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FORM 2A
THE PATENTS ACT. 1970
CONVENTION **APPLICATION** FOR PATENT

1485 DEL 98

By **the** assignee or Legal Representative of the Applicant in Convention country.
[See Sections 5. 7 and 135]

24 AUG

We. BOEHR1NGER INGELHEIM **PHARMACEUTICALS.** INC.. of 900 Ridgebury Road. P.O. Box 368. Rldgcfield. Conn. 06877-0368. United States of America.

hereby declare -
il that we are in possession of an invention for
"PHARMACEUTICAL SUSPENSION COMPRISING NEVI RAPINE H EMI HYD RATE"

iijthat application for protection of invention has been made in the following country on the following official date **namely:-**

in U.S.A. on 25.8.1997 by **KARL** GEORG GROZINGER. a Canadian citizen of 171 High Ridge Avenue. Ridgefield. CT. USA and AMALE AYOUB HAWI. a US citizen of 166 Old Brookfieid Road 3 12-3. Danbury. CT 06810. USA.

for: "PHARMACEUTICAL SUSPENSION COMPRISING NEVI RAPINE HEMIHYDRATE" & PWSC

and that the said application or each of the said application, was the first application in a Convention countries in respect of the relevant invention by the said KARL GEORG GROZINGER AND AMALE AYOUB HAWI.

fllthat we arc the legal assignees of KARL GEORG GROZINGER AND AMALE AYOUB **HAWI.** .

ivjthat the complete specification filed with this application is and any amended specification which may hereafter be filed in this behalf will be true of the invention to which this application relates:

v|that we believe that we are entitled to a patent for the said invention having regard to the provisions ofThe Patents Act.- 1970;

vijthat to the best of our knowledge, information and belief, the facts and matters stated herein arc correct and that there is no lawful ground of objection to the grant of patent to us on this application.

We request that a patent may be granted to us for the said invention, **with** priority based on the above-mentioned application in a Convention country under the provisions of sub-section |1| of section **135** of the Act.

We request that all notices, requisitions, and communications relating to this application may be sent to REMFRY & SAGAR. Attorney s-at-Law, Re m fry House. 8. Nangal Raya Business Centre, New Delhi-1 10 046.

Dated this 24th day of August. 1998

JT*

OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

TO
Till-; CONTROLLER OF PATENTS
'nilC PATENT OFFICE. DELHI

THE PATENTS ACT, 1970

COMPLETE

SPECIFICATION
Section 10

"PHARMACEUTICAL SUSPENSION COMPRISING NEVIRAPINE HEMIHYDRATE"

BOEHRINGER INGELHEIM PHARMACEUTICALS. INC., of 900 Ridgebury Road. P.O. Box 368, Ridgefield. Conn. 06877-0368. United States of America.

The following specification particularly describes and ascertains the nature of Lhis invenLion and the manner in which it is to be performed:-

PHARMACEUTICAL SUSPENSION COMPRISING NEV-IRAPFNE HEMIHYDRATE •

Background of the Invention

(1) • Field of the Invention

The invention relates to a novel composition of matter which is a pharmaceutica! suspension comprising nevirapine hemihydrate.

(2) Description of the Related Art

Nevirapine, or 1 l-cyclopropyt-5,1 l^ihydro-4-methyl-6H-dipyrido[3,2-b:2',3^{t}-eJ[l,4]diaze-pin-6-one, is a known agent for the treatment of infection by HIV-1 (human immunodefi-ciency virus, type 1), which acts through specific inhibition of HIV-1 reverse transcri'ptase. Its synthesis and use are described in various publications including, *inter alia,* U.S. Patent No. 5,366,972; European Patent Application No. 0 429 987, U.S. Patent 5,571,912 and U.S Patent No. 5,569,760 . Viramune " tablets, a pharmaceutical comprising nevirapine in tablet form, has recently been approved by the U.S. Food and Drug Administration for use in the treatment of HIV-l infection.

