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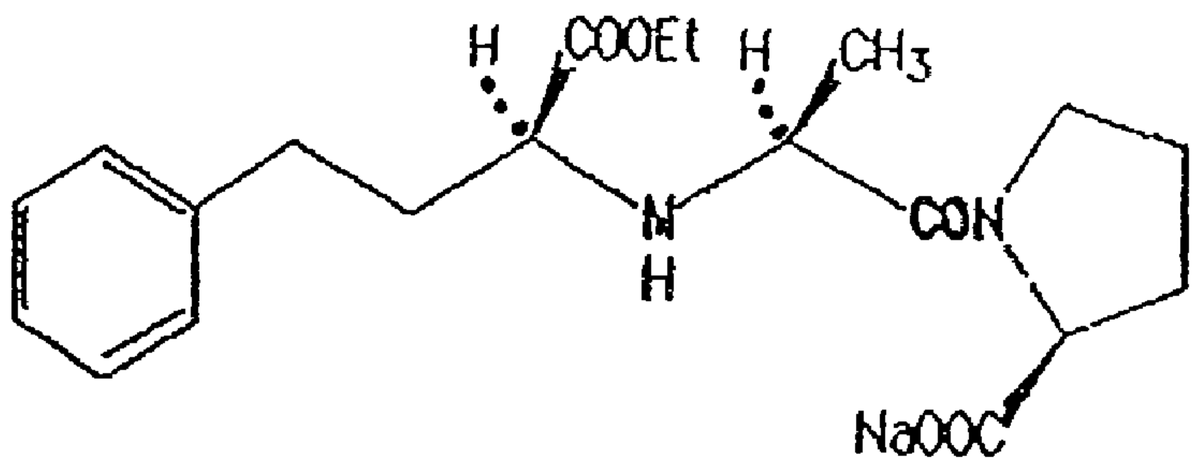
(30) 1991/11/25 (P-1842/91) YU

(54) **FORMULATION STABLE A BASE DE SEL D'ANALAPRIL; METHODE DE PREPARATION ET UTILISATION**

(54) **STABLE FORMULATION OF ANALAPRIL SALT, A PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF**



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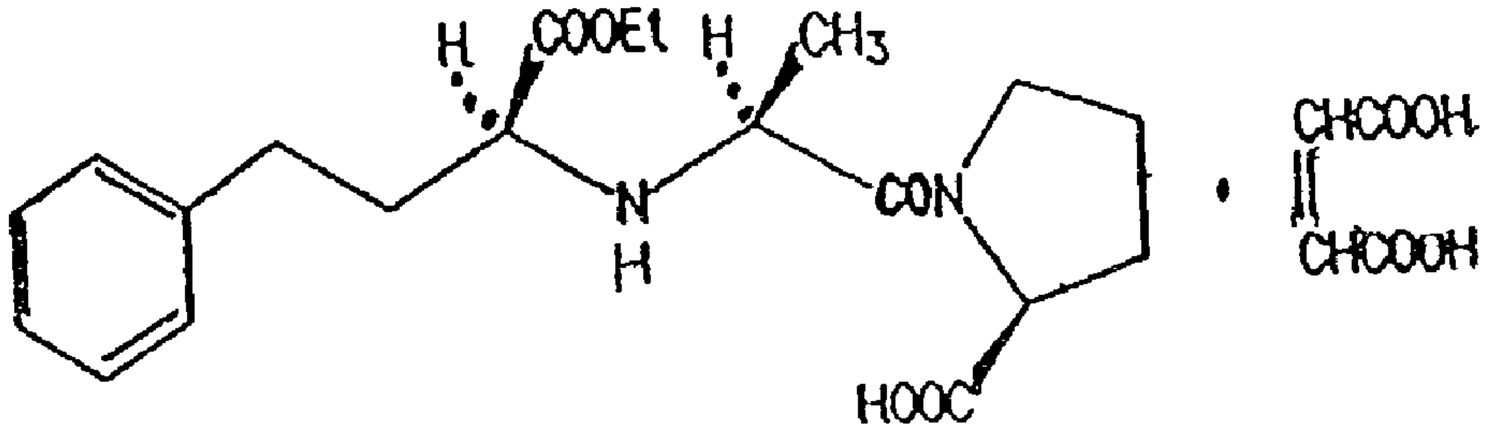
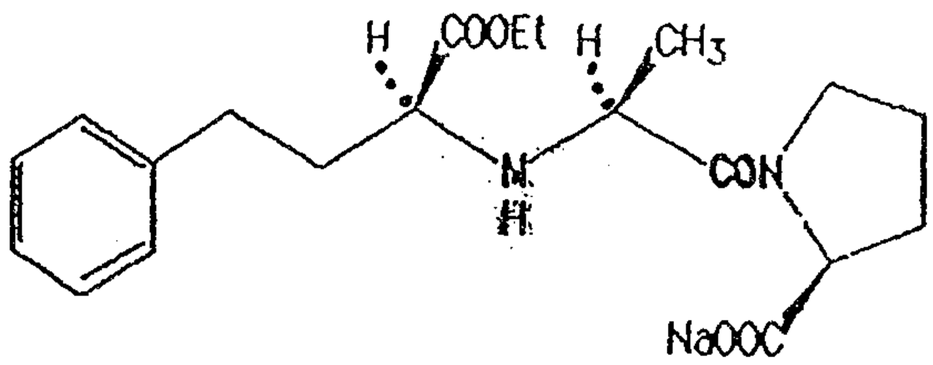


