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Spectrophotometric and polarographic determination of enalapril and lisinopril using 2,4-dinitrofluorobenzene

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Abstract

The reaction of enalapril maleate and lisinopril with 2,4-dinitrofluorobenzene has been used to form colored products and polarographically active derivatives. The different experimental conditions have been optimized. The proposed methods have been validated and applied to the determination of both drugs in their commercial tablets. The results have been statistically compared with those obtained using the official HPLC methods.

Keywords: Spectrophotometry; Differential pulse polarography; 2,4-Dinitrofluorobenzene (Sanger's reagent)

1. Introduction

Enalapril maleate (*N*-{*N*-[(*S*)-1-ethoxycarbonyl-3-phenylpropyl]L-alanyl}-proline hydrogen maleate) and lisinopril (*N*-{*N*-[(*S*)-1-carboxy-3-phenylprolyl]L-lysyl}-L-proline dihydrate) are angiotensin-converting enzyme (ACE) inhibitors used in the treatment of hypertension and heart failure. Both drugs and their tablets are official in USP 24 [1], where HPLC methods are described for their quantitation.

The analytical profiles of the two drugs have been reviewed [2,3]. Enalapril has been assayed spectrophotometrically by ion pair-extraction technique [4,5]. Potentiometric [6,7] and HPLC [8–10] procedures were also developed. In tablets, lisinopril has been determined by GC [11], derivative spectrophotometric [12,13], calorimetric and fluorimetric [12] procedures. Capillary electrophoresis has been used to separate closely related ACE inhibitors and to quantitate them in their pharmaceutical preparations [14].

In biological fluids, enalapril has been quantitated by radio-enzymic assay [15], GC–MS [16]

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Table 1
Assay parameters for the determination of enalapril maleate and lisinopril through the reaction with 2,4-dinitrofluorobenzene

Item	Drug			
	EM		LD	
	Procedure I	Procedure II	Procedure I	Procedure II
Standard concentration (mg ml^{-1})	0.2	0.2	0.2	0.2
Volume of standard solution (ml)	0.6–1.8	1–4	0.2–1.2	0.2–0.7
Borate buffer pH	9		10	
Borate buffer volume (ml)	0.2		0.5	
Reagent volume (ml)	2.5	1.0	2.5	0.5
Heating temperature (°C)	100	Room temperature	80	60
Heating time (min)	25		30	20
λ_{max} (nm)	356	420	400	364
E_p (mV)	−844		−802	

and GC–negative ion CIMS [17]; lisinopril has been analyzed by GC [18,19], HPLC [20] and fluoroimmunoassay [21].

Several kinds of interactions can occur between the electron-deficient polynitro aromatic compounds and nucleophiles depending upon reactant structure and solvent environment. In aqueous borate buffer, 2,4-dinitrofluorobenzene (DNFB) or Sanger's reagent yields yellow colored products when reacting with primary and secondary amines through nucleophilic aromatic substitution reaction [22]. On the other hand, in the presence of dipolar aprotic solvent (DMSO), a Meisenheimer complex is formed [23]. Both types of reactions have been utilized for the spectrophotometric determination of norfloxacin [24] in its pharmaceutical preparations. 2,4-Dinitrofluorobenzene has also been used as precolumn derivatizing reagent for the HPLC assay of sulphonylurea drugs with ultraviolet detection [25]. To our knowledge, one polarographic procedure has been reported in the analytical abstract for the determination of histidine after substitution reaction with Sanger's reagent [26].

This paper reports direct spectrophotometric and polarographic procedures for the analysis of the two antihypertensive drugs enalapril maleate (EM) and lisinopril dihydrate (LD), after reacting with 2,4-dinitrofluorobenzene.

2. Experimental

2.1. Materials and reagents

- Enalapril maleate (EM) and lisinopril dihydrate (LD) were obtained from Pharco-Pharmaceuticals (Alexandria, Egypt) and were used as such without any purification.
- Borate buffer was prepared as 0.02 M sodium tetraborate solution and pH was adjusted with 0.2 M sodium hydroxide or 0.2 M boric acid.
- 2,4-Dinitrofluorobenzene (Hopkin and Williams Co., Essex, UK) was prepared as 0.25% (w/v) solution in methanol for procedure I and as 0.2% (w/v) solution in DMSO for procedure II. The solutions of 2,4-dinitrofluorobenzene should be freshly prepared.
- Silver oxide was prepared in our lab [27].
- Analytical reagent grades of DMSO, methanol, diethyl ether, sodium hydroxide and sodium tetraborate were used.

