AUSTRALIA

639354

PATENTS ACT 1990

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

Sandoz Ltd.

of

Lichtstrasse 35, CH-4002 Basle, Switzerland

[54] Invention Title:

"Hydrochloric acid donors as stabilizers for ACE inhibitor compositions".

[72] Name(s) of actual inventor(s):

Bruce Allan ROSS
Richard Victor VIVILECCHIA

[74] Address for service in Australia:

DAVIES & COLLISON, Patent Attorneys, 1 Little Collins Street, Melbourne, Victoria, Australia. Attorney Code: DM

Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
557234	United States of America	US	25 July 1990

DATED this TWENTY THIRD day of JULY 1991

.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

MELBOURNE S.O.

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PATENTS ACT 1990
NOTICE OF ENTITLEMENT

We, Sandoz Ltd., the applicant named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors.

The Nominated Person is entitled to claim priority from the basic application listed on the patent request because the Nominated Person is the assignee of the applicants in respect of the basic application, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY THIRD day of JULY 1991

.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

(D&C ref: 1419820)

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(54) Title
HYDROCHLORIC ACID DONORS AS STABILIZERS FOR ACE INHIBITOR COMPOSITIONS

(51)[5] International Patent Classification(s)
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(71) Applicant(s)
SANDOZ LTD.

(72) Inventor(s)
BRUCE ALLAN ROSS; RICHARD VICTOR VIVILECCHIA

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 609168 20421/88
FR 2318636
US 4900559

(57) Claim

1. A pharmaceutical composition comprising as an active component an ACE inhibitor; and a hydrochloric acid donor that releases hydrochloric acid to stabilise the ACE inhibitor.

16. A pharmaceutical composition comprising spirapril, in free base form or acid addition salt form; and a hydrochloric acid donor.

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COMPLETE SPECIFICATION

NAME OF APPLICANT(S):

Sandoz Ltd.

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

INVENTION TITLE:

"Hydrochloric acid donors as stabilizers for ACE inhibitor compositions".

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

Hydrochloric Acid Donors as stabilizers for ACE inhibitor compounds

The present invention relates to the use of certain acid donors as stabilizers in pharmaceutical compositions containing ACE inhibitors, and to the pharmaceutical compositions resulting therefrom.

Background of the Invention

There are a number of pharmaceutical compositions which suffer from instability problems due to the fact that the active component is susceptible to certain types of degradation, thereby diminishing their attractiveness and, in some cases, rendering them unsuitable from a commercial standpoint. For example, several ACE (Angiotensin Converting Enzyme) inhibitor-containing compositions suffer from this drawback since certain ACE inhibitors degrade readily in pharmaceutical dosage forms. More particularly, and as is the case with other ACE inhibitors such as Quinapril and Enalapril, Spirapril may degrade in dosage forms to the diketo piperazine (the internal cyclization product) and the diacid (the ester hydrolysis product). Accordingly, in view of their usefulness in treating hypertension, a number of research endeavors have been directed to overcoming the instability problem associated with ACE inhibitor-containing compositions.

Description of the Prior Art

European Patent Application 264,888 is directed to the stabilization of ACE inhibitor-containing pharmaceutical compositions employing ascorbic acid alone or a combination of ascorbic acid with fumaric acid, maleic acid and/or citric acid as the stabilizing component(s).of ACE inhibitor-containing pharmaceutical compositions

employing ascorbic acid alone or a combination of ascorbic acid with fumaric acid, maleic acid and/or citric acid as the stabilizing component(s).

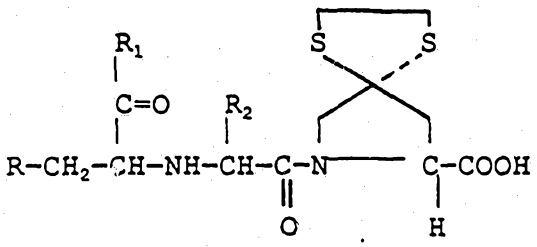
USP 4,743,450 is also directed to the stabilization of ACE inhibitor-containing pharmaceutical compositions employing, as the stabilizer component, a combination of an alkali or alkaline earth metal salt (preferably, magnesium carbonate) and a saccharide (preferably, mannitol or lactose).

