**Title:** PROCESS FOR THE PREPARATION OF DESLORATADINE ADDUCT FORMED WITH CARBON DIOXIDE

![Chemical Structure](image)

\[
x \frac{1}{2} \text{CO}_2
\]

**Abstract:** Process for the preparation of a desloratadine adduct form with carbon dioxide of the formula: (I)
Process for the preparation of desloratadine adduct formed with carbon dioxide

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of desloratadine adduct formed with carbon dioxide of the formula

![Chemical Structure Image]

 Particularly, the present invention relates to an improved process for the preparation of desloratadine adduct formed with carbon dioxide of the formula (I), wherein acetone is used as reaction medium. The desloratadine adduct formed with carbon dioxide of the formula (I) prepared according to the present invention has good long term stability and is useful for the preparation of a stable pharmaceutical composition.
8-chloro-6,1-dihydro-11-(4-piperyldene)-5H-benzo[5,6]cyclohepta[1.2-b]pyridine (INN name: desloratadine) of the formula

![Molecule structure](image)

is a known antihistamine drug, which is an active metabolite of the compound 8-chloro-6,11-dihydro-1-(1-ethoxy-carbonyl-4-piperyldene)-5H-benzo[5,6]cyclohepta[1.2-b]pyridine (INN name: loratadine) of the formula
In case of oral use of desloratadine the anti-allergic effect is 3 or 4 times higher than the effect of loratadine and the duration of the effect is almost 24 hours, which is advantageous in case of once a daily use [Arzneim. Forch. Drug. Res. 40(1), Nr. 4: 345 (2000)].

Desloratadine of the formula 8-chloro-6,1 1-dihydro-1-(4-piperilydene)-5H-benzo[5,6]cyclohepta[1.2-b]pyridine (I) is prepared from 8-chloro-6,1 1-dihydro-1-(1-ethoxy-carbonyl-4-piperilydene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine of the formula (III) by basic or acidic hydrolysis and decarboxylation.

Desloratadine of the formula (II) is used as a base or in salt form for the preparation of pharmaceutical compositions. Two
known polymorph forms and the amorphous form of desloratadine are known in the literature. Inventors of the US patent application No. US 2004/0242619 describe the polymorph forms 1, 2 and the mixtures thereof. Inventors of the US patent application No. US 2006/0135547 describe the preparation of the polymorphous formula 2 using a different solvent.

According to the international patent application No. WO 2005/084674 an amorphous form of desloratadine is prepared by spray-drying method.

Although in the description of the Hungarian patent No. 194864 it is mentioned that desloratadine salts can be prepared with hydrochloric acid, methane sulphonie acid, sulphuric acid, acetic acid, maleic acid, fumaric acid and phosphoric acid, the process for the preparation of these salts is not disclosed.

Some of above-mentioned salts and preparation thereof are described in the description of Hungarian patent application No. P0004701. The ethoxycarbonyl group of loratadine is eliminated by hydrolysis with mineral acids at high temperature.
Salts of desloratadine with two moles of the acid (1:2 salts) can be isolated directly from the reaction mixture. Preparation of desloratadine disulphate, dihydrochloride, dihydrobromide salts is shown. Among the examples the process for the preparation of hemisulphate salt of desloratadine from disulphate salt is also described. Salts of desloratadine formed with one mole acid (1:1 salts) are prepared by reacting desloratadine base with hydrochloric acid, benzene sulphonic acid, methane sulphonate acid, fumaric acid and tartaric acid in a medium containing dichloromethane.

Two polymorphs of desloratadine hemifumarate are described in international PCT patent application No. 2004/012738. The difference between the melting points of these polymorphs is some degrees of Celsius.

The desloratadine adduct called as desloratadine pseudopolymorph of the formula (I) is described first in the international patent application No. WO2006/003479. The advantages of adduct make this product better than other salts for the preparation of different pharmaceutical compositions, e.g. tablets or other forms. According to the description of said patent application an adduct precipitates containing 1/2 mole of carbon dioxide with 1 mole desloratadine according to the
formula (I.) by adding carbon dioxide into the solution of desloratadine base in tetrahydrofurane or ethyl acetate.

