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(54) Title: PROCESS FOR PREPARATION OF HIGH-PURITY MELOXICAM AND MELOXICAM POTASSIUM SALT

(57) Abstract: The invention provides a process for the preparation of high purity meloxicam of the Formula (II). The meloxicam raw product is reacted with the solution of potassium hydroxide or potassium carbonate, whereby high purity meloxicam potassium salt monohydrate is produced. Said salt is subsequently treated with mineral or organic acid to yield high-purity meloxicam.

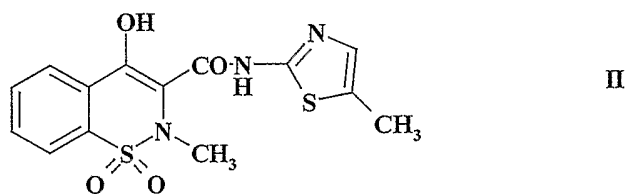
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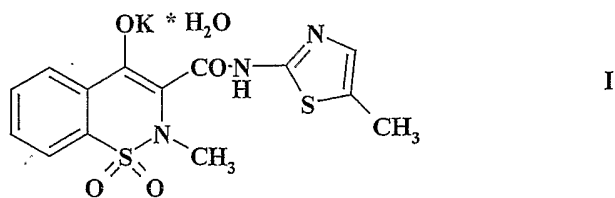
**Process for preparation of high-purity meloxicam and  
meloxicam potassium salt**

**FIELD OF THE INVENTION**

The present invention relates to a process for the preparation of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (II),



also known by the International Nonproprietary Name (INN)  
meloxicam and its potassium salt monohydrate of the Formula (I)

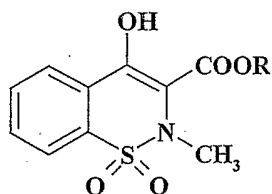


in high purity.

### TECHNICAL BACKGROUND OF THE INVENTION

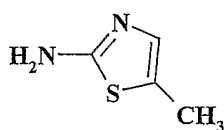
Meloxicam belongs to the group of non-steroidal antiinflammatory drugs. It exerts its pharmacological effect by the inhibition of the cyclooxygenase (COX) enzyme system, which has significant role in the development of inflammatory processes. The medicinal importance of meloxicam resides in the fact that meloxicam selectively inhibits the COX-2 enzyme. This phenomenon results in less adverse effects during the medication period. It was found that the probability of the development of kidney-related or gastrointestinal adverse effects is significantly lower during the treatment using meloxicam than in those cases, when different, non-selective COX-inhibitors were administered.

Processes for the preparation of meloxicam have been disclosed in European Patent No. 2482. According to the first process, an activated form of 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylic acid of the Formula (III),



III

such as its methyl-, ethyl- or isopropyl ester (wherein the meaning of the R group in the Formula(III) is methyl, ethyl or isopropyl, respectively) is reacted with 2-amino-5-methyl-thiazole of the Formula (IV)

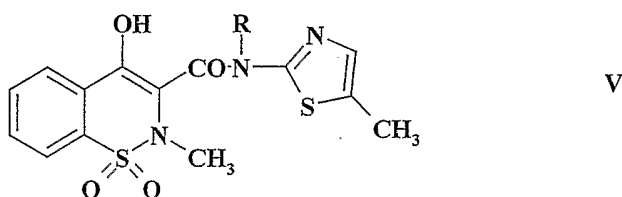


IV

at high temperature. During this reaction, by-products with similar chemical structure to meloxicam and some tar are also formed, therefore further purification of the raw product is required. Solvents most often used for the recrystallization of raw meloxicam are dichloroethane and dichloromethane. The above mentioned process has the disadvantage that toxic and costly solvents are used, which are harmful to the environment as well. During the subsequent drying, it must be assured that the residual solvent concentration in the finished active ingredient should not exceed a threshold concentration set by health authorities and pharmacopoeias. At the drying temperature, thermal decomposition of the active ingredient also takes place. Use of halogenated organic solvents requires extensive analytical testing, because the residual solvent concentration must be determined in costly analytical measurements.

In the second known process, the nitrogen atom of the 2H-1,2-benzothiazine ring is methylated using either the very expensive methyl iodide or the extremely toxic dimethyl sulfate. Due to its low yield and high production costs, this process is not used on an industrial scale.