2.2. Apparatus

- Perkin–Elmer double-beam UV–Vis spectrophotometer Model Lambda 3B attached to a Panasonic KX-3626 printer and using 1 cm quartz cells.
- Metrohm 693 VA Processor with a Model 694 VA Stand assembly containing a multimode working electrode, a Pt rod as auxiliary electrode and a reference Ag/AgCl 3 M KCl electrode.
- HPLC Shimadzu Model C-R7A Plus Chromatopac equipped with a UV detector SPD-10A.
- Schott-Gerate pH meter Model CG 710 calibrated with standard buffers.

2.3. Preparation of standard drug base solutions

Standard enalapril base solution was prepared by transferring about 20 mg of EM to a 100 ml volumetric flask using methanol. For each 1 mg amine salt, 2 mg silver oxide was added and the flask was shaken continuously for 3 min, thereafter the volume was completed to the mark with methanol. The solution was filtered and the first portion of the filtrate was discarded.

Lisinopril standard solutions were prepared as 0.2 mg ml^{-1} solution in distilled water for procedure I as well as the polarographic method and as 0.2 mg ml^{-1} in DMSO (after dissolving in the least amount of methanol) for procedure II.

2.4. General procedures and construction of calibration curves

2.4.1. Procedure I

Into different sets of screw-capped test tubes, accurate volumes of standard bases solutions (Table 1) were transferred (for enalapril, the volume was kept constant with methanol). A 0.2 ml borate buffer (pH 9 and 10 for enalapril and lisinopril, respectively) was added followed by 2.5 ml of DNFB methanolic solution. The test tubes were placed in a waterbath (the temperature and time are specified in Table 1), then cooled and the contents were transferred quantitatively into 10 ml volumetric flasks.

2.4.1.1. For spectrophotometric measurement. The solutions were completed to the mark with methanol. The absorbance was measured at the specified wavelengths (Table 1) against similarly treated blank.

2.4.1.2. For polarographic measurement. The volumes were adjusted to the mark using the same previously used buffer for each drug. The solutions were extracted twice with ether (each 15 ml). The etherial extracts were discarded and the aqueous solutions were heated at 40 °C. Aliquots from the aqueous solutions (2 ml for enalapril and 1 ml for lisinopril) were transferred into the polarographic cell, followed by 10 ml of borate buffer pH 9 and 10 for enalapril and lisinopril, respectively. The solutions were purged with pure nitrogen for 5 min. The differential pulse polarographic measurement was performed with a −50 mV pulse amplitude. The polarograms were recorded from −500 to −1200 mV vs. Ag/AgCl reference electrode at a scan rate of 10 mV s^{-1}.

