Title: PROCESS FOR THE PREPARATION OF DICLOFENAC EPOLAMINE

Abstract: The present invention concerns a process for the preparation of the salt diclofenac epolamine comprising the following steps: a) reacting 1-(2,6-dichlorophenyl)-2-indolinone with a base selected from sodium hydroxide or potassium hydroxide in an aqueous solvent, thus obtaining sodium or potassium diclofenac salt; b) dissolving the so obtained sodium or potassium diclofenac salt in a solvent mixture comprising water and an organic solvent selected from the group consisting of ethyl acetate, methyl isobutyl ketone, toluene, isobutyl acetate, n-butyl acetate, n-propyl acetate, isopropyl acetate; c) adding a strong acid to give diclofenac acid and removing the water phase; d) anhydrifying the remaining organic solvent phase; and e) adding l-(2-hydroxyethyl)-pyrrolidine.
"PROCESS FOR THE PREPARATION OF DICLOFENAC EPOLAMINE"

FIELD OF THE INVENTION
The present invention concerns a process for the preparation of the salt of diclofenac with hydroxyethylpyrrolidine, defined also either DHEP or diclofenac epolamine.

STATE OF THE ART
Diclofenac (i.e. [2-(2,6-dichlorophenyl)-amino] benzeneacetic acid) is an anti-inflammatory medicament, which has been known for a long time and shows the property of cyclizing in an acid environment to give the corresponding indolinone. In order to obtain stabilisation of the open form, it is salified with some bases.

From the document EP271709 the preparation of the salt of diclofenac with hydroxyethylpyrrolidine is known. Such a salt is soluble in water and allowed the commercialization of aqueous pharmaceutical forms of diclofenac. Specifically, according to such a document the salt is prepared by reaction of diclofenac acid with distilled hydroxyethylpyrrolidine in acetone, followed by firstly a step of treatment with hexane after removal of the solvent under vacuum at 40°C and secondly a step of separation of the crystalline salt following to the stirring of the mixture. The yield of the reaction indicated in the document is 83% and the product is obtained pure after the dissolution in acetone, decoloration with charcoal and treatment again with hexane. In the corresponding United States patent the preparation of the salt of interest is also proposed as comprising the reaction between diclofenac acid and hydroxyethylpyrrolidine in ethyl acetate solvent.

The salt diclofenac epolamine is also known in the dihydrate form other than anhydrate. In the article titled "Effect of the temperature on a hydrate diclofenac salt" (A.Fini et al, International Journal of Pharmaceutics 181 (1999) 95-106), the salt dihydrate diclofenac epolamine is obtained by reacting diclofenac acid with N-(2-hydroxyethyl)pyrrolidine in water, whereas the corresponding anhydrate form is
obtained by reacting the same reagents in ethyl acetate instead of water.

All the described preparations therefore provide for diclofenac acid as starting material, which is not a commercially available product, that therefore must be purposely prepared in order to proceed with the synthesis by salification reaction with the base N-(2-hydroxyethyl)pyrrolidine.

An object of the present invention is therefore to provide an alternative synthesis of the salt diclofenac epolamine, which is industrially convenient and which guarantees at the same time yields at least comparable to those until now described the prior art documents.

SUMMARY OF THE INVENTION

The above stated object has been achieved through a process for the preparation of the salt diclofenac epolamine comprising the following steps:

a) reacting 1-(2,6-dichlorophenyl)-2-indolinone with a base selected from sodium hydroxide and potassium hydroxyde in an aqueous solvent, thus obtaining sodium or potassium diclofenac salt;
b) dissolving the so obtained sodium or potassium diclofenac salt in a solvent-mixture comprising water and an organic solvent selected from the group consisting of ethyl acetate, methyl isobutyl ketone, toluene, isobutyl acetate, n-butyl acetate, n-propyl acetate, isopropyl acetate;
c) adding a strong acid to give diclofenac acid and removing the water phase;
d) anhydriding the remaining organic solvent phase; and
e) adding 1-(2-hydroxyethyl)-pyrrolidine.

The salt diclofenac epolamine is obtained in yields higher than 85% and in high purity, without the need of carrying out specific recrystallization or purification as in the prior art.
DETAILED DESCRIPTION OF THE INVENTION

The process according to the invention for the preparation of diclofenac epolamine comprises the step a) of reaction between 1-(2,6-dichlorophenyl)-2-indolinone and a base selected from the group consisting of sodium hydroxide and potassium hydroxide. Such a step takes place in an aqueous solvent, preferably water, and more preferably in the presence of a reducing agent of the family of sulfites, hydrosulfites, bisulfites. Such a reducing agent is advantageously sodium hydrosulfite. More advantageously, the reaction mixture of the step a) is refluxed for at least 5 hours, preferably 6 hours, and cooled at 30-50 °C, preferably 35-37 °C. The product sodium or potassium diclofenac salt is then filtered and washed, preferably at 30-50 °C, more preferably at 35-37 °C, with water or an aqueous solution of potassium or sodium in the form of hydroxides, chlorides and sulfates, preferably chlorides.