II

(57) There is disclosed a stable formulation of enalapril salt of the formula I (see formula I) which is prepared in such manner that a compound of formula II (see formula II) is suspended in demineralized water and a stoichiometric amount of the corresponding sodium compound such as sodium carbonate, sodium hydrogen carbonate or sodium hydroxide is added thereto, to this enalapril sodium salt prepared in situ of the formula I (see formula I) formulating additives are added, the whole is homogenized and formulated.

Abstract

There is disclosed a stable formulation of enalapril salt of the formula I



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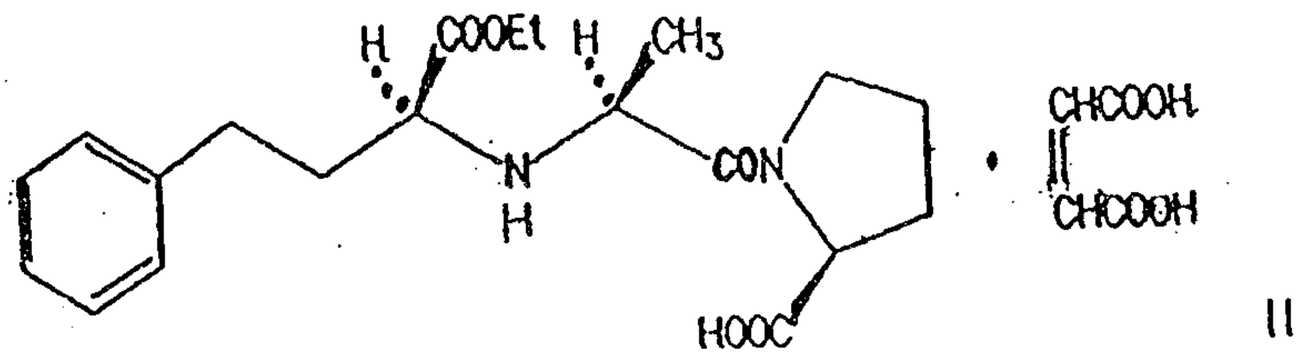
which is prepared in such manner that a compound of formula II