It was found that when using the above mentioned processes, the by-product 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V),



wherein the alkyl group corresponds identical to the R group in the starting compound of the Formula (III), i.e. methyl, ethyl or isopropyl, is formed in an amount of 1-20 % by weight. Compounds of the Formula (V) are crystalline compounds poorly soluble in organic solvents and having their melting point above 250 °C. Impurities of the Formula (V) can be removed partly by filtering the hot solution of meloxicam crude product. However, a dissolved portion of the compounds of Formula (V) amounting to a few tenth percent crystallizes together with meloxicam upon cooling, therefore compounds of the Formula (V) appear in the final

pharmaceutical active ingredient as impurity. It was observed that the compounds of the Formula (V) are produced in the largest quantity (10-20 % by weight), if the compound of the Formula (III) is used as starting material wherein R is methyl. The smallest amount of the compound of Formula (V) is produced in the case when R is isopropyl in the starting compound of the Formula (III). According to the specifications of the pharmacopoeias, threshold concentration of the compounds of the Formula (V) is 0.1 % by weight, which could be achieved only after recrystallizing the crude product several times from dichloromethane.

United States Patent Application No. 20030109701 discloses processes for the preparation of several meloxicam polymorph forms by dissolving meloxicam in sodium-hydroxide solution prepared in water or in the mixture of water and an organic solvent, subsequently acidifying the solution of meloxicam sodium salt, thus setting meloxicam free from its sodium salt. In this way, different crystalline modifications of meloxicam are obtained, depending upon the conditions used during dissolution and precipitation. Subsequently, the polymorph form obtained in the above described process is converted into the pharmaceutically acceptable polymorph I form.

#### SUMMARY OF THE INVENTION

The objective of our research has been to develop a process for the preparation of high purity meloxicam suitable as pharmaceutical

active ingredient and said high purity meloxicam being essentially free of 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide impurity of the Formula (V), wherein the meaning of alkyl is methyl, ethyl or isopropyl.

The above objective is solved according to the present invention.

Surprisingly, it has been found that meloxicam potassium salt monohydrate of the Formula (I) can be crystallized from aqueous solution in exceptionally high purity, thus allowing the purification of raw meloxicam.

According to an aspect of the present invention, there is provided a process for the preparation of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam) of the Formula (II) of high purity, which comprises

- (a) dissolving meloxicam potassium salt monohydrate of the Formula (I) in water or in the mixture of water and an organic solvent, removing insoluble impurities and treating the resulting solution with an organic or inorganic acid, and crystallizing meloxicam; or
- (b) transforming meloxicam raw product into crystalline meloxicam potassium salt monohydrate of the Formula (I), dissolving said meloxicam potassium salt monohydrate of the Formula (I) in water or in a mixture of water and an

organic solvent, removing insoluble impurities and treating the dissolved potassium salt of meloxicam with an organic or inorganic acid, followed by crystallization meloxicam of the Formula (II); or

- (c) reacting a compound of the general Formula (III), wherein R is methyl, ethyl or isopropyl with 2-amino-5-methyl-thiazole of the Formula (IV), transforming the resulting meloxicam of the Formula (II) into its potassium salt, separating insoluble impurities from aqueous or aqueous-organic solution of said meloxicam potassium salt, treating said solution with an organic or inorganic acid and crystallizing meloxicam.

According to a further aspect of our invention, there is provided a process for the preparation of meloxicam potassium salt of the Formula (I), by reacting meloxicam of the Formula (II) with potassium hydroxide or potassium carbonate dissolved in water or in the mixture of water and an organic solvent and if desired, crystallizing the meloxicam potassium salt monohydrate of the compound of the Formula (I) thus formed.

In the above mentioned process directed to the preparation of meloxicam potassium salt of the Formula (I) or monohydrate thereof, the molar amount of potassium hydroxide or potassium carbonate is 1-10 molar equivalent, preferably 4-5 molar equivalent of the molar amount of meloxicam.



If desired, any of the processes can be performed in water or in the mixture of water and an organic solvent. As organic solvent, an alcohol containing 1-4 carbon atoms, for example, methanol, ethanol or isopropanol, preferably ethanol can be used.

In the above mentioned process variants a) to c), meloxicam of the Formula (II) is set free from its potassium salt dissolved in water or in the mixture of the water and an organic solvent by treatment with an inorganic or an organic acid. Said acidic treatment is carried out by mixing the solution of meloxicam potassium salt of the Formula (I) with concentrated acid or an aqueous solution thereof. Suitable acids include any mineral or organic acids, for example, sulphuric acid, hydrochloric acid, phosphoric acid, tartaric acid, acetic acid.

