

Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations

M.M. Al-Omari ^a, M.K. Abdelah ^a, A.A. Badwan ^a, A.M.Y. Jaber ^{b,*}

^a *The Jordanian Pharmaceutical Manufacturing Co. (JPM), P.O. Box 94, Naor 11710, Jordan*

^b *King Fahd University of Petroleum and Minerals, Chemistry Department, Dhahran 31261, Saudi Arabia*

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Abstract

The chemical stability of enalapril maleate in tablet dosage forms consisting of different formulation excipients has been studied in this work. The influence of various parameters such as heat, moisture, light and the drug-matrix was investigated. The degradation of enalapril maleate has been followed by using an HPLC method, which was demonstrated to be specific, stability indicating, accurate and precise. The degradation kinetics of enalapril maleate in phosphate buffer solutions of pH values in the range of 2.2–10.5 were observed to be pseudo first order throughout the whole pH range studied. Enalapril maleate alone showed high stability for temperature under dry and humid conditions, however it became unstable when mixed with the drug-matrix in its tablet formulations and exposed to the same conditions. The pathway of degradation of enalapril maleate was found to be pH dependent. The extent of degradation of two different enalapril maleate tablet formulations (product A of a basic drug-matrix and product B of an acidic drug-matrix) has been investigated. The degree of degradation of the product with acidic matrix was significantly less than that of the basic matrix under same temperature and humidity conditions. In fact, diketopiperazine and enalaprilat degradants were mainly associated with the degradation of the product with the acidic matrix and that with the basic matrix, respectively. Dry enalapril maleate powder showed some photolysis, which was more significant with daylight (3.3%) compared with that under UV light (0.2%). Although the product with the acidic matrix showed some photolysis but the effect was not pronounced and the % recovery of enalapril was almost complete and within the acceptable experimental errors. However, the product with the basic matrix showed almost no response for photolysis. © 2001 Elsevier Science B.V. All rights reserved.

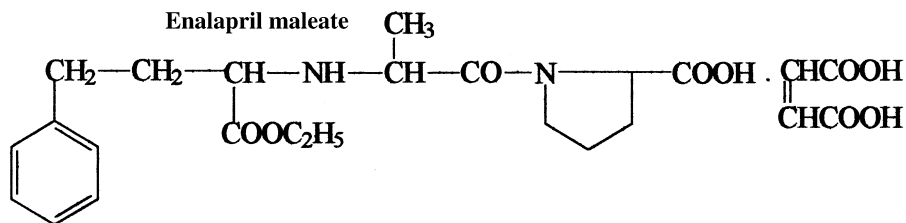
Keywords: Enalapril maleate; Lubricating agents; Enalaprilat; Diketopiperazine; Drug stability; HPLC

1. Introduction

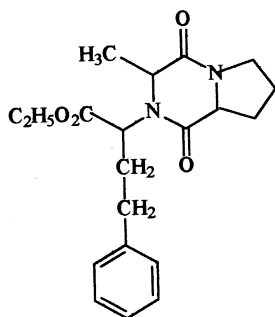
Enalapril maleate, angiotensin-converting enzyme inhibitor, is 1-*N*-[(*s*)-1-carboxyl-3-phenylpropyl]-L-alanyl-}-L-proline 1-ethyl ester maleate with the following structural formula,

* Corresponding author. Tel.: +966-3-8602611; fax: +966-3-8604277.

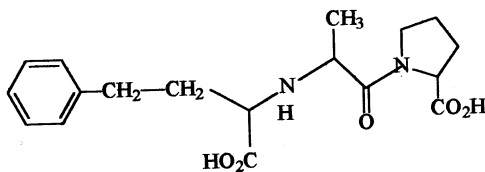
E-mail address: amjaber@kfupm.edu.sa (A.M.Y. Jaber).



Chemical and physical stability of enalapril maleate have been reported earlier in the literature. Enalapril maleate tablets formulated in lactose matrix containing magnesium stearate lubricant have shown an increase in the disintegration times at very high humidities. The drug degrades slightly to form diketopiperazine (DKP) by dehydration and the diacid enalaprilat by hydrolysis and these products increase with temperature [1]. It was also found that less than 2% of degradation of solid enalapril took place at 80°C when kept so for 3 weeks and a degradation of less than 1% when kept for 16 weeks at 40°C and 75% relative humidity (RH). When enalapril maleate was transferred into solution, the rate and the pathway of degradation, where dependent upon pH of the solution [2]. Below pH 5, the major degradation product was DKP, however, at pH 5 or above, the major degradation product was the diacid, enalaprilat. The structural formulas for these two products are shown below.



