

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 April 2009 (16.04.2009)

PCT

(10) International Publication Number
WO 2009/047634 A2

(51) International Patent Classification:
A61K 9/08 (2006.01) A61K 31/167 (2006.01)

(21) International Application Number:
PCT/IB2008/003217

(22) International Filing Date: 18 June 2008 (18.06.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/929,192 18 June 2007 (18.06.2007) US

(71) Applicant (for all designated States except US): **COM-BINO PHARM, S.L.** [ES/ES]; Fructuós Gelabert, 6-8 Sant Joan Despí, E-08970 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LLORET PEREZ, Sergio** [ES/ES]; Coroleu 22, Esc. A, 2º, 1a, E-08030 Barcelona (ES). **FERNANDEZ PEÑA, Agnès** [ES/ES]; Aristides Maillol 9 2 2a, E-08029 Barcelona (ES).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: AQUEOUS FORMULATIONS OF ACETAMINOPHEN FOR INJECTION

(57) Abstract: The invention relates to novel stable aqueous formulations of acetaminophen for injection as well as processes for preparing and using the same.



WO 2009/047634 A2

AQUEOUS FORMULATIONS OF ACETAMINOPHEN FOR INJECTION**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to United States Provisional Application No. 60/929,192, filed June 18, 2007, which application is expressly incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION**1. Field of the Invention**

[0002] The invention relates to novel stable aqueous formulations of acetaminophen for injection as well as processes for preparing and using the same.

2. Discussion of the Related Art

[0003] Acetaminophen, also known as paracetamol, is a common analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics.

[0004] It has been known for many years the poor stability of acetaminophen in aqueous solutions and its inadequate solubility. Acetaminophen forms undesired degradation products by reaction with the oxygen in the air or with the oxygen dissolved in the aqueous solution. The rate of decomposition is accelerated as the temperature is increased and upon exposure to light. The stability is also a function of the solution's pH.

[0005] The instability of acetaminophen in aqueous solutions and the specific regulatory requirements to assure the safety, efficacy and quality of pharmaceutical drugs have prevented the development of intravenous dosage forms in comparison with tablet and suppository forms.

[0006] U.S. Pat. No. 6,028,222 describes aqueous formulations of acetaminophen containing a buffering agent and a free radical antagonist and/or a free radical scavenger which need to be bubbled with an inert gas through the aqueous solvent in order to remove oxygen from the medium and maintain the stability of acetaminophen.

[0007] U.S. Pat. No. 6,992,218 B2 relates to aqueous formulations with an active principle susceptible to oxidation, for example acetaminophen, wherein the essential means for stabilizing them is deoxygenating by bubbling with an inert gas and/or placing under vacuum until the oxygen content is below 2 ppm.

[0008] Thus, there is thus still a need for acetaminophen aqueous formulations, free of any organic solvent, which are stable at ambient and room temperature and avoids removing the dissolved oxygen by bubbling an inert gas and/or placing under vacuum. The fact of not having to bubble an inert gas and/or to applying vacuum is traduced to an improved manufacturing process that requires less steps and therefore less cost.

SUMMARY OF THE INVENTION

[0009] The invention relates to novel stable aqueous formulations of acetaminophen for injection as well as processes for preparing and using the same.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0010] Reference will now be made in detail to the preferred embodiments of the invention. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. In addition, and as will be appreciated by one of skill in the art, the invention may be embodied as a method, system or process.

[0011] The invention provides new, stable, aqueous acetaminophen formulations.

[0012] In one aspect, the invention relates to a new stable, aqueous acetaminophen formulation that includes:

- a. approximately 200.0 mg to approximately 1,400.0 mg of acetaminophen;
- b. approximately 200.0 mg to approximately 10,000.0 mg of mannitol for injection;
- c. approximately 0.0 mg to approximately 30.0 mg of monobasic sodium phosphate;
- d. approximately 0.0 mg to approximately 300.0 mg of povidone;

- e. a sufficient amount of sodium hydroxide (as needed) is added to adjust the pH between approximately 4.0 and approximately 8.0;
- f. a sufficient amount of hydrochloric acid (as needed) is added to adjust the pH between approximately 4.0 and approximately 8.0; and
- g. an injection volume of water for injection up to a volume of approximately 100 mL.

[0013] In another aspect, the invention includes a new stable, aqueous composition that includes acetaminophen having the following composition:

- a. approximately 1,000.0 mg of acetaminophen;
- b. approximately 3,750.0 mg of mannitol for injection;
- c. approximately 13.0 mg of monobasic sodium phosphate;
- d. approximately 100.0 mg of povidone;
- e. a sufficient amount of sodium hydroxide is added to adjust the pH until approximately 5.5;
- f. a sufficient amount of hydrochloric acid is added to adjust the pH until approximately 5.5; and
- g. an injection volume of water for injection up to a volume of approximately 100 mL.