Although each of the above patents represents an attempt to overcome the instability problems associated with ACE inhibitor-containing compositions, there still exists a dire need for ACE inhibitor-containing compositions exhibiting improved stability, especially in the presence of moisture. To this end, the present invention is directed to pharmaceutical compositions, particularly ACE inhibitor-containing compositions, exhibiting improved stability.

Description of the Invention

Accordingly in one aspect the present invention provides a pharmaceutical composition comprising as an active component an ACE inhibitor; and a hydrochloric acid donor that releases hydrochloric acid to stabilise the ACE inhibitor

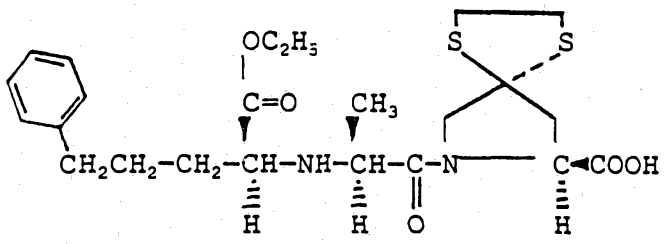
Preferably, the ACE inhibitor is a compound of the formula III



III

in which R is C_1-C_6 alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy; R_1 is hydroxy or C_1-C_6 alkoxy; and R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 aminoalkyl.

More preferably the ACE inhibitor is the compound Spirapril having the formula



All of the compounds of formula III are known, having been previously described e.g. in USP 4,470,972. Moreover, their usefulness in treating hypertension as well as methods for their preparation are set forth therein.

Accordingly in another aspect this invention provides a process for the production of a stabilized pharmaceutical composition as defined above which comprises admixing an ACE inhibitor with a hydrochloric acid donor that releases hydrochloric acid.

The pharmaceutical compositions may exhibit advantages as follows:-

1) The active component may be preserved from degradation, and/or

2) They may exhibit an extended shelf-life under normal storage conditions, and/or

3) They may be less sensitive to moisture and even the stability may improve with an increase in moisture, and/or

4) They may exhibit less discoloration over a significant period of time, and/or

5) They may exhibit less instability when employed in the presence of colorants.

In comparison to certain acidifiers which have previously been employed as stabilizers in pharmaceutical compositions, e.g. citric acid, maleic acid, ascorbic acid, etc., preferably the acid donors are chosen which release the more volatile hydrochloric acid and, therefore, effect a greater diffusion through the dosage form matrix. Although any compounds which produce hydrochloric acid would be suitable in the practice of the instant invention, preferred acid donors include an amino acid hydrochloride, such as glycine hydrochloride, glutamic acid hydrochloride, betaine hydrochloride, alanine hydrochloride, valine hydrochloride, lysine hydrochloride, arginine hydrochloride, aspartic acid hydrochloride and a Lewis acid chloride, such as ferric chloride, zinc chloride and aluminium chloride.

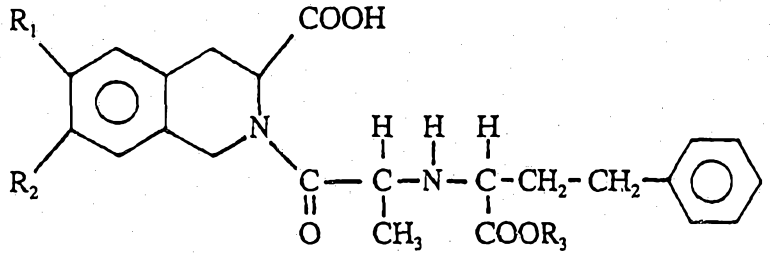
The more preferred acid donors are glycine hydrochloride, glutamic acid hydrochloride and betaine hydrochloride. The most preferred acid donor is glycine hydrochloride.

