1317234

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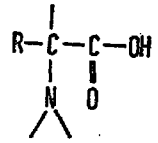


(54) METHOD OF INHIBITING THE HYDROLYSIS OF ACETYLSALICYLIC ACID AND d-PROPOXYPHENE HYDROCHLORIDE

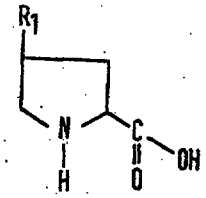
(71) We, ELI LILLY AND COMPANY, a Corporation organised and existing under the laws of the State of Indiana, United States of America, of 307 East McCarty Street, Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method for stabilizing pharmaceutical compositions comprising d-propoxyphene hydrochloride and acetylsalicylic acid.

The present invention provides a method of inhibiting the hydrolysis of acetylsalicylic acid, hereinafter referred to as aspirin, to yield free acetic acid and salicylic acids in pharmaceutical compositions in which d-propoxyphene hydrochloride is present. This hydrolysis can be substantially inhibited, or even essentially prevented, by admixing the hydrochloride of a compound selected from the group having as a general formula either



or



wherein

R is hydrogen, methyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxymethyl, 1-hydroxyethyl, carboxymethyl, carboxyethyl, carboxy-(1-hydroxy)ethyl, aminobutyl, methylthioethyl, mercaptomethyl, carboxy - (2 - aminoethyl)dithiomethyl, p-hydroxyphenyl, benzyl, indolylmethyl, guanidinopropyl, imidazolylmethyl and ureidopropyl; and

R_1 is hydrogen or hydroxyl.

The present invention also provides a pharmaceutical composition stabilised against hydrolysis comprising acetylsalicylic acid, d-propoxyphene hydrochloride and the hydrochloride of a naturally occurring amino acid.

The useful compounds described above comprise the 23 naturally occurring amino acids popularly known as essential amino acids. The designation "essential" is not intended to denote indispensable as contrasted with dispensable as applied to human nutritional requirements, but incorporates those amino acids which are characterized as both, and includes the following naturally occurring amino acids listed by both the common and scientific name.

Glycine, 2-aminoacetic acid;
Alanine, 2-aminopropanoic acid;
Valine, 2-amino-3-methylbutanoic acid;
Norleucine, 2-aminohexanoic acid;
Leucine, 2-amino-4-methylpentanic acid;
Isoleucine, 2-amino-methylpentanoic acid;
Serine, 2-amino-3-hydroxypropanoic acid;
Threonine, 2 - amino - 3 - hydroxybutanoic acid;
Aspartic acid, aminosuccinic acid;
Glutamic acid, 2-aminopentanedioic acid;
Hydroxyglutamic acid, 2 - ammino - 3-hydroxypentanedioic acid;
Lyhine, 2,6-diaminohexanoic acid;
Methionine, 2 - amino - 4 - methylthiobutanoic acid;
Cystein, 2 - amino - 3 - mercaptopropanoic acid;

Cystine, 3,3′ - dithiobis(2 - aminopropanoic acid);
Tyrosine, 2 - amino - p - hydroxyhydrocinnamic acid;
Phenylalanine, 2 - amino - 3 - phenylpropanoic acid;
Tryptophane, 2 - amino - 3 - indolylpropanoic acid;
Arginine, 2 - amino - 5 - guanidovaleric acid;
Histidine, 2 - amino - 3 - (5 - imidazolyl)-propanoic acid;
Citrulline, 2 - amino - 5 - ureidovaleric acid;
Proline, 2-pyrrolidinecarboxylic acid;
Hydroxyproline, 4 - hydroxy - 2-pyrrolidinecarboxylic acid.

The term naturally occurring amido acids will be employed hereinafter to denote the above described class of compounds.

The hydrochlorides of naturally occurring amino acids useful in this invention are prepared by reacting such amino acids with hydrochloric acid in either an aqueous or ethanolic solution and are purified by crystallization following procedures well known to those skilled in the art. The scope of this invention embraces both the dihydrochlorides and monohydrochlorides of the diaminocarboxylic acids, arginine, lysine and citrulline.

