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(54) **PROCESS FOR TREPROSTINIL SALT PREPARATION**

(75) Inventors: **Walter Giust**, Toronto (CA); **Fabio Souza**, Mississauga (CA); **Jan Oudenes**, Aurora (CA); **Boris Gorin**, Oakville (CA); **Elena Bejan**, Brantford (CA)

(73) Assignee: **EON LABS, INC.**, Princeton, NJ (US)

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(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Sudhakar Katakam
Assistant Examiner — Jennifer C Sawyer
(74) *Attorney, Agent, or Firm* — Nixon Peabody LLP

(57) **ABSTRACT**

Disclosed is a process for preparing a treprostinil salt. The process involves the step of dissolving treprostinil in a water-miscible organic solvent to form a treprostinil solution. The treprostinil solution is reacted with an aqueous basic solution containing an alkali metal cation to form treprostinil salt. Allowing crystallization of the treprostinil salt to take place, and then collecting the treprostinil salt formed.

34 Claims, 1 Drawing Sheet

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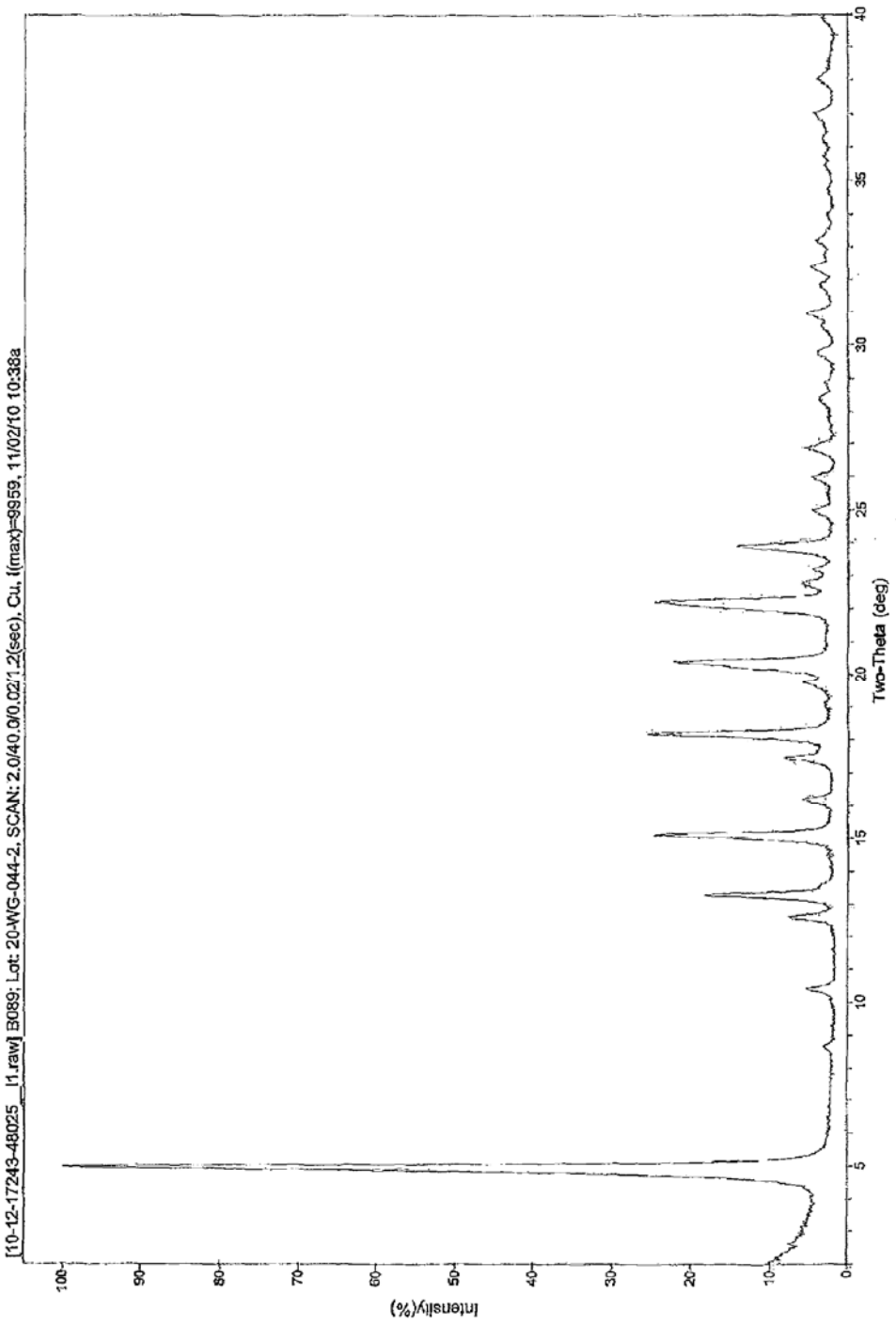