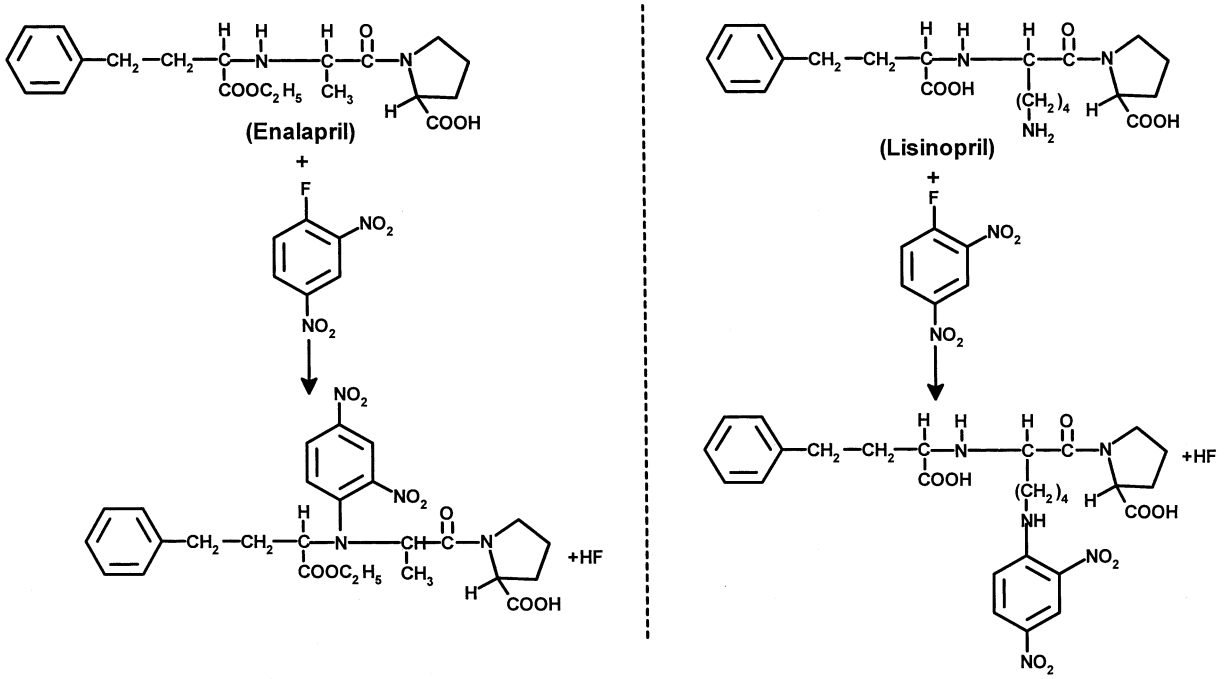
2.4.2. Procedure II

Aliquots from standard bases solutions (Table 1) were pipetted into 10 ml volumetric flasks (in case of enalapril) or screw-capped test tubes (in case of lisinopril). For enalapril, the volumes were kept constant with methanol. The specified volume of the reagent solution in DMSO was added (Table 1). For enalapril, the reaction occurs spontaneously at room temperature; while for lisinopril, the test tubes were heated in a waterbath at 60 °C for 20 min then cooled and transferred quantitatively into 10 ml volumetric flasks. The solutions were finally adjusted to volume with DMSO. The absorbances of the resulting solutions were measured at their corresponding λ_{max} (Table 1) against a reagent blank.

2.5. Procedures for commercial tablets

2.5.1. Enalapril maleate tablets

Twenty tablets were weighed and powdered. A quantity of the powder equivalent to 20 mg drug was quantitatively transferred into a 100 ml volumetric flask using methanol, followed by 40 mg silver oxide to liberate the base. The flask was



Scheme 1.

shaken mechanically for 30 min and the volume was completed to the mark with methanol. The solution was filtered into a dry flask and the procedure was completed as mentioned above under the general procedures.

2.5.2. Lisinopril tablets

Twenty tablets were weighed and powdered. An accurately weighed amount of the powder equivalent to one tablet was transferred into separate 100 ml volumetric flasks using about 40 ml distilled water or methanol for procedures I and II, respectively. The flasks were shaken mechanically for 30 min, completed to the mark with either distilled water or DMSO for procedures I and II, respectively, and finally filtered. The general procedures were then followed as described above.

3. Results and discussion

The two ACE inhibitors (EM and LD) are weakly UV absorbing and polarographically inactive compounds. The fact that EM contains a

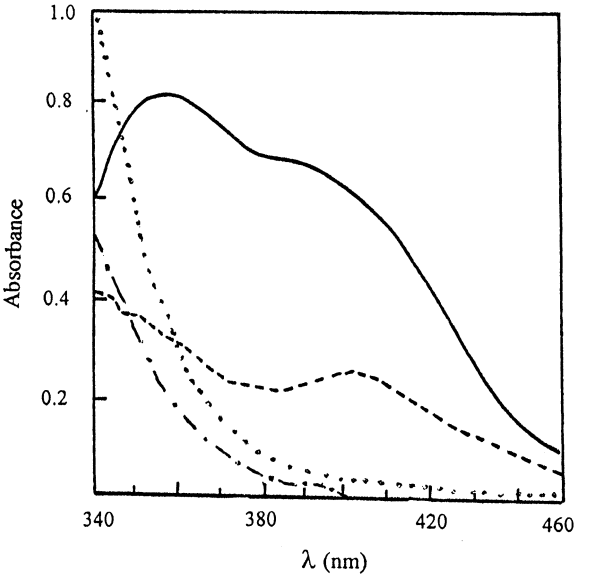


Fig. 1. Absorption curves of the dinitrophenyl derivatives of enalapril maleate (34.13 μg ml^{-1}) (—) and lisinopril (10.76 μg ml^{-1}) (- - -), and blank with (·-·-·) and without (...) acidification.