[0014] Another embodiment of the invention provides a process for preparing the above-described aqueous composition that includes the following steps:

- a. adding monobasic sodium phosphate, povidone, mannitol for injection and acetaminophen in a volume of water for injection to form the aqueous formulation;
- b. if necessary, adding sodium hydroxide or hydrochloric acid to adjust the pH of the aqueous formulation between approximately 4.0 and approximately 8.0;
- c. adjusting the final volume of the aqueous formulation by adding additional water for injection;

- d. filtering the aqueous formulation;
- e. filling the aqueous formulation into bottles;
- f. closing the bottles containing the aqueous formulation under an inert (*e.g.*, nitrogen) atmosphere; and
- g. sterilizing the bottle containing the aqueous formulation.

[0015] It should be understood that the word “bottles” is meant to convey glass or plastic containers or any other materials suitable for containing the aqueous formulations of acetaminophen described herein.

[0016] The invention further includes the use of the aqueous pharmaceutical formulations of acetaminophen according to the invention for the treatment of pain. In particular, the invention further includes the use of the aqueous pharmaceutical formulations of acetaminophen for the treatment of pain after surgery and treatment of short period of fever when intravenous administration is justified or when others routes of administration are not possible.

[0017] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention and specific examples provided herein without departing from the spirit or scope of the invention. Thus, it is intended that the present invention covers the modifications and variations of this invention that come within the scope of any claims and their equivalents.

[0018] The following example is for illustrative purposes only and is not intended, nor should it be interpreted, to limit the scope of the invention.

[0019] **EXAMPLE 1: Aqueous solution of acetaminophen**

[0020] Table 1 illustrates a formulation of an aqueous acetaminophen solution with the following constituents:

Description	Amount per bottle
Acetaminophen	1,000.0 mg
Mannitol (for injection)	3,750.0 mg
Monobasic Sodium Phosphate	13.0 mg
Povidone	100.0 mg
Sodium Hydroxide	q.s. pH 5.5
Hydrochloric Acid	q.s. pH 5.5
Water (for injection)	q.s. 100 mL

Table 1

[0021] The aqueous acetaminophen formulation of Table 1 was prepared by dissolving 13.0 mg of monobasic sodium phosphate, 100.0 mg of povidone, 3,750.0 mg of mannitol for injection and 1,000.0 mg of acetaminophen in 80 mL of water for injection. Then, the pH is checked, and if necessary was adjusted until 5.5 by adding sodium hydroxide or hydrochloric acid. The solution was adjusted to 100 mL by the addition of water for injection. Next, the solution was filtered and filled into a 100 mL bottle. The bottle was then closed under a nitrogen atmosphere and sterilized.

[0022] The stability of acetaminophen solution was evaluated until 6 weeks. The solution was stored at 25° C/60% HR and 40° C/75% HR. During the stability period time, relative substances, color and pH were studied and we can conclude that acetaminophen solution is stable and no acetaminophen degradation occurred and none of its physicochemical characteristics has changed significantly.

[0023] Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the disclosure has been made only by way of example, and that numerous changes in the conditions and order of steps can be resorted to by those skilled in the art without departing from the spirit and scope of the invention.

CLAIMS

1. A stable aqueous formulation of acetaminophen for injection comprising:
 - a. approximately 200.0 mg to approximately 1,400.0 mg of acetaminophen;
 - b. approximately 200.0 mg to approximately 10,000.0 mg of mannitol for injection;
 - c. approximately 0.0 mg to approximately 30.0 mg of monobasic sodium phosphate;
 - d. approximately 0.0 mg to approximately 300.0 mg of povidone;
 - e. a sufficient amount of sodium hydroxide and hydrochloric acid as needed in order to adjust the pH to between approximately 4.0 and approximately 8.0;and
 - f. a volume of water for injection up to a volume of approximately 100 mL.
2. The aqueous formulation of acetaminophen of claim 1 comprising approximately 1,000.0 mg of said acetaminophen; approximately 3,750.0 mg of said mannitol for injection; approximately 13.0 mg of said monobasic sodium phosphate; and approximately 100.0 mg of said povidone.
3. A process for preparing the aqueous formulation of acetaminophen of any of claims 1 and 2 comprising:
 - a. adding said monobasic sodium phosphate, said povidone, said mannitol for injection and said acetaminophen in a volume of water for injection to form the aqueous formulation;
 - b. if necessary, adding sodium hydroxide or hydrochloric acid to adjust the pH of the aqueous formulation to between approximately 4.0 and approximately 8.0; and
 - c. adjusting the final volume of the aqueous formulation by adding additional water for injection.
4. The process of claim 3, further comprising at least one of:
 - a. filtering the aqueous formulation;

- b. filling the aqueous formulation into a bottle;
 - c. closing a bottle containing the aqueous formulation under an inert atmosphere; and
 - d. sterilizing a bottle containing the aqueous formulation.
5. Use of the aqueous formulation of acetaminophen according to any of claims 1 and 2 or made by any of the methods of claims 3 and 4 comprising administering a sufficient amount of the aqueous formulation of acetaminophen to a patient in need thereof to eliminate pain.
6. The use of claim 5, wherein the pain occurs following surgery.