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(71) Applicant *(for all designated States except US):* PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* SMITH, Ward, M. [US/US]; 7 Schooner Drive, Mystic, New London County, CT 06355 (US). APPLETON, Troy, A. [US/US]; 18 Whittle Street, Mystic, New London County, CT 06355 (US).

(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

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(54) Title: HEMIPHOSPHATE HEMIHYDRATE OF 2-(1-PENTYL-3-GUANIDINO-4-IMIDAZOLYL)THIAZOLE

(57) Abstract

The hemiphosphate hemihydrate salt of 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole is the preferred salt of this antiulcer agent.

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HEMIPHOSPHATE HEMIHYDRATE OF 2-(1-PENTYL-3-GUANIDINO-4-IMIDAZOLYL)THIAZOLE

Background of the Invention

The present invention is directed to a hemiphosphate hemihydrate salt of 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole having advantageous properties.

U.S. Patent 4,560,690, which is herein included by reference, describes 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole and analogs as having antiulcer activity. The form of this preferred compound, reported in said patent is the anhydrous dihydrochloride salt, which is noncrystalline, difficult to purify and possesses properties which are generally less suitable for formulation and use as a medicinal agent in man.

International Application No. PCT/US86/02308 reports a further improvement in salts of this preferred antiulcer agent and describes the preparation and properties of the dihydrochloride trihydrate salt.

Summary of the Invention

It has now been found that a yet unreported salt of 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole, namely, the hemiphosphate hemihydrate, offers many advantages especially a high weight percent of active agent.

Detailed Description of the Invention

2-(1-Pentyl-3-guanidino-4-imidazolyl)thiazole hemiphosphate hemihydrate is prepared by solubilizing the dihydrochloride trihydrate salt (10 mg free base equivalent) per ml in a pH 6.6, 0.2 M Phosphate buffer

containing acetone in the ratio one part (weight) acetone to four parts (weight) buffer. After standing overnight at room temperature, the desired product is removed by filtration and dried under vacuum at room temperature.

This hemiphosphate hemihydrate salt has all the characteristics desired in a drug to be formulated for human use; it is crystalline, stable, non-hygroscopic and contains a high weight percent of active agent. This latter characteristic is especially important in allowing the formulation of smaller tablets, capsules, etc., for oral administration. This can readily be seen from the following comparison of the various reported forms of 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole:

Form	Molecular Formula	Molecular Wt.(gr/mole)	%Potency[1]
free base	$C_{13}H_{20}N_6S_1$	292.4	100%
dihydro-chloride trihydrate	$C_{13}H_{20}N_6S_1$ $2HCl$ $3H_2O$	419.4	292.4/419.4 69.7%
hemi-phosphate hemihydrate	$C_{13}H_{20}N_6S_1$ $1/2H_3PO_4$ $1/2H_2O$	350.4	292.4/350.4 83.4%

[1] Potency is defined as the ratio of the molecular weights of the free base to the salt form.

The following example is given by way of illustration and is not to be construed as a limitation of this invention.

EXAMPLE 1

2-(1-Pentyl-3-guanidino-4-imidazolyl)thiazole Hemiphosphate Hemihydrate Salt

Sufficient 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole dihydrochloride trihydrate was added to 100 ml. of a solution consisting, by weight, of 1 part acetone and 4 parts of a 0.2H phosphate buffer to give a drug concentration of 10 mg free base equivalent/ml. The mixture was stirred until all the solids had dissolved and was then allowed to remain undisturbed at room temperature overnight. The precipitated crystals were filtered and dried at room temperature in vacuo for 24 hours.

The DSC data gathered on this material shows it to possess two low temperature endotherms and one high temperature endotherm associated with melting.

The TGA data shows a loss of approximately 3% of the total weight when heated to 170°C. This weight loss is likely due to water loss, since Karl Fischer readings show 3.2% water on the material.

Samples of the hemiphosphate hemihydrate were submitted for elemental analysis. The amount of carbon, hydrogen and nitrogen are within 3% of the theoretical value whereas phosphorous is slightly higher that the theoretical value. The titratable water is slightly higher than the theoretical water content for a hemihydrate (2.6%). The slightly higher % water could be accounted for by the presence of some surface water on the bulk.

The habit of the hemiphosphate hemihydrate crystals is more rod-like or bladed in character than the needle crystalline habit of the dihydrochloride trihydrate form. Single crystal studies showed that there are 8 molecules per unit cell. The single crystal data confirms that this is the hemiphosphate hemihydrate. X-ray powder diffraction patterns generated for the new form and for the dihydrochloride trihydrate form also verifies that these are two completely different forms.

Samples of the hemiphosphate hemihydrate were stored at 50°C. After 55 days, TGA data still shows a weight loss of 2.7% up to 170°C and microscopically shows birefringence indicating that the form is physically stable under these conditions.

A tabulation of this information is as follows:

TABLE 1

Some Physicochemical Properties of 2-(1-pentyl-3-guanidino-4-imidazolyl)thiazole hemiphosphate hemihydrate

1. Thermal Properties	
Melting Point °C (Onset of endothermic peak, DSC heating rate = 10°C/min)	214°C
Heat of Fusion (kcal/M)	4.1 kcal/M
Percent weight loss (TGA heating rate = 10°C/min) to 170°C	2.9 (103°-169°C)

2. X-ray and Microscopic Analysis

Single Crystal	crystalline, consistent with proposed composition
Powder Diffraction	crystalline
Microscopic Crystallinity	birefringent

3. Elemental Analysis (lot #16362-120-1)

Element	Theoretical % ($1/2H_3PO_4$ $1/2H_2O$)	Actual %
C	44.6	44.23
H	6.5	6.48
N	24.0	23.67
P	4.4	4.79
H_2O	2.6	3.2 (KF)

4. Physical Stability after Storage at 50°C (55 Days)

Percent Weight Loss (TGA) to 170°C.	2.7%
Microscopic Crystallinity	birefringent

CLAIMS

1. 2-(1-Pentyl-3-guanidino-4-imidazolyl)thiazole hemiphosphate hemihydrate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/03019

I. **CLASSIFICATION OF SUBJECT MATTER** (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07D 417/04 A61K 31/425

U.S.Cl.: 548/193; 514/370

II. **FIELDS SEARCHED**

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	548/193 514/370

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Chemical Abstracts 1-109

III. **DOCUMENTS CONSIDERED TO BE RELEVANT** [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	U.S., A, 4,560,690 (REITER) 24 DECEMBER 1985 (24.12.85), see column 2, lines 21-28.	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. **CERTIFICATION**

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 FEBRUARY 1989	11 APR 1989
International Searching Authority	Signature of Authorized Officer
ISA/US	ROBERT GERSTL