Enalaprilat



Diketopiperazine

The drug-excipient interaction followed by degradation as a result of hydrolysis and dehydration was not restricted to enalapril maleate but it was a major stability problem for the formulation of all the *N*-carboxyalkyl dipeptide analogs that work as potent angiotensin converting enzyme

inhibitors [3]. This degradation pattern took place in both solid state of the drug and in water, however the degradation in water was pH dependent [4–7]. It was reported that moexipril (RS-10085) degrades to diketopiperazine at pH 4 or below and suffers ester hydrolysis to a diacid product at pH above 5. A similar behavior has been reported for the moexipril (RS-10029), where the intramolecular aminolysis leading to diketopiperazine takes place at pH 8 or below. At pH values above 8, the diketopiperazine product starts decreasing while the amide hydrolysis increases and the hydrolysis predominates at pH above 11[5]. The drug-excipient incompatibility has been investigated for various excipients with moexipril hydrochloride in powder form at 60°C and different relative humidities [7]. The major degradation product of the drug raw material and all the 1:1 drug-excipient mixtures was diketopiperazine and the drug was more stable in a lower moisture environment. It has been also found that the basic excipients accelerate the

degradation of moexipril hydrochloride significantly at 60°C and 50% RH.

Interaction of active ingredients with the drug excipients in tablet formulations has also been reported for other drugs. For example, acylation and subsequent loss of potency have been observed

for aspirin-codeine [8] and aspirine–phenylephrine [9] combinations.

The effect of various formulation factors such as the type of excipient and packaging materials, temperature, light, pH of the matrix and humidity play an important role in the product design. Consequently, the influence of formulation factors should be considered during stability studies. This work aimed at studying the effect of two different types of tablet formulations (formulations with acidic and basic matrices) on the stability and pathway of degradation of enalapril maleate in solid matrices and tablets with respect to temperature and humidity. Furthermore, the effect of light on the stability of enalapril maleate alone and in tablet formulations was also investigated.

2. Experimental

2.1. Materials and instrumentation

Enalapril maleate of USP grade was obtained from JPM, Jordan. The excipients used were of pharmaceutical grades (USP or BP). All chemicals were of analytical or HPLC grade. Enalapril maleate, diketopiperazine, enalaprilat, enalapril lactone I and enalapril lactone II were supplied by JPM. Two commercial products of enalapril maleate tablets, product A (the tablet comprises 20 mg enalapril maleate, lactose, starch, magnesium stearate, red iron oxide, yellow iron oxide and sodium bicarbonate with aluminium/aluminium packaging material) and product B (the tablet comprises 20 mg enalapril maleate, lactose, starch and triglyceride palmitic acid with PVC/aluminum packaging material) were obtained from the Jordan market.

High performance liquid chromatograms have been run on a Du Pont Instrument/Series 8800 equipped with the Merck column, Lichrosphere C₈, 250 × 4.6 mm of 5 μm.

Ultraviolet rays sterilizer (AH POONG AP602) connected to germicidal lamp G15T8-AN 15W (SANKYO DENKI, Japan) was used to study the photolysis of enalapril maleate and the tablet formulations.

2.2. Chromatographic method

The standard USP HPLC method [10] in which the column oven was kept at 65°C has been employed. The mobile phase used was a mixture of phosphate buffer (pH 2)–acetonitrile (17:8, v/v). Phosphate buffer was prepared by adjusting the pH of 0.001 M potassium dihydrogen phosphate with phosphoric acid to 2. The flow rate was 1.5 ml/min. Chromatographic detection was set at 215 nm using a UV detector. The injection volume was 50 μl.

2.3. pH measurement

Powdered tablets equivalent to 40 mg enalapril maleate were dispersed in 10 ml of distilled water and the pH was measured using a Jenway 3030 pH meter.

2.4. Kinetics studies

Phosphate buffer solution of 0.010 M was prepared and sodium chloride was added to adjust the ionic strength of the buffer solution to 0.20 M. The pH of the buffer solutions was adjusted to the desired values (2.2–10.5) by the addition of aqueous sodium hydroxide solution. Samples of enalapril maleate (100 mg each) were dissolved in 250 ml of the phosphate buffers. The samples were kept in an incubator at 80°C for different storage intervals after which they have been withdrawn from the incubator and analyzed by the HPLC method.