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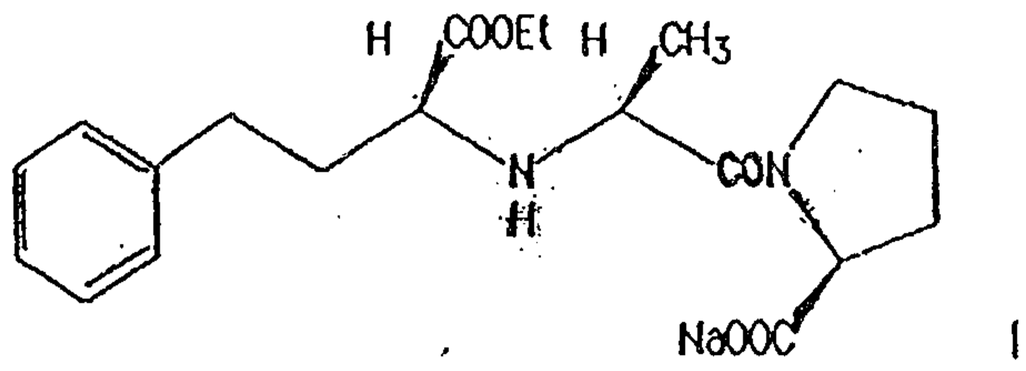
is suspended in demineralized water and a stoichiometric amount of the corresponding sodium compound such as sodium carbonate, sodium hydrogen carbonate or sodium hydroxide is added thereto, to this enalapril sodium salt prepared *in situ* of the formula I



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formulating additives are added, the whole is homogenized and formulated.

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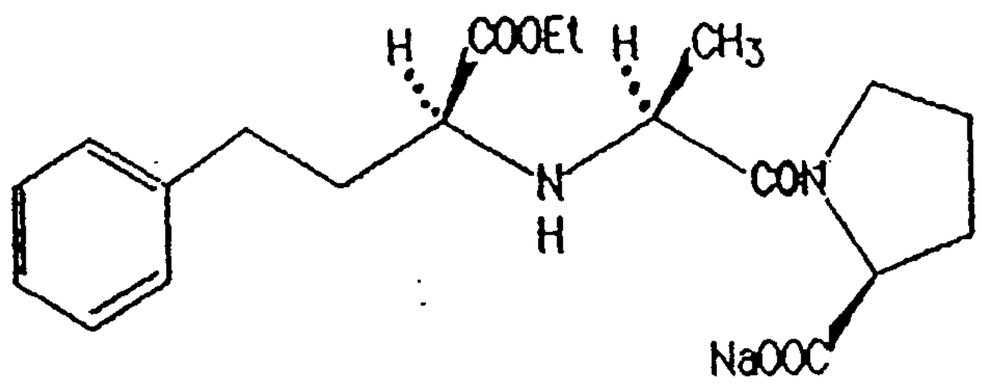
STABLE FORMULATION OF ENALAPRIL SALT, A PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF

Field Of The Invention

The present invention relates to a stable formulation of enalapril salt of the formula I:



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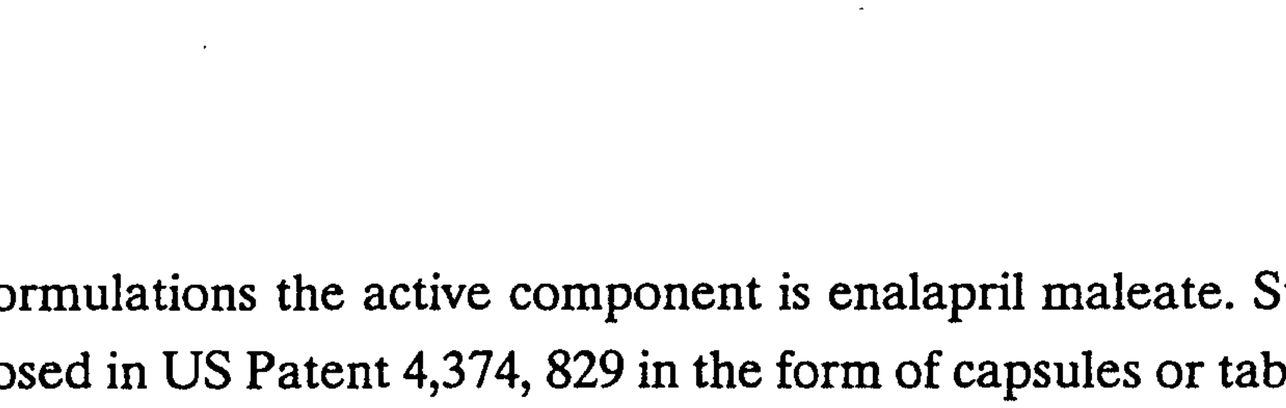
to a process for the preparation thereof as well as to the use thereof.

