



FASCICULE DEBREVET D'INVENTION

21 Numéro de dépôt:1201200464
(PCT/EP11/002482)

22 Date de dépôt :18/05/2011

30 Priorité(s) :
EP n° 10005258.8 du 19/05/2010

24 Délivré le :31/01/2014

45 Publié le : 10.04.2015

73 Titulaire(s) :

Uni-Pharma KleonTsetis Pharmaceutical Laboratories S.A.
14th Km, National Road 1,
GR-145 64 KIFISSIA (GR)

TSETI Ioulia
3 Streit Street, GR-145 61 KIFISSIA (GR)

72 Inventeur(s) :

TSETI Ioulia (GR)

74 Mandataire :Cabinet ÉKÉMÉ LYSAGHT SARL,
B.P. 6370, YAOUNDE (CM).

54 Titre :Stable ready to use injectable paracetamol formulation.

57 Abrégé :

The invention concerns a stable aqueous paracetamol solution for use in IV infusion comprising at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, at least one stabilizing compound bearing at least one thiol functional group and at least one stabilizing compound selected from the group consisting of Thiamine salts.

- 1) Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.
- 2) TSETI Ioulia

Stable ready to use injectable paracetamol formulation

The present invention refers to a pharmaceutical composition comprising paracetamol for parenteral administration by IV infusion, with an optimum pH 6.0 (ranging between 5.5 and 6.5) comprising at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, at least one stabilizing compound bearing at least one thiol functional group and at least one stabilizing compound selected from the group consisting of Thiamine salts in a suitable concentration, able to stabilize and solubilize the paracetamol even at elevated temperatures.

Description

Field of the Invention

The present invention relates to an injectable liquid paracetamol composition according to claim 1, which is stable even at elevated temperatures over a longer period of time.

Background of the Invention

Paracetamol is considered to be the main active metabolite of phenacetin and acetanidile having analgesic and antipyretic properties. Paracetamol has equivalent analgesic and antipyretic action to that of aspirin whilst it expresses weak anti-inflammatory action therefore its use in inflammatory rheumatic diseases is limited.

A large number of pharmaceutical preparations to be administered orally or even topically are known. However, it is difficult to obtain a pharmaceutical preparation for injection and particularly, a ready-to-use solution for intravenous perfusion, due to the fact that paracetamol is not very soluble in water and its solutions in aqueous medium are unstable in the presence of oxygen and/or light, being decomposed through a plurality of degradation pathways which are well known and are described for example in the article "Stability of aqueous solutions of N-acetyl-p-aminophenol",

by K.T. Koshy and J.L. Lach, J. Pharmaceutical Sciences, Vol 50 (2) (February 1961), p. 113-118. This instability in aqueous medium is shown by the appearance of degradation substances causing a coloring in the solution. The different substances causing the coloring of the solution include benzoquinoidines which are hepatotoxic
5 in humans.

However, the development of color in pharmaceutical solutions and especially in injectable formulations, which must be completely transparent, involves a serious problem, because the presence of said color is indicative of the existence of
10 unwanted compounds in the formulation and therefore leads to the rejection of the injectable product without being used.

One of the causes of paracetamol degradation is based on chemical oxidation reactions in which the oxygen present in the solution is the main precursor of this
15 degradation. The secondary cause of degradation may be the deacetylation of the amino group generating p-aminophenol which is also quickly degraded producing p-benzoquinoneimine. This deacetylation takes place both at acid pH and (much faster) at basic pH once the phenolate form is present.

20 Obtaining stable paracetamol solutions in aqueous medium can be solved by means of several joint actions.

1) Establishing an optimal pH in which the formation of 4-aminophenol is prevented or minimized, as has been indicated by K. Thomas Koshy and Jon L. Lach in the
25 previous indicated reference "Stability of aqueous solutions of N-acetyl-p-aminophenol", J. of Phar. Sci., Vol 50 No. 2 (1961), 113-118, the hydrolysis of the acetate group of paracetamol is minimized between pH= 4.5 and pH 6.0.