Naturally occurring amino acids useful as the hydrochloride in the novel processes and compositions of this invention, occur naturally in the L-form. The DL-amino acid racemic mixtures have been synthesized, and the D-form is recognized. All three forms are available in the form of their hydrochloride salts, and as the hydrochloride salts are operative in the present invention. The L-form is the most commercially available of the forms of naturally occurring amino acid hydrochlorides and represents the preferred embodiment herein exemplified.

In the practice of the present invention, it has been found that the quantity of the amino acid hydrochloride required to inhibit the hydrolysis of the aspirin is related to the amount of d-propoxyphene hydrochloride present in the aspirin/d-propoxyphene hydrochloride combination. Effective hydrolysis inhibition is achieved when a naturally occurring amino acid as the hydrochloride is admixed into the pharmaceutical composition in an amount of from about 5 to about 130 percent by weight of the amount of d-propoxyphene hydrochloride present. Preferably, the naturally occurring amimno acid hydrochloride is employed in an amount of from about 5 to about 50 percent of the quantity of d-propoxyphene hydrochloride present. The naturally occurring amino acid hydrochloride employed in the useful processes of this invention can be admixed with the other ingredients in the pharmaceutical composition in any order and an effective inhibition of aspirin hydrolysis will be achieved. Preferably, the naturally occurring amino acid hydrochloride and d-propoxyphene hydrochloride are intimately admixed before commingling with the aspirin. In an especially preferred embodiment of the present invention, a naturally occurring amino acid hydrochloride and d-propoxyphene hydrochloride are intimately admixed and granulated together with a pharmaceutically acceptable solvent in which one of the ingredients is substantially soluble, such as water, methanol, ethanol, isopropanol, acetone, methylethyl ketone, methylisobutyl ketone, chloroform, methylene chloride, trichloroethylene, trichlorofluoromethane, 1,2 - dichloro - 1,1,2,2-tetrafluoroethane, and the like, preferably ethanol, the solvent removed therefrom by evaporation, and the dried granules commingled with the aspirin.

The admixing of a naturally occurring amino acid hydrochloride, preferably in the L-form, with the aspirin and d-propoxyphene hydrochloride combination results in a manyfold decrease in the rate and amount of aspirin hydrolysis in the presence of moisture.

An eminently satisfactory utilization of a naturally occurring amino acid hydrochloride for the inhibition of aspirin hydrolysis is accomplished by substituting L-glutamic acid hydrochloride for all of the inert ingredient, starch, in one of the pharmaceutical compositions illustrated above, resulting in a pharmaceutical composition composed of: aspirin, 40.0 percent; d-propoxyphene hydrochloride, 11.4 percent phenacetin, 28.4 percent; caffeine, 5.7 percent; and L-glutamic acid hydrochloride, 14.5 percent. The rate of hydrolysis of aspirin in such a composition decreased from 70 to 90 percent by comparison with the unstabilized composition.

When L-lysine dihydrochloride is added in an amount of about 18 percent of the d-propoxyphene hydrochloride content in a pharmaceutical composition containing aspirin, 52.4 percent; d-propoxyphene hydrochloride 10.5 percent; and kaolin, 37.1 percent, resulting in a pharmaceutical composition in which the naturally occurring amino acid as the hydrochloride comprised about two percent of the total, the rate of hydrolysis is decreased more than 50 percent.

Other compatible active agents and pharmaceutically acceptable inert ingredients can coexist in the pharmaceutical composition comprising the combination of aspirin, d-propoxyphene hydrochloride and naturally occurring amino acid hydrochloride, or the latter combination can comprise the sole contents of the composition. In either case, the rate of aspirin hydrolysis will be significantly retarded in the presence of the naturally occurring amino acid hydrochloride.

Other pharmaceutically acceptable water soluble salts of naturally occurring amino acids, such as phosphate, sulfate, and the like

can also be effectively employed to impede the hydrolysis of aspirin in pharmaceutical compositions comprising d-propoxyphene hydrochloride and aspirin.

The novel pharmaceutical compositions of this invention can be filled into gelatin capsules or formed into compressed tablets, by processes known to those skilled in the art, in suitable quantities to provide unit dosage forms containing the appropriate amounts of the therapeutic agents for oral administration.

This invention is further illustrated by the following examples.