This adduct is a new pseudopolymorph form of desloratadine with half a mole of carbon dioxide. According to the results of HPLC examinations this adduct of the formula (I) has a very high purity. The reason of the high purity is that the contaminants having basic properties in the solution containing raw desloratadine base do not produce adducts, therefore these contaminants remain in the solution, meanwhile the only crystallised product is the adduct of desloratadine.

According to the international patent application No. W02006/003479 the preparation of the adduct of the formula (I) is carried out in a mixture of an ester type solvent, preferably in ethyl acetate or in an ether type solvent, e.g. tetrahydrofurane or diethyl ether and a C₄OH alcohol, preferably ethanol or methanol. If carbon dioxide is added into a solution of desloratadine base in an organic solvent or desloratadine is added to an organic solvent, meanwhile carbon dioxide is added into the mixture, a product having appropriate carbon dioxide content can be prepared. Solubility of desloratadine base in ether or ester type solvents is relative low, in methanol or ethanol is good,
therefore according to the preferable embodiment of the
process a solution of desloratadine in alcohol is added to the
reaction mixture.

The product according to the formula (I) is practically
insoluble in the reaction mixture containing ethyl acetate and
approx. 10 % of alcohol, therefore the yield of the product is
high. According to the description of international patent
application No. W02006/003479 the media containing ethyl
acetate is especially preferable for the preparation of the
adduct of the formula (I).

The adduct of the formula (I) prepared from a medium
containing ethyl acetate contains ethyl acetate as contaminant
evidently.

In case of reproduction of the preparation of the product
according to the patent application No. W02006/003479 in
laboratory scale the amount of this contaminant is lower than
the amount allowed by pharmacopoeias, but an unexpected
problem appears during the examination of the pharmaceutical
composition prepared from the product contaminated by this
contaminant.
During the storage of the pharmaceutical composition containing active ingredients having an ester type contaminant, N-acetyl-desloratadine according to the formula

![Formula Image](IV)

is formed and the amount of this contaminant increases to a higher level than allowed by pharmaceutical authorities.

Scaling up the processes described in the patent application No. W02006/003479 in case of using other solvents, e.g. tetrahydroforane or diethyl ether entails further difficulties. The elimination of the residual solvents in industrial scale to the level required by authorities can only be achieved by using elevated temperature and vacuum simultaneously, which destructs the stoichiometric composition of the product.

Based on the facts above, the preparation of the compound of the formula (I) can not be carried out in industrial scale in an appropriate quality.
The purpose of present invention is to work out a new process for the preparation of the adduct of desloratadine of the formula (I) which allows the preparation of the adduct of the formula (I) in industrial scale having a purity and stability appropriate for the requirements of pharmaceutical industry.

SUMMARY OF THE INVENTION

The present invention relates to a new process for the preparation of desloratadine adduct with carbon dioxide according to the formula (I) in which acetone or a mixture of acetone and aliphatic alcohols is used as reaction medium resulting a product which is suitable for the preparation of pharmaceutical compositions acceptable by pharmaceutical authorities.

DETAILED DESCRIPTION OF THE INVENTION

We found surprisingly, that acetone as dipolar aprotic solvent having a high dielectric constant (20.7) is especially useful for the preparation of the adduct of desloratadine with carbon dioxide of the formula (I). The thus obtained pharmaceutical active ingredient is appropriate for the preparation of a pharmaceutical composition.
A U the more surprising that the use of acetone having a high dielectric constant (20.7) is favourable for the preparation of the adduct of the formula (I) because the ester type solvents found to be advantageous (e.g. ethyl acetate, butyl acetate) and the ether type solvents (e.g. diethyl ether or tetrahydrofurane) used according to the international patent application No. W02006/003479 are apolar solvents having low dielectric constants of approximately 4-6.

Although we have found that the adduct is not formed in alcohols having a high dielectric constant (over 20), moreover, in the case when the adduct was added into alcohol, its destruction was detected with the evolution of carbon dioxide gas, the use of small amount of alcohol (max. 15% by volume) in the reaction mixture is acceptable.

The polarities of different materials including solvents are characterized with their dielectric constants, which can be found in different chemical handbooks, e.g. on pages of E-49-52 of the issue 64 of CRC Handbook of Chemistry and Physics.

The basis of the present invention for the preparation of the pseudopolymorph of desloratadine of the formula (I) is the
reaction of desloratadine base of the formula (II) with carbon dioxide in the presence of acetone.

Desloratadine base is added to the reaction mixture in a finely powdered form or in a solution of the base in alcohol.

