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COMMUNICATION

Search for Related Substances in Market Products Containing Enalapril Maleate as the Active Principle

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ABSTRACT

This study's main object was the determination of substances, by means of high-performance liquid chromatography (HPLC), that are related to enalapril maleate in medicinal tablets. The research was on products containing a 20 mg active principle with a 12-month Δt *and on those batches near their expiration date with an enalapril maleate concentration of 10, 5, and 2.5 mg.*

INTRODUCTION

Enalapril maleate is prescribed for the treatment of arterial hypertension; its action occurs by the inhibition of the converter enzyme of angiotensin (3). After oral administration, bioactivation by hydrolysis of the ethylic ester to enalaprilat takes place, which is responsible for the pharmacological action (Fig. 1). Given that the oral absorption of enalapril is higher than that of enalaprilat, the former is the active principle chosen for oral pharmaceutical forms. At the same time, enalaprilat is the active drug chosen for the pharmaceutical form for intravenous administration.

The two main ways of degradation are the hydrolysis of ethylic ester to enalaprilat and the cyclization to diketopiperazine from enalapril (Fig. 2). The active drug is very stable in the solid state, if kept at environmental temperatures and in an amber glass container, and does not show the presence of degradation products by high-performance liquid chromatography (HPLC). The pharmaceutical tablet form is stable in environments protected from high temperatures and humidity. When

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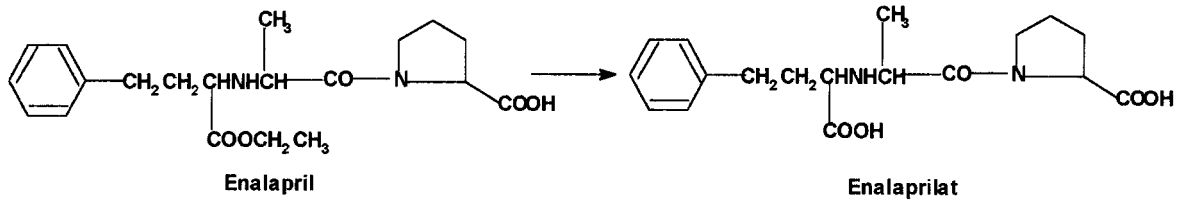


Figure 1. Bioactivation.

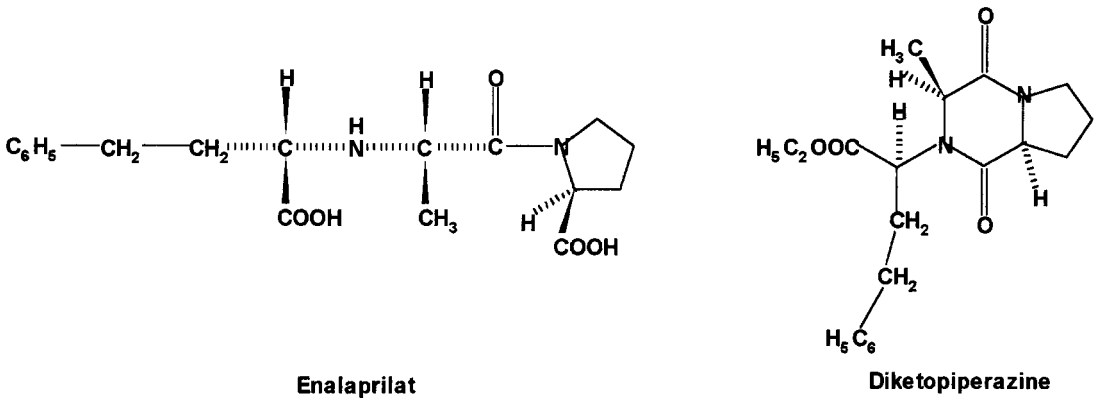


Figure 2. Main ways of degradation.

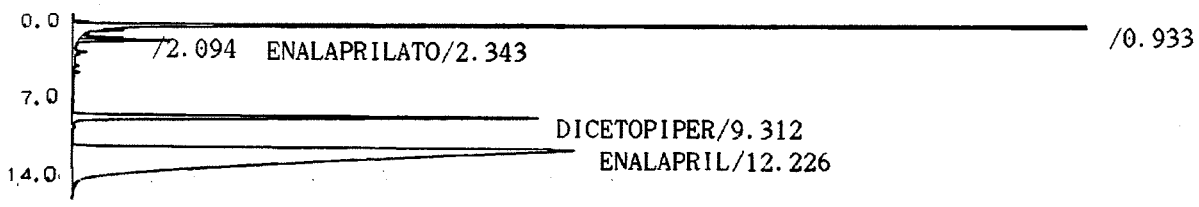
stocked in open packages at a temperature of 40°C and 75% relative humidity, a decrease of about 10% of active principle after 3 months, with enalapril diketopiperazine the main product of degradation (1).

MATERIALS AND METHODS

The quantity of sample that permitted follow-up for a period of time for the 20-mg medicinal specialty was taken form the respective certificate owner's manufacturing laboratory specifications. For those tablets containing 10, 5, and 2.5 mg active principle, the analysis was made on samples from batch files 15 to 23 months from manufacture.