2) Preventing the presence of oxygen in solution. This action is described in Spanish patent no. 2,201,316, from the validation in Spain of European patent EP 858,329 B1, issued to Pharmatop SCR. This document discloses a process whereby
30 paracetamol oxidation is prevented by means of eliminating the main element activating the reaction, oxygen, with nitrogen bubbling. By further keeping the solution in a completely hermetic bottle, the stability of paracetamol in solution is ✓

ensured for long time periods, with minimal impurity levels and the total absence of color in the solution. It may be presumed that this product of the prior art must be kept in suitable bottles preventing the incorporation of oxygen into the solution and therefore these solutions cannot be stored in individual oxygen-permeable bottles such as plastic materials.

Further, US Patent 6,028,222 discloses the use of free radical antagonists or free radical scavengers, which may be a polyol or an organic compound substituted by one or more thiol functional groups, to provide stable analgesic formulations of paracetamol. US Patent 4,727,064 discloses the use of alkylated cyclodextrins to improve the solubility of drugs, inter alia paracetamol, in water.

Despite the achievements of the prior art, there is due to raising quality and safety requirements a constant need to further improve the stability of aqueous paracetamol solution for use in IV infusion even at elevated temperatures over a longer period of time without the need of keeping the solutions in a completely hermetic bottle.

The present invention therefore concerns a stable aqueous paracetamol solution for use in IV infusion comprising at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, at least one stabilizing compound bearing at least one thiol functional group and at least one stabilizing compound selected from the group consisting of Thiamine salts.

The at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, the at least one stabilizing compound bearing at least one thiol functional group and the at least one stabilizing compound selected from the group consisting of Thiamine salts are preferably present in a total concentration between 0.001% and 20 % m/v.

The stable aqueous paracetamol solution according to the invention may have a pH between 4.0 and 7.0. Typically, the solution may be a buffer with a buffer

composition selected from at least one of the acid form and the ionized form of:
citric, malic, acetic, sorbic, phosphoric, fumaric, lactic, gluconic and tartaric acids or
mixtures thereof. Preferably, the pH is between 5.5 and 6.5 and more preferably the
pH is adjusted to 6. A typical buffer includes phosphate or sodium citrate/acetate and
5 is preferably disodium phosphate dihydrate.

The preferred cyclodextrin is a hydroxyalkyl-cyclodextrin, in particular 2-
hydroxypropyl-beta-cyclodextrin. Typically, the at least one stabilizing-dissolving
compound for paracetamol in solution selected from the group consisting of
10 cyclodextrins is provided in a concentration between 0.2% m/v and 19% m/v,
preferably in a concentration between 0.2% m/v and 6.0% m/v and more preferably
between 0.5% and 3.0% m/v.

15 The 2-hydroxypropyl beta-cyclodextrin (HPBCD) is preferably selected from
derivatives with a degree of substitution of between 2.5 and 10 hydroxypropyl
substituents per beta-cyclodextrin molecule, more preferably between 3.5 and 8
hydroxypropyl substituents per beta-cyclodextrin molecule. The molar ratio of
Paracetamol to 2-hydroxypropyl beta-cyclodextrin is preferably 100:1 to 0.1:1 , more
20 preferably 5:1, most preferably 1.5:1.

The at least one stabilizing compound bearing at least one thiol functional group is
selected from the group consisting of thioglycerols, cystein, acetylcystein,
thioglycolic acid and/ or salts thereof, dithiothreitol, reduced glutathione, thiolactic
25 acid and/ or salts thereof, thiourea and mercaptoethanesulfonic acid and is typically a
thioglycerol, preferably monothioglycerol, present in a concentration between
0.001% m/v and 0.2% m/v.

The at least one stabilizing compound selected from the group consisting of Thiamine
30 salts is preferably Thiamine HCl and is preferably present in a concentration between
0.001% m/v and 0.2% m/v. √

In addition, the aqueous solution may further comprise other chelating agents or complexing agents. The chelating or complexing agent in solution may be selected from the group consisting of EDTA, nitrilotriacetic acid, ethylenediamine-N,N'-diacetic-N,N'-dipropionic acid, ethylenediamine-tetra(methylene phosphoric acid), 2,2' (ethylenediamino)-dibutyric acid, ethylene glycol bis(2-aminoethylether)-N,N,N',N'-tetra acetic acid, and/or salts thereof, and is preferably EDTA. Preferably the chelating or complexing agent is present in a concentration between 0.001% m/v and 0.2% m/v.