Acidic treatment can be preferably carried out under the control of the acidity (pH value) of the solution of meloxicam potassium salt of the Formula (I). The acidic treatment is continued until pH 3 to 6, preferably until pH 6 is reached.

According to a further aspect of the present invention, there is provided 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam) of the Formula (II) essentially free from 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V), wherein the R alkyl group of the Formula (V) is methyl, ethyl or isopropyl.

The invention further relates to meloxicam potassium salt monohydrate of the Formula (I), preferably in a purified state wherein said salt is essentially free from 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V), wherein alkyl (Group R in the Formula (V)) is methyl, ethyl or isopropyl.

According to a still further aspect of the invention, there are provided pharmaceutical preparations comprising meloxicam potassium salt monohydrate of the Formula (I) as active ingredient and one or more pharmaceutically acceptable vehicle or auxiliary agent, preferably in a purified state wherein said salt is essentially free from 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V), wherein alkyl (Group R in the Formula (V)) is methyl, ethyl or isopropyl.

The invention further relates to pharmaceutical preparations comprising high purity meloxicam of the Formula (II) as active ingredient and one or more pharmaceutically acceptable vehicle or auxiliary agent, wherein the active ingredient meloxicam is essentially free from 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V), wherein alkyl (Group R in the Formula (V)) is methyl, ethyl or isopropyl.

#### DETAILED DESCRIPTION OF THE INVENTION

Organic acids and phenols form salt with metals, which are usually well soluble in water. This phenomenon is often exploited for the purification of said compounds by dissolving the product in alkaline-aqueous medium and removing the alkaline- and water-insoluble organic impurities by filtration or extraction with a suitable non-miscible solvent.

It is known according to the state of the art that potassium salts crystallize less easily and have greater solubility in water and in organic solvents, than sodium salts. Potassium salts can be hygroscopic, therefore said salts are preferably isolated from their solution in organic solvents.

The preparation of sodium salt of meloxicam was disclosed in Example 2 of European Patent No. 2482. The methanolic solution of meloxicam is mixed with approximately equimolar amount of sodium methylate, the reaction mixture is evaporated to dryness, the sodium salt is suspended in the mixture of acetone-ether and filtered.

United States Patent Application No. 20030109701 discloses the preparation of meloxicam sodium salt by dissolving meloxicam in aqueous-organic solution of sodium hydroxide.

Although according to the state of the art, among alkaline metal salts of meloxicam, the potassium salt is also mentioned, no

disclosure is available for the preparation of the potassium salt of meloxicam in solid form and no data can be found with regard to its stability, solubility and purity. According to the state of the art, salts prepared from meloxicam and inorganic or organic bases are prepared exclusively with the purpose to increase the solubility of meloxicam.

According to the state of the art, there is no disclosure for the preparation of meloxicam in high purity form or its purification via its salt formed with inorganic or organic base.

It has been found very surprisingly, that the meloxicam potassium salt of the Formula (I) can be isolated easily in especially pure monohydrate form from the solution of the raw product prepared with water or, if desired, with aqueous-organic solvents, even in the case when the impurity of the Formula (V) is present in the amount of approximately 20% by weight.

The advantage of the preparation of the potassium salt of the Formula (I) resides in the fact that in this way impurities of the Formula (V) as well as other alkaline-insoluble contaminants can be completely and very easily removed from the raw product.

Despite of the fact that the compounds of Formula (V) contain an aromatic hydroxy group, they do not form salt with alkali metals, therefore they are insoluble in alkaline aqueous solution and can be removed from the solution of meloxicam potassium salt by

filtration. The small amount of impurity present on the surface of the solid crystalline meloxicam potassium salt monohydrate of the Formula (II), including the traces of the compounds of Formula (V) can be removed by simple washing with an appropriate solvent, since meloxicam potassium salt monohydrate of the Formula (I) is practically insoluble in organic solvents, for example, in ethyl-acetate.

According to a further aspect of the present invention, there is provided a process for the preparation of high purity, crystalline meloxicam potassium salt monohydrate of the Formula (I). In the first step, meloxicam is produced starting from the compound of the Formula (III), wherein the meaning of R is methyl, which is reacted with the compound of Formula (IV). In this process, a by-product of the Formula (V), wherein the meaning of R is methyl, is produced in an amount of 10-15 % by weight. The raw product is dissolved in aqueous potassium hydroxide or potassium carbonate solution at the temperature of 50 to 60 °C, the impurities insoluble in the alkaline-aqueous solvent are removed by filtration or centrifugation, the clear solution is cooled and the crystalline, high purity meloxicam potassium salt monohydrate of the Formula (I) is isolated by filtration or centrifugation.