According to the advantageous embodiment of the present invention the desloratadine base is dissolved in a C₁-C₄ alcohol or in a mixture thereof, preferably dissolved in ethanol and added to the acetone, in which carbon dioxide gas is added continuously. The proportion alcohol used is 3-20 % by volume preferably 5-20 % by volume, most preferably 5-17 % by volume based on the amount of used acetone.

According to another embodiment of the present invention carbon dioxide or dry ice is added into a suspension of desloratadine base of the formula (II) formed in acetone or in a mixture of acetone and alcohol.

The reaction can be carried out between 20-60°C. The shape of the crystallines highly depends on the used reaction temperature. The shape of crystallines influences the drying properties and the amount of the remained solvent content of the product.
The preferred reaction temperature is between 40-55°C, more preferably is between 45-55°C, because in this case the adduct of the formula (I) precipitates from the reaction mixture in a form having good drying properties.

The process according to the present invention is carried out in the presence of an amount of 2-20 times volume acetone, preferably in 10-20 times volume acetone based on the weight of the used desloratadine base.

The X-ray diffractogram of the product prepared according to the present invention is identical to that of the adduct product which was produced according to the description of the international patent application No. W02006/003479.

A further object of the present invention is a process for the preparation of desloratadine of the formula (II) and acid addition salts thereof in a high purity using the adduct of desloratadine with carbon dioxide as starting material.

Particularly, desloratadine of the formula (II) is prepared by heating or if necessary boiling a mixture of the adduct of desloratadine with \( \frac{1}{2} \) mole of carbon dioxide with an organic solvent or a mixture of organic solvents, then the organic solvent is removed partly or fully forming the reaction mixture.
and the thus obtained desloratadine is crystallised. The obtained raw desloratadine base can be recrystallised.

According to a preferable embodiment of the present invention, desloratadine of the formula (II) can be prepared by dissolution of the adduct of desloratadine with 3/4 mole of carbon dioxide in an aliphatic alcohol, then the solution is heated at its boiling point, boiled for 0.5-3 hours if necessary, then the organic solvent is evaporated and the residue is recrystallised from a mixture of acetone and methanol.

The different polymorph forms of desloratadine known from the literature can be prepared using specific circumstances and solvents of the recrystallisation process.

Taking into consideration that the amine type side products have been eliminated in course of the preparation of the adduct of the desloratadine with 1/2 mole of carbon dioxide, the obtained desloratadine base is free from hardly removable contaminants.

Salts of desloratadine are prepared according to processes described in the international patent application No. WO2006/003479 with the proviso that the adduct of the desloratadine with 1/2 mole of carbon dioxide prepared in the
presence of acetone according to the present invention. The adduct is dissolved in an organic solvent then reacted with a solution of the appropriate acid in an organic solvent.

As an acid e.g. hydrochloric acid, hydrogen bromide, sulphuric acid, methane sulphonic acid, benzene sulphonatic acid, maleic acid or fumaric acid can be used.

According to an embodiment of the present invention the acid is used in an approx. equimolar amount based on the amount of the adduct of the formula (I). In this case the salt obtained contains 1 mole of acid based on 1 mole of desloratadine.

According to another embodiment of the present invention the acid is used in a 2:1 molar equivalent amount, preferably in a 2:1-3:1 molar equivalent amount based on the amount of the adduct of the formula (I). In this case the salt obtained contains 2 moles of acid based on 1 mole of desloratadine.

The advantage of the process of the present invention is that the stable adduct of the formula (I) can be prepared in a pharmaceutically acceptable purity. The drying of the product does not require such circumstances which change the stoichiometric composition of the product. Acetone as residual
solvent does not cause formation of contaminants even during a long storage time.

Other advantage of the present invention is that the adduct of desloratadine with 1 A mole of carbon dioxide is extremely suitable for the preparation of desloratadine of the formula (II) and salts thereof in high purity. The reason is that the pseudopolymorph form of desloratadine of the formula (I) can be prepared in such a high purity, which is acceptable for pharmaceutical use without further purification. The separation of the adduct of the formula (I) is a much more efficient purification process than the recrystallisation of the desloratadine base. The reason of this fact is that the basic contaminants formed in a small amount during the removal of ethoxycarbonyl group in course the preparation of desloratadine from loratadine do not react with carbon dioxide. Therefore these contaminants remain in the mother liquor during filtering off the obtained adduct of desloratadine with 1 A mole of carbon dioxide. Thus, desloratadine can be purified easily from amine type contaminants.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.
Example 1

Preparation of adduct of desloratadine with half a mole of carbon dioxide (I)

Dry ice is placed into a 250 ml round flask, the evolved carbon dioxide is added continuously under the fluid level into an apparatus, in which 1200 ml of acetone is stirred vigorously at 45°C. A solution of 80 g of desloratadine in 140 ml of ethanol is added dropwise during 30 minutes.