Angel et al. [Proc. 50th Annual Meeting of the Electron Microscopy Society of America, pp. 1326-1327 (1992)] have disclosed that nevirapine exists as the hemihydrate stable form and as the anhydrous metastable form. This same reference describes an attempt to make an aqueous suspension of nevirapine, suitable for pediatric use, from the anhydrous form of the compound. The attempt was unsuccessful because, when formulated in aqueous suspension, the anhydrous nevirapine slowly converted to the hemihydrate form, yielding crystals of the hemihydrate which, over time, grew so large as to adversely affect drug dissolution and pharmaceutical per-formance.

Summary of the Invention

The invention is an aqueous suspension of the hemihydrate form of nevirapine. It has been found, unexpectedly, that, when placed in aqueous suspension, the crystal size of the hemi-hydrate remains stable over time. For this reason, aqueous suspensions of nevirapine hemi-hydrate are pharmaccuticaily acceptable.

Detailed Description of the Invention

Anhydrous nevirapinc can be made by any of several known methods, including those described in the references mentioned above.

The hemihydrate is conveniently produced by recrystallization of the anhydrous material from an aqueous medium. This can be accomplished by treating an aqueous suspension of the anhydrous material, which is a free base, with a strong acid, such as HC1, to yield the acid addition salt. The salt is, in turn, treated with a strong base, such as NaOH, to yield the free base as a precipitate, in the hemihydrate form. The precipitate is removed from the aqueous medium by filtration, washed with water and dried until the water content is between about 3.1 and 3.9% by weight. Further drying, which would convert the hemihydrate to the anhydrous form is to be avoided. The term hemihydrate is intended to refer to nevirapine which contains about 0.5 mole of water.

For use in a pharmaceuticaily acceptable aqueous suspension, the particle size of the hemihydrate should be between about I and 150 microns in diameter. The hemihydrate produced as described above can be milled, if necessary, so that particle size will fall within this range.

A pharmaceuticaily acceptable aqueous suspension of nevirapine hemihydrate can be made by adding the hemihydrate to purified water, in ratios from 1 to 50 mg nevirapine hemihydrate to I mL of water, followed by agitation. The formulation can additionally comprise conventional pharmaceutical additives, such as, but not limited to, suspending agents and/or viscosity thickening agents such as, for example cellulose-based polymers or synthetic polymers, preferably cross-linked polymers such as the carbomers; wetting agents such as, for example, polyethylene oxides or polyoxyethylene sorbitan fatty acid esters (polysorbates); sweetening or flavoring agents, such as sucrose; and preservatives, such as, for example, the parabens.

By way of non-limiting description, a typical formulation in accordance with the invention would be one as described in the following table.

Constituent	Range of Amount (g/100 mL)
Nevirapine Hemihydrate	0.1-50
Carbomer934P,NF	0.17-0.22
Polysorbate 80, NF	0.01 -0.2
Sorbitol Solution, USP	5-30
Sucrose, NF	5-30
Methylparaben, NF	0.15-0.2
Propyiparabcn, NF	0.02 - 0.24
Sodium Hydroxide, N.F.*	q.s. to pH 5.5 - 6.0
Purified Water, USP	q.s. ad 100.0 mL

*20% solution prepare.'

The invention is further illustrated by the following non-limiting examples.

Example 1
Preparation of nevirapine hemihydrate

A glass lined reactor containing 318 Kg of nevirapinc (anhydrous) is charged with 319 Kg of 37% HC1 at a flow rate to maintain the internal temperature below 35°C. The mixture is agitated at 25-35°C until all material is dissolved. The solution is filtered and diluted with 160 liters of purified water. The solution is neutralized with a 25% sodium hydroxide solution, while maintaining the temperature below 40°C. The resulting crystalline suspension is cooled to I5-20°C for 30 minutes. The crystals are centrifuged and washed with purified water and dried at 30-40°C. The crystals are then dried under vacuum using a conventional vacuum tumble dryer for 8-24 hours, an air circulation tray dryer for 24-72 hours, or a Titus* centrifuge dryer (TZD) for 1 to 8 hours. The drug substance, which is the hemihydrate, is dried until the water content is between 3.1 - 3.9% as determined by a moisture balance on 100°C for 30 min.