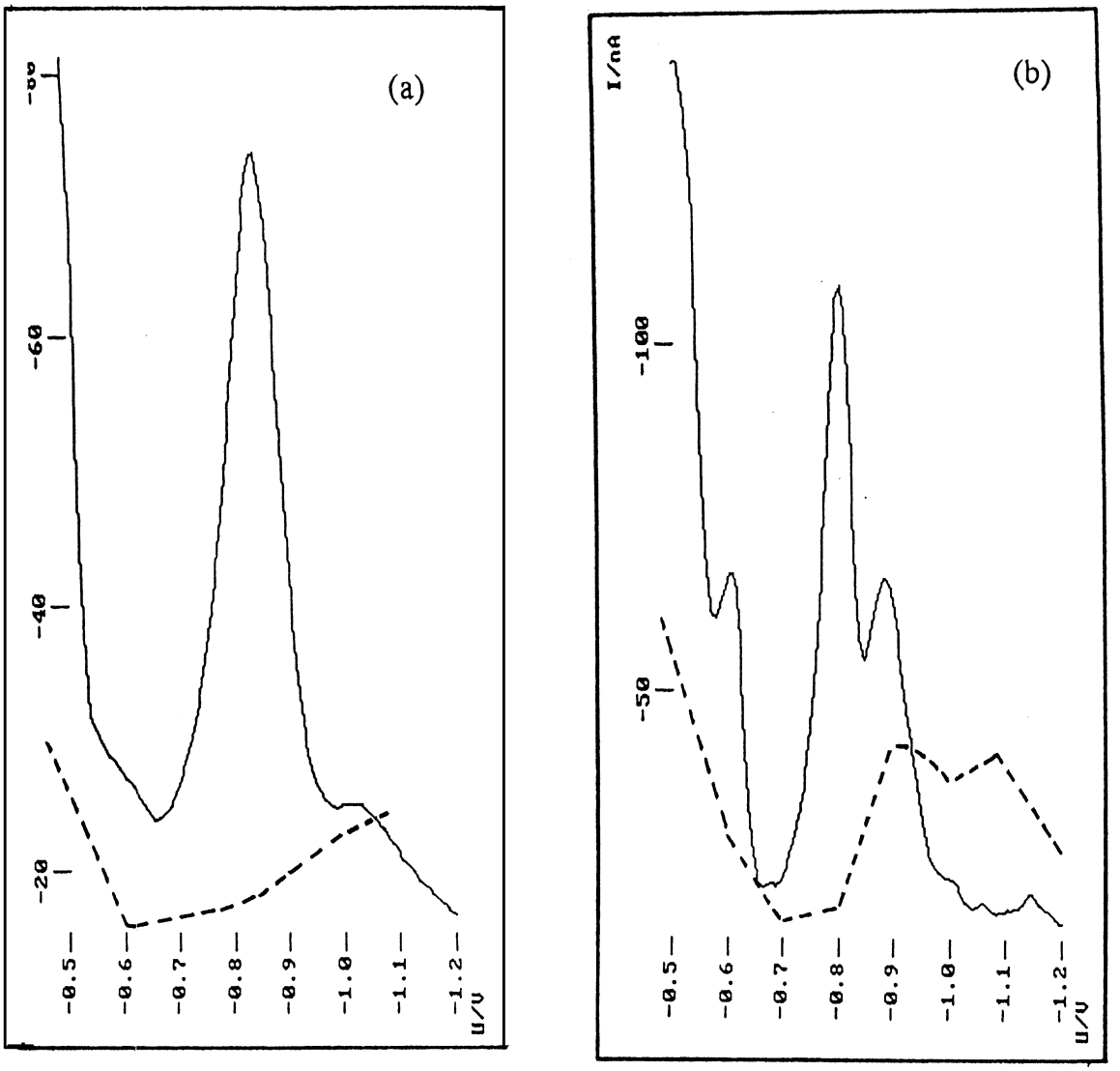


Fig. 2. Differential pulse polarograms of the dinitrophenyl derivatives of: (a) enalapril maleate (6.5 μg ml^{-1}) in borate buffer (pH 9) and (b) lisinopril (1.7 μg ml^{-1}) in borate buffer (pH 10). Each with the corresponding blank (- - -).

secondary amino group and LD contains a primary as well as a secondary amino group directed our thoughts to the possibility of using DNFB to introduce the electroactive chromophoric nitro group to their molecules. To liberate enalapril base, we cannot apply the traditional method (alkalinization with alkali hydroxide then extraction with volatile organic solvent) because it contains a carboxylic group which forms a water-soluble alkali salt. Silver oxide was used to provide the required alkalinity to liberate enalapril base, and the excess unconsumed silver oxide is removed by filtration.

3.1. Method I

In borate buffer, the nucleophilic aromatic substitution reaction between 2,4-dinitrofluorobenzene and each of enalapril and lisinopril proceeds as proposed in Scheme 1. Lisinopril

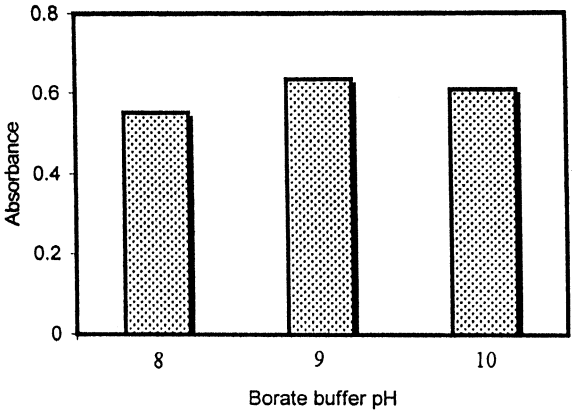


Fig. 3. Effect of buffer pH on the substitution reaction of enalapril maleate with 2,4-dinitrofluorobenzene.