2.5. Degradation of enalapril maleate and tablet formulations in solid matrices

2.5.1. Degradation under stress conditions

Samples of enalapril maleate powder (100 mg each), mixtures of enalapril maleate powder (100 mg each) and different formulation excipients including sodium bicarbonate, magnesium stearate and triglyceride palmitic acid were separately mixed and compressed using IR disc compressor (10 tons). The samples were placed in 100 ml quick fitted flasks, 0.1 ml of water was added to create high degree of humidity, and they were exposed to 100°C for 2 h. The samples were then

dispersed in 100 ml of phosphate buffer of pH 2 in the cases of enalapril maleate alone and mixtures of enalapril maleate–sodium bicarbonate, and in 100 ml of ethanol when enalapril maleate was mixed with triglyceride palmitic acid or magnesium stearate. The samples were then sonicated and centrifuged when necessary. Further dilution was made to obtain solutions having concentrations of about 40 mg enalapril maleate per 100 ml before analyzing them by the HPLC method.

2.5.2. Degradation under mild conditions

Samples of enalapril maleate powder (1.0 g each) were kept in open containers incubated at 40°C under dry and 75% RH (saturated solution of lead nitrate was employed to obtain the required range of humidity) conditions for a period of 6 months. Samples of about 80 mg were then withdrawn and dissolved in 200 ml phosphate buffer of pH 2.0 in order to get solutions having about 40 mg of enalapril maleate per 100 ml. The samples were then analyzed by the HPLC method.

Samples of blistered and nonblistered tablets of product A and product B were kept at 40°C under dry and 75% RH conditions for 6 months. Each sample of the two products was then treated and analyzed as above.

2.6. Photolysis studies

Samples of enalapril maleate powder (100 mg each) and powdered enalapril maleate tablets (equivalent to 100 mg enalapril maleate) were placed in quick fitted pyrex flasks and exposed to daylight or low intensity UV light for 15 days. The samples were then diluted with the mobile phase to obtain solutions having concentrations of about 20 mg enalapril maleate per 100 ml and analyzed by HPLC.

Another set of samples of enalapril maleate powder (100 mg each) were placed in 100 ml quick fitted pyrex flasks, 50 ml of distilled water (pH 2.3) or sodium bicarbonate solution (pH 6.5) were added to each flask. The flasks were then exposed to light and the resultant solutions were analyzed by HPLC after a suitable dilution to obtain solutions having concentrations of 20 mg enalapril maleate per 100 ml of mobile phase.

3. Results and discussion

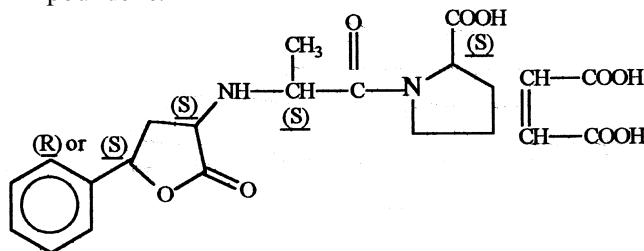
3.1. Validation of the HPLC method

Enalapril maleate and its degradation products were determined by HPLC according to the USP method [10]. The validity of the method was checked by running chromatograms for enalapril maleate and the known degradation products under the experimental set by the USP method given in the Section 2.

3.1.1. Specificity and stability indication tests of the HPLC method

Chromatograms were recorded for samples of enalapril maleate alone and after spiking with the expected impurities. The relative retention times recorded for enalapril maleate and the degradation products, enalaprilat and diketopiperazine, were 1.0, 0.30, 1.30, respectively. The photolysis and the oxidation (oxidation by H₂O₂) products of enalapril maleate were also separated well and appeared at relative retention times of 0.24 and 0.80, respectively.

Furthermore, it was possible to separate two synthesis impurities, namely, enalapril–lactone I and enalapril–lactone II which appeared at relative retention times of 0.45 and 0.52, respectively. These impurities could be formed as by-products resulting from the incomplete hydrogenation of the oxo-enalapril intermediate during the synthesis process. These enalapril–lactones were identified as, (5S)-N-(5-phenyl-dihydro-2(3H)-furanone-3(S)-yl)-L-alanyl-L-proline maleate (enalapril–lactone I) and (5R)-N-(5-phenyl-dihydro-2(3H)-furanone-3(S)-yl)-L-alanyl-L-proline maleate (enalapril–lactone II). The structural formula for these two compounds is:



Enalapril-lactone I (S) and Enalapril-lactone II (R)

The separation of all these impurities by the

HPLC method using a UV detector set at 215 nm assures the specificity of the method for enalapril maleate and all possible impurities.