10 The stable aqueous paracetamol solution according to the invention may further comprise isotonicizing agents, preferably sodium chloride.

The stable aqueous paracetamol solution for IV infusion may be sterilized by heat or by filtration.

15 A typical concentration of paracetamol is between 0.20% and 10% m/v, preferably 0.5% and 1.5% m/v.

20 The aqueous medium of the solution according to the invention may have been deoxygenated by a water-insoluble inert gas (N₂).

The compositions according to the invention will be administered intravenously and they are stable when stored for more than 24 months at room temperature. Moreover, the compositions may be even stable when stored for more than 30 days at elevated temperatures, for example 70°C.

25 A composition may be prepared in solution and stored in clear glass containers or bottles made of a polymer material such as polyethylene, or in soft material bags made from polyethylene, polyvinylchloride or polypropylene.

30 The molar ratio of paracetamol to cyclodextrin is preferably 100:1 to 0.1:1, more preferably 5:1 and most preferably 1.5:1. $\sqrt{\quad}$

Typically, the solution comprises 2 mg to 200 mg, preferably more than 5 mg, most preferably 10 mg paracetamol per millilitre solution.

5 The complexing or chelating agent may comprise 0.001 to 5 mg, preferably 0.0015 to 1 mg, most preferably 0.1 mg per millilitre solution.

Further, the solution comprises typically 2 mg to 150 mg, preferably more than 3 mg, most preferably between 6 mg and 7 mg cyclodextrin per millilitre solution.

10 The at least one stabilizing compound bearing at least one thiol functional group, which is preferably monothioglycerol, may comprise 0.01 to 5 mg, preferably 0.015 to 1 mg, most preferably 0.1 mg per millilitre solution.

15 The at least one stabilizing compound selected from the group consisting of Thiamine salts, which is preferably Thiamine HCl, may comprise 0.01 to 5 mg, preferably 0.015 to 1 mg, most preferably 0.1 mg per millilitre solution.

Advantageously, the solution is in the form of a unit dose that does not exceed 100 millilitres.

20 The inventor has found a way to prepare a stable aqueous solution comprising at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, at least one stabilizing compound bearing at least one thiol functional group and at least one stabilizing compound selected from
25 the group consisting of Thiamine salts in a suitable concentration, which is not only capable of having a concentration of paracetamol of more than 10 mg per millilitre of solution, but is also stable and does not need to be refrigerated when packed in clear glass sealed vials, or in stoppered glass vials or in bottles made of a polymer material such as polyethylene, or in soft material bags made from polyethylene, polyvinyl
30 chloride or polypropylene. By "stable" is meant that the solution can be stored for at least 24 months at room temperature and at least 30 days at elevated temperature ✓

(70°C) without the appearance of colour and particulate matter which is visible to the eye.

5 The use of the stabilizing-dissolving and stabilizing compounds according to the invention and preferably the chelating agent has been found to not only increase the paracetamol solubility to the extent that it is possible to dissolve 1000 mg of paracetamol into a final volume of 100 ml but also effectively stabilises the solution preventing the formation of particulate matter and colour at elevated temperature in ampoules, vials and bags.

10

The solution may be formulated in unit dose form, each unit dose containing from 100 mg to 1500 mg paracetamol inclusive, more preferably from 600 mg to 1000 mg inclusive, most preferably 1000 mg, in a volume not exceeding 100 millilitres.

15 The injectable stabilised solution of the invention may be prepared by methods known in the art.

20 The stabilised injectable solution of the invention may be packed into suitable containers known in the art (for example glass ampoules, vials, cartridges, glass sealed vials, or in stoppered glass vials or in bottles made of a polymer material such as polyethylene, or in soft material bags made from polyethylene, polyvinyl chloride or polypropylene). The glass should preferably be clear glass.