PROCESS FOR TREPROSTINIL SALT PREPARATION

CROSS REFERENCE TO RELATED APPLICATIONS

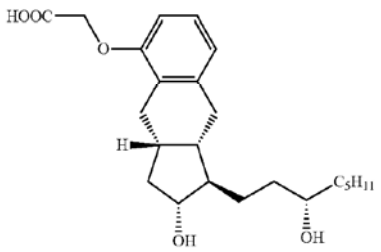
This application is a 35 U.S.C. §371 National Stage Entry Application of International Application No. PCT/CA2011/050804, filed Dec. 22, 2011, which designates the U.S., and which claims benefit under 35 U.S.C. §119(b) of Canadian Patent Application No. 2,726,599, filed Dec. 30, 2010, the content of the above patent application is hereby expressly incorporated herein by reference into the detailed description hereof in its entirety.

TECHNICAL FIELD

This specification relates to a process for treprostinil salt preparation.

BACKGROUND

Prostacyclin derivatives are useful pharmaceutical compounds possessing pharmacological activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, vasodilation and bronchodilation. Treprostinil is a prostacyclin analogue, having the following chemical structure:



Treprostinil sodium solution is marketed as Remodulin® and Tyvaso® for treatment of pulmonary arterial hypertension.

Process for preparation of treprostinil, treprostinil derivatives and intermediates useful in preparation of treprostinil are described in U.S. Pat. Nos. 4,306,075; 6,700,025; 6,809,223 and 6,765,117. U.S. Pat. No. 4,306,075 (col. 40, l. 41-62) discloses a general procedure for preparation of pharmacologically acceptable salts of treprostinil, where preparation of an inorganic salt of treprostinil can be carried out by dissolution of treprostinil in water, followed by neutralization with appropriate amounts of corresponding inorganic base. However, a commercially viable synthetic route for preparation of the sodium salt of treprostinil is desired.

Preparation of treprostinil sodium can be difficult, as the salt is soluble in water and difficult to precipitate, while the treprostinil acid is only sparingly soluble in water. Salts of a compound can be useful due in part to their increased stability, bioavailability and solubility in water. Availability of treprostinil salt can also help in preparation of a formulation, including a pharmaceutical formulation.

Therefore, there is a need in the art for a process for the preparation of a salt of treprostinil. Moreover, there is a need

the art for a process for the synthesis of treprostinil sodium, including a commercially viable process.

SUMMARY OF THE INVENTION

In one aspect, the specification relates to a process for preparing a treprostinil salt, comprising:

- dissolving treprostinil in a water-miscible organic solvent to form a treprostinil solution;
- reacting the treprostinil solution with an aqueous basic solution containing an alkali metal cation to form a reaction mixture containing the treprostinil salt;
- allowing crystallization of the treprostinil salt; and
- collecting the treprostinil salt formed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a powder X-ray diffraction spectrum of treprostinil sodium obtained according to the reaction described herein.