The cooling temperature of the product and the temperature of the water washing of about 35-45 °C resulted to be particularly advantageous, allowing a good drainage/washing of the product.

The product obtained after step a), i.e. sodium or potassium diclofenac salt, can be advantageously used directly in step b) without the need of a drying step, therefore as wet grains.

In step b) sodium or potassium diclofenac salt is firstly dissolved in a mixture-solvent comprising water and organic solvent selected from the group consisting of ethyl acetate, methyl isobutyl ketone, toluene, isobutyl acetate, n-butyl acetate, n-propyl acetate, isopropyl acetate. Preferably the organic solvent is an organic solvent selected from ethyl acetate and methyl isobutyl ketone, more preferably ethyl acetate. Advantageously, the so obtained solution is heated to a temperature in the range of 55-70 °C, preferably 60-65 °C in case of ethyl acetate.

In step c) a strong acid is added to the system of water/organic solvent. Such an
acid is added in order to achieve a pH not higher than 3.5, preferably a pH of about 3 (+/-0.1). Such an acid is more preferably hydrochloric acid, but sulfuric acid can be used. After the separation of the phases, the aqueous phase is removed and the organic phase is washed with water.

In step d) the organic phase is anhydriified. Preferably, in the anhydriification step a fraction of the organic solvent is distilled and the organic solvent is added again, which is then distilled. In a preferred embodiment of the invention, the organic solvent of step b) is ethyl acetate and the organic solvent of the anhydriification d) is ethyl acetate. In another preferred embodiment of the invention, the organic solvent of step b) is methyl isobutyl ketone and the organic solvent of the anhydriification d) is ethyl acetate. In this case, after the removal of the water phase of step c) the methyl isobutyl ketone phase is concentrated under vacuum, thus obtaining a stirrable slurry, which is then added with ethyl acetate. In a further preferred embodiment of the invention, the organic solvent of step b) is methyl isobutyl ketone and the anhydriification step d) is carried out by concentrating under vacuum.

In step e) 1-(2-hydroxyethyl)pyrrolidine is added to the organic solution of step d). 1-(2-hydroxyethyl)pyrrolidine is preferably added at a temperature in the range from 45 to 60°C, preferably about 50°C. This range of temperatures for the addition of 1-(2-hydroxyethyl)pyrrolidine resulted extremely advantageous, because it allows the immediate obtainment of diclofenac epolamine of a pharmaceutically acceptable grade. At the end of step e) the product diclofenac epolamine precipitated in a yield higher than 85%.

The product is then filtered off and washed with ethyl acetate. After drying, the product has an high purity. The purity of the obtained diclofenac epolamine according to the invention through HPLC analysis resulted to be not less than 99.80 % and in the assay (HClO₄) 99.0 - 101 %. Advantageously, the product diclofenac epolamine obtained according to the present process resulted to be in accordance with known required analytical specifications without the need of
further purification steps.

The solution of step b) can be optionally subjected to a decoloration step before the addition of the strong acid in step c).

The invention will be now described with reference to some examples given in a illustrating and non-limiting way.

**Example 1**

**Step a) of preparation of sodium diclofenac**

In a four-necked glass flask the following ingredients were charged:

- 1-(2,6-dichlorophenyl)-2-indolinone g 592
  (M.W. 278.1 3 moles: 2.1 28)
- Water cc 2368
- Sodium hydrosulfite g 40
- Sodium hydroxide 30 % g 851
  (M.W.: 40; moles: 6.38)

The mixture was refluxed for 6 hours, then cooled to 35 - 37 °C. The precipitate was filtered on buchner funnel, then washed with water (cc 1600) preheated to 35 - 37 °C. Wet 1016 grams of sodium diclofenac were obtained corresponding to dry 625 grams (Theor. g 677.1 )

The resulting yield was 92.3% with respect to the theoretical yield.

**Steps b)-e) Preparation of diclofenac epolamine**

In a four-necked glass flask the following ingredients were charged:

- Sodium diclofenac salt as wet grams g 227.6
  (estimation of dry grams: g 140)
The mixture was heated to \( T = 60 - 65 \, ^\circ C \). At pH of about 3, hydrochloric acid 36 % (cc 39) was added, thus letting the phases to be separated. The exhausted aqueous phase was discarded and the organic phase was washed for twice at 60 - 65 °C with water (cc 60 for twice). 340 cc of solvent were distilled off and ethyl acetate (cc 340) was added.