A Shimadzu (Kyoto, Japan) liquid chromatograph with a Lichrocart 125 × 4 mm Lichrospher 100 C8 (5 μm) column was used. The mobile phase was phosphate buffer at pH 2.5 and acetonitrile (ACN) (68:32). Injection volume was 20 μl, with flow at 1 ml/min. Detection wavelength was 215 nm. Column oven temperature was 50°C.

For the concentrated standard, 25 mg of maleate enalapril secondary standard was weighed accurately and transferred quantitatively to a 50-ml glass flask. About 30 ml of pH 2.5 buffer was added, and the mixture was



Chromatogram 1. Method specificity.

Table 1

Results for Enalapril 20-mg Tablets (for up to 3 Determinations)

Product	Batches	Months as of Manufacture Date	Primary Container	Impurities (%)	Title (%)
A	1. Expiration date 11/98	11		6.0	91.7
	2. Expiration date 11/97 (files sample)	12	Polyvinyl chloride (PVC)	6.3	87.0
B	1. Expiration date 3/98	12	PVC	2.3	101.0
C	1. Expiration date 3/98	13	Aluminum-aluminum (Al-Al)	1.4	103.7
D	1. Expiration date 11/97	12	PVC	6.0	97.9
	2. Expiration date 8/97 (file sample)	16		8.6	87.8
E	1. Expiration date 5/98	11	Al-Al	0.6	95.5
F	1. Expiration date 5/98	11	Al-Al	2.6	96.9
G	1. Expiration date 10/98	7		1.7	96.9
	2. Expiration date 9/97 (file sample)	16	Amber PVC inside an Al paper envelope	2.7	94.9
	3. Expiration date 1/98 (file sample)	20		8.4	87.7
H	1. Expiration date 6/98	10	Al-Al	1.5	95.0
I	1. Expiration date 12/97	16	Al-Al	1.2	97.5
J	1. Expiration date 4/98	9	Al-Al	0.3	87.2
K	1. Expiration date 3/98	13	Al-Al	1.5	96.0

Table 2

Results for Enalapril 10-mg Tablets

Product	Batches	Months as of Manufacture Date	Primary Container	Impurities (%)	Title (%)
A	1. Expiration date 5/98	14		9.1	84.0
	2. Expiration date 11/97	20	Amber PVC	13.4	72.9
B	1. Expiration date 5/98	15		1.9	99.0
	2. Expiration date 11/97	20	PVC	8.0	85.8
C	1. Expiration date 10/97	21	Al-Al	1.3	106.0
D	1. Expiration date 8/97	23	PVC	10.2	94.9
E	1. Expiration date 9/97	22	Al-Al	1.0	95.8
F	1. Expiration date 5/98	14		2.7	96.2
	2. Expiration date 12/98	19	Al-Al	2.6	96.0
	3. Expiration date 8/97	23		2.7	90.3
G	1. Expiration date 11/98	8	Amber PVC inside an	2.6	99.9
	2. Expiration date 1/98	18	aluminum paper envelope	21.8	74.0
H	1. Expiration date 3/98	15	Al-Al	4.8	90.8
	2. Expiration date 8/97	23		6.6	92.2
I	1. Expiration date 12/97	19	Al-PVC titanium	5.5	88.5
	2. Expiration date 9/97	22		5.3	89.3
K	1. Expiration date 8/97	23	Al-Al	0.8	100.0
L	1. Expiration date 4/99	4	PVC	19.7	75.0
M	1. Expiration date 7/98	8	PVC	9.6	86.9

Table 3

Results for Enalapril 5-mg Tablets

Product	Batches	Months as of Manufacture Date	Primary Container	Impurities (%)	Title (%)
C	1. Expiration date 3/98	16	Al-Al	2.2	103.9
	2. Expiration date 9/97	22		1.9	108.5
E	1. Expiration date 9/97	22	Al-Al	1.1	101.0
F	1. Expiration date 4/98	15	Al-Al	3.5	96.1
	2. Expiration date 8/97	23		4.5	92.0
G	1. Expiration date 10/98	9	Amber PVC inside an	6.6	74.0–84.0
	2. Expiration date 4/98	15	aluminum paper envelope	36.6	76.1
	3. Expiration date 10/97	21		19.8	79.0
H	1. Expiration date 2/99	5		3.8	90.0
	2. Expiration date 11/98	8	Al-Al	7.1	85.8
	3. Expiration date 7/97	24		7.1	90.0
K	1. Expiration date 8/97	23	Al-Al	1.0	102.2