Example 1

Pharmaceutical compositions comprising aspirin and d-propoxyphene hydrochloride were prepared according to the following formulae and filled into gelatin capsules. The filled capsules were stored at 50°C. for four days and the contents analyzed for free salicylic acid using the procedure outlined on page 607 of N. F. XIII (1970). The percent salicylic acid found is shown in Table I below:

FORMULA A

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
Starch	84 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 570 mg.

FORMULA B

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
Kaolin	84 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 570 mg.

FORMULA C

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
L-Glutamic acid hydrochloride	84 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 570 mg.

FORMULA D

Ingredient	Amount
Aspirin	227 g.
Phenacetin	163 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
L-Glutamic acid hydrochloride	30 g.
Starch	54 g.

The d-propoxyphene hydrochloride and L-glutamic acid hydrochloride were admixed together in a Hobart (Trade Mark) mixer for 5 minutes, and 10 ml. of ethyl alcohol were added to the blended powder and the mixer was run for another 5 minutes. The moistened mass was removed from the mixer, passed through a No. 6 mesh (U.S.) screen, and spread on trays. The ethyl alcohol was removed from the granulation *in vacuo* for 2 hours at 25°C. The dried granules were worked through a 16 mesh (U.S.) screen and added to a laboratory size ribbon blender. The remainder of the ingredients were added to the blender and admixed together for 15 minutes and then filled into size 0 gelatin capsules, each capsule containing 570 mg.

FORMULA E

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
L-Glutamic acid hydrochloride	30 g.
Kaolin	54 g.

The ingredients were processed and combined as described under Formula D above.

FORMULA F

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
L-Glutamic acid hydrochloride	15 g.
Starch	69 g.

The ingredients were processed and combined as described under Formula D above.

FORMULA G

Ingredient	Amount
Aspirin	227 g.
Phenacetin	162 g.
Caffeine	32 g.
d-Propoxyphene hydrochloride	65 g.
L-Glutamic acid hydrochloride	15 g.
Kaolin	69 g.

The ingredients were processed and combined as described under Formula D above.

TABLE I

Free Salicyclic Acid Contained in Pharmaceutical Compositions after Four Days Storage in Filled Capsules at 50°C.

Formula	d-Propoxyphene Hydrochloride mg./Capsule	L-Glutamic Acid Hydrochloride mg./Capsule	L-Glutamic Acid Hydrochloride as % of d-Propoxyphene Hydrochloride	% Free Salicyclic Acid Contained in Pharmaceutical Compositions
A	65	None	—	2.93
B	65	None	—	2.28
C	65	84	129	0.67
D	65	30	46	0.25
E	65	30	46	0.30
F	65	15	23	0.55
G	65	15	23	0.66

The data clearly shows that the commingling of L-glutamic acid hydrochloride with aspirin and d-propoxyphene hydrochloride results in a 3- to 10-fold reduction in the rate of aspirin hydrolysis as measured by the development of free salicylic acid in the pharmaceutical composition.

Example 2

Pharmaceutical compositions comprising aspirin and d-propoxyphene hydrochloride were prepared containing respectively 84 mg. per capsule of glutamic acid hydrochloride in the D-form, DL-form, and L-form. The capsules were stored at 50°C. for 4 days, and the contents were analyzed for free salicylic acid using the procedure outlined on page 607 of N.F. XIII (1970). Table II shows the percent salicylic acid found.

TABLE II

Free Salicylic Acid Contained in Pharmaceutical Compositions after Four Days Storage in Filled Capsules at 50°C.

Aspirin mg./Capsule	d-Propoxyphene Hydrochloride mg./Capsule	Glutamic Acid Hydrochloride mg./capsule	Glutamic Acid Hydrochloride Form Used	% Free Salicylic Acid Contained in Pharmaceutical Compositions
227	65	None	—	2.93
227	65	None	—	2.28
227	65	84	L-form	0.67
227	65	84	DL-form	1.47
227	65	84	D-form	1.25

The data in Table II show that all three forms of glutamic acid hydrochloride were effective in inhibiting the hydrolysis of aspirin in the presence of d-propoxyphene hydrochloride, the L-form showing the greatest effect, as measured by a lessening of the amount of free salicylic acid contained in the pharmaceutical composition in which glutamic acid hydrochloride was included as one of the ingredients.

