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Differential Pulse Polarographic Determination of Enalapril Maleate

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A differential pulse polarographic (DPP) method has been developed for the quantitative analysis of enalapril maleate. Enalapril maleate gives a peak at -1.4 V in methanol.

A calibration curve was constructed for the 20 -100 μg ml^{-1} concentration range. As a reference method, a reversed phase high performance liquid chromatographic procedure has been developed. Commercially available tablets were analysed by the two methods. Statistical evaluations indicated that there was no significant difference between the mean values and precisions of the two methods at a 95% confidence level.

Key Words: Differential pulse polarography, high performance liquid chromatography, enalapril maleate, tablets.

Introduction

Enalapril maleate ((S)-1-{N-[1- (ethoxycarbonyl)-3-phenylpropyl]-L-alanyl}-L-proline, (Z)-2 -butenedioate (1 : 1) salt, ENM) (I) is a salt of enalapril (EN) and maleic acid (MA). EN is a pro-drug which is hydrolysed to enalaprilate (DIAC), acting as an inhibitor of enzyme antiotensin convertase[1].

It is indicated for the treatment of renivascular hypertension (Figure 1).

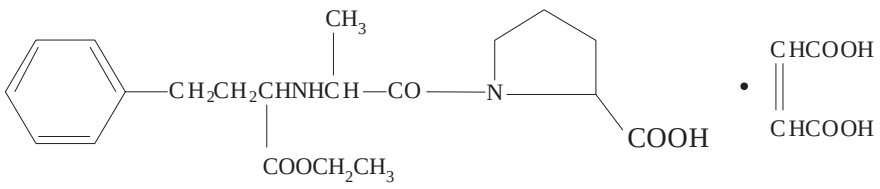

Figure 1. Enalapril Maleate

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Enalapril shows its inhibition activity by metabolizing to its diacid form in vivo. The acid and diketopiperazine derivative are the major potential degradation products resulting from the hydrolysis and intramolecular cyclization of enalapril. High performance liquid chromatography (HPLC) has been the only practical technique for the determination of enalapril in pharmaceutical dosage forms without interference from degradation products. However, severe conditions that shorten column life, such as low pH of the solvent and high column temperature, are required for acceptable peak shape, because enalapril exists as two rotational isomers owing to the alanyl-proline moiety in its structure[2].

For the determination of enalapril maleate in dosage forms, various analytical techniques including spectrophotometric[3,4] capillary electrophoresis[5−7], liquid chromatographic[8−12], GC-MS[13] and flow injection analysis[14] are used.

This study describes a new differential pulse polarographic (DPP) method for the quantitative analysis of enalapril maleate (1) in tablets[15−16].

Experimental

Materials

Pharmaceutical grade enalapril maleate (Ilsan/İstanbul) was used as received. HPLC grade acetonitrile and other analytical grade chemicals were purchased from E. Merck. Milli Q water was used.

Apparatus

A Metrohm Herisau Polarograph E 506 polarecord VA 526 in conjunction with the following three electrode system was used. Working electrode: static mercury dropping electrode (SMDE); reference electrode: Ag/AgCl (3 M KCl); auxiliary electrode: glassy carbon rod.

The HPLC system consisted of the component C_{18} 10 μm Bondapak column (300 x 3.9 mm i.d.); a model 481 model variable wavelength spectrophotometer was from Waters.

Solutions

A stock solution of (I) (1000 μg ml^{-1}) was prepared with CH_3OH. Standard solutions were obtained by diluting the stock solution with methanol for the preparation of the calibration curves in the concentration ranges 20-100 μg ml^{-1} for DPP.

Polarographic Conditions

U_{start} : -0.8 V, ΔU: -1.5 V, t_{drop}: 1 s, sensitivity: 1.5 x 10^{-9} A/mm, supporting electrolyte: tetramethylammonium bromide (TMAB).

Polarographic Procedure

Twenty tablets were weighed and powdered. An accurately weighed portion of the powder equivalent to ca. 20 mg of (I) was transferred into a 50 ml volumetric flask with 20-25 ml of CH_3OH and 2 ml TMAB added. The mixture was shaken for 30 min and diluted to volume with methanol. After filtration, 3 ml of the filtrate was transferred into a 25 ml volumetric flask and diluted to volume with CH_3OH. The DP

polarogram of this solution was recorded between -0.8 and -2.3 V after deaeration with N_2 for 10 min. The quantity of (I) in tablets was calculated by regression equation of the calibration curve.