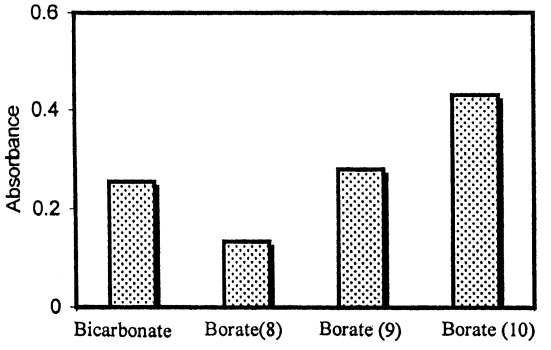


Fig. 4. Effect of buffer type and pH on the substitution reaction of lisinopril with 2,4-dinitrofluorobenzene.

molecule features primary and secondary amino groups. The presence of a carboxylic group adjacent to its secondary amino group leads to a Zwitter-ion-like structure. So, most probably, the nucleophilic attack occurs through its primary amino group. For enalapril, the secondary amino group is of sufficient basicity to attack 2,4-dinitrofluorobenzene.

The dinitrophenyl derivatives of enalapril and lisinopril have been measured spectrophotometrically and polarographically (DPP). The absorption spectra and polarograms are shown in Figs. 1 and 2.

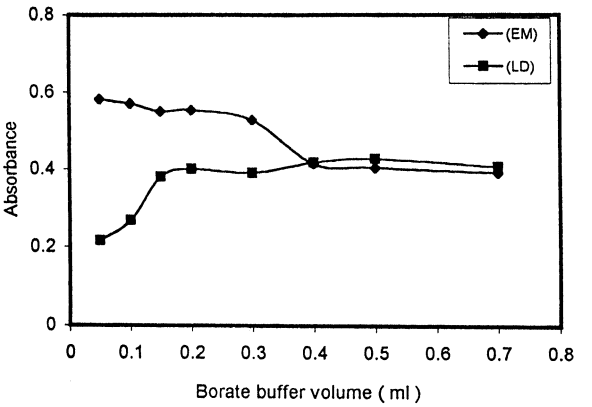


Fig. 5. Effect of borate buffer volume on the substitution reaction of enalapril maleate and lisinopril with 2,4-dinitrofluorobenzene.

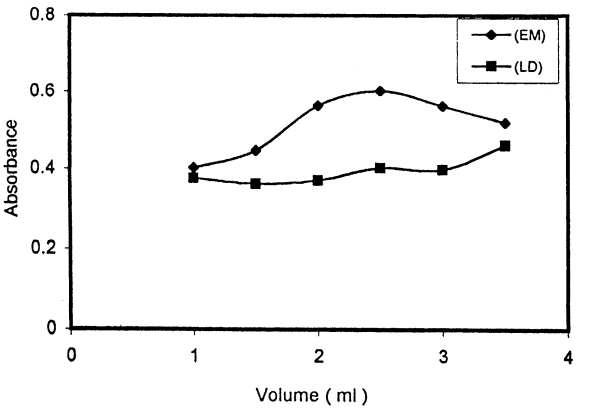


Fig. 6. Effect of 2,4-dinitrofluorobenzene (0.25%, w/v) volume on the substitution reaction of enalapril maleate and lisinopril with 2,4-dinitrofluorobenzene.

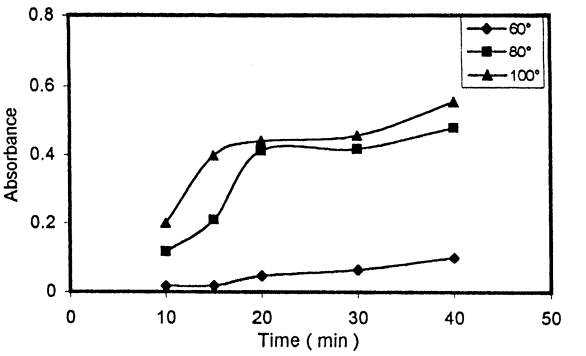


Fig. 7. Effect of heating temperature and time on the substitution reaction of enalapril maleate with 2,4-dinitrofluorobenzene.

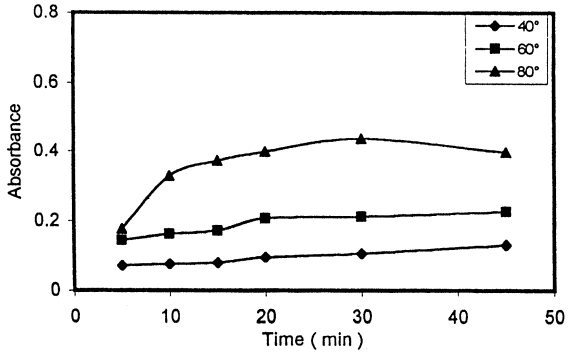


Fig. 8. Effect of heating temperature and time on the substitution reaction of lisinopril with 2,4-dinitrofluorobenzene.