DETAILED DESCRIPTION

As noted above, the specification relates to a process for preparing a treprostinil salt, the process containing the steps of:

- dissolving treprostinil in a water-miscible organic solvent to form a treprostinil solution;
- reacting the treprostinil solution with an aqueous basic solution containing an alkali metal cation to form a reaction mixture containing the treprostinil salt;
- allowing crystallization of the treprostinil salt; and
- collecting the crystals of the treprostinil salt.

The water-miscible organic solvent used for dissolving treprostinil is not particularly limited, and can contain one or more functional groups, as long as the organic solvent is miscible and can form a solution with water. In one embodiment, for example and without limitation, the water-miscible organic solvent is a water-miscible ketone solvent, water-miscible alcohol or water-miscible ether.

In one embodiment, for example and without limitation, the water-miscible organic solvent is a water-miscible ketone solvent. The number of carbon atoms in the water-miscible ketone solvent is not particularly limited but can be any number, as long as the water-miscible ketone solvent is miscible in water. In one embodiment, the water-miscible ketone solvent contains from 3 to 8 carbon atoms. In another embodiment, for example and without limitation, the water-miscible ketone solvent is a hydrocarbon based water-miscible ketone solvent. A hydrocarbon based water-miscible ketone solvent contains a ketone functional group and a hydrocarbon chain having carbon and hydrogen atoms. In a further embodiment, for example and without limitation, the water-miscible ketone solvent is a linear or branched alkyl ketone. The number of carbon atoms in the alkyl ketone is not particularly limited and contain, for example and without limitation, 3 to 6 carbon atoms. In one embodiment, for example and without limitation, the water-miscible solvent is acetone.

Examples of water-miscible ketone solvents for use in preparation of treprostinil salt can include, for example and without limitation, acetone, butanone, 2-pentanone, 3-pentanone, methyl isopropyl ketone, 2-hexanone, 3-hexanone, methyl isobutyl ketone (MIBK), ethyl isopropyl ketone, cyclopentanone, 2-methyl cyclopentanone, 3-methyl cyclopentanone, cyclohexanone and others.

In another embodiment, the water-miscible organic solvent is a water-miscible alcohol. The number of carbon atoms in the water-miscible alcohol is not particularly limited but can be any number, as long as the alcohol is miscible in water. In one embodiment, for example and without limitation, the water-miscible alcohol contains from 3 to 8 carbon atoms. In another embodiment, for example and without limitation, the water-miscible alcohol is a hydrocarbon based water-miscible alcohol. A hydrocarbon based water-miscible alcohol contains an alcohol functional group and a hydrocarbon chain having carbon and hydrogen atoms. In a further embodiment, for example and without limitation, the water-miscible alcohol is a linear or branched alkyl alcohol. The number of carbon atoms in the linear or branched hydrocarbon based alcohol is not particularly limited and contain, for example and without limitation, 3 to 6 carbon atoms. In one embodiment, for example and without limitation, the water-miscible alcohol is methanol, ethanol, propanol, isopropanol and others.

Similar to the water-miscible organic ketones solvent and water-miscible alcohols noted above, other water-miscible organic solvents can also be used. Examples of other water-miscible organic solvents can include, for example and without limitation, tetrahydrofuran, acetonitrile and others. In addition, two or more organic solvents can also be used so long the organic solvents together are miscible in water.

The ratio of treprostinil to the water-miscible organic solvent as described herein is not particularly limited. In one embodiment, for example and without limitation, the ratio of treprostinil to the water-miscible organic solvent is 1 g of treprostinil to from 5 to 50 mL of the water-miscible organic solvent. In another embodiment the ratio of treprostinil to the water-miscible organic solvent is, for example and without limitation, 1 g of treprostinil to from 15 to 30 mL of the water-miscible organic solvent.

The aqueous basic solution for reaction with treprostinil to form treprostinil salt contains an aqueous solution and a base, which can deprotonate carboxylic acid moiety of treprostinil. The base in the aqueous basic solution for use in the reaction described herein is not particularly limited and contains an anion and an alkali metal cation. In one embodiment, for example and without limitation, the anion is hydroxide, carbonate or bicarbonate anion. The alkali metal cation for use in the reaction described herein can be, for example and without limitation, lithium, sodium or potassium. Appropriate anion and alkali metal cation can be determined based on the reaction conditions and the desired treprostinil salt. In one embodiment, for example and without limitation, the aqueous basic solution contains sodium hydroxide for reaction with treprostinil to form treprostinil sodium.