Prior Art

In the known formulations the active component is enalapril maleate. Such a formulation is e.g. disclosed in US Patent 4,374, 829 in the form of capsules or tablets.

Summary Of The Invention

The stable formulation of enalapril salt is prepared in such manner that a compound of formula II:



II

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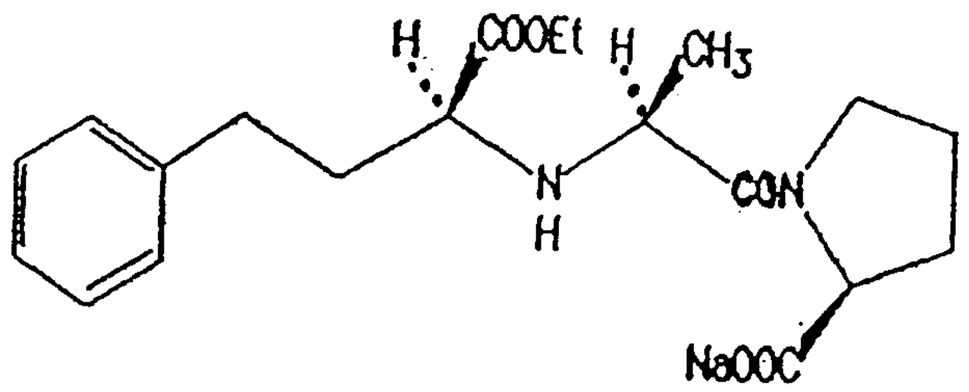
is suspended in demineralized water, a stoichiometric amount of a sodium compound such as sodium carbonate, sodium hydrogen carbonate or sodium hydroxide is added thereto, to this enalapril sodium salt prepared *in situ* of the formula I



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formulating additives are added, the whole is homogenized and formulated.

Formulating additives are e.g. cellulose, lactose of different sizes, alcohols, acids, bases, dyestuffs, starch, talc, polyvinyl pyrrolidone, magnesium stearate etc. Sodium salt may also be in combination with other antihypertensive agents (atenolol) and/or diuretics (hydrochlorothiazide).

The invention also provides a stable formulation of enalapril sodium salt obtained obtained according to the above process, preferably in the form of tablets. Such a formulation has not been disclosed as yet.

Enalapril sodium salt of the formula I is a prodrug useful in the treatment of cardiovascular diseases, especially hypertension. It delivers the same active substance as any other prodrug having enalapril moiety in its molecule.

Detailed Description Of The Invention

It should be pointed out that the stable formulation of enalapril according to the invention is designed in such a manner that enalapril maleate is temporarily converted into enalapril sodium salt. After the dissolution of such a formulation, especially a tablet, enalapril is liberated from the temporary form, enabling the absorption process to be carried out completely (see Example 8 and Graph 1).

Plasma concentrations determined after oral application of tablets prepared from 2.5 to 30 mg of enalapril maleate and having 2 to 16 mg enalapril in the form of sodium salt provide a therapeutical activity necessary for the treatment of the hypertension.

Daily doses amount to 4 to 64 mg of enalapril in the form of Na salt.

The invention is illustrated in detail by the following Examples, which should not be considered as a limitation thereof.

Example 1

To enalapril maleate (250 g) suspended in demineralized water (800 ml), a solution of sodium hydroxide (60 g in 400 ml of demineralized water) was added. To thus prepared clear solution of enalapril sodium salt, corn starch (400 g) and dyestuff (30 g) were added and it was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (3125 g) was added and the wet mass was dried at 40 to 50 °C. Corn starch (125 g), talc (150 g) and magnesium stearate (43 g) were added to the dried mass and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 2

To enalapril maleate (250 g) suspended in demineralized water (800 ml), a solution of sodium carbonate (81 g of Na_2CO_3 in 400 ml of demineralized water) was added. To thus prepared clear solution of enalapril sodium salt, corn starch (400 g) and dyestuff (30 g) were added and it was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (3125 g) was added and the wet mass was dried at 40 to 50 °C. Corn starch (125 g), talc (150 g) and magnesium stearate (43 g) were added to the dried mass and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 3