Subsequently, 260 cc of solvent were distilled off and 54.2 g of 1-(2-hydroxyethyl)pyrrolidine (M.W: 115.17 moles: 0.47) were added at a temperature of about 50°C. The pH of the mixture could optionally be corrected to 8.8 - 9 with further 1-(2-hydroxyethyl)pyrrolidine.

The product therefore precipitated, filtered off under vacuum at a temperature of 0/5°C and then washed with ethyl acetate (cc 160). The product was also dried under vacuum at 40°C for one night.

168.8 g of diclofenac epolamine were obtained in a yield of about 93.2%. (Theoretical amount from sodium diclofenac salt: g 181.0 ).

**Example 2**

The step a) of Example 1 was repeated and sodium diclofenac was obtained, which was subsequently used as wet grams in the following step b).

**Steps b)-e) Preparation of diclofenac epolamine**

In a four-necked glass flask the following ingredients were charged:

- Sodium diclofenac salt as wet grams \( g \) 227.6
  (estimation of dry grams g 140)
Hydrochloric acid 36% (cc 40) was then added up to pH 1-2 (M.W.: 36.46; moles: 0.46), thus letting the phases to be separated. The aqueous phase was discarded and the organic phase was washed twice with water (cc 60 x 2).

The organic phase was concentrated under vacuum up to a small volume, thus obtaining a slurry, which was still stirrable. Ethyl acetate (cc 200) was then added. 1-(2-hydroxyethyl)pyrrolidine (g 52.8; moles: 0.458) was added at a temperature of 55 - 60 °C. The product started to precipitate and, subsequently, was filtered off under vacuum at a temperature of 0/5 °C. It was then washed with ethyl acetate (cc 160) and dried under vacuum at 40 °C for 18 hours.

Dry 168.3 grams of diclofenac epolamine were obtained (corresponding to a theoretical amount of sodium diclofenac salt of g 181.0). The resulting yield was 93% with respect to theoretical yield.

**Example 3**

The step a) of Example 1 was repeated and sodium diclofenac was obtained, which was subsequently dried and used as dry grams in the following step b).

**Steps b)-e) Preparation of diclofenac epolamine**

In a four-necked glass flask the following ingredients were charged:

- Dry sodium diclofenac salt  
  g  74,55  
  (moles: 0.2343)
- Water  
  cc  450

The mixture was heated to 70 - 75 °C, decolored with carbon and the filter was
then washed with hot water (cc 30).

Methyl isobutyl ketone was then added (cc 280) and the mixture was then acidified with 36 % hydrochloric acid (g 23), thus letting the phases to be separated. The exhausted aqueous phase was discarded and the organic phase was hot-washed with water (cc 50). The reaction mixture was concentrated under vacuum, by condensing about 100 cc of solvent, while checking the water amount of the mixture. When this amount was < 0.5 %, 1-(2-hydroxyethyl)pyrrolidine (g 28.3; moles: 0.245) was added to the mixture at 50 - 55 °C.

The product was then left to be crystallized and, subsequently, filtered under vacuum at a temperature of 0/5°C and washed with Methyl isobutyl ketone (cc 100). The final product was then dried at 40 °C for one night. Dry 83.1 grams of diclofenac epolamine were obtained (theoretical amount from sodium diclofenac salt was g 96.39). The yield was 86.2% with respect to theoretical yield.

Example 4

Step a) of preparation of Potassium diclofenac

In a four-necked glass flask the following ingredients were charged:

- 1-(2,6-dichlorophenyl)-2-indolinone g 100 (moles: 0.359)
- Water cc 435
- Sodium hydrosulfite g 4
- Potassium hydroxide 90 % g 33.6 (moles: 0.539)

The mixture was refluxed for 8h 30 min, then cooled to 35 - 37 °C. The precipitate was filtered on buchner funnel, then washed with a 1% NaCl solution in water (cc 70) preheated to 35 °C. Wet 180,2 grams of potassium diclofenac were obtained
Steps b)-e) Preparation of diclofenac epolamine

In a four-necked glass flask the following ingredients were charged:

- Potassium diclofenac salt  g 73,5  
  (moles: 0.22)
- Water  cc 252
- Ethyl acetate  cc 28

and the mixture was heated to $T = 60 - 65 \, ^\circ C$: the solution obtained was treated with charcoal and filtered.

Ethyl acetate (cc 232) was added and hydrochloric acid 36% (g 23) was then added up to pH 3 at $T = 60 - 65 \, ^\circ C$, thus letting the phases to be separated. The aqueous phase was discarded and the organic phase was washed twice with water (cc 60 x 2).