Example 3

Pharmaceutical compositions comprising aspirin, d-propoxyphene hydrochloride, and L-lysine dihydrochloride were prepare according to the following formulae and filled into gelatin capsules. The filled capsules were stored at 50°C. for four days and the contents analyzed for free salicylic acid using the procedure outlined on page 607 of N.F. XIII (1970). The percent salicylic acid found is shown in Table III below:

FORMULA H

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	230 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

FORMULA J

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	228 g.
L-Lysine dihydrochloride	2 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

FORMULA K

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	226 g.
L-Lysine dihydrochloride	4 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

FORMULA L

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	224 g.
L-Lysine dihydrochloride	6 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

FORMULA M

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	218 g.
L-Lysine dihydrochloride	12 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

TABLE III

Free Salicylic Acid Contained in Pharmaceutical Compositions After Four Days Storage in Filled Capsules at 50°C.

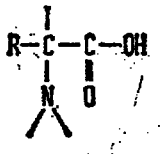
Formula	d-Propoxyphene Hydrochloride mg./Capsule	L-Lysine dihydrochloride mg./Capsule	L-Lysine dihydrochloride as % of d-Propoxyphene Hydrochloride	% Free Salicylic Acid Contained in Pharmaceutical Compositions[1]
H	65	None	—	1.96
J	65	2	3.08	1.56
K	65	4	6.15	1.22
L	65	6	9.23	1.05
M	65	12	18.46	0.81

[1]Each result is the average of 6 separate assays.

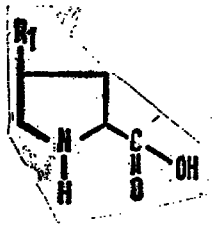
The data indicate that the addition of L-lysine dihydrochloride to a pharmaceutical composition comprising aspirin and d-propoxyphene hydrochloride has a significant effect on the rate of aspirin hydrolysis as measured by the development of free salicylic acid.

WHAT WE CLAIM IS: —

1. The method of inhibiting the hydrolysis of acetylsalicylic acid in a pharmaceutical composition comprising acetylsalicylic acid and d-propoxyphene hydrochloride which comprises incorporating into such pharmaceutical composition the hydrochloride of a compound selected from the group having as a general formula either



or



wherein

R is hydrogen, methyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxymethyl, 1-hydroxyethyl, carboxymethyl, carboxyethyl, carboxy-(1-hydroxy)ethyl, aminobutyl, methylthioethyl, mercaptomethyl, carboxy - (2 - aminoethyl)dithiomethyl, p-hydroxyphenyl, benzyl, indolylmethyl, guanidinopropyl, imidazolylmethyl and ureidopropyl; and,

R_1 is hydrogen or hydroxyl.

2. The method of claim 1 wherein the compound is incorporated into the pharmaceutical composition in an amount of from 5 to 130 percent by weight of the amount of d-propoxyphene hydrochloride in such pharmaceutical composition.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

FORMULA M

Ingredient	Amount
Aspirin	325 g.
d-Propoxyphene hydrochloride	65 g.
Starch	218 g.
L-Lysine dihydrochloride	12 g.

The ingredients were admixed together in a laboratory size ribbon blender for 15 minutes and filled into size 0 gelatin capsules, each capsule containing 620 mg.

TABLE III

Free Salicylic Acid Contained in Pharmaceutical Compositions After Four Days Storage in Filled Capsules at 50°C.

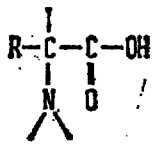
Formula	d-Propoxyphene Hydrochloride mg./Capsule	L-Lysine dihydrochloride mg./Capsule	L-Lysine dihydrochloride as % of d-Propoxyphene Hydrochloride	% Free Salicylic Acid Contained in Pharmaceutical Compositions[1]
H	65	None	—	1.96
J	65	2	3.08	1.56
K	65	4	6.15	1.22
L	65	6	9.23	1.05
M	65	12	18.46	0.81

[1]Each result is the average of 6 separate assays.