To assess the HPLC method as a stability indicator for enalapril maleate, chromatograms were recorded for enalapril maleate in different matrices under various stress conditions where degradation was stimulated by heat, light or hydrogen peroxide (Table 1). Table 1 shows a decrease in the assay of enalapril maleate under different degradation conditions associated with the formation of degradation products. These results indicate the possibility of simultaneous detection of the degradation products resulted from hydrolysis in basic media, cyclization in acidic media, photolysis or oxidation, thus the method is a stability indicator for enalapril maleate.

3.1.2. Linearity, accuracy, repeatability and intermediate precision

Calibration graphs were plotted for certain concentration ranges of enalapril maleate and its possible degradation products in pure or drug-matrix solutions. The concentration range of enalapril maleate was about 50–400 $\mu\text{g ml}^{-1}$ and that of diketopiperazine and enalaprilat was about 0.4–5 $\mu\text{g ml}^{-1}$. All calibration plots showed excellent linear-

ity with correlation coefficients of better than 0.9999. The limit of detection, LOD, and limit of quantification, LOQ, for enalapril maleate in the pure solutions were 2.0 and 6.6 $\mu\text{g ml}^{-1}$, respectively, and in drug-matrix solutions were 3.1 and 10.4 $\mu\text{g ml}^{-1}$, respectively. However, in drug-matrix solutions, LOD and LOQ for diketopiperazine were respectively, 0.068 and 0.23 $\mu\text{g ml}^{-1}$, meanwhile they were 0.019 and 0.063 $\mu\text{g ml}^{-1}$ for enalaprilat.

The accuracy of the method towards enalapril maleate was checked by analyzing various samples of enalapril maleate in the drug-matrix solutions using different concentrations covering a range of about 50–400 $\mu\text{g enalapril maleate ml}^{-1}$ (25–200% of the target concentration that is 200 $\mu\text{g ml}^{-1}$). The percent recovery was in the range of 99.1–100.5 with a bias of -0.9 to $+0.2$. The overall percent recovery was 99.7 with a relative standard deviation of 0.66%. The overall percent recoveries of diketopiperazine and enalaprilat in the drug matrix solutions were 97.4 and 103.8 with relative standard deviations of 0.67 and 1.2%, respectively.

Various samples of enalapril maleate in the drug-matrix solutions were analyzed by three analysts as a means to test the repeatability and intermediate precision of the method. The percent

Table 1

Degradation of enalapril maleate alone and with drug-excipients when stored for various storage intervals under different stress conditions in solid matrices and high humidity or in solution

Material/storage conditions	% Enalapril recovered	% Degradation		
		Diketopiperazine	Enalaprilat	Others
Enalapril maleate (disc)/100°C/2 h	77.2	21.0	2.6	–
Enalapril maleate and triglyceride palmitic acid (disc)/100°C/2 h	77.0	21.0	2.6	–
Enalapril maleate and magnesium stearate (disc)/100°C/2 h	50.0	18.0	21.0	–
Enalapril maleate and sodium bicarbonate (disc)/100°C/2 h	80.7	0.1	14.9	–
Enalapril maleate in phosphate buffer solution, pH 10.5/80°C/2 h	65.7	–	28.0	–
Enalapril maleate in phosphate buffer solution, pH 2.2/80°C/24 h	83.5	10.0	–	–
Enalapril maleate in water solution (pH 2.3)/daylight/room temperature/15 days	97.5	–	–	5.0 (photolysis product)
Enalapril maleate in 3.5% H_2O_2 solution/65°C/12 h	66.0	3.0	–	5.0 (oxidation product)

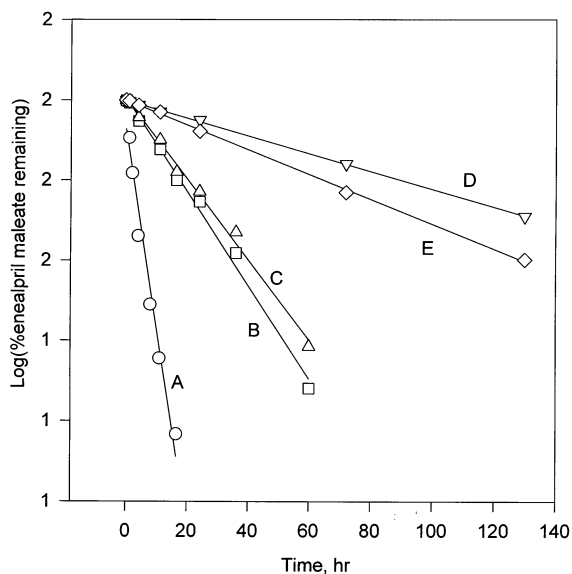


Fig. 1. Plots of log (% enalapril maleate remaining) against time for the degradation of enalapril maleate in samples of about $400 \mu\text{g ml}^{-1}$ enalapril maleate in aqueous buffers of pH 10.5 (A); 7.0 (B); 5.5 (C); 3.4 (D); and 2.2 (E) at 80°C .