Other preferred hydrochloric acid donors may be chosen e.g. on the basis of vapour pressure measurements determining the release of hydrochloric acid, e.g. having similar properties to the preferred acid donors mentioned above.

Although, in general, the hydrochloric acid donor may be employed in any amount which will prevent degradation of the active component, e.g. as indicated by standard stability tests, the amount of the hydrochloric acid donor employed is between 1% and 25%, preferably between 1% and 20%, more preferably between 1% and 15%, e.g. from 1 to 10%, or 1 to 5%, e.g. 2% based on the total weight of the pharmaceutical composition.

The weight ratio of active component to the hydrochloric acid donor may be determined in conventional manner. The preferred weight ratio of active component to the hydrochloric acid donor is 2.5:1 to 1:7, more preferably 2:1 to 1:2.

The instant invention, viz., the use of a select group of hydrochloric acid donors as stabilizers in pharmaceutical compositions, applies to all ACE inhibitors in pharmaceutical compositions where buffering to a low pH for required stability is desired. It may be of particular interest for active components which are in acid addition salt form, e.g. hydrochloride salt form. In general, ACE inhibitor-containing pharmaceutical compositions wherein the ACE inhibitor employed is prone to form diketopiperazine degradation products would benefit from the use of a select group of hydrochloric acid donors as stabilizers therefor. For example, one class of ACE inhibitors to which the instant invention would apply are compounds of formula I:

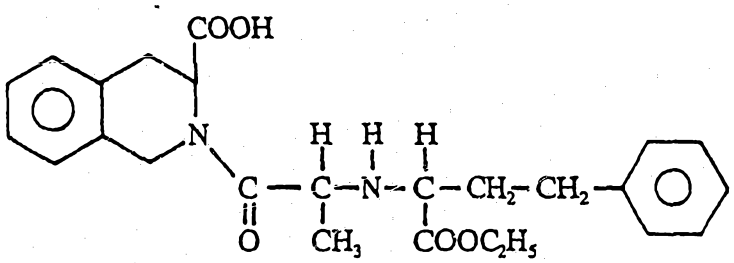


I

wherein R_1 and R_2, independently, are hydrogen or a group $-OC_nH_{2n+1}$, where n is 1 to 5; and

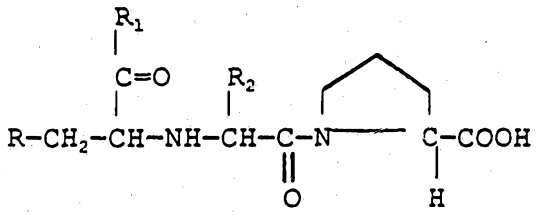
R_3 is hydrogen or a group $-C_nH_{2n+1}$, where n is as defined above.

In the above formula, preferred compounds are those where R_1 and R_2 have the same significance. More preferred compounds of the above formula are those where R_1 and R_2 are both hydrogen or methoxy and R_3 is hydrogen or methyl. The most preferred compound of the above formula is Quinapril having the formula



All of the above compounds are known, having been previously described e.g. in USP 4,344,949. Moreover, their usefulness in treating hypertension as well as methods for their preparation are set forth therein.

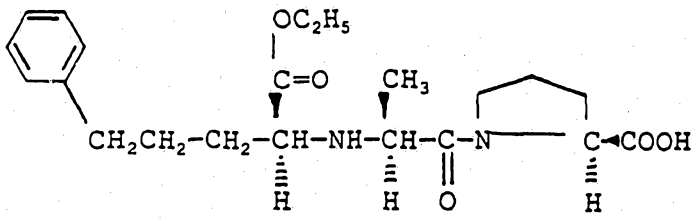
Another class of ACE inhibitors to which the invention would apply are compounds of formula II:



II

wherein R is C_1-C_6alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;
R_1 is hydroxy or C_1-C_6alkoxy; and
R_2 is hydrogen, C_1-C_6alkyl or C_1-C_6aminoalkyl.