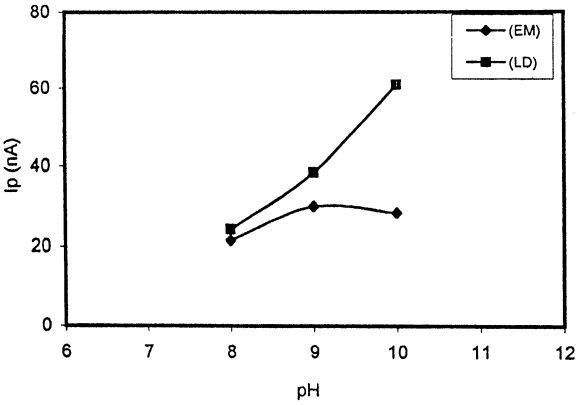
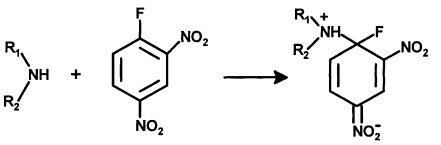


Fig. 9. Effect of borate buffer pH on the differential pulse peak current resulting from the reduction of the dinitrophenyl derivatives of enalapril maleate and lisinopril.



R_1 and R_2 stand for the rest of the drugs molecules

Scheme 2.

3.1.1. Optimum reaction conditions

The reaction conditions were optimized spectrophotometrically.

- The reaction was investigated over the pH range 8–10 using either bicarbonate or borate medium. For enalapril, no reaction occurred when using bicarbonate, while maximum sensitivity was achieved when using borate buffer of pH 9 (Fig. 3). For lisinopril, borate buffer (pH 10) gave the best results (Fig. 4). The optimum volume of the buffer solution was found to be 0.2 and 0.5 ml, respectively (Fig. 5).
- Concerning the reagent volume, it was found that 2.5 ml of DNFB solution is the optimum volume (Fig. 6).
- The effect of heating time and temperature was studied (Figs. 7 and 8); the optimal values are presented in Table 1.
- The reaction products were stable for at least 30 min.

3.1.2. The spectrophotometric measurement

It has been reported [24] that the excess reagent must be hydrolyzed to 2,4-dinitrophenol by acidification to get rid from the excess reagent spectral interference. Comparing the absorbance values of the blank solutions with and without acidification at 356 and 400 nm (λ_{max} of the reaction products; Fig. 1), it is clear that the acidification leads to a small decrease, which could be easily eliminated through the instrumental background correction (auto zero of blank); so acidification step has been omitted to render the procedure more simple.

3.1.3. The differential pulse polarographic measurement

- Before measurement, the excess unused reagent must be eliminated by extraction with ether [26].
- The polarographic reduction of the dinitrophenyl amine derivatives involves four electrons for each nitro group when carried out in buffer of pH 8–10 in order to be converted to the hydroxylamine [26]. The effect of borate buffer on the peak current was investigated over this range as it is reported that beyond pH 10, DNFB can hydrolyze, moreover, the dinitrophenyl amine derivatives are soluble at alkaline pH and precipitate in acidic medium [26]. The study showed that maximum peak current was obtained at pH 9 and 10 for enalapril and lisinopril, respectively (Fig. 9).

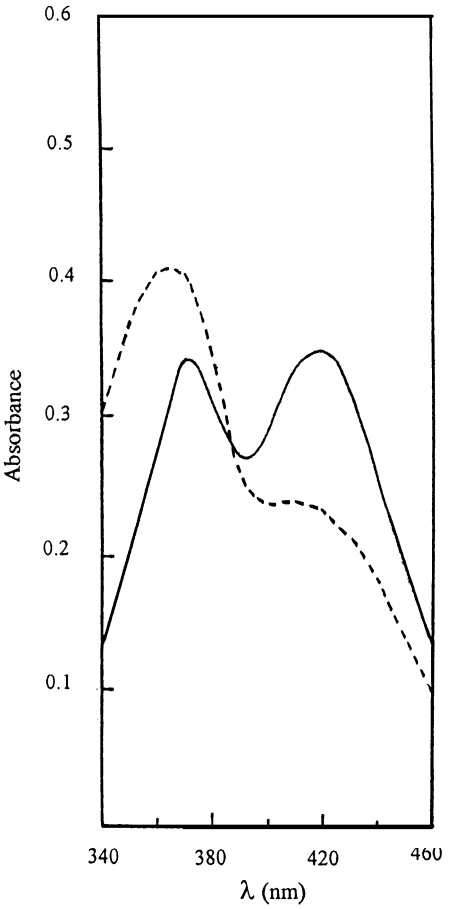


Fig. 10. Absorption curves of the Meisenheimer complexes formed between each of enalapril maleate (30.98 μg ml^{-1}) (—) and lisinopril (10 μg ml^{-1}) (- - -) and 2,4-dinitrofluorobenzene in DMSO.