After adding of approx. the half of the desloratadine solution crystallisation of the product begins. The crystal suspension is cooled to 20°C during one hour. The suspension is stirred for an hour at 5°C then the precipitated product is filtered, the filter cake is washed with 150 ml of acetone of 5°C and dried at 25°C for 2-3 hours until weight uniformity.

Yield: 80.7 g (94.3 %) white powder.

Analysis: C_{19}H_{19}ClN_{2} x \frac{1}{2} CO_{2} (332.87)
Calculated:  C:70.71   H:5.79   Cl:10.62   N:8.41
Found:  C:70.85   H:5.66   Cl:10.81   N:8.383

IR spectra and powder X-ray diffractogram are identical to the IR spectra and X-ray diffractogram of the product prepared according to the process described in international patent application No. WO2006/003479;

Example 2

Preparation of pseudopolymorph of desloratadine with half a mole of carbon dioxide (I)

Dry ice is placed in a 50 ml round flask and the evolved carbon dioxide is added continuously under the fluid level into an apparatus, in which 120 ml of acetone is stirred vigorously at 40°C. A solution of 8.0 g of desloratadine in 10 ml of methanol is added dropwise to the acetone during 30 minutes.

After adding of approx. the half of the desloratadine solution crystallisation of the product begins. The crystal suspension is cooled to 20°C during one hour. The suspension is stirred for an hour at 5°C, then the precipitated product is filtered, the filter cake is washed with 15 ml of acetone of 5°C and dried at 45°C for 3 hours.
Yield: 8.26 g (96.0 %) white powder.

IR spectra and powder X-ray diffractogram are identical to the IR spectra and X-ray diffractogram of the product prepared according to the process described in international patent application No. WO2006/003479.

Example 3

Preparation of pseudopolymorph of desloratadine with half a mole of carbon dioxide (I).

The reaction is carried out according to Example 2 with the proviso that desloratadine base is dissolved in 20 ml of 2-propanol having a temperature of 60°C and the solution is added to acetone of 55°C.

Yield: 8.20 g (95.2 %) white powder.

IR spectra and powder X-ray diffractogram are identical to the IR spectra and X-ray diffractogram of the product prepared according to the process described in international patent application No. WO2006/003479.
Example 4

Preparation of pseudopolymorph of desloratadine with half a mole of carbon dioxide (I).

The reaction is carried out according to Example 2 with the proviso that desloratadine base is dissolved in 20 ml of 1-butanol of 60°C and the solution of desloratadine base in 1-butanol is added to acetone of 50°C.

Yield: 8.12 g (94.3 %) white powder.

IR spectra and powder X-ray diffractogram are identical to the IR spectra and X-ray diffractogram of the product prepared according to the process described in international patent application No. WO2006/003479.

Example 5

Preparation of pseudopolymorph of desloratadine with half a mole of carbon dioxide (I)

Dry ice is placed in a 50 ml round flask and the evaporated carbon dioxide is added continuously under the fluid level into an equipment in which 150 ml of acetone is stirred vigorously
at 50°C. In small portions 8.0 g of finely powdered desloratadine is added to the acetone. The suspension is stirred for two hours after the addition, then boiled for an hour. The crystal suspension is cooled to 20°C during one hour. The suspension is stirred for an hour at 5°C, then the precipitated product is filtered, the filter cake is washed with 15 ml of acetone of 5°C and dried at 40-45°C for 1 hour.

Yield: 8.37 g (97.5%) white powder.

IR spectra and powder X-ray diffractogram are identical to the IR spectra and X-ray diffractogram of the product prepared according to the process described in international patent application No. WO2006/003479.