To enalapril maleate (250 g) suspended in demineralized water (1200 ml), sodium hydrogen carbonate (125 g) was added in portions. To thus prepared clear solution of enalapril sodium salt, corn starch (400 g) and dyestuff (30 g) were added and it was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (3125 g) was added and the wet mass was dried at 40 to 50 °C. Corn starch (125 g), talc (150 g) and magnesium stearate (43 g) were added to the dried mass and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 4

To enalapril maleate (200 g) suspended in demineralized water (1200 ml), a solution of sodium hydroxide (48 g in 400 ml of water) was added. To thus prepared clear solution of enalapril sodium salt, polyvinyl pyrrolidone K 25 (136 g), ethanol (400 g), corn starch (766 g) and dyestuff (24 g) were added and it was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (5160 g) was added and the wet mass was dried at 40 to 50 °C. Starch 1500 (200 g), talc (240 g) and magnesium stearate (68 g) were added to the dried mass and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 5

To enalapril maleate (200 g) suspended in demineralized water (1600 ml), sodium hydrogen carbonate (100 g) was added in portions. To thus prepared clear solution of enalapril sodium salt polyvinyl pyrrolidone K 25 (136 g), ethanol (400 g), corn starch (766 g) and dyestuff (24 g) were added and it was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (5160 g) was added and the wet mass was dried at 40 to 50 °C. Starch 1500 (200 g), talc (240 g) and magnesium stearate (68 g) were added to the dried mass and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 6 (comparative)

A mixture of enalapril maleate (200 g), polyvinyl pyrrolidone K 25 (136 g), corn starch (766 g), dyestuff (24 g) and sodium hydrogen carbonate (100 g) was stirred until a homogeneously coloured mixture was obtained. To the homogeneously coloured mixture lactose 80 (5160 g), starch 1500 (200 g), talc (240 g) and magnesium stearate (68 g) were added and it was homogenized for 15 to 30 minutes. The homogenate thus prepared was used in preparing tablets.

Example 7

Stability test

Stability studies were made with tablets of Examples 5 and 6 under conditions as disclosed in Table 1. The content of enalapril sodium salt (NaE) and the presence of decomposition product 2-(1-ethoxycarbonyl-3-phenylpropyl-3-methyl-hexahydro-pyrrolo)-[1,2-a]-pirazine-1,4-dione (DKP) were controlled.

Table 1

Stability of enalapril sodium salt in tablets

	Example 5 content in %		Example 6 content in %	
	NaE	DKP	NaE	DKP
initial content	100.0	<0.1	98.8	0
RT 3 months	100.0	<0.1	97.5	2.1
35 °C 3 months	98.7	0.1	85.5	~10.0
50 °C 3 months	94.2	4.2	13.8	~80.0
31 °C 70% RH 3 months	100.0	<0.1	92.0	~10.0
37 °C 85% RH 3 months	98.9	0.5	70.9	~30.0

RT = room temperature
RH = relative humidity

From the above Table it is evident that the enalapril sodium salt prepared *in situ* is more stable in a pharmaceutical formulation than in case of only physical mixing of enalapril maleate and sodium hydrogen carbonate.

Example 8

Dissolution test

Tablets prepared according to Examples 5 and 6 were tested for their dissolution characteristics. A standard method (USP XXII) was used to evaluate the dissolution profiles. The results are presented in Graph 1 in % of enalapril maleate dissolved.

Example 9

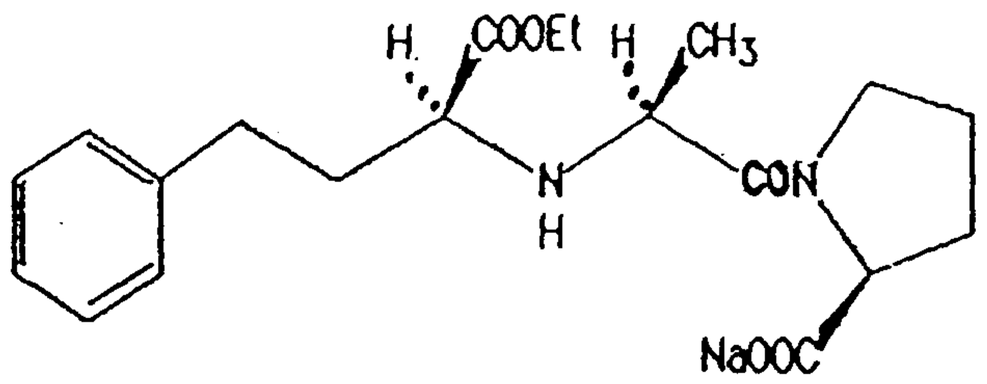
Plasma levels of enalaprilate

After *p.o.* application of tablets with 6 mg of enalapril in the form of sodium salt, plasma samples were analysed. The following enalaprilate concentrations were determined.