In the above formula, preferred compounds are those wherein R is benzyl, R_1 is C_1-C_6 alkoxy and R_2 is hydrogen, methyl or aminobutyl. More preferred compounds of the above formula are those wherein R is benzyl, R_1 is C_1-C_4 alkoxy and R_2 is hydrogen or methyl. The even more preferred compounds of the above formula are those wherein R is benzyl, R_1 is ethoxy and R_2 is methyl. The most preferred compound of the above formula is Enalapril having the formula



All of the above compounds of formula II are known, having been previously described e.g. in European Patent 12,401. Moreover, their usefulness in treating hypertension as well as methods for their preparation are set forth therein.

It should be noted that all of the compounds of formulae I, II and III form salts with various inorganic and organic acids and bases, which salts may be prepared by conventional methods. Therefore, it should be understood that all of such salts would also benefit from the use of the select group of hydrochloric acid donors as stabilizers therefor in accordance with the instant invention.

The amount of the active component in the pharmaceutical compositions of the instant invention is between 0.5% and 50%, preferably between 0.75% and 25%, e.g. between 1% and 25%, more preferably between 0.75% and 20%, e.g. between 1% and 20%, most preferably between 0.75% and 15%, e.g. between 1% and 15%, based on the total weight of the pharmaceutical composition.

As indicated above, all of the compounds of formulae I, II and III are known and their usefulness in daily dosages at which said compounds are employed as well as typical unit dosages of said compounds are well documented in the literature.

Although the pharmaceutical compositions may be in any form, the solid forms are preferred, more preferably tablets, capsules and caplets.

In addition to the active components and the stabilizing component, e.g., glycine hydrochloride, the pharmaceutical compositions of the instant invention will typically contain a pharmaceutically acceptable carrier. Generally, they are compounds which do not contain groups which would significantly interfere with either the active component or the stabilizing component. For example, sugars such as lactose, sucrose, mannitol and sorbitol are quite suitable; as are starches such as corn starch and tapioca starch; cellulose and derivatives thereof such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate; sodium sulfate; and polyvinyl alcohol. Such type compounds are generally present in amounts of between 5% and 90%, preferably between 10% and 80%, based on the total weight of the pharmaceutical composition.

The stabilized compositions of the instant invention may also contain optional ingredients that are normally employed in pharmaceutical formulations, the only qualification being that they must be compatible with the select group of hydrochloric acid donors so as not to interfere with their stabilizing function. Typical optional ingredients include lubricants, e.g., talc, alkaline earth metal stearates such as magnesium stearate and calcium stearate, and hydrogenated vegetable oils such as hydrogenated cottonseed oil; binders such as polyvinylpyrrolidone (povidone) and gelatin; and disintegrants such as microcrystalline cellulose, cross-linked polyvinylpyrrolidone and alginic acid. Other optional ingredients are fillers, water scavengers, buffers, preservatives, anti-oxidants, colorants and flavouring agents. The total amount of the optional ingredients in the stabilized compositions of the instant invention is not critical. In general, the total amount of the optional ingredients is consistent with the amount of the active component, stabilizer and pharmaceutically acceptable carrier, i.e., the total amount will be equivalent to the remainder of the pharmaceutical compositions.

The stabilized compositions of the instant invention can be prepared by any of the conventionally employed processing techniques such as the wet granulation process. The technique is preferably chosen to ensure a homogeneous distribution of the active component and a homogeneous distribution of the hydrochloric acid donor over or

among the active component particles. Conveniently the hydrochloric acid donor is distributed in a liquid form, e.g. an aqueous solution used as a granulating liquid.

Examples of other active components that are contemplated include those with a -NH-CH-CO-N-C-COOH moiety as in the above formulae I, II,and III, e.g the di-acid form of spirapril, spiraprilate. Such compounds include ramipril, perindopril, indolapril, lisinopril, alacepril, trandolapril, benazapril, libenzapril, delapril, and cilazapril.