recoveries for enalapril maleate obtained by the analysts was in the range of 100.0–101.8 and the relative standard deviation (R.S.D.) was in the range of 0.1–0.9%. However, the overall percent recovery obtained by the three analysts for enalapril maleate was 101.1 and R.S.D. was 0.57%.

3.2. Kinetics of enalapril maleate degradation

The stability of enalapril maleate was investigated in aqueous matrix containing 0.010 M phosphate buffer of pH values of 10.5, 7.0, 5.5, 3.4 and 2.2 with ionic strength adjusted to 0.2 M and stored at 80°C . Enalapril maleate left after various storage intervals was assessed by the stability indicating HPLC method mentioned above. The linearity of the plots of log (% enalapril maleate) remaining against time (Fig. 1) indicates that the degradation follows a first-order kinetics. Since water and other matrix components are in large excess to enalapril maleate, the kinetics would be a typical pseudo first-order process. Fig. 1 shows that the rate of enalapril loss is depen-

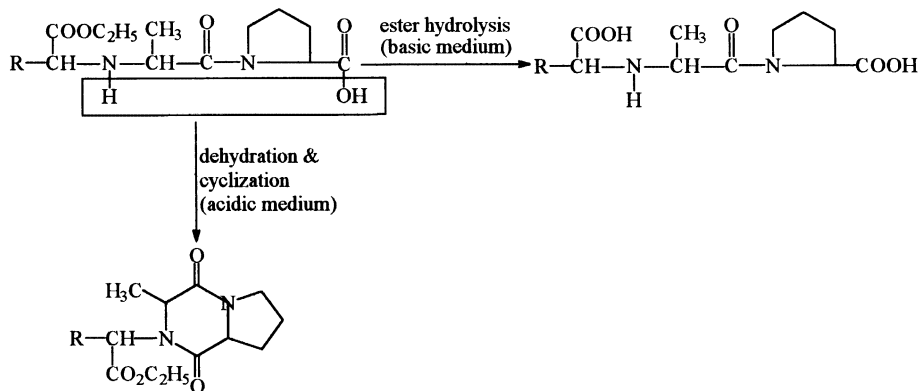
dent upon the solution pH and it is obvious that the degradation at pH 10.5 is more significant than that at lower pH values. This kinetic behavior is compatible with the earlier reports for enalapril maleate [2] and the *N*-carboxyl dipeptide angiotensin converting enzyme inhibitors [3–7].

3.3. Degradation of enalapril maleate in solid formulations

The stability and pathway of degradation of enalapril maleate alone or in the presence of possible drug-excipients in solid matrices were first investigated under stress conditions where the components were kept for 2 h under a temperature of 100°C and relative humidity of $>90\%$. Table 1 shows that enalapril maleate alone or in the presence of triglyceride palmitic acid drug-excipient decomposes mainly into diketopiperazine (21.0%) with a small proportion of enalaprilat (2.6%). However, the main degradation product in the presence of sodium bicarbonate is enalaprilat (14.9%) with insignificant proportion of diketopiperazine (0.1%). Enalapril maleate in the presence of magnesium stearate showed, significantly, a higher degree of degradation with almost similar proportions of diketopiperazine (18.0%) and enalaprilat (21%) degradation products (Table 1).

It is obvious from the above results that the degree and pathway of degradation of enalapril maleate are dependent upon humidity and the pH of the drug-matrix. This degradation may be ascribed to the drug-matrix interaction in the solid form at elevated temperatures in the presence of moisture. The pathway of degradation has been attributed to the dehydration followed by intramolecular cyclization in the acidic medium, which leads to the formation of diketopiperazine and to the ester hydrolysis of enalapril maleate that leads to the formation of enalaprilat in the basic medium [1,2]. Scheme 1 below, represents these two reactions.