According to a further aspect of the present invention, there is provided a process to transform meloxicam potassium salt monohydrate of the Formula (I) into high purity meloxicam. The meloxicam potassium salt monohydrate of the Formula (I) is

dissolved in water or in a mixture of water and an organic solvent, the solution is filtered, the filtrate is acidified by aqueous acid solution and cooled. Subsequently the crystalline meloxicam is collected, washed and dried.

According to another aspect of the present invention, there is provided a process for the production of high purity meloxicam polymorph I form. The potassium salt of the Formula (I) is dissolved in water at a temperature between 50 and 60 °C, the aqueous solution is filtered, and the yellow solution is acidified until pH 6 using concentrated acid solution, the solution is cooled and the precipitated crystalline meloxicam polymorph I form is isolated by centrifugation or filtration.

The advantage of the process according to the present invention resides in the fact that the only solvent used during the purification process is water, therefore it is not necessary to remove organic solvent residues from the product. At the acidity (pH value) given above, the product is almost insoluble in water, therefore the yield is almost quantitative. During the above described process, heat stress of the product and thermal decomposition thereof is minimal, which allows the production of high purity product. The above described process does not involve hazardous chemicals, therefore it is advantageous from the environmental viewpoint. The use of the above described process results in significant cost reduction as well.

The above inventive concept according to our invention can be applied more generally. Among esters of the Formula (III), the methyl ester is the cheapest and is produced on the greatest scale. However, said methyl ester of the Formula (III), wherein R is methyl, has received but limited attention during the production of meloxicam, because of the fact that the by-product of the Formula (V), wherein R is methyl, is produced during the amidation reaction in a significant amount, about 10-15% by weight, which could not be removed by crystallization. Using the process according to the present invention, contaminated raw products containing the above mentioned high amounts of the compound of the Formula (V), wherein R is methyl, can be purified. In this manner, it has become possible to use the cheaper methyl ester of the Formula (III), wherein R is methyl, instead of the isopropyl ester of Formula (III), wherein R is isopropyl.

The preparation of the raw meloxicam of the Formula (II) is carried out according to state of the art by reacting an ester of the Formula (III), wherein R is methyl, ethyl or isopropyl and 2-amino-5-methyl-thiazole of the Formula (IV) in solvents having high boiling point, for example, in chloro-benzene, decaline or xylene, preferably, in xylene. The reaction takes place at the boiling point of the reaction mixture, at the temperature between about 130 and about 170 °C. The reaction time is usually 12-24 hours. Besides the product meloxicam, the reaction mixture contains a significant amount of the compound of the Formula (V) corresponding to the starting compound of the Formula (III) with respect to the R group

and tar-like substance as well. If desired, the reaction can be carried out in presence of activated carbon to decrease the amount of tar. During the reaction, meloxicam and the by-product of the Formula (V) crystallizes and precipitates from the reaction mixture, and can be removed by filtration together with activated carbon, if present.

The raw meloxicam, which may contain activated carbon as well, is dissolved in a 20-50-fold weight amount of aqueous potassium hydroxide solution at a temperature between 50 and 80 °C under stirring. If desired, the dissolution rate of meloxicam can be increased by adding about 3-5 volume% of low molecular weight alcohol, for example, methanol, ethanol or isopropanol. The volume of the potassium hydroxide solution is determined taking into account the quality and quantity of the low molecular weight alcohol.

The aqueous-alkaline solvent dissolves meloxicam only. The compound of the Formula (V), which is insoluble in alkaline medium is filtered together with activated carbon, if present. The clear yellow filtrate is cooled while the precipitation of crystalline meloxicam potassium salt monohydrate of the Formula (I) takes place.

Crystallization of meloxicam potassium salt monohydrate can be enhanced by salting-out. To achieve salting-out effect, an amount of potassium hydroxide or potassium carbonate is added to the solution of meloxicam potassium salt as solid or as concentrated



aqueous solution in excess to the equimolar amount required for salt formation. Total amount of potassium ions present in the solution according to the present invention can be between 1-10 molar equivalents, preferably 4-5 molar equivalents relative to the molar amount of meloxicam.

The solid crystalline meloxicam potassium salt monohydrate of the Formula (I) is isolated, the impurities present on the surface of the crystals are washed away using cold water or an organic solvent or a mixture of thereof, for example, using ethylacetate, ethanol, methanol, isopropanol as organic solvent.

According to our observations, using the process of the present invention, meloxicam potassium salt monohydrate can be obtained in high purity even in the unfavourable case when the reaction mixture contained 15-20 % of the compound of the Formula (V) by weight.

According to the present invention, there is provided a process for the preparation of meloxicam polymorph I form of the Formula (II) in high purity, which comprises dissolving meloxicam potassium salt monohydrate of the Formula (I) in water or in the mixture of water and 1-20 volume% of a low molecular weight alcohol at a temperature between 50 and 100 °C, preferably at a temperature between 60 and 70 °C. The solvent preferably comprises 2-5 volume% ethanol in water.

The solution is filtered, and the clear yellow filtrate is acidified to pH 6 using a mineral or organic acid. For acidification, any mineral or organic acid, for example, hydrochloric acid, sulphuric acid or phosphoric acid, acetic acid, tartaric acid can be used. The crystalline meloxicam is filtered off and washed with water and ethanol.

According to a further aspect of the present invention, there are provided pharmaceutical preparations comprising meloxicam potassium salt monohydrate of the Formula (I) in admixture with one or more conventional carrier(s) or auxiliary agent(s), essentially free of the impurity of the Formula (V).

Another further aspect of the present invention relates to pharmaceutical preparations comprising meloxicam of the Formula (II) in admixture with one or more conventional carrier(s) or auxiliary agent(s), essentially free from the impurity of the Formula (V).

The pharmaceutical compositions according to the present invention contain generally 0.1-95 % by weight, preferably 1-50 % by weight, particularly 5-30 % by weight active ingredient.

The pharmaceutical compositions of the present invention may be suitable for oral (e.g. powders, tablets, coated tablets, capsules, microcapsules, pills, solutions, suspensions or emulsions),

parenteral (e.g. injection solutions for intravenous, intramuscular, subcutaneous or intraperitoneal use), rectal (e.g. suppositories) transdermal (e.g. plasters) or local (e.g. ointments or plasters) administration or for the application in form of implants. The solid, soft or liquid pharmaceutical compositions according to the invention may be produced by methods conventionally applied in the pharmaceutical industry.

The solid pharmaceutical compositions for oral administration containing the compound of the Formula (I) may comprise vehicles, fillers or carriers (such as lactose, glucose, starch, potassium phosphate, micro-crystalline cellulose), binding agents (such as gelatine, sorbite, polyvinyl pyrrolidone), disintegrants (such as croscarmellose, Na-carboxy-methyl cellulose, crospovidone), tableting auxiliary agents (such as magnesium stearate, talc, polyethylene glycol, silicic acid, silicon dioxide) and surface-active agents (e.g. sodium lauryl sulfate).

The liquid compositions containing meloxicam potassium salt of the Formula (I) in dissolved form are known according to the state of the art. Liquid pharmaceutical preparations suitable for oral administration according to the present invention can be suspensions or emulsions. Such compositions may contain suspending agents (e.g. gelatine, carboxymethyl cellulose), emulsifiers (e.g. sorbitane monooleate, solvents (e.g. water, oils, glycerol, propylene glycol, ethanol), buffering agents (e.g. acetate,

phosphate, citrate buffers) or preservatives (e.g. methyl-4-hydroxybenzoate).

Soft pharmaceutical compositions containing as active ingredient a compound of the general Formula (I) or a pharmaceutically acceptable acid addition salt thereof, such as suppositories, contain the active ingredient evenly dispersed in the basic material of the suppository (e.g. in polyethylene glycol or cocoa butter).

The pharmaceutical compositions according to the present invention can be prepared by known methods of the pharmaceutical industry. The active ingredient is admixed with pharmaceutically acceptable solid or liquid carriers and/or auxiliary agents and the mixture is brought to galenic form. The carriers and auxiliary agents together with the methods which can be used in the pharmaceutical industry are disclosed in the literature (Remington's Pharmaceutical Sciences, Edition 18, Mack Publishing Co., Easton, USA, 1990).

The pharmaceutical compositions according to the present invention contain generally a dosage unit.

Further details of the present invention are provided in the following examples without limiting the scope of protection to said examples.

**Example 1**

4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide potassium salt monohydrate (compound of the Formula I)

350 ml of xylene are transferred into an apparatus equipped with Marcusson head and provided with means for inert gas purging. Purging with argon is started and 35.0 g (130 mmol) 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methylester of the Formula (III) [wherein the meaning of R is methyl], 15.0 g (132 mmol) of 2-amino-5-methyl-thiazole of the Formula (IV) and 6.0 g of activated carbon are added during continuous stirring and argon purge.