The following examples are for the purpose of illustration only and are not intended in any way to limit the scope of the instant invention.

EXAMPLE 1:

Below are stabilized compositions in accordance with the instant invention in white tablet form:

Ingredient	Amount (mg)	
	A	B
Quinapril hydrochloride	40.0	-
Enalapril hydrochloride	-	40.0
glycine hydrochloride	40.0	40.0
lactose	277.5	277.5
corn starch	25.0	25.0
talc	15.0	15.0
magnesium stearate	2.5	2.5
	400.0	400.0

EXAMPLE 2:

The following compositions A-D represent stabilized compositions in accordance with the instant invention in white tablet form whereas composition E does not contain a stabilizer of the instant invention:

Ingredient	Amount (mg)				
	A	B	C	D	E
Spirapril hydrochloride	3.06	3.06	3.06	3.06	3.19
lactose, NF	99.94	94.74	99.94	94.74	80.21
starch,NF	19.50	19.50	19.50	19.50	12.00
povidone, USP	2.60	2.60	2.60	2.60	2.00
glycine hydrochloride	-	-	2.60	2.60	-
glutamic acid hydrochloride	2.60	2.60	-	-	-
silica gel, NF	-	5.20	-	5.20	1.90
colloidal SiO_2, NF	1.30	1.30	1.30	1.30	0.10
magnesium stearate, NF	1.00	1.00	1.00	1.00	0.60
total	130.00	130.00	130.00	130.00	100.00

EXAMPLE 3:

To demonstrate the effectiveness of the stabilizers of the instant invention against added moisture, the following results were obtained when the compositions of Example 2A-2D were stored for 3 months at 30°C and 75% relative humidity:

	* Assay %	Diketo	Diacid
Example 2A	99.6	0.0	0.1
Example 2B	100.0	0.0	0.2
Example 2C	99.6	0.0	0.1
Example 2D	99.9	0.0	0.2

* per cent of original Spirapril hydrochloride content

EXAMPLE 4:

To demonstrate the effectiveness of the stabilizers of the instant invention against an increase in temperature, the following results

were obtained when the compositions of Example 2A and 2C were stored at 50°C for varying periods of time. For purposes of comparison, below are the results obtained when the composition of Example 2E was stored at 50°C for three months.

	Period (months)	* Assay %	Diketo	Diacid
Example 2A	1	99.0	0.2	0.1
	2	100.8	0.6	0.3
	3	99.1	0.9	0.3
Example 2C	1	100.3	0.1	0.2
	2	101.3	0.8	0.2
	3	98.4	1.0	0.3
Example 2E	3	91.2	7.3	0.4

* per cent of original Spirapril hydroch oride content

EXAMPLE 5:

The following compositions A and B and D represent stabilized compositions in accordance with the instant invention in colored tablet form whereas composition C contains maleic acid, an acidifier disclosed in the prior art:

Ingredient	Amount (mg)			
	A	B	C	D
Spirapril hydrochloride	3.06	3.06	3.06	6
lactose, NF	96.94	96.94	96.94	99.77
starch, NF	19.50	19.50	19.50	22.50
povidone, USP	2.60	2.60	2.60	3.0
alginic acid	-	-	-	13.0
glycine hydrochloride	2.60	-	-	3.0
glutamic acid hydrochloride	-	2.60	-	-
maleic acid	-	-	2.60	-
carmine	3.00	3.00	3.00	-
iron oxide, red	-	-	-	0.03
colloidal SiO_2, NF	1.30	1.30	1.30	1.5
magnesium stearate, NF	1.00	1.00	1.00	1.2
total	130.00	130.00	130.00	150.00

Representative production process

A batch of 1.6 million tablets of Example 5D is made as follows:

a) Spirapril hydrochloride (4.8 kg), 79.576 kg lactose, starch (18 kg) and povidone (2.4 kg) are sieved separately (typically 1600 µm) and mixed together in a high speed mixer.