time (h)	concentration (μg/l)
0	0
0.5	1.22
1	13.99
2	63.13
3	84.07
4	68.64
6	49.63
8	27.30
12	14.36
24	2.73

CLAIMS:

1. A process for preparing a stable formulation of an enalapril salt of the formula I:



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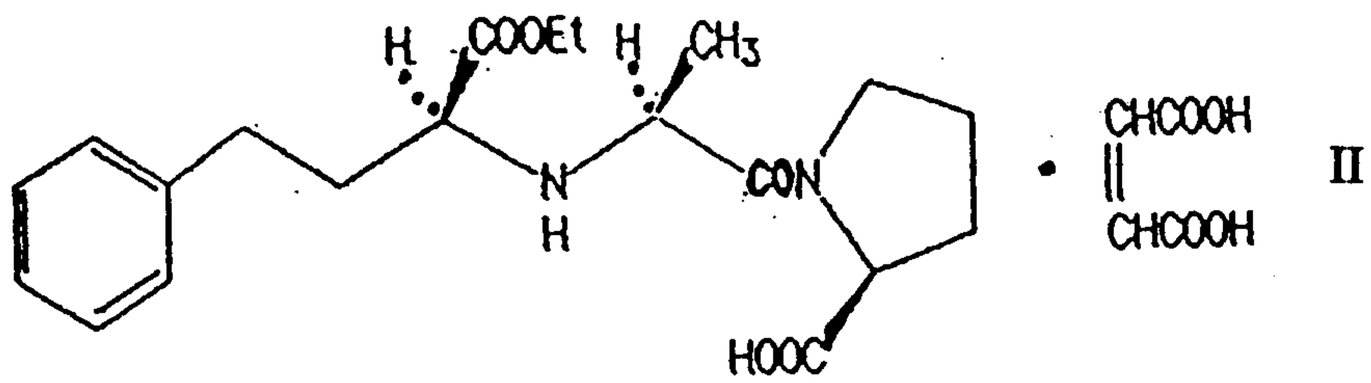
wherein a compound of formula II:



II

is suspended in demineralized water and a stoichiometric amount of a sodium compound is added thereto, and to the enalapril sodium salt prepared *in situ* of the formula I formulating additives are added, and the resultant mixture is homogenized and formulated.

2. The process of claim 1, wherein the sodium compound is sodium carbonate, sodium hydrogen carbonate or sodium hydroxide.

3. A stable formulation of an enalapril sodium salt prepared according to the process of claim 1 or 2.

4. The formulation according to claim 2 in the form of a tablet.

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5. The use of the formulation of claim 2 or 3 as prodrug for the treatment of cardiovascular diseases.