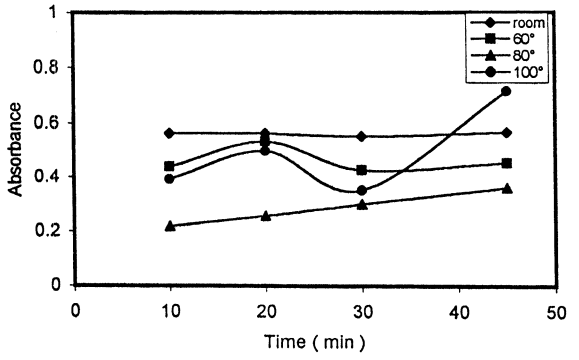


Fig. 11. Effect of heating temperature and time on Meisenheimer complex formation between enalapril maleate and 2,4-dinitrofluorobenzene in DMSO.

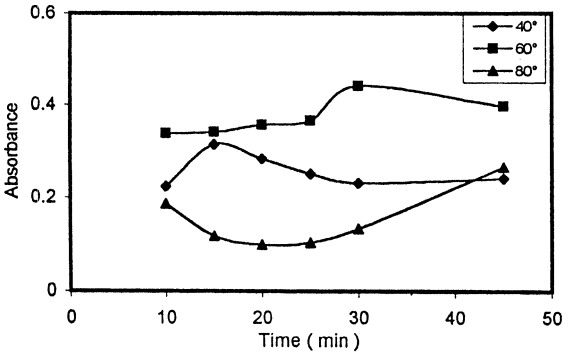


Fig. 12. Effect of heating temperature and time on Meisenheimer complex formation between lisinopril and 2,4-dinitrofluorobenzene in DMSO.

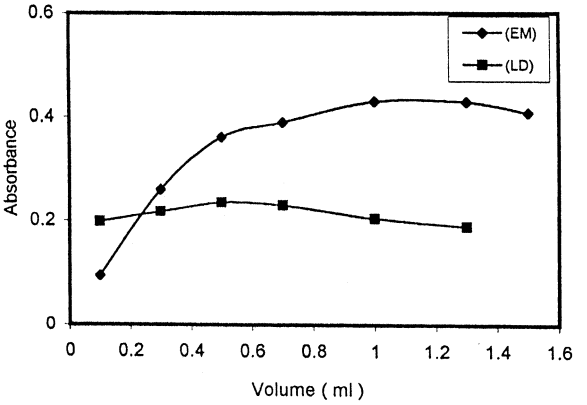


Fig. 13. Effect of 2,4-dinitrofluorobenzene (0.2%, w/v) volume on Meisenheimer complex formation between each of enalapril maleate and lisinopril and the reagent in DMSO.

3.2. Method II

The reaction of amines with polynitro compounds in DMSO has been shown to produce anionic σ-complexes of the Meisenheimer type [23]. The charge transfer from the nucleophile (enalapril or lisinopril) to the DNFB results in a covalently bonded σ-complex as shown in Scheme 2. The large polarizable complex formed is well solvated and stabilized in DMSO [28]. The visible spectra of the Meisenheimer complexes formed between DNFB and enalapril or lisinopril are shown in Fig. 10.

Table 2
Validation data for the determination of enalapril maleate through the reaction with 2,4-dinitrofluorobenzene

Item	Procedure I		Procedure II
	Spectrophotometry	DPP	
λ_{max} (nm) or E_p (mV)	356 nm	−844 mV	420 nm
Concentration range (μg ml^{-1})	12.90–38.70	2.41–7.75	20.80–83.20
Regression equation			
Intercept, a	-1.7×10^{-2}	−8.22	0.13
Variance of intercept, S_a^2	8.3×10^{-5}	2.73	5.2×10^{-5}
Slope, b	2.4×10^{-2}	12.34	7.1×10^{-3}
Variance around slope, S_b^2	1.1×10^{-7}	9.8×10^{-2}	2.0×10^{-8}
Correlation coefficient, r	0.9996	0.9990	0.9992
Variance, $S_{y,x}^2$	5.7×10^{-5}	1.90	5.3×10^{-5}
Accuracy (mean ± S.D.)	102.03 ± 1.16	101.02 ± 1.79	100.63 ± 1.86
Precision (RSD%)	1.89	1.98	1.15
Limit of detection (μg ml^{-1})	3.62	0.60	5.72
Limit of quantitation (μg ml^{-1})	12.07	2.00	19.07

Table 3
Validation data for the determination of lisinopril through the reaction with 2,4-dinitrofluorobenzene