The organic phase was distilled (Ethyl acetate cc 170 was condensed) and Ethyl acetate (cc 170) was then added. The organic phase was distilled again (Ethyl acetate cc 130 was condensed), then 1-(2-hydroxyethyl)pyrrolidine (g 27.4) was added at a temperature of 50 \, ^\circ C. The product started to precipitate and, subsequently, was filtered off under vacuum at a temperature of 0/5 \, ^\circ C. It was then washed with ethyl acetate (cc 80) and dried under vacuum at 50 \, ^\circ C for 18 hours.

Dry 82.8 grams of diclofenac epolamine were obtained (corresponding to a theoretical amount from potassium diclofenac salt of g 90.45). The resulting yield was 91.5% with respect to theoretical yield.
CLAIMS

1. A process for the preparation of the salt diclofenac epolamine comprising the following steps:
   a) reacting 1-(2,6-dichlorophenyl)-2-indolinone with a base selected from sodium hydroxide or potassium hydroxide in an aqueous solvent, thus obtaining sodium or potassium diclofenac salt;
   b) dissolving the so obtained sodium or potassium diclofenac salt in a solvent-mixture comprising water and an organic solvent selected from the group consisting of ethyl acetate, methyl isobutyl ketone, toluene, isobutyl acetate, n-butyl acetate, n-propyl acetate, isopropyl acetate;
   c) adding a strong acid to give diclofenac acid and removing the water phase;
   d) anhydrying the remaining organic solvent phase; and
   e) adding 1-(2-hydroxyethyl)-pyrrolidine.

2. The process according to claim 1, wherein the aqueous solvent of step a) is water.

3. The process according to claim 1 or 2, wherein step a) takes place in the presence of sodium hydrosulfite.

4. The process according to anyone of claims 1-3, wherein the reaction mixture of the step a) is refluxed for at least 5 hours and cooled at 30-50 °C.

5. The process according to claim 4, wherein the reaction mixture of the step a) is refluxed for 6 hours and cooled at 35-37 °C.

6. The process according to anyone of claims 1-5, wherein the product sodium or potassium diclofenac coming from step a) is then filtered and washed with water or an aqueous solution of potassium or sodium in the form of hydroxides, chlorides and sulfates.

7. The process according to anyone of claims 1-6, wherein the product sodium or potassium diclofenac coming from step a) is filtered off and washed at 30-50 °C, preferably 35-37 °C.

8. The process according to anyone of claims 1-7, wherein in step b) sodium or potassium diclofenac is dissolved in a mixture-solvent comprising water and ethyl acetate.

9. The process according to anyone of claims 1-7, wherein in step b) sodium or
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topassium diclofenac is dissolved in a mixture-solvent comprising water and methyl isobutyl ketone.

10. The process according to anyone of claims 1-8, wherein the solution of sodium or potassium diclofenac and the solvent-mixture comprising water and ethyl acetate is heated to a temperature in the range of 55-70°C, preferably 60-65°C.

11. The process according to anyone of claims 1-10, wherein a strong acid is added to the system of water/organic solvent in order to achieve a pH not higher than 3.5, preferably a pH of about 3 (+/-0.1).

12. The process according to anyone of claims 1-11, wherein in the anhydridification step a fraction of the organic solvent is distilled off and the organic solvent is again added.

13. The process according to anyone of claims 1-12, wherein the organic solvent of step b) is ethyl acetate and the organic solvent of the anhydridification d) is ethyl acetate.

14. The process according to anyone of claims 1-12, wherein the organic solvent of step b) is methyl isobutyl ketone and the organic solvent of the anhydridification d) is ethyl acetate.

15. The process according to anyone of claims 1-12, wherein the organic solvent of step b) is methyl isobutyl ketone and the anhydridification step d) is carried out by concentration under vacuum.

16. The process according to anyone of claims 1-15, wherein in step e) 1-(2-hydroxyethyl)pyrrolidine is added to the organic solution of step d) at a temperature in the range from 45 to 60°C.

17. The process according to anyone of claims 1-16, wherein in step e) 1-(2-hydroxyethyl)pyrrolidine is added to the organic solution of step d) at a temperature of about 50°C.
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C229/42 C07C227/18 C07D207/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>Y P. MOSER ET AL: &quot;Synthesis and quantitative structure-activity relationships of diclofenac analogues&quot; JOURNAL OF MEDICINAL CHEMISTRY., vol. 33, no. 9, 1990, pages 2358-2368, XP002543586 USAHERICAN CHEMICAL SOCIETY. Scheme 1 ; page 2366, left column, line 20 - line 30 ; page 2366, last paragraph - page 2367, left column, line 10</td>
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<td>Y EP 0 271 709 A (ALTERGON SA [CH]) 22 June 1988 (1988-06-22) cited in the application claims 1-4; example 1</td>
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D Further documents are listed in the continuation of Box C.

X See patent family annex.

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search 1 September 2009

Date of mailing of the international search report 10/09/2009

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Authorized officer Voyiazoglou, D
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