Enalapril maleate powder stored for 6 months at 40°C in the absence and presence of humidity showed insignificant degradation; 0.1–0.2% of diketopiperazine and 0.1% of enalaprilat were detected (Fig. 2, chromatogram A and Table 2).



Scheme 1. Degradation of enalapril maleate in acidic and basic media.

Thus, the mild temperature, humidity and moderate pH values for the drug-matrix do not effect the degradation of enalapril maleate.

When nonblistered tablets of product A and product B were kept at 40°C and 75% RH for 6 months, a degradation to diketopiperazine and enalaprilat has been detected by the HPLC chromatograms; this degradation was relatively more significant for product A compared with product B; 85.3 and 97.4% of enalapril have been recovered from samples of product A and product B, respectively, (Table 2 and Fig. 2, chromatogram B). Infact, enalaprilat was the main degradant (11.9%) from product A and diketopiperazine was the main degradant (5.7%) from product B.

Blistered tablets of product B showed an insignificant degradation (Table 2) when stored at 40°C under dry (a recovery of 101.5% enalapril with a total degradation of 1.4%) and 75% RH (a recovery of 101.2% enalapril with a total degradation of 1.3%). Meanwhile, blistered tablets of product A under the same conditions showed a relatively more tendency for degradation when stored at 40°C under dry (a recovery of 97.8% enalapril) and 75% RH (a recovery of 95.0% enalapril) conditions with a total degradation of 3.5 and 4.4%, respectively.

It is obvious from the above results that the degree and pathway of degradation of the tablet formulations are similar to those for enalapril maleate under the stress conditions mentioned above and they are dependent on the pH of the

drug-matrix, temperature and humidity. The product with an acidic matrix showed a less significant degradation compared with that with a basic matrix when both were stored under the same conditions. Furthermore, blistering of the tablets in both formulations reduces the degradation significantly even in the presence of 75% RH.

3.4. Photolysis of enalapril maleate alone and in its tablet formulations

Photolysis of enalapril maleate as powder or in aqueous acidic or basic solution and in tablet formulations (products A and B) was investigated by exposing them to the daylight and low intensity UV light for 15 days. HPLC chromatograms for enalapril maleate alone or in acidic (pH 2.3) aqueous solutions when exposed to daylight or to low intensity UV light, showed new peak at a retention time of about 1.9 min in addition to those for enalapril, diketopiperazine and enalaprilat (Fig. 3). It was not possible to quantify this peak accurately since the photodegradation product is unknown. Thus, the quantity of this product was estimated based on its relative peak areas in the HPLC chromatograms. The estimation for the photodegradation product indicated that enalapril maleate alone had a significant photodegradation (3.3% for the dry powder and 5.0% for the aqueous solution of pH 2.3, Table 3) when exposed to daylight. The photolysis degradation was negligible in the basic solutions of pH