6. The use of claim 5 for hypertension.

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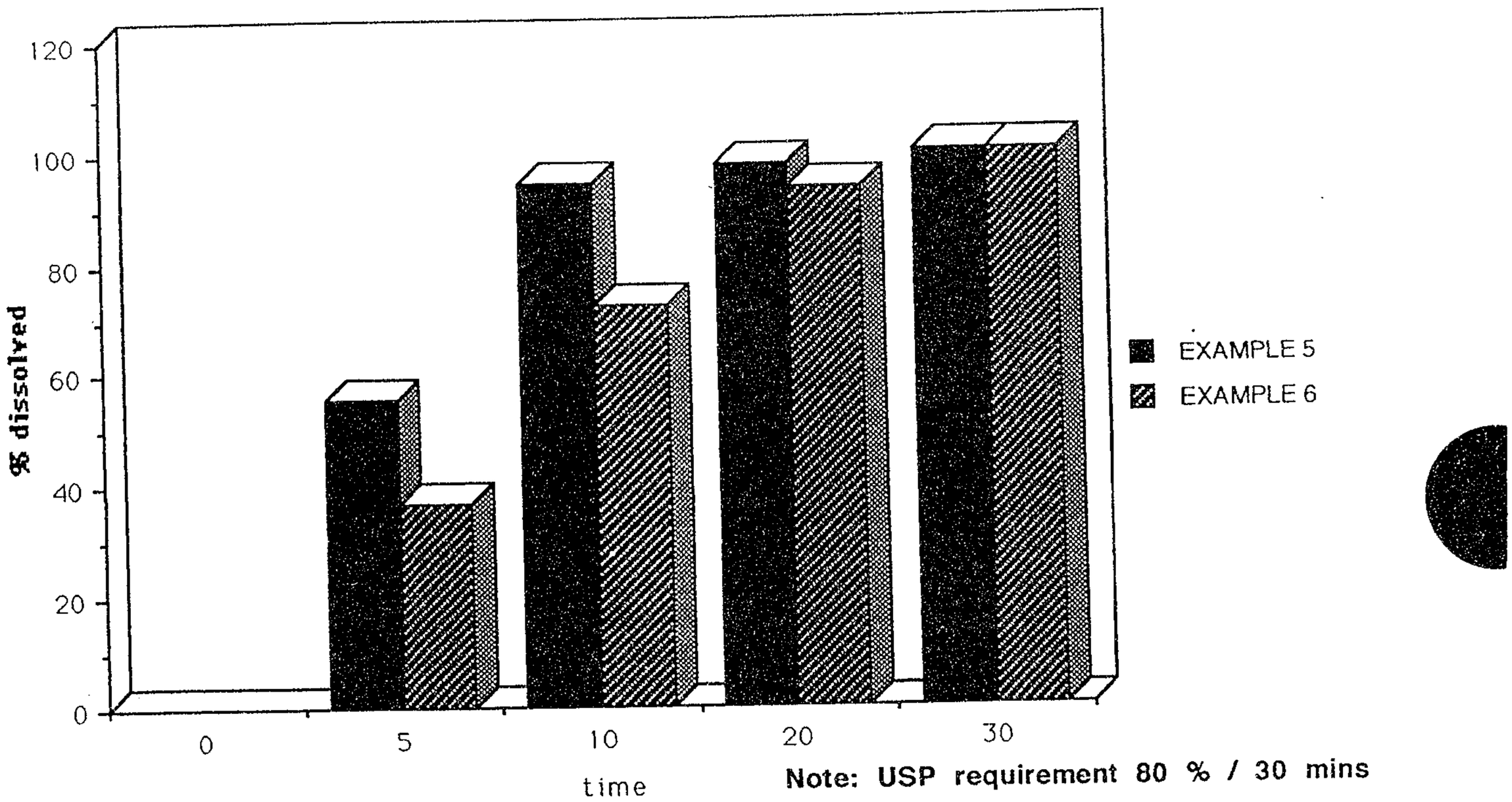
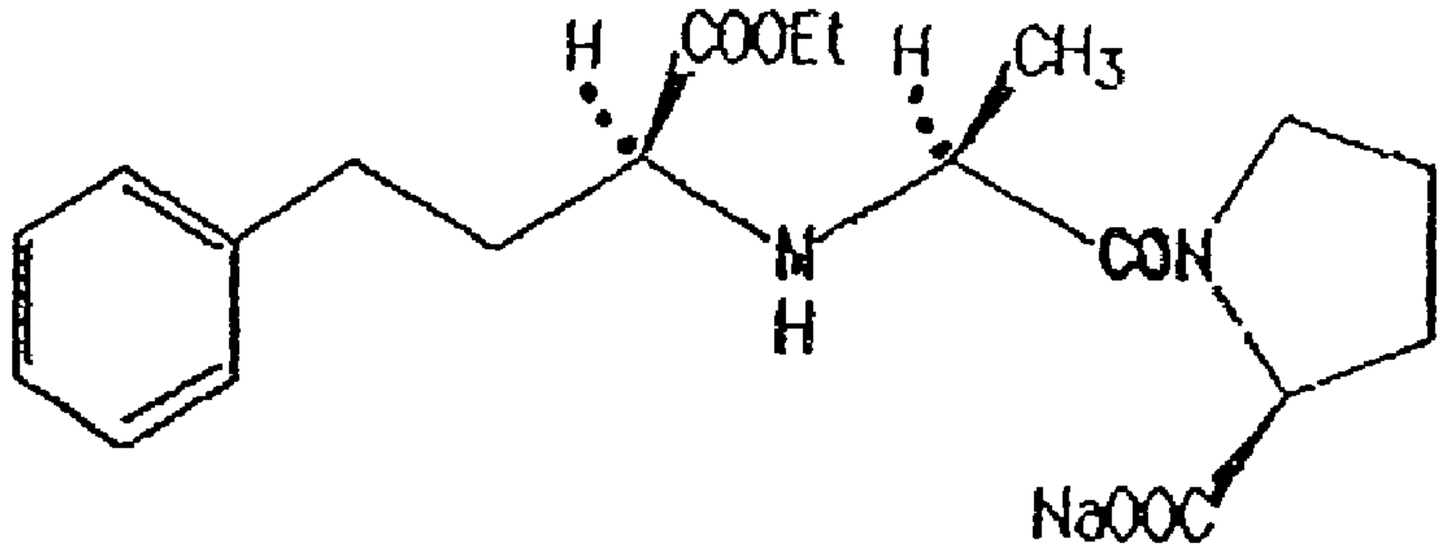
GRAPH 1

