Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
Description

Technical Field

[0001] The invention deals with a new crystalline salt of the selective estrogen receptor modulator 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyfenyl)-3-methyl-1H-indol-5-ol with acetic acid.

Background Art

[0002] Bazedoxifene (1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyfenyl)-3-methyl-1H-indol-5-ol) of formula 1:

![Formula 1](image1)

belongs to selective estrogen receptor modulators (SERMs). A more detailed description of its biological activity can be found e.g. in Drugs of the Future, 2002, 27(2), 117-121.


[0004] Use of a substance for pharmaceutical purposes places high demands on the substance quality. The most efficient purification operation is crystallization. In the case of substances that cannot crystallize it is very difficult to achieve internationally appreciated quality criteria defined by the ICH instructions. In addition, amorphous forms of substances are more susceptible to decomposition, in particular hydrolysis or oxidation, which is caused by their large surface. According to well-known and verified information bazedoxifene and its hitherto known forms can be classified among such substances that are difficult to purify and prone to decomposition.

[0005] Bazedoxifene as well as bazedoxifene ascorbate are non-crystalline forms that can be obtained by concentrating the solution until dry. Due to this, however, all undesired, nonvolatile substances coming from the synthesis or decomposition of API remain in the resulting substance. This is mainly the case of 2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol of formula 2 and 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-5-benzyloxy-2-(4-hydroxyphenyl)-3-methyl-1H-indole of formula 3, coming from the synthesis, and 1-(4-hydroxybenzyl)-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol of formula 4 and 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol N-oxide of formula 5, generated by decomposition of bazedoxifene.

![Formulas 2-5](image2)
The allegedly crystalline acetate does not solve the problem of quality. The presence of even small quantities of the above mentioned or other impurities precludes crystallization of bazedoxifene acetate prepared in accordance with the patent documents US 5,998,402; US 6,479,535 or US 2005/0227965. The acetate can be successfully obtained in the amorphous form by a modified procedure with yields of about 40%. The acetate is subject to decomposition reactions producing undesired impurities, especially oxidation that produces the undesired substance of formula 5. To suppress this decomposition process the addition of ascorbic acid as an antioxidant is commonly used. Therefore, a more suitable form of bazedoxifene has been looked for that could be easily prepared in high yields and in particular in the quality corresponding to API and would not be susceptible to undesired decompositions at the same time.

Disclosure of Invention

The invention relates to a new stable crystalline salt of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (bazedoxifene) with acetic acid and to a method of their preparation, characterized by the reaction of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol of formula 1 with acetic acid in a suitable solvent.

The selection of the solvent depends on the solubilities of the starting substance and product and especially on the capability of the product to form a strong lattice in the given solvent. As the solvents, one can use C1-C5 alcohols (e.g. methanol, ethanol, 1-propanol, 2-propanol, butanols), esters of carboxylic acids (e.g. ethyl acetate), ethers (e.g. dioxan, tetrahydrofuran or diethyl ether), ketones (e.g. acetone or cyclobutanone), acetonitrile, their arbitrary mixtures and mixtures with water in any proportions. A preferable embodiment of the invention comprises using ethanol or its mixtures with water, with ethyl acetate or with toluene as the solvent in the proportions of 97.5:2.5 to 90:10.

The crystalline structure of said salt has been unambiguously characterized by the results of the following analytic methods: X-Ray Powder Diffraction (hereinafter XRPD only), melting point and Differential Scanning Calorimetry (hereinafter DSC only). The results of the analyses are presented in the examples and attached drawings.

Preferably, the salt is characterized by the following reflections in the X-Ray diffraction pattern: 13.17; 15.97; 17.95; 19.62; 20.54; 22.08; 25.27.

It is especially beneficial to prepare the crystalline form of the salt of the present invention if an alcohol (C1-C5) or its mixtures with toluene, DMF or ethyl acetate in the proportions of 90: 10 to 95:5 are used as the solvent. The process exclusively leads to a defined crystal modification (determined by means of DSC and XRPD) and a defined particle size and, in addition, this process manifests high quality and high yields, which are achieved in a reproducible manner. The above mentioned characteristics of the crystalline salt are very advantageous for its manufacture and pharmaceutical use.

In the process of the invention a new polymorph of the salt with acetic acid (CH₃COOH) (bazedoxifene acetate) has been prepared, which can be used in practice for the preparation of pharmaceutically useful compositions.

The object of the invention will be elucidated in a more detailed way in the following examples, which, however, do not have any impact on the scope of protection defined by the claims.

Brief Description of Drawings

Fig. 1 shows the X-Ray Powder Diffraction of the crystalline salt of acetic acid with bazedoxifene polymorph C) prepared according to Example 10 (bazedoxifene acetate).