Example 2
Preparation of nevirapine hemihydrate

26 g of nevirapine (anhydrous) are suspended in 100 mL of water. To the stirred mixture is added 30 mL of concentrated hydrochloric acid with cooling to maintain the temperature below 30°C. After 10 to 20 minutes, the colored solution is filtered and neutralized by ihe addition of 14.4 g sodium hydroxide in 50 mL of water. The resulting precipitate is filtered and washed with water. The wet crystalline material is transferred to trays and dried at 35-45°C until a water content of 3.1 to 3.9% is obtained. The melting point of the resulting hemihydrate is 242-245°C and analyzes for 3.1 to 3.6% of water, or about 0.5 mole of water.

Example 3
Preparation of aqueous 50 mg/5 ml pharmaceutical suspension of nevirapine hemihydrate

Composition

Constituent	Amount (g/lOOmL)
Nevirapine Hemihydrate	1.035
Carbomer 934P, NF	0.2100
Polysorbate80,NF	0.05000
Sorbitol Solution, USP	23.13
Sucrose, NF	15.00
Methylparaben, NF	0.1800
Propylparaben, NF	0.02400
Sodium Hydroxide, N.F.*	q.s. to pH 5.5-6.0
Purified Water, USP	q.s. ad 100.0 mL

*20% solution prepared

Processing Method

A portion of purified water is heated to approximately 70°C and the methylparaben and propylparaben are added while continuously mixing. Once the parabens have completely dissolved, the solution is allowed to cool to less than 35°C, and then the carbomer 934P is dispersed in the preservative solution while mixing. The pH is adjusted to pH 5.5 - 5.8 with 20% sodium hydroxide solution. The gel is continually stirred for approximately 20 minutes and the pH remeasured. The sorbitol solution is added while mixing. Then the sucrose is added and mixing continued for 30 minutes. The polysorbate 80 is dissolved in a portion of purified water, the nevirapine is then added to the polysorbate 80 solution, and the mixture is homogenized for at least 40 minutes. The nevirapine/polysorbate 80 drug concentrate is thoroughly blended into the carbomer gel. The suspension is adjusted to volume or weight with purified water and blended for 30 minutes.

What is claimed is:

1. A method for preparing an aqueous suspension of nevirapine which method comprises admixing nevirapine hemihydrate, having a particle size between about I and 150 microns, with water.

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2. A pharmaceutical composition consisting essentially of nevirapine hemihydrate, having a particle size between about 1 and 150 microns, and water.

3. A pharmaceutical composition consisting essentially of the following constituents in the specified relative range amounts:

Constituent	Range of Amount (g/lOOmL)
Nevirapine Hemihydrate	0.1-50
Carbomer 934P, NF	0.17-0.22
Polysorbate 80, NF	0.01 -0.2
Sorbitol Solution, USP	5-30
Sucrose, NF	5-30
Methylparaben, NF	0.15-0.2
Propylparaben, NF	0.02 - 0.24
Sodium Hydroxide, N.F.*	q.s. to pH 5.5-6,0
Purified Water, USP	q.s. ad 100.0 mL

*20% solution prepared

wherein the nevirapine particle size is between about 1 and 150 microns in diameter.

4. A pharmaceutical composition, in accordance with claim 3, consisting essentially of the following constituents in the specified relative amounts:

constituent	amount (g/lOOmL)
Nevirapine Hemihydrate	1.035
Carbomer 934P, NF	0.1900
Polysorbate 80, NF	0.05000
Sorbitot Solution, USP	23.13
Sucrose, NF	15.00
Methylparaben, NF	0.1800
Propylparaben, NF	0.02400
Sodium Hydroxide, N.F.*	q.s. to pH 5.5 - 6.0
Purified Water, USP	q.s. ad 100.0 mL

*20% solution prepared

wherein the nevirapine particle size is between about 1 and 150 microns in diameter.

5. Use of nevirapine hemihydrate for preparing a pharmaceutical composition for the treatment of HIV-1 infection.

6. A pharmaceutical composition substantially as hereinbefore described with reference to the foregoing examples.

Dated this 24th day of August. 1998.

(V.B. MEHRISH)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS