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(72) Inventeurs/Inventors:

Santos, Pedro Paulo De Lacerda E Oliveira, PT;
Mendes, Zita Maria De Mouro Vaz Azevedo, PT;
Heggie, William, PT

(73) Propriétaire/Owner:

HOVIONE INTER LTD., CH

(74) Agent: MCCARTHY TETRAULT LLP

(54) Titre : METHODE DE PURIFICATION ET DE CRISTALLISATION DE L'IOPAMIDOL

(54) Title: PROCESS FOR THE PURIFICATION AND CRYSTALLISATION OF IOPAMIDOL

(57) **Abrégé/Abstract:**

The present invention describes a process for the purification and crystallisation of lopamidol, wherein 1-propanol, or 2-propanol, is added to an aqueous solution of lopamidol followed, if necessary, by azeotropic distillation to reduce the quantity of water in relation to the quantity of propanol, and thereby ensure an high yield. The aqueous solution can be prepared either by the dissolution of crude lopamidol in water or directly from the reaction in which the lopamidol is formed. The present invention presents advantages for the routine production of lopamidol since the crystallisation is straightforward to perform, can be easily controlled and is reproducible at an industrial scale.



ABSTRACT

- The present invention describes a process for the purification and crystallisation of Iopamidol, wherein 1-propanol, or 2-propanol, is added to an aqueous solution of Iopamidol followed, if necessary, by azeotropic distillation to reduce the quantity of water in relation to the quantity of propanol, and thereby ensure an high yield. The aqueous solution can be prepared either by the dissolution of crude Iopamidol in water or directly from the reaction in which the Iopamidol is formed.
- 10 The present invention presents advantages for the routine production of Iopamidol since the crystallisation is straightforward to perform, can be easily controlled and is reproducible at an industrial scale.

PROCESS FOR THE PURIFICATION AND CRYSTALLISATION OF
IOPAMIDOL

It has been shown that non-ionic X-ray contrast media, such as Iopamidol, present
5 advantages in relation to prior art ionic compounds. All of these products depend on
the presence of large quantities of iodine in the molecule to provide an opaque
background, allowing their use to visualise internal organs. However, the quantities
needed for this purpose are extremely high, being many times higher than those
needed for compounds used as medicines. It is normal to inject between 100 g and
10 200 g of contrast media agent into a patient. For this reason, the above mentioned
substances should be of very high purity, have extremely low toxicity and a minimal
interference with the normal organ functions. Therefore, there is an increasing need
to develop manufacturing processes for the production of contrast media giving
product of the highest purity.

15 There exist several methods which can be used to produce high purity bulk
pharmaceutical products. Possibly the most efficient method for the production of
high purity product is a chromatographic process. However, in the present instance,
such a method is difficult to implement given the extremely large quantities that are
20 necessary. Chromatographic methods are usually associated with low volume and
high value product.

Crystallisation methods are the most suitable but they do not always allow the
successful removal of impurities with molecular structures that are very similar to
25 that of the primary product. In the case of Iopamidol, for example, one of the most
problematic impurities is that formed by the loss of one of the iodine atoms bonded
to the central benzene ring. In terms of the molecular configuration in the crystal,
the properties of this substance are very similar to those of Iopamidol, being easily
introduced in the crystalline structure with the consequent difficulty in its removal.

30 Another general consideration is the fact that the molecules used as X-ray contrast
media are extremely soluble, especially in aqueous media, and hence their difficult
crystallisation. It is believed that this is due to the high degree of freedom
associated with the hydrophilic side chains containing alcohol functions.

35 The prior art cites two solvent systems considered adequate for the crystallisation of
Iopamidol. The first of these systems comprises the use of ethanol and/or aqueous
ethanol, as described in US Patent N° 4.001.323. The crystallisation is usually
carried out by dissolution of Iopamidol in the minimum amount of water, addition of
40 ethanol, followed by distillation of the excess water until an adequate ethanol:water

ratio, usually of the order of 95:5, is obtained, after which purified Iopamidol separates. A disadvantage of this method is that the product tends to retain a certain amount of ethanol in the crystal structure, which can only be removed by drying at high temperatures under vacuum.

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PCT Patent Application N° 94/02415 (publication number WO95/04031) claims an improvement in relation to the use of ethanol. Butyl alcohols, especially 2-butanol, are used in a manner similar to that mentioned above for ethanol. It is claimed that butyl alcohols are more easily removed than ethanol from the final product in the
10 drying step.

However, these two solvent systems present the same disadvantage when used at a large scale, namely the separation of the product is too rapid, even at high temperature, causing the crystallisation process to pass through an intermediate
15 phase in which there is formation of a pasty product which only solidifies after an extended stirring period at a reduced temperature. It is well known that the formation of this type of pasty product can give rise to the occlusion of impurities, which, otherwise, would have remained in the mother liquors of the crystallisation, and hence the final bulk product may not have the high purity level desired. There
20 can also be losses of product which sticks to the walls, to the stirrer, etc. of the reactor where the crystallisation takes place. This situation is obviously undesirable during routine production.

It has been unexpectedly found that the use of propanol and isopropanol solves these
25 problems. When propyl alcohols are used, the crystallisation process is much slower than with ethanol or the butyl alcohols, thereby eliminating the tendency to form pastes. Crude solid Iopamidol is dissolved in water, or if the aqueous solution is obtained directly from the reaction in which the Iopamidol is formed, any non-aqueous solvents being previously removed by conventional methods, then propanol
30 or isopropanol is added and the ratio of propanol or isopropanol to water is corrected by means of the azeotropic properties of propanol or isopropanol with water. Alternatively, di-isopropyl ether can be used so as to obtain a ternary azeotropic system in order to attain more quickly the desired ratio of propanol or isopropanol and water. The percentage of water in the final solvent mixture is
35 usually between 1% and 15% in relation to the propanol or isopropanol. After cooling, during which efficient stirring is maintained, Iopamidol is isolated from the solution in a well defined crystalline form.

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Preferably the quantity of propanol is comprised between 5 and 15 times, in volume, with respect to the weight of the iopamidol present.

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A further advantage of this method is the fact that the so formed Iopamidol can be more easily filtered than any of the products resulting from the crystallisation with ethanol or the butyl alcohols. From an industrial point of view, this fact has obvious advantages.

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Residual quantities of propanol, or isopropanol, are also easily removed by conventional drying procedures. Therefore, the use of either propanol or isopropanol to carry out the purification of Iopamidol provides a practical industrial scale process.

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The table appearing hereinbelow summarises the results obtained and establishes a comparison between 2-butanol, 1-propanol and 2-propanol.

Comparative crystallisations of Iopamidol

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Solvent	Paste formation	Time to beginning of crystallisation	Time of filtration	Yield (%)	% Purity (by HPLC)
2-BuOH	YES	--	4'	99.2	99.80
1-PrOH	NO	2'	3'30"	99.1	99.84
20 2-PrOH	NO	5'	3'	99.3	99.84
2-PrOH	NO	3'	3'30"	98.9	99.86

The tests were carried out at a 30 g scale and the filtration time relates to tests carried out in identical equipment, under the same conditions.

25 The following examples serve to illustrate the present invention and are not, in any way, to be considered as a limitation thereof.

EXAMPLE 1

30 Crude, crystalline and desalinated Iopamidol (30 g), resulting from the normal production process, was dissolved in water (30 ml) and concentrated to a volume of 17.5 ml. After heating to 75°-80°C, 1-propanol (212 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. A mixture of propanol/water (12 ml) was removed by
35 azeotropic distillation at atmospheric pressure, with the concentration of water in the final mixture being 3.3%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.4 g.

EXAMPLE 2

Crude, crystalline and desalinated Iopamidol (30 g) was dissolved in water (30 ml) and concentrated to a volume of 17.5 ml. After heating to 75°-80°C, 2-propanol
5 (230 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. A mixture of propanol/water (30 ml) was removed by azeotropic distillation at atmospheric pressure, with the concentration of water in the final mixture being 3.8%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and
10 dried at 60°C. The yield of Iopamidol was 29.5 g.

EXAMPLE 3

An aqueous and desalinated solution of crude Iopamidol (containing 30.1 g of
15 product) resulting from the normal production process, was concentrated to a volume of 17.5 ml. After heating to 75°-80°C, 1-propanol (225 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. A mixture of propanol/water (25 ml) was removed by azeotropic distillation at atmospheric pressure, with the concentration of water in
20 the final mixture being 2.6%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.8 g.