Fig. 2 shows the DSC curve of the crystalline salt of acetic acid with bazedoxifene polymorph C) prepared according to Example 10 (bazedoxifene acetate).

Examples

EXAMPLE 1

Preparation of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-benzyloxyphenyl)-5-benzyloxy-3-methyl-1H-indole (benzylated bazedoxifene)

[0015]
In an inert atmosphere NaH (2.7 g; 112 mmol) was suspended in DMF (80 ml). At 0-5 °C 5-benzyloxy-2-(4-benzyloxyphenyl)-3-methyl-1H-indole (11 g; 26 mmol) was added and the suspension was stirred for 30 minutes. Then a solution of 4-(2-azepan-1-yl-ethoxy)benzyl chloride (8 g; 26 mmol) in DMF (30 ml) was added dropwise within 1 hour. The cooling was shut down and the reaction mixture was stirred for another 2.5 hours. Then, water (1.2 ml) was carefully added dropwise to the reaction mixture and the reaction mixture was filtered through a thin layer of celite. Another 35 ml of water were added dropwise to the brightly yellow filtrate under intensive stirring.

The separated white product was filtered and washed with methanol. The yield of the crude product was 13.7 g (81 %). The crude product was dissolved in 70 ml of ethyl acetate with a small quantity of activated charcoal and filtered while hot. 100 ml of methanol were added to the filtrate. The yield of crystallization was 80.5 %. Melt. point = 109-112 °C. HPLC content 99.8%.

EXAMPLE 2

Preparation of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (bazedoxifene).

The starting compound, benzylated bazedoxifene of formula 7 (4.8 g; 7.38 mmol) was dissolved in an ethanol/THF mixture (1:1) (80 ml) and the catalyst, 2.34%-Pd/C (0.4 g) was added in an inert atmosphere. Then, the reaction mixture was stirred in the hydrogen atmosphere for 5 hours. The catalyst was filtered off through a celite layer in an inert atmosphere. The obtained clear, colourless filtrate was concentrated until dry.

3.43 g (99%) of the bazedoxifene base were obtained in the form of off-white, solid foam. HPLC content 98.8%.

EXAMPLE 3

Preparation of the salt of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol with acetic acid (bazedoxifene acetate).

The starting compound, benzylated bazedoxifene of formula 7 (3 g; 4.6 mmol) was dissolved in ethyl acetate (30 ml) and the catalyst, 2.34%-Pd/C (0.25g) was added in an inert atmosphere. Then, the reaction mixture was stirred in the hydrogen atmosphere for 24 hours. The catalyst was filtered off through a celite layer in an inert atmosphere. The obtained clear, colourless filtrate was added to a solution of acetic acid (0.3 ml, 5.1 mmol) in the ethyl acetate (9 ml) and ethanol (2.5) mixture dropwise while being cooled with ice. The separated white substance was filtered and suspended in 30 ml of a mixture of ethyl acetate and ethanol (95:5) and the suspension was refluxed for 5 minutes. After cooling with ice and filtration the product was dried in a vacuum drier at 50 °C.

1 g of bazedoxifene acetate was obtained (yield 41%). Melt. point =139-163 °C.
Claims

1. A salt of 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol of formula 1 with acetic acid (bazedoxifene acetate), which salt is characterized by the following reflections in the X-Ray diffractogram pattern: 13.17; 15.97; 17.95; 19.62; 20.54; 22.08; 25.27.

2. Use of the salt according to claim 1 for the preparation of pharmaceutically useful compositions.

Patentansprüche

1. Salz von 1-[4-(2-Azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol der Formel 1 mit Essigsäure (Bazedoxifenacetat), wobei das Salz durch die folgenden Reflexe im Röntgenbeugungsmuster gekennzeichnet ist: 13,17; 15,97; 17,95; 19,62; 20,54; 22,08; 25,27.

2. Verwendung des Salzes gemäß Anspruch 1 für die Herstellung von pharmazeutisch nützlichen Zusammensetzungen.

Revendications

1. Un sel de 1-[4-(2-azépan-1-yl-éthoxy)benzyl]-2-(4-hydroxyphényl)-3-méthyl-1H-indol-5-ol de formule 1:
et d'acide acétique (acétate de bazédoxifene), lequel sel est caractérisé par le spectre de diffraction aux rayons X présentant les réflexions suivantes : 13,17 ; 15,97 ; 17,95 ; 19,62 ; 20,54 ; 22,08 ; 25,27.

2. Utilisation du sel selon la revendication 1, pour la préparation de compositions utiles du point de vue pharmaceutique.
Fig. 2
REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5998402 A [0003] [0006]
- US 6479535 B [0006]
- US 20050227965 A [0006]

Non-patent literature cited in the description

- Drugs of the Future, 2002, vol. 27 (2), 117-121 [0002]