b) Iron oxide (0.024 kg) and lactose (0.24 kg) are mixed together and

sieved, and added to the mixture obtained in step a).

c) Glycine hydrochloride (2.4 kg) in 13.40 kg of demineralised water is pumped into the mixture obtained in step b), mixed and kneaded until suitable for granulation. The granulate is dried in a fluidized bed drier at 60°C e.g. until a loss on drying of about 2.1% is reached, then broken by sieving (typically 1000 µm). A batch of 107.44 kg results.

d) A second batch of 107.44 kg is produced following steps a), b) and c), and the batches are combined (214.88 kg).

e) In another vessel 20.8 kg alginic acid, 2.4 kg colloidal SiO_2 are mixed together and sieved (typically 1000 µm) and sieved with almost the whole of the granulate obtained in step d).

f) 1.92 kg magnesium stearate and the remaining part of the granulate obtained in step d) are mixed together, sieved (typically 1000 µm) and combined with the mixture in step e). 240 kg of tabletting mixture is obtained and this is compressed into tablets.

EXAMPLE 6:

To demonstrate the effectiveness of the stabilizers of the instant invention against an increase in temperature in the presence of colorants, the following results were obtained when the carmine colored compositions of Example 5A and 5B were stored at 50°C for three months.

	* Assay %	Diketo	Diacid
Example 5A	96.3	2.7	**
Example 5B	96.0	1.8	**

* per cent of original Spirapril hydrochloride content

** interference from dye

EXAMPLE 7:

To show the superiority of the pharmaceutical compositions of the present invention, the following results were obtained when the compositions of Example 5A and 5C were stored at 50°C for varying periods of time:

	Period (months)	* Assay %)	Diketo	** Diacid
Example 5A	1	98.4	1.1	1
	2	15.2	3.1	2
	3	96.3	2.7	2
Example 5C	1	91.6	5.1	1
	2	89.2	14.8	2
	3	84.6	10.0	2

* per cent of original Spirapril hydrochloride content

** interference from dye

EXAMPLE 8:

The following compositions A-D represent stabilized compositions in accordance with the instant invention in white tablet form whereas composition E does not contain a stabilizer of the instant invention:

Ingredient	Amount (mg)				
	A	B	C	D	E
Spirapril hydrochloride	3.0	3.3	3.3	3.3	3.3
lactose, NF	360.0	360.0	360.0	360.0	360.0
glycine hydrochloride	20.0	-	-	-	-
ferric chloride	-	20.0	-	-	-
betaine hydrochloride	-	-	20.0	-	-
glutamic acid hydrochloride	-	-	-	20.0	-
colloidal SiO_2, NF	1.0	1.0	1.0	1.0	1.0
stearic acid, NF	16.0	16.0	16.0	16.0	16.0
total	400.3	400.3	400.3	400.3	380.3

EXAMPLE 9

To demonstrate the effectiveness of the pharmaceutical compositions of the instant invention against an increase in temperature and added moisture, the following results were obtained when the compositions of Examples 8A-8D stored for 72 hours. For purposes of comparison, below are the results obtained when the composition of Example 8E was stored for 72 hours under the same conditions.

	Temp.(°C)	% Water	*Assay %	Diketo	Diacid
Example 8A	0	0	94	0.1	0.10
	65	0	91	0.6	0.05
	65	5	-	-	-
	65	10	92	0.7	0.10
Example 8B	0	0	62	0.3	0.80
	65	0	66	0.4	0.60
	65	5	72	0.7	1.40
	65	10	66	1.3	3.10
Example 8C	0	0	94	0.1	0.40
	65	0	91	4.0	0.03
	65	5	94	0.9	0.07
	65	10	95	0.8	0.14
Example 8D	0	0	95	0.2	0.03
	65	0	91	3.6	0.03
	65	5	97	0.4	0.10
	65	10	94	0.4	0.20
Example 8E	0	0	93	0.1	0.05
	65	0	87	6.0	0.04
	65	5	79	9.0	0.20
	65	10	65	17.0	0.30