Table 4

Results for Enalapril 2.5-mg Tablets

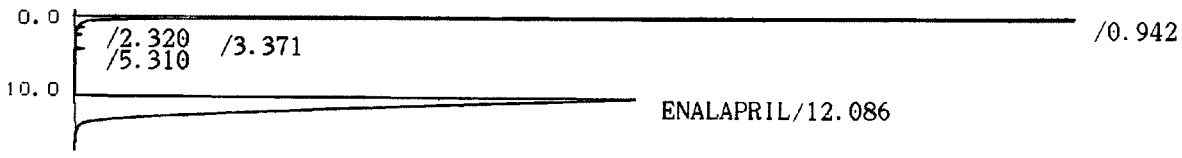
Product	Batches	Months as of Manufacture Date	Primary Container	Impurities (%)	Title (%)
C	1. Expiration date 4/98	15	Al-Al	2.7	102.9
	2. Expiration date 1/98	18		9.4	87.1
E	1. Expiration date 9/97	22	Al-Al	1.9	93.0
H	1. Expiration date 9/97	22	Al-Al	15.1	76.0
K	1. Expiration date 8/97	23	Al-Al	1.5	99.6

sonicated for 10 min. The mixture was brought up to volume using the same dissolvent. For the dilute standard, 5 ml of the previous solution was transferred using a double gauge pipette to a 50-ml glass flask. This was brought up to volume with pH 2.5 buffer. For the enalaprilat standard, 10 mg was weighed and brought to 100 ml with pH 2.5 buffer. The diketopiperazine standard followed the same procedure.

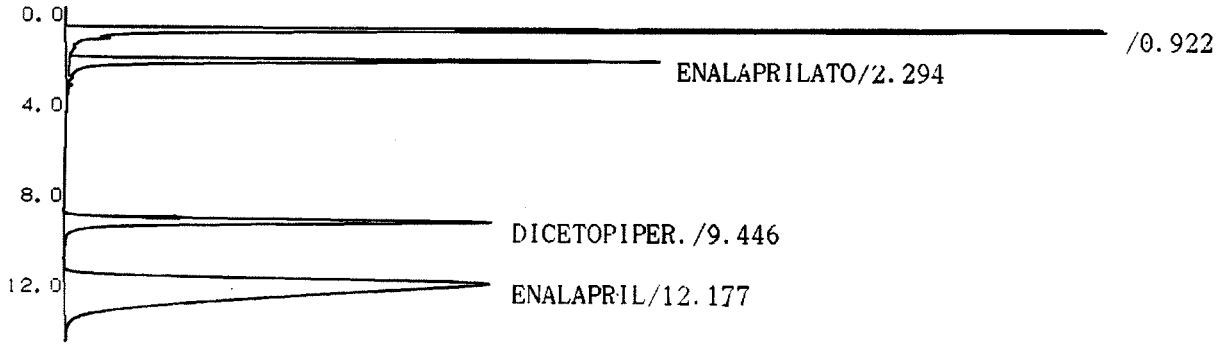
For the test solution, an average weight for 20 tablets was obtained. Fine powder equivalent to 25 mg of enalapril maleate was weighed and poured into a 50-ml glass flask. This was diluted with approximately 30 ml of pH 2.5 buffer, shaken mechanically for 15 min, and sonicated for the same period of time. The solution was brought to volume and filtered with white band paper, discarding 10 ml of filtered material.

All solutions were filtered using 0.45-μm membranes.

A solution containing enalapril maleate and the impurities was injected with enalaprilat and diketopiperazine to identify them in the chromatogram (Chromatogram 1).



Chromatogram 2. Raw material 15 months old.



Chromatogram 3. Contribution of diketopiperazine to degradation.

The calculation for the sample was made taking into account the sum of the areas of the mentioned products.

The developed methodology was validated according to the chromatographic conditions of the USP XXIII method (2).

A Shimadzu liquid chromatograph with a Lichrocart (Merck, Darmstadt, Germany) C8 125 × 4 mm, Lichrospher 100 (5 μm) column was used. The mobile phase was phosphate buffer at pH 2.5 and ACN (68:32). The injection volume was 20 μl, with flow at 2 ml/min. Detection wavelength was 215 nm, and column oven temperature was 80°C.

RESULTS AND DISCUSSION

From the studies, the following can be stated (Tables 1–4). First, the active drug is stable, given that the raw materials used as secondary standards for the standardization of the commercial products, at different times, did not show enalaprilat and diketopiperazine in significant quantities (Chromatogram 2). Second, in all the analyzed products presenting an impurities percentage higher than 5%, this is because of the presence of diketopiperazine, with its contribution higher than that of enalaprilat (Chromatogram 3). Third, when the active principle/excipient proportion is lower, the degradation is more significant. Fourth, the presence of impurities depends directly on the container used.

CONCLUSIONS

The results obtained during this study show the necessity for standardizing the formulation, the manufacturing process, and the container used in products containing enalapril maleate as the active principle to guarantee stable pharmaceutical specialties during the fixed shelf-life period.

REFERENCES

1. D. P. Ip and G. S. Brenner, Enalapril Maleate, in *Analytical Profiles of Drug Substances*, Vol. 16 (K. Florey, Ed.), Academic Press, 1987, pp. 207–243.
2. U.S. Pharmacopeial Convention, Enalapril maleate tablets, in *U.S. Pharmacopeia 23*, Author, Washington, DC, 1995, p. 587.
3. P. A. Todd and R. C. Heel, Enalapril. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure, Drugs, 31, 198–248 (1986).