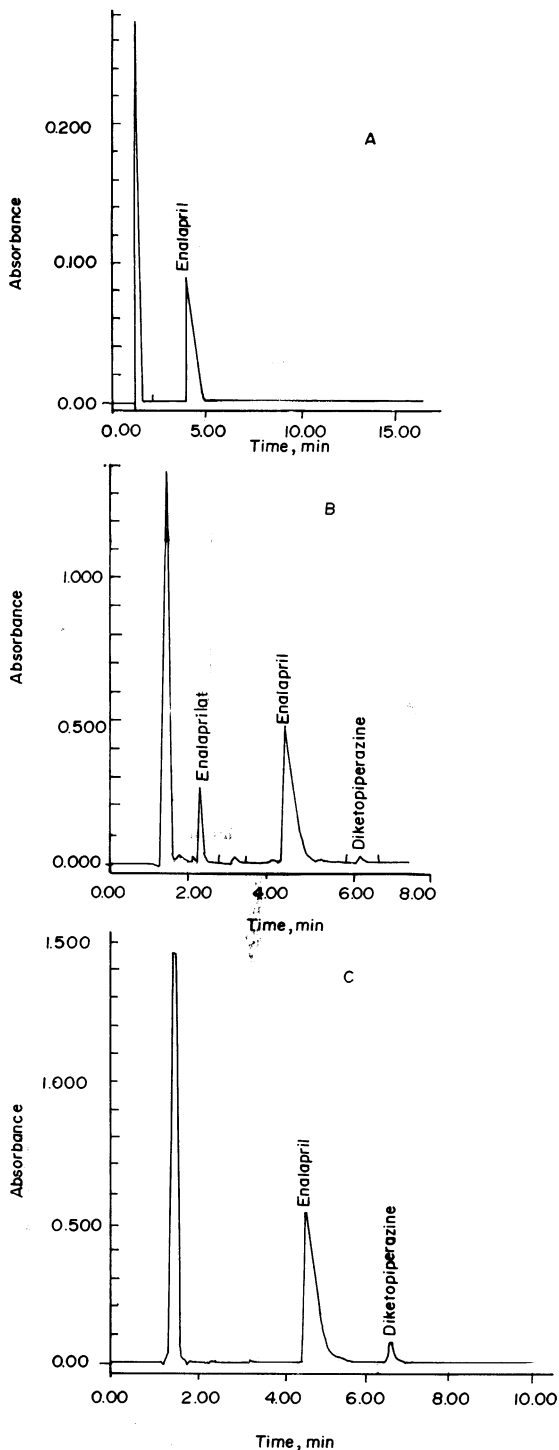


Fig. 2. HPLC chromatograms for enalapril maleate alone (chromatogram A), tablets of product A (chromatogram B) and tablets of product B (chromatogram C) after storage at 40°C and 75% RH for 6 months.

6.5 (Table 3). Also, under UV light the photolysis of enalapril maleate in powder or in basic solutions was insignificant (0.2% for the dry powder, Table 3).

The photodegradation peak had appeared in the chromatograms of product B (Fig. 3, chromatogram C) after exposure to daylight although its contribution to the total area was relatively insignificant (0.9%, Table 3). However, chromatograms of product A showed an insignificant photolysis (traces, Fig. 3, chromatogram B, Table 3). The reduction in the photodegradation of product B with an acidic drug-matrix in comparison to enalapril maleate powder may be ascribed to the decrease in the surface area exposed to light in the presence of formulation excipients. On the other hand, the better light stability showed by product A might be ascribed to the basicity of the drug-matrix and/or the presence of red and yellow iron oxide.

4. Conclusion

The degradation of enalapril maleate can be studied by an HPLC stability indicating method. Enalapril maleate powder is stable against moderate heat and humidity; 40°C and 75% RH. However, in tablet formulations, enalapril maleate would show some instability, which may be ascribed to its interaction with the drug-matrix. The major degradation kinetics of enalapril maleate was observed to be a pseudo first order.

Enalapril maleate tablet formulations with an acidic matrix would have a better stability against temperature and humidity over those formulations comprising a basic matrix. Humidity, type of the drug-matrix and its pH and blistering of the tablets may be the major factors that affect the stability of the drug in its tablet formulations. Enalapril maleate in the tablets with a basic matrix may have a relatively improved stability against light compared with the tablets of the acidic matrix.

Consequently, enalapril maleate tablet formulations with basic matrices should not be exposed to high temperature and moisture due to its instability under these conditions, meanwhile, the formu-

Table 2

Stability of enalapril maleate powder alone and in tablet formulations stored for 6 months at 40°C under dry and humid conditions

Material	Storage conditions	% Enalapril recovered	% Degradation	
			Diketopiperazine	Enalaprilat
Enalapril maleate powder	Dry	100.0	0.1	0.1
Enalapril maleate powder	75% RH	100.0	0.2	0.1
Product A (nonblistered tablets)	75% RH	85.3	1.3	11.9
Product B (nonblistered tablets)	75% RH	97.4	5.7	0.3
Product A (blistered tablets)	Dry	97.8	2.7	0.8
Product A (blistered tablets)	75% RH	95.0	3.2	1.2
Product B (blistered tablets)	Dry	101.5	1.2	0.2
Product B (blistered tablets)	75% RH	101.2	1.0	0.3