EXAMPLE 10

To demonstrate the extended shelf-life of a stabilized composition in accordance with the instant invention, the following results were obtained when the composition of Example 5A was stored for an extended period under various conditions:

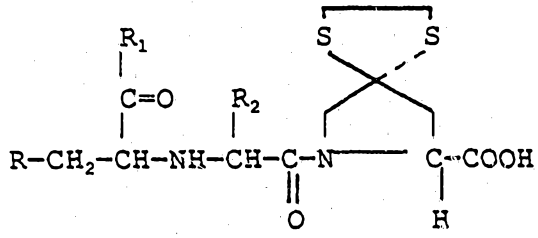
Period (months)	30°C		40°C		50°C		30°C/75% RH	
	DK	DA	DK	DA	DK	DA	DK	DA
0	0.4	0.0	-	-	-	-	-	-
3	0.4	0.1	1.3	0.2	2.5	0.2	0.4	0.1
6	0.5	0.2	1.7	0.2	3.0	0.1	0.5	0.1
9	0.9	0.2	-	-	-	-	-	-
12	1.1	0.2	2.6	0.1	-	-	-	-
24	1.5	0.2	-	-	-	-	-	-

DK = diketopiperazine
DA = diacid

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising as an active component an ACE inhibitor; and a hydrochloric acid donor that releases hydrochloric acid to stabilise the ACE inhibitor.

2. A composition according to claim 1 in which the ACE inhibitor is a compound of the formula III



III

in which R is C_1-C_6 alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy; R_1 is hydroxy or C_1-C_6 alkoxy; and R_2 is hydrogen, C_1-C_6 alkyl or C_1-C_6 aminoalkyl.

3. A composition according to claim 2 wherein the ACE inhibitor is spirapril.

4. A composition according to claim 1 wherein the ACE inhibitor is quinapril or enalapril.

5. A composition according to any one of the preceding claims wherein the ACE inhibitor is in the form of its hydrochloride acid addition salt.

6. A composition according to any one of the preceding claims wherein the hydrochloric acid donor is an amino acid hydrochloride or a Lewis acid chloride.

7. A composition according to claim 6 wherein the hydrochloric acid donor is an amino acid hydrochloride selected from glycine hydrochloride, glutamic acid hydrochloride, betaine hydrochloride, alanine hydrochloride, valine hydrochloride, lysine hydrochloride, arginine hydrochloride and aspartic acid hydrochloride.

8. A composition according to claim 7 wherein the hydrochloric acid donor is glycine hydrochloride.

9. A composition according to claim 6 wherein the hydrochloric acid donor is a Lewis acid chloride selected from ferric chloride, zinc chloride and aluminium chloride.

10. A composition according to any one of the preceding claims wherein the hydrochloric acid donor is present in an amount between 1% and 25%, based on the total weight of the composition.

11. A composition according to any one of the preceding claims wherein the weight ratio of the active component to hydrochloride acid donor is from about 2.5:1 to about 1:7.

12. A composition according to any one of the preceding claims in the form of a tablet.

13. A stabilised pharmaceutical composition according to claim 1 and substantially as described in this specification with reference to any one of the examples.

14. A process for the production of a stabilized pharmaceutical composition as defined in any one of claims 1 to 13 which comprises admixing an ACE inhibitor with a hydrochloric acid donor that releases hydrochloric acid.

15. A method according to claim 14 and substantially as described in this specification with reference to example 5.

16. A pharmaceutical composition comprising spirapril, in free base form or acid addition salt form; and a hydrochloric acid donor.

DATED this 5th day of May, 1993
Sandoz Ltd.
By Its Patent Attorneys
DAVIES COLLISON CAVE

Abstract of the Disclosure

The invention relates to the use of certain acid donors as stabilizers in pharmaceutical compositions, and to the pharmaceutical compositions resulting therefrom.