**Example 6**

Polymorph form 1 of desloratadine base

In 120 ml of ethanol 40 g of adduct of desloratadine with ½ mole of carbon dioxide is boiled for an hour, then the solvent is evaporated. 360 ml of acetone and 20 ml of methanol are added to the warm residue. The mixture is boiled and decolourised with carbon, filtered, the filtrate is left to cool to 25°C during half an hour and stirred for an additional hour.
The crystal suspension is stirred at -10°C for four hours, then filtered.

The product is dried at 50°C for two hours, until weight uniformity.

Yield: 23.5 g (63.0 %)
Melting point: 257-258°C

Based on the IR spectra and powder X-ray diffractogram the product is pure desloratadine base of the polymorph form 1.

**Example 7**

Preparation of desloratadine hydrochloride (1:1) from the carbon dioxide pseudopolymorph of desloratadine formed with half a mole of carbon dioxide

To a suspension of 7.1 g (20 mmoles) of the carbon dioxide adduct of desloratadine in 100 ml ethyl acetate, a solution of 0.73 g (20 mmoles) of hydrogen chloride in ethyl acetate is added at 20-25°C within 10 minutes. The suspension is stirred for 3 hours until the gas evolution is finished, then cooled to 0°C, filtered, and the crystals are washed with ethanol.
Yield: 6.61 g (95.2 %) white crystals.

Mp.: 261-263 °C

Analysis: for the formula of C_{19}H_{19}ClN_{2} \cdot HCl (347.29)

Calculated: C:65.71 H:5.80 Cl:20.42 N:8.07

Found: C:65.39 H:5.75 Cl:20.26 N:8.02

HPLC purity >99.8 %
What we claim is,

1. Process for the preparation of the pseudopolymorph of desloratadine of the formula

\[
\text{II.} \quad \text{N} \quad \text{H}
\]

characterized in that desloratadine base of the formula

\[
\text{I.} \quad \text{N} \quad \text{H}
\]

is reacted with carbon dioxide in the presence of acetone.
2. Process according to Claim 1 characterized in that the desloratadine base is added dissolved in alcohol or in a powdered form to the acetone.

3. Process according to Claims 1 or 2 characterized in that C₁⁻C₄ alcohols, preferably ethanol are used to dissolution of desloratadine base.

4. Process according to Claims 2 or 3 characterized in that the volume of alcohol used for the dissolution of desloratadine base is 3-20%, preferably 5-20%, more preferably 5-17% by volume of used acetone.

5. Process according to any of Claims 1-4 characterized in that the reaction is carried out between 20-60°C, preferably between 40-55°C, more preferably between 45-55°C.

6. Process according to any of Claims 1-5 characterized in that the reaction is carried out in acetone of 2-50 times volume, preferably 10-20 times volume based on the weight of desloratadine base.
7. Process according to any of Claims 1-6 characterized in that carbon dioxide gas or dry ice is added to a solution of desloratadine base in acetone.

8. Process for the preparation of desloratadine, characterized in that the adduct of desloratadine prepared according to any of the claims 1-7 is heated in an organic solvent, then evaporated and recrystallised if necessary.

9. Process for the preparation of polymorph form I of desloratadine characterized in that the adduct of desloratadine with $\frac{1}{2}$ of carbon dioxide of the formula (I) is boiled in ethanol then evaporated in vacuum, the residue is recrystallised from a mixture of acetone and methanol, then filtered and dried.

10. Process for the preparation of acid addition salts of desloratadine characterized in that the solution of pseudopolymorph form of desloratadine with carbon dioxide prepared according to Claims 1-7 in an organic solution is reacted with a solution of the appropriate acid in an organic solvent.
# A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04

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)

C07D

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/003479 A (EGYT GYOGYSZERVEGESZETI GYAR [HU]; MEZEI TIBOR [HU]; SIMIG GYULA [HU]) 12 January 2006 (2006-01-12) cited in the application page 11 - page 12 examples 2,4 page 14 - page 15 examples 5-11 claims 14-18</td>
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<td>A</td>
<td>WO 85/03707 A (SCHERING CORP [US]) 29 August 1985 (1985-08-29) cited in the application example II</td>
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| D | Further documents are listed in the continuation of Box C | X | See patent family annex |

- Special categories of cited documents
  - 'A' document defining the general state of the art which is not considered to be of particular relevance
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- 'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search: 7 February 2008

Date of mailing of the international search report: 14/02/2008

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Seitner, Irmgard
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