The reaction mixture is heated for 24 hours using an oil bath at a temperature between 170 and 180 °C. The heating is adjusted in a way that only a minimal amount of distillate (2-5 ml/hour) is produced in the head. Distillation of methanol is ceased by the end of the reaction.

The reaction mixture is cooled to 25 °C, crude meloxicam containing carbon and approximately 12% of the impurity of Formula (V) are filtered off and washed on the filter with xylene and ethanol. The crude product containing carbon is stirred in 1200 ml of 0.5 % aqueous potassium hydroxide solution at the temperature of 50 °C for one hour, carbon and the impurity of Formula (V) insoluble in the alkaline solution are filtered off and the clear yellow solution at 25 °C are added dropwise the solution of 30 g potassium hydroxide in 100 ml water. The potassium salt of

meloxicam is precipitated in the form of yellow crystals which are easily separable by filtration. The crystal suspension is stirred for two hours at 10 °C, filtered and washed with water.

Yield, 42.9 g [81.0 %, calculated on the amount of the compound of Formula (III)]

Content (on the basis of potassium content): 99.5 %

Water (Karl Fischer method): 4.6 %

Melting point, 170-171 °C

Elemental analysis [ $C_{14}H_{12}KN_3O_4S_2 \cdot H_2O$  (407,5)]:

Calculated	C:41.26	H:3.46	N:10.31	S:15.74
Measured	C:41.20	H:3.52	N:10.21	S:15.61

Purity (HPLC): 99.8 % .

Thermogravimetry: the product loses 4.75% water at 175-245 °C

**Example 2**

4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (compound of Formula (II), polymorph I form of meloxicam

34.1 g (83.7 mmol) meloxicam potassium salt monohydrate are dissolved in the mixture of 1500 ml of 0.5 % aqueous potassium hydroxide solution and 25 ml of ethanol at the temperature of 40-45 °C by stirring for 30 minutes. The yellow solution are added 2.0 g of activated carbon and after stirring for ten minutes, the carbon is filtered off. The filtrate are added 100 ml aqueous hydrochloric acid solution prepared by diluting 20 ml (23.6 g) concentrated hydrochloric acid to 100 ml final volume, at 30 °C in 30 minutes (pH 3-5). The suspension is stirred for two hours at 10 °C temperature, filtered and the product is washed on the filter with water.

Yield: 28.5 g (97.1 % calculated on the basis of the weight of meloxicam potassium salt monohydrate as starting compound)

Melting point: 246-248 °C

Elemental analysis (C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> (351,4)

Calculated	C:47.85	H:3.73	N:11.96	S:18.25
Measured	C:47.80	H:3.82	N:11.87	S:18.20

Purity (HPLC): 99.8 %.

### Example 3

4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide potassium salt monohydrate (compound of the Formula (I))

One proceeds according to Example 1 with the difference that instead of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methylester [compound of the Formula (III), wherein R is methyl], 36.83 g (130 mmol) 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid ethylester [compound of the Formula (III), wherein R is ethyl] are used.

Yield: 46.9 g (88.5 % calculated on the basis of the weight of the starting compound 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methylester of the Formula (III)).

Content (on the basis of potassium content): 99.6 %

Water (Karl Fischer method): 4.7 %



Elemental analysis [ $C_{14}H_{12}KN_3O_4S_2 \cdot H_2O$  (407,5)]

Calculated	C:41.26	H:3.46	N:10.31	S:15.74
Measured	C:41.22	H:3.38	N:10.25	S:15.69

Purity (HPLC): 99.8 % .

#### Example 4

Meloxicam polymorf I form

One proceeds according to Example 2 with the only difference that the solution of the potassium salt is treated with 6.0 ml 96% acetic acid instead of hydrochloric acid.

Yield: 29.0 g (98.5 % calculated on the basis of the amount of meloxicam potassium salt monohydrate of the Formula (I) used as starting compound).

Melting point: 246-248 °C

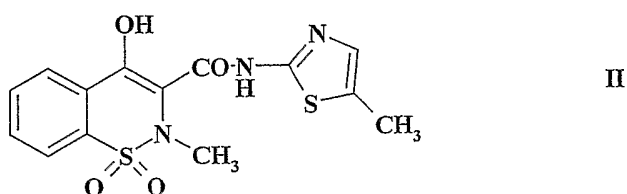
Elemental analysis ( $C_{14}H_{13}N_3O_4S_2$  (351,4):

Calculated	C:47.85	H:3.73	N:11.96	S:18.25
Measured	C:47.89	H:3.68	N:11.91	S:18.29

Purity (HPLC) 99.8 % .