EXAMPLE 4

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An aqueous and desalinated solution of crude Iopamidol (containing 29.4 g of product) was concentrated to a volume of 17.5 ml. After heating to 75°-80°C, 2-propanol (240 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. A mixture of
30 propanol/water (40 ml) was removed by azeotropic distillation at atmospheric pressure, with the concentration of water in the final mixture being 3.9%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.1 g.

EXAMPLE 5

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Crude, crystalline and desalinated Iopamidol (5 g) was dissolved in water (5 ml). After heating to 68°-72°C, 2-propanol (40 ml), previously heated to 68-72°C. was added and the mixture refluxed for 60 minutes, with crystallisation occurring after a

30 minute period. After cooling to 0°-5°C and stirring for 30 minutes, the product was filtered, washed with 5 ml of 2-propanol and dried at 60°C. The yield of Iopamidol was 4.1 g.

5 EXAMPLE 6

An aqueous and desalinated solution of crude Iopamidol (containing 30 g of product), resulting from the normal production process, was concentrated to a volume of 20 ml. After heating to 75°-80°C, 1-propanol (270 ml), previously heated
10 to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. After addition of di-isopropyl ether (60 ml), a mixture of 1-propanol/di-isopropyl ether/water (90 ml) was removed by azeotropic distillation at atmospheric pressure, with the concentration of water in the final mixture being 3.1%. After reflux for 30 minutes, cooling to room temperature and stirring for 3
15 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.9 g.

EXAMPLE 7

20 An aqueous and desalinated solution of crude Iopamidol (containing 30 g of product) was concentrated to a volume of 20 ml. After heating to 75°-80°C, 2-propanol (270 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30 minutes, during which crystallisation occurred. After addition of di-isopropyl ether (90 ml), a mixture of 2-propanol/di-isopropyl ether/water (90 ml)
25 was removed by azeotropic distillation at atmospheric pressure, with the concentration of water in the final mixture being 3.9%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.9 g.

30 EXAMPLE 8

Crude, crystalline and desalinated Iopamidol (30 g) was dissolved in water (30 ml) and concentrated to a volume of 20 ml. After heating to 75°-80°C, 2-propanol (270 ml), previously heated to 75°-80°C, was added and the mixture refluxed for 30
35 minutes, during which crystallisation occurred. A mixture of propanol/water (90 ml) was removed by azeotropic distillation at atmospheric pressure, the concentration of water in the final mixture being 5.0%. After reflux for 30 minutes, cooling to room temperature and stirring for 3 hours, the product was filtered and dried at 60°C. The yield of Iopamidol was 29.6 g.

CLAIMS

1. Process for the purification and crystallisation of Iopamidol, characterised by the fact that propanol is added to an aqueous solution of Iopamidol, obtained either
5 by the dissolution of Iopamidol in water or directly from the reaction in which the Iopamidol is formed, followed, if necessary, by azeotropic distillation to reduce the amount of water with respect to the amount of propanol.
2. Process according to claim 1, characterised by the fact that the propanol is 1-
10 propanol.
3. Process according to claim 1, characterised by the fact that the propanol is 2-propanol.
- 15 4. Process according to claim 1, characterised by the fact that the starting material is crude Iopamidol, in the solid form.
5. Process according to claim 1, characterised by the fact that the starting material is crude Iopamidol, in aqueous solution.
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6. Process according to any of claims 4 or 5, characterised by the fact that propanol is added to an aqueous solution of Iopamidol, followed, if necessary, by azeotropic distillation to reduce the amount of water with respect to the amount of propanol.
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7. Process according to any of claims 4 or 5, characterised by the fact that the quantity of propanol is comprised between 5 and 15 times, in volume, with respect to the weight of the Iopamidol present.
- 30 8. Process according to any of claims 4 or 5, characterised by the fact that the ratio of water to propanol is comprised between 1:99 and 15:85.
9. Process according to claim 8, characterised by the fact that the ratio of water to propanol is established by the use of a binary azeotropic distillation, the two
35 components being water and propanol.
10. Process according to claim 8, characterised by the fact that the ratio of water to propanol is established by the use of a ternary azeotropic distillation, the three components being water, di-isopropyl ether and propanol.