25 The stabilized injectable solution of the invention is suitable for intravenous use.

The stabilized injectable solution of the invention need not be stored under refrigerated conditions to provide a shelf life of at least 24 months, saving refrigeration costs during transport and storage, and alleviating patient discomfort during administration.

30

The invention will now be described in more detail with reference to the following non-limiting examples. ✓

Examples

Example 1

A preferred pharmaceutical composition according to the invention comprises:

5 Table 1:

Ingredient	Quantity/100 ml
Paracetamol	1000 mg
Hydroxypropyl-beta-cyclodextrin HPBCD	666 mg
Monothioglycerol (MTG)	10 mg
EDTA	10 mg
Thiamine HCl	10 mg
NaCl	600 mg
Disodium phosphate dihydrate	35.6 mg
Water for Injection to	100 ml
Final pH (HCl or NaOH) 1M	5.5-6.5

Example 2

The unit composition of a second formulation (Control, comparative example) is
 10 provided in Table 2 below:

Table 2:

Ingredient	Quantity/100 ml
Paracetamol	1000 mg
Hydroxypropyl-beta-cyclodextrin HPBCD	666 mg
Monothioglycerol (MTG)	10 mg
EDTA	10 mg
NaCl	600 mg
Disodium phosphate dihydrate	35.6 mg
Water for Injection to	100 ml
Final pH (HCl or NaOH) 1M	5.5-6.5

Example 3

Laboratory-scale formulations given in Examples 1 and 2 of the present invention were manufactured and filled into clear glass vials and polymer material (soft material bags) and placed on a stability program. Tables 3 – 4 below summarize the results obtained:

Table 3:

Stability of 1000mg/100ml (Paracetamol- HPBCD) Batches at 70°C for 20 days			
Example	Chemical stability	Appearance	Comments
Example 1	Acceptable level of known degradant	Stable, clear solution	Complies, trial continued
Control Example 2	Acceptable level of known degradant	Yellow color	Not stable, trial continued to 30 days as control

Table 4:

Stability of 1000mg/100ml (Paracetamol- HPBCD) Batches at 70°C for 30 days			
Example	Chemical stability	Appearance	Comments
Example 1	Acceptable level of known degradant	Stable, clear solution	Complies, trial continued
Control Example 2	Acceptable level of known degradant	Yellow color	Not stable, trial continued to 40 days as control

After 40 Days at 70 °C the solution according to example 1 still remained clear and colourless (both in clear glass vials and soft material bags), free from visible particulate matter. ✓

Tables 3-4 show stability evaluations of 1000 mg per 100 ml paracetamol formulations and the solution according to the invention shows advantages over a control solution with a different composition of stabilizing compound.


5

Example 4

To produce 100 1000mg/100 ml paracetamol units for IV injection, 8000 ml water for injection (WFI) is purged with nitrogen gas to reduce the oxygen. The water was
10 heated to 50°C. Processing continues under a nitrogen gas blanket. 66.675 g of HPBCD (DS 4.69) is added to 60 % of the WFI batch volume and is mixed until dissolved. The solution is then allowed to cool to room temperature. The solution is pre-filtered with a 0.45Pµ filter, followed by the addition of 1 g MTG, 1 g EDTA, 60 g NaCl, 1 g Thiamine HCl and 3.56 g Disodium phosphate dihydrate. The solution is
15 stirred until all the MTG, EDTA, NaCl, Thiamine HCl and Disodium phosphate dihydrate is dissolved. The pH is then adjusted to 6 with HCl 1M. 100 g paracetamol is added to the solution and stirred until dissolved. pH is adjusted to 6, should it be required and made up to 100% volume with WFI. The resultant 1000mg/100 ml paracetamol solution is sterilized by filtration with 0.22Pµ filters and filled into pre-
20 sterilized vials or bags, under aseptic conditions. The vials or bags are sealed aseptically under nitrogen. The formulation contains 1000 mg/100 ml paracetamol, as determined by validated HPLC. ✓