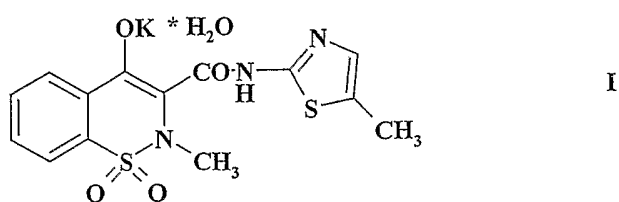
What we claim is,

1. Process for the preparation of 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam) of the Formula (II)



of high purity, which comprises

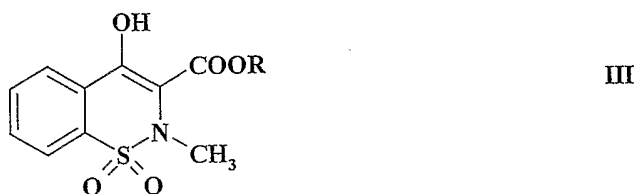
- a. dissolving meloxicam potassium salt monohydrate of the Formula (I)



in water or in the mixture of water and an organic solvent, removing the insoluble impurities and treating the resulting solution with an organic or inorganic acid, and crystallizing meloxicam; or

(b) transforming meloxicam raw product into crystalline meloxicam potassium salt monohydrate of the Formula (I), dissolving said meloxicam potassium salt monohydrate of the Formula (I) in water or in a mixture of water and an organic solvent, removing the insoluble impurities and treating the dissolved potassium salt of meloxicam with an organic or inorganic acid, followed by crystallization meloxicam of the Formula (II); or

(c) reacting a compound of the general Formula (III)



wherein R is methyl, ethyl or isopropyl with 2-amino-5-methyl-thiazole of the Formula (IV)



transforming the resulting meloxicam of the Formula (II) into its potassium salt, separating the insoluble impurities from aqueous or aqueous-organic solution of said meloxicam potassium salt,

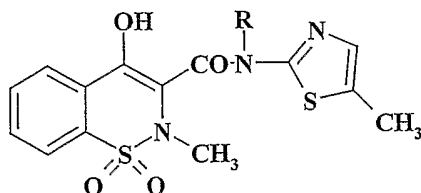
treating said solution with an organic or inorganic acid and crystallizing meloxicam.

2. Process according to variants a), b) and c) of claim 1, characterized in that meloxicam potassium salt monohydrate of the Formula (I) is prepared by reacting meloxicam of the Formula (II) with potassium hydroxide or potassium carbonate dissolved in water or in the mixture of water and an organic solvent and if desired, crystallizing the meloxicam potassium salt monohydrate of the compound of the Formula (I) thus formed.
3. Process for the preparation of meloxicam potassium salt monohydrate of the Formula (I), which comprises reacting meloxicam of the Formula (II) with potassium hydroxide or potassium carbonate dissolved in water or in the mixture of water and an organic solvent and if desired, crystallizing the meloxicam potassium salt monohydrate of the Formula (I) thus formed.
4. Process according to claim 2, characterized in that the molar amount of potassium hydroxide or potassium carbonate is 1-10 molar equivalent, preferably 4-5 molar equivalent of the molar amount of meloxicam.

5. Process according to claim 1, characterized in that as organic solvent, an alcohol containing 1-4 carbon atoms, for example, methanol, ethanol or isopropanol, preferably ethanol is used.
6. Process according to variants a), b) or c) of claim 1, characterized in that the acidic treatment of the solution of meloxicam potassium salt in water or in a mixture of water and an organic solvent is carried out by mixing said solution with an organic or inorganic acid, for example, sulphuric acid, hydrochloric acid, phosphoric acid, tartaric acid, acetic acid, preferably, with acetic acid or hydrochloric acid.
7. Process according to claim 6, characterized in that the treatment with an acid is continued until pH 3 to 6, preferably until pH 6.
8. 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam) of the Formula (II) essentially free of 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V), wherein the R alkyl group of the Formula (V) is methyl, ethyl or isopropyl.
9. Meloxicam potassium salt monohydrate of the Formula (I).
10. Meloxicam potassium salt monohydrate of the Formula (I) essentially free of 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of

the Formula (V), wherein alkyl (Group R in the Formula (V)) is methyl, ethyl or isopropyl.