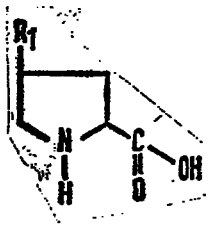
The data indicate that the addition of L-lysine dihydrochloride to a pharmaceutical composition comprising aspirin and d-propoxyphene hydrochloride has a significant effect on the rate of aspirin hydrolysis as measured by the development of free salicylic acid.

WHAT WE CLAIM IS: —

1. The method of inhibiting the hydrolysis of acetylsalicylic acid in a pharmaceutical composition comprising acetylsalicylic acid and d-propoxyphene hydrochloride which comprises incorporating into such pharmaceutical composition the hydrochloride of a compound selected from the group having as a general formula either



or



wherein

R is hydrogen, methyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxymethyl, 1-hydroxyethyl, carboxymethyl, carboxyethyl, carboxy-(1-hydroxy)ethyl, aminobutyl, methylthioethyl, mercaptomethyl, carboxy - (2 - aminoethyl)dithiomethyl, p-hydroxyphenyl, benzyl, indolylmethyl, guanidinopropyl, imidazolylmethyl and ureidopropyl; and,

R_1 is hydrogen or hydroxyl.

2. The method of claim 1 wherein the compound is incorporated into the pharmaceutical composition in an amount of from 5 to 130 percent by weight of the amount of d-propoxyphene hydrochloride in such pharmaceutical composition.

* C L M S *

3. The method of claim 1 or 2 wherein the compound is intimately admixed with the d-propoxyphene hydrochloride before incorporation into the pharmaceutical composition.

4. The method of claim 1 or 2 wherein the compound and the d-propoxyphene hydrochloride are granulated together employing a pharmaceutically acceptable solvent, the solvent is evaporated therefrom, and the dried granules are incorporated into the pharmaceutical composition.

5. The method of claim 1, 2, 3 or 4 wherein the compound is L-glutamic acid hydrochloride.

6. The method of claim 1, 2, 3 or 4 wherein the compound is L-lysine di-hydrochloride.

7. A pharmaceutical composition stabilized against hydrolysis comprising acetylsalicylic acid, d-propoxyphene hydrochloride and the hydrochloride of a naturally occurring amino acid.

8. The pharmaceutical composition of claim 7 wherein the naturally occurring amino acid is L-glutamic acid.

9. The pharmaceutical composition of claim 7 wherein the naturally occurring amino acid is L-lysine.

10. The method of inhibiting the hydrolysis of acetylsalicylic acid in a pharmaceutical composition substantially as herein described.

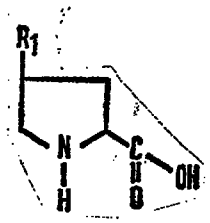
11. A pharmaceutical composition stabilized against hydrolysis substantially as herein described.

12. A method according to any one of claims 1 and 3 to 6 wherein the compound is incorporated into the pharmaceutical composition in an amount of from 5 to 50 percent by weight of the quantity of d-propoxyphene hydrochloride.

13. A pharmaceutical composition comprising acetylsalicylic acid, d-propoxyphene hydrochloride and the hydrochloride of a compound of the formula:—



or



wherein

R is hydrogen, methyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxymethyl, 1 - hydroxyethyl, carboxymethyl, carboxyethyl, carboxy - (1 - hydroxy)ethyl, aminobutyl, methylthioethyl, mercaptomethyl, carboxy-(2-aminoethyl)dithiomethyl, p-hydroxyphenyl, benzyl, indolylmethyl, guanidinopropyl, imidazolylmethyl and ureidopropyl; and,

R_1 is hydrogen or hydroxyl.

14. A method according to any one of claims 1 to 6 and 12 or a composition as claimed in any one of claims 7, 8, 9 and 13 wherein the hydrochloride of the amino acid is replaced with another pharmaceutically acceptable water soluble salt of an amino acid.

15. A composition according to claim 7 or a method according to claim 1 substantially as described with reference to any one of the specific Examples.

16. A composition whenever prepared by a method as claimed in any one of claims 1 to 6, 10, 12, 14 and 15.

17. A method of relieving pain in an animal, excluding man, which comprises the oral administration of an effective amount of a composition as claimed in any one of claims 7, 8, 9, 11 and 13 to 15.

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