablet formulation	
	Mean (±SD) amount (µg) found (n = 6)	Mean (±SD) % recovery (n = 6)	Mean (±SD) amount (µg) found (n = 6)	Mean (±SD) % recovery (n = 6)
16	15.82 ± 0.12	98.89 ± 0.05	15.76 ± 0.19	98.53 ± 0.08
20	19.21 ± 0.32	97.01 ± 0.62	19.35 ± 0.38	98.71 ± 0.82
24	23.56 ± 0.27	98.17 ± 0.13	23.61 ± 0.32	98.39 ± 0.54

TABLE-4
ASSAY OF TRANDOLAPRIL DOSAGE FORMS

Brand name of the tablet	Labeled amount of drug (mg)	Mean (±SD) amount (mg) found by the proposed method (n = 6)	% Mean (±SD) labeled amount (n = 6)
AAA	4	4.02 ± 0.92	100.5 ± 0.13
BBB	2	1.98 ± 0.87	99.02 ± 0.27

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