11. Pharmaceutical preparations comprising meloxicam potassium salt monohydrate of the Formula (I) according to claim 9 and one or more pharmaceutically acceptable vehicle or auxiliary agent.
12. Pharmaceutical preparations comprising high purity meloxicam of the Formula (II) according to claim 8 and one or more pharmaceutically acceptable vehicle or auxiliary agent.
13. 4-hydroxy-2-methyl-N-alkyl-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the Formula (V)



V

wherein alkyl (the R group in the Formula (V)) is methyl, ethyl or isopropyl.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2005/000136

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/12 A61K31/427 A61P29/00

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 A61K A61P

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, PAJ, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 002 482 A (DR. KARL THOMAE) 27 June 1979 (1979-06-27) cited in the application	8,12
Y	claims; example 1 -----	13
X	US 2003/109701 A1 (COPPI ET. AL.) 12 June 2003 (2003-06-12) cited in the application	8,12
	claims; examples -----	
A	EP 0 945 134 A (BOEHRINGER INGELHEIM) 29 September 1999 (1999-09-29) claims; examples ----- -/-	1-13

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

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\*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

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Date of the actual completion of the international search

10 May 2006

Date of mailing of the international search report

29/05/2006

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/HU2005/000136

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. S. LAZER ET. AL.: "Effect of Structural Modification of Enol-Carboxamide Type Nonsteroidal Antiinflammatory Drugs on COX-2/COX-1 Selectivity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, 1997, pages 980-989, XP002379086	1-12
Y	tables 1,2	13
E	----- EP 1 645 559 A (A.M.S.A. ANOMIA MATERIE SINTETICHE E AFFINI) 12 April 2006 (2006-04-12) claims; examples -----	1-13



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/HU2005/000136

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0002482	A	27-06-1979	AT 365589 B	25-01-1982
			AT 863078 A	15-06-1981
			AU 522538 B2	10-06-1982
			AU 4253078 A	21-06-1979
			BG 33286 A3	14-01-1983
			BG 60475 B2	28-04-1995
			CA 1102802 A1	09-06-1981
			CS 9104100 A3	17-06-1992
			CS 202515 B2	30-01-1981
			DD 140354 A5	27-02-1980
			DE 2756113 A1	21-06-1979
			DK 562078 A	17-06-1979
			ES 475677 A1	16-04-1979
			FI 783867 A	17-06-1979
			GR 65626 A1	15-10-1980
			HU 175846 B	28-10-1980
			IE 48042 B1	05-09-1984
			IL 56206 A	30-04-1982
			JP 1474086 C	27-12-1988
			JP 54092976 A	23-07-1979
			JP 63024997 B	23-05-1988
			LU 88557 A9	21-03-1995
			MX 9202949 A1	01-07-1992
			NL 940002 I1	16-03-1994
			NO 784231 A	19-06-1979
			NZ 189186 A	16-03-1981
			PL 211753 A1	13-08-1979
			PT 68915 A	01-01-1979
			RO 75792 A1	28-02-1981
			SU 841588 A3	23-06-1981
			US 4233299 A	11-11-1980
			YU 294978 A1	31-10-1982
US 2003109701	A1	12-06-2003	AT 318813 T	15-03-2006
			AU 2002350753 A1	24-07-2003
			CA 2470164 A1	17-07-2003
			EP 1462451 A1	29-09-2004
			WO 03057692 A1	17-07-2003
			ES 2223209 A1	16-02-2005
			HU 0402536 A2	28-04-2005
			JP 2005516030 T	02-06-2005
			MX PA04005338 A	31-03-2005
			NZ 533521 A	29-07-2005
EP 0945134	A	29-09-1999	ZA 200404475 A	07-06-2005
			AT 254920 T	15-12-2003
			AU 762322 B2	26-06-2003
			AU 3417199 A	18-10-1999
			BR 9909192 A	05-12-2000
			CA 2326517 A1	07-10-1999
			CN 1295478 A	16-05-2001
			DE 59907871 D1	08-01-2004
			DK 1083902 T3	29-03-2004
			WO 9949867 A1	07-10-1999
			ES 2212547 T3	16-07-2004
			HK 1034183 A1	21-01-2005
			HU 0101246 A2	29-05-2002
			JP 3639532 B2	20-04-2005

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/HU2005/000136

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0945134	A	JP 2002509886 T NO 20004823 A NZ 507382 A PL 342988 A1 PT 1083902 T TR 200002786 T2 ZA 200004178 A	02-04-2002 22-11-2000 29-08-2003 16-07-2001 30-04-2004 22-01-2001 20-02-2002
EP 1645559	A	12-04-2006	NONE