Item	Procedure I		Procedure II
	Spectrophotometry	DPP	
λ_{max} (nm) or E_p (mV)	400 nm	−802 mV	364 nm
Concentration range (μg ml^{-1})	4.04–20.20	0.40–2.39	4.40–15.40
Regression equation			
Intercept, a	9.4×10^{-2}	8.36	-6.0×10^{-2}
Variance of intercept, S_a^2	1.1×10^{-4}	11.39	2.3×10^{-4}
Slope, b	1.7×10^{-2}	58.40	4.7×10^{-2}
Variance around slope, S_b^2	6.8×10^{-7}	6.06	2.3×10^{-6}
Correlation coefficient, r	0.9977	0.9973	0.9984
Variance, $S_{y,x}^2$	9.7×10^{-5}	16.47	1.7×10^{-5}
Accuracy (mean ± S.D.)	100.79 ± 1.68	101.38 ± 1.83	100.79 ± 1.96
Precision (RSD%)	1.92	1.77	1.56
Limit of detection (μg ml^{-1})	1.16	4.3×10^{-3}	0.87
Limit of quantitation (μg ml^{-1})	3.87	0.14	2.89

3.2.1. Optimum reaction conditions

- The complex formed between enalapril through its secondary amino group and DNFB is formed instantaneously at room temperature; moreover, the sensitivity decreased by increasing temperature (Fig. 11), while lisinopril required heating at 60 °C for 20 min for maximum color formation (Fig. 12).
- The effect of the reagent concentration on the developed color was investigated. Full color intensity was obtained when using 1.0 and 0.5 ml of DNFB solution for enalapril and lisinopril, respectively (Fig. 13).

Table 4
Assay results of enalapril maleate and lisinopril in their pharmaceutical preparations by the proposed methods

Item	Procedure I		Reference method	Procedure II
	Spectrophotometry	DPP		
Ezapril tablets[a] (10 mg enalapril maleate per tablet)				
Recovery (%)*	103.20	103.17	103.61	103.54
S.D.	0.91	0.83	0.75	0.85
t	0.78	0.88		0.14
F	1.47	1.22		1.27
Renitec tablets[b] (20 mg enalapril maleate per tablet)				
Recovery (%)*	103.19	102.00	102.40	103.57
S.D.	1.14	1.87	0.79	0.89
t	1.28	0.44		2.20
F	2.08	5.61		1.27
Zestril tablets[c] (equivalent of 20 mg anhydrous lisinopril per tablet)				
Recovery (%)*	103.66	101.71	102.14	101.94
S.D.	0.82	1.16	1.62	1.22
t	1.87	0.48		0.22
F	3.87	0.93		1.77

[a] Product of Kahira Pharm. and Chem. Ind. Co. for Multipharma Co., Egypt.
[b] Product of Merck Sharp & Dohme. Packed by Novartis Pharma S.A.E., Cairo.
[c] Product of Sedico Pharmaceutical Co., 6 October City, Egypt, under license of Zeneca Limited, Macclesfield Chesshire, England.
* Each value is the mean of five measurements. Theoretical values for *t* and *F* at $P = 0.05$ are 2.31 and 6.39, respectively.

- The Meisenheimer complex was found to be stable for 90 min for both drugs.

3.3. Validation of the proposed procedures

3.3.1. Linearity

Under the optimal experimental conditions, the absorbance values (for procedures I and II) and the differential pulse peak current values (for procedure I) were found to be proportional to drugs concentrations over the ranges stated in Tables 2 and 3. The good linearity was manifested by the values of the variances around the slopes (S_b^2) and correlation coefficients (r) as evident from Tables 2 and 3.

3.3.2. Accuracy

The accuracy of the proposed procedures was assessed by calculating the recovery of the drugs spiked ($\pm 50\%$ from the labeled content) in common tablet excipients (starch, talc, lactose, acacia, magnesium stearate and microcrystalline cellulose). The results are presented in Tables 2 and 3.

3.3.3. Precision

The precision of the methods was evaluated by calculating the relative standard deviation of the assay results of three different drugs concentrations each in three replicates. The values presented in Tables 2 and 3 are quite satisfactory.

3.3.4. Limit of detection and limit of quantitation

Tables 2 and 3 show the values of the limits of detection and quantitation for each drug by the proposed procedures.

3.4. Application to the analysis of tablets

The analysis of EM and LD in their commercial tablets was performed using the proposed procedures and the official HPLC methods [1]. The results obtained were compared statistically by the student's *t*-test and variance ratio *F*-test (Table 4). The experimental values did not exceed the theoretical ones in both tests, indicating the absence of any significant difference between the compared methods.

In conclusion, the proposed procedures are likely to be suitable for the analysis of EM and LD in their commercial tablets. Procedure II is more simple than procedure I since no pH adjustment is required; however, the polarographic measurement based on procedure I is more sensitive than the spectrophotometric ones.

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