09 NOV 2012
YACOUDE - YACOUDE Sarl
YACOUDE - YACOUDE
Tel. - Fax. 22 31 67 53

Claims

1. A stable aqueous paracetamol solution for use in IV infusion comprising at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, at least one stabilizing compound bearing at least one thiol functional group and at least one stabilizing compound selected from the group consisting of Thiamine salts.
2. The stable aqueous solution according to claim 1, where the at least one stabilizing-dissolving compound for paracetamol in solution selected from the group consisting of cyclodextrins, the at least one stabilizing compound bearing at least one thiol functional group and the at least one stabilizing compound selected from the group consisting of Thiamine salts are present in a total concentration between 0.001% and 20 % m/v.
3. The stable aqueous solution according to claim 1 or 2, wherein the at least one stabilizing-dissolving compound for paracetamol in solution is selected from the group consisting of hydroxyalkyl-beta-cyclodextrins.
4. The stable aqueous paracetamol solution according to anyone of claims 1 to 3, wherein the at least one stabilizing-dissolving compound for paracetamol in solution is 2-hydroxypropyl-beta-cyclodextrin.
5. The stable aqueous solution according to anyone of claims 1 to 4, wherein the concentration of the at least one stabilizing-dissolving compound for paracetamol in solution is between 0.2% m/v and 19% m/v, preferably between 0.2% m/v and 6.0% m/v, particularly preferably between 0.5% m/v and 3.0% m/v.
6. The stable aqueous paracetamol solution according to anyone of claims 1 to 5, wherein the at least one stabilizing compound bearing at least one thiol functional group is selected from the group consisting of thioglycerols, cystein, acetylcystein, 

thioglycolic acid and/ or salts thereof, dithiothreitol, reduced glutathione, thiolactic acid and/ or salts thereof, thiourea and mercaptoethanesulfonic acid.

7. The stable aqueous paracetamol solution according to anyone of claims 1 to 6,
5 wherein the at least one stabilizing compound bearing at least one thiol functional group is a thioglycerol, preferably monothioglycerol.

8. The stable aqueous paracetamol solution according to anyone of claims 1 to 7,
10 wherein the at least one stabilizing compound bearing at least one thiol functional group is present in a concentration between 0.001% m/v and 0.2% m/v.

9. The stable aqueous paracetamol solution according to anyone of claims 1 to 6,
wherein the at least one stabilizing compound selected from the group consisting of Thiamine salts is Thiamine HCl.

10. The stable aqueous paracetamol solution according to anyone of claims 1 to 9,
wherein at least one stabilizing compound selected from the group consisting of Thiamine salts is present in a concentration between 0.001% m/v and 0.2% m/v.

11. The stable aqueous paracetamol solution according to any one of the preceding claims, further comprising a chelating agent.

12. The stable aqueous paracetamol solution according to claim 11, wherein the chelating agent is selected from the group consisting of EDTA, nitrilotriacetic acid,
25 ethylenediamine-N,N'-diacetic-N,N'-dipropionic acid, ethylenediamine-tetra(methylene phosphoric acid), 2,2'-(ethylenediamino)-dibutyric acid, ethylene glycol bis(2-aminoethylether)-N,N,N',N'-tetra acetic acid, and/or salts thereof, and is preferably EDTA. ✓

13. The stable aqueous paracetamol solution according to claim 11 or 12, wherein the chelating agent is present in a concentration between 0.001% m/v and 0.2% m/v.

5 14. The stable aqueous paracetamol solution according to any one of the preceding claims, wherein the pH is between 4.0 and 7, and the solution is buffered with a buffer composition selected from at least one of the acid form and the ionized form of: citric, malic, acetic, sorbic, phosphoric, fumaric, lactic, gluconic and tartaric acids or mixtures thereof and is preferably disodium phosphate dihydrate.

10 15. The stable aqueous paracetamol solution according any one of the preceding claims, wherein the concentration of paracetamol is between 0.20% and 10% m/v, preferably between 0.5% and 1.5% m/v. ✓

09 NOV 2012

YACUBDE - CAME
Tél- Fax: 22 31