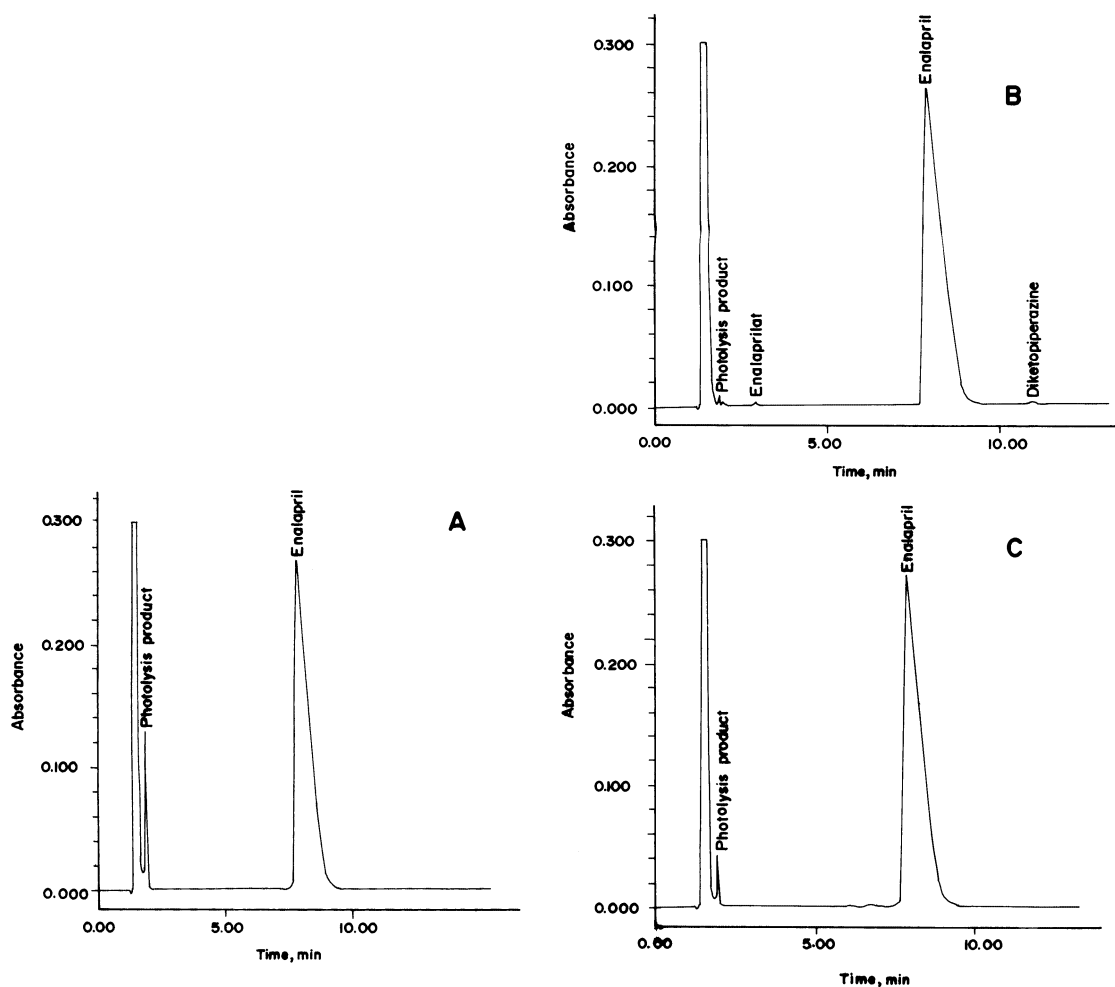


Fig. 3. HPLC chromatograms for enalapril maleate powder (chromatogram A), tablets of product A (chromatogram B) and tablets of product B (chromatogram C) after storage at room temperature exposed to daylight for 15 days.

Table 3

Photolysis of enalapril maleate as dry powder alone, in tablet formulations and in aqueous solutions after exposure to daylight and low intensity UV light for 15 days^a

Sample	Storage condition	% Enalapril recovered	% Degradation		
			DKP	EA	PD
Enalapril maleate	Dark	99.6	–	–	–
Enalapril maleate	Daylight	99.5	–	–	3.3
Enalapril maleate	UV light	99.8	–	–	0.2
Product B	Dark	103.0	–	–	–
Product B	Daylight	102.7	–	–	0.9
Product B	UV light	103.3	–	–	0.2
Product A	Dark	100.6	0.7	0.3	–
Product A	Daylight	97.7	0.5	0.3	Traces
Product A	UV light	97.8	0.7	0.3	Traces
Enalapril maleate	Aqueous solution (pH 2.3)/dark	99.4	0.4	0.5	–
Enalapril maleate	Aqueous solution(pH 2.3)/daylight	97.5	–	–	5.0
Enalapril maleate	Aqueous solution (pH 2.3)/UV light	100.0	0.4	0.6	–
Enalapril maleate	Aqueous solution + NaHCO ₃ (pH 6.5)/dark	86.0	–	13.2	–
Enalapril maleate	Aqueous solution + NaHCO ₃ (pH 6.5)/daylight	90.5	–	8.1	Traces
Enalapril maleate	Aqueous solution + NaHCO ₃ (pH 6.5)/UV light	82.0	–	16.2	–

^a EA: enalaprilat; DKP: diketopiperazine; PD: photodegradation product.

lations with acidic matrices should be protected from light.

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