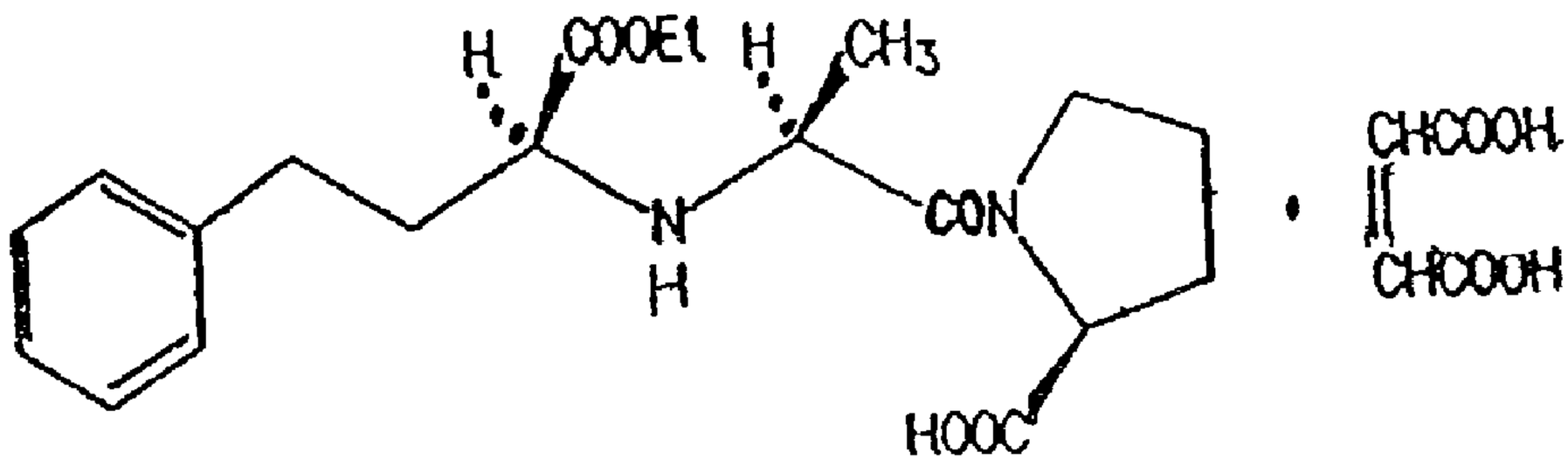
COMPARISON EXAMPLE 5 VS. EXAMPLE 6
DISSOLUTION



Note: USP requirement 80 % / 30 mins


H
COOEt
H
CH3
N
H
CON
NaOOC

I


H
COOEt
H
CH3
N
H
CON
HOOC
CHCOOH
CHCOOH

II