Chromatographic Procedure

Enalapril maleate, using 0.025 M ortophosphoric acid [(adjusted to pH 3.0 with triethylamine (TEA)]: Acetonitrile (84:16 v/v) as a mobile phase at a flow rate of 1.0 ml/min and 10 μm Bondapak C_{18} column (300 x 3.9 mm) as a stationary phase. Detection was carried out using a UV detector at 226 nm. Hydrochlorothiazide was used as an internal standard. The flow rate was 1.0 ml/min^{-1} (3100 pSI), and under these conditions the retention times were 2.4 min for enalapril maleate and 4 min for the internal standard.

Results and Discussion

For the recording of the best polarogram, the type of extraction solvent, various buffer solutions (pH 1-14) and polarographic conditions were investigated. The best solvent for enalapril maleate is methanol. With this solvent, enalapril maleate solution with tetramethylammoniumbromide (TMAB) supporting electrolyte was examined by using a DPP method.

The method involves the extraction of (I) from tablets with methanol, filtration, appropriate dilution and recording of DP polarograms between -0.8 and -2.3 V. E_{peak} was observed at -1.4 V v.s Ag/AgCl (3 M KCl) (Figure 2).

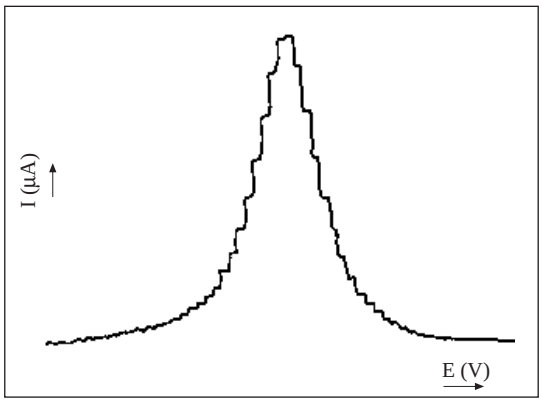

Figure 2. Polarographic peak of enalapril maleate (c = 60 μg ml^{-1}).

Polarographic conditions are U_{start} = -0.8 V, ΔU = -1.5 V, mm/t_{drop} = 2.0 s, t_{drop} = 1.0 s and pulse amplitude: 50 mV.

Five different DP polarograms were recorded using the stock solution of (I) in methanol (0.5-2.5) 2 ml TMAB was added and diluted to 25 ml with methanol. A calibration graph was plotted between i $_{peak}$ and drug calibration (c). The regression equation of the calibration curve was calculated as

$$i_{\text{peak}} = 1.61c + 9.39(r = 0.9999)(i_{\text{peak}} = \mu A, c : \mu g m l^{-1})$$

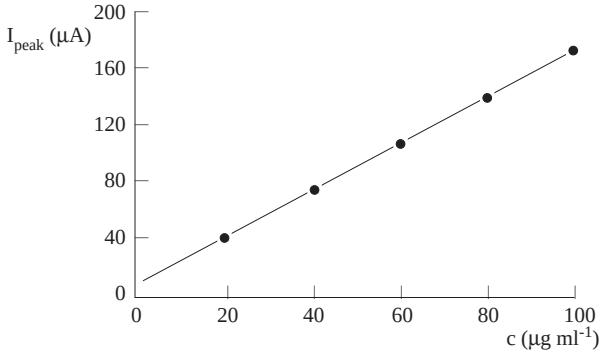

Figure 3. Calibration curve.

Commercially available tablets containing (I) were analysed by the developed DPP method and HPLC method for comparison. The results obtained by both methods and statistical comparison in terms of t- and F-tests of significance at a 95% confidence level are tabulated in the Table. Calculated t- and F-values are both lower than corresponding table values.

Table. Analysis of enalapril maleate in tablets (labelled to contain 20 mg of enalapril maleate per tablet).

Statistical value	Proposed method (DPP)	Reference method (HPLC)
X	20.65	20.12
Recovery	99.40	98.50
RSD	1.16	0.65
n	5	5
t-test of significance*	t = 0.07	
F-test of significance**	F = 0.29	

*t = 2.31 (p = 0.05)
**F = 6.39 (p = 0.05)

In conclusion, the developed method is simple and does not require expensive solvents, and presents new alternatives for the rapid and precise determination of enalapril maleate. Detection limits were 5 μg ml^{-1} and 2 μg ml^{-1} for the DPP and HPLC methods respectively. It has good precision and accuracy for the determination of (I) in tablets. It is suitable for routine analyses. Common excipients in tablets, such as sugars, cellulose and magnesium stearate, did not interfere.

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