The concentration of the base in the aqueous basic solution for reaction with treprostinil is not particularly limited. Sufficient concentration of the aqueous basic solution can be used to allow reaction with treprostinil and to allow formation of treprostinil salt. In one embodiment, for example and without limitation, the base in the aqueous basic solution has a concentration of from about 2 to about 8 molar. In another embodiment, for example and without limitation, the base in the aqueous basic solution has a concentration of from about 5 molar.

The mole ratio of the base in the aqueous basic solution to treprostinil in the treprostinil solution is not particularly limited. The mole ratio used can be chosen to maximize yield, by reaction of the base with treprostinil and allowing crystallization of treprostinil salt. In general, the ratio of the base to treprostinil used allows for deprotonation of treprostinil. In one embodiment, for example and without limitation, the mole ratio of base in the basic solution to treprostinil in the treprostinil solution ranges from 1:1 to 2:1. In another embodiment, the mole ratio of base in the basic solution to treprostinil in the treprostinil solution is, for example and without limitation, about 1.05:1, 1.1:1 or 1.2:1.

The volumetric ratio of the water-miscible organic solvent to the aqueous basic solution for preparation of treprostinil salt from treprostinil is not particularly limited. The volumetric ratio can be set to maximize yield and/or quality of treprostinil salt obtained. In one embodiment, for example and without limitation, the volumetric ratio of the water-miscible organic solvent to the aqueous basic solution is from 10:1 to 70:1. In another embodiment, the volumetric ratio of the water-miscible organic solvent to the aqueous basic solution is, for example and without limitation, about 40:1.

In one embodiment, the process for preparation of treprostinil salt from treprostinil is carried out by warming the treprostinil solution prior to reaction of the treprostinil solution with the aqueous basic solution. The temperature the treprostinil solution is warmed is not particularly limited. In one embodiment, for example and without limitation, the treprostinil solution is warmed up to about 60° C. prior to reacting it with the aqueous basic solution. In another embodiment, the treprostinil solution is warmed, for example and without limitation, up to about 30° C. prior to reacting it with the aqueous basic solution. The temperature the treprostinil solution is warmed can include all temperature values between those noted above.

The addition of reactants for performing the reaction of treprostinil in the treprostinil solution with the aqueous basic solution is not particularly limited. In one embodiment, for example and without limitation, the aqueous basic solution is added to the treprostinil solution for reaction with treprostinil.

The temperature for carrying out the reaction of treprostinil in the treprostinil solution with the aqueous basic solution is not particularly limited. In one embodiment, for example and without limitation, the reaction of the treprostinil solution with the aqueous basic solution is carried out at an internal temperature below about 60° C. In another embodiment, the reaction of the treprostinil solution with the aqueous basic solution is carried out at an internal temperature, for example and without limitation, below about 30° C. The temperature for carrying out the reaction can include all values between those noted above.

The reaction of treprostinil in the treprostinil solution with the aqueous basic solution as described herein can be carried out, for example and without limitation, by agitating the reaction. The rate of agitation for carrying out the reaction is not particularly limited. The rate of agitation can be set to maximize yield and/or quality of treprostinil salt. In one embodiment, for example and without limitation, agitation is continued even after allowing crystallization of treprostinil salt. The time period for the agitation is also not particularly limited and can be, for example and without limitation, for at least about 4 hours. In another embodiment, the agitation is carried out, for example and without limitation, for about 1 hour.

The temperature at which the reaction mixture is agitated after allowing crystallization of treprostinil salt and prior to collecting treprostinil salt is not particularly limited. In one embodiment, for example and without limitation, the reaction mixture is agitated at room temperature.

In another embodiment, the reaction mixture is cooled prior to collecting treprostinil salt. The temperature to which

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