CRYSTALLINE POLYMORPH OF URIC ACID

Field of the invention

The present invention relates to the pharmaceutical and biomedical field and the delivery of active agents, specifically of a new delivery form of uric acid as a crystalline polymorph, and the obtention and purification thereof.

Background art

The potential therapeutical medical effect of uric acid against neurological disease has been extensively disclosed in the art.

Uric acid is a powerful antioxidant agent that blocks the reaction between superoxide anion and nitric oxide, which would damage cells by nitrosylating tyrosine residues of proteins. The plasma concentration of uric acid is almost 10 times higher than other antioxidant substances, such as vitamins C or E, and its antioxidant capacity is also higher.

Beyond these antioxidant effects, uric acid acts on transcription factors as therapeutic targets, among others activating the nuclear factor erythroid 2-related factor2 / heme oxygenase 1 (Nrf2 / HO-1) pathway or having a positive regulation in the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).

It is known that the administration of uric acid before an occlusion of the middle cerebral artery or after reperfusion significantly reduces resulting cerebral infarction, suppresses accumulation of Reactive Oxygen Species (ROS) and decreases lipid peroxidation. Further, the administration of uric acid has been shown neuroprotective in a thromboembolic model of focal cerebral ischemia. The relationship between higher uric acid levels in the blood at the time of a cerebral infarction and a lower neurological severity is also well known in the art.

Patent application WO 2010112113 A1 discloses the combined use of uric acid and citicoline for the treatment of stroke, demonstrating an effect in ischemic model cell cultures.

WO 2018206826 A1 demonstrates the efficacy of uric acid in the treatment of cerebral infarction in patients treated by mechanical thrombectomy.

It is also noted, however, that the use of uric acid as an eventual therapeutical agent involves a serial of preventions that need to be watched out. Namely, uric acid has limited solubility in organic fluids with tendency to crystallize, which complicates its medical use and the incorporation of same in pharmaceutical formulations. Besides, the presence of excess levels of uric acid in blood is usually the cause of the appearance of kidney stones and gout processes due to the accumulation of monosodium urate crystals; at this respect, WO 2015181412 A1 teaches about the use of theobromine for the prevention of these related clinical damages.

The formation of crystals of uric acid in organic fluids has been reported in a serial of publications, always referring to undesired crystallization at an excess of compound. These crystals are prejudicial because they harm the organs where they show up and have by themselves no therapeutical effect. For example, RU 2260801 C1 reports the formation of atypical crystals of uric acid of different forms in combination with cholesterol crystals at purine exchange disorders.

To overcome these difficulties, transport systems or platforms by nanomaterials and controlled release scaffolds have been developed as an alternative to the use of free uric acid as a therapeutical agent. These delivery agents facilitate solubilization and stability, allowing better logistics in the clinical setting and a suitable administration into the body in therapeutically relevant doses. At this respect, EP 4173616 A discloses the encapsulation of uric acid in liposomes as a transport-controlled release platform for an effective administration with high yields in therapeutical doses for the treatment of stroke, without exceeding pathological limits of free compound in the blood.

A disposal of uric acid able to be delivered at better bioavailability still needs to be achieved. With this aim, the obtention and characterization of crystals may offer improved pharmaceutical features that enable an effective dosage of the compound for medical uses. However, the isolation of uric acid crystals from organic sources raises problems on their purity and the presence of unwanted side compounds. The withdrawal of contaminations can be difficult and hazardous, never ensuring a complete absence of same in the final product, let apart the dependency on the disposal of the organic source.

In this sense, US 2302204 A discloses the recovery and purification of uric acid from bird guano to obtain a crude precipitate that is crystallized in the sodium urate form and then further recrystallize redissolving said sodium urate crystals in a sodium hydroxide solution, charcoal treatment and addition of sulphuric acid.

The patent US 4,007,186 isolates uric acid from poultry feces to obtain ultra-pure crystals of 99.9% purity by a recrystallization step with perchloric acid, capable of serving as "reference standard".

The obtention of uric acid from organic sources raises additional needs con controlling eventual organic contaminations that make this source not appropriate for pharmaceutical uses, among other concerns.

On the search of synthetic pathways to avoid these issues, CN 113912606 A discloses a method for the obtention of sodium urate crystals and their use in the treatment of gout. The method comprises dissolving uric acid and potassium hydroxide in water and reacting the solution with calcium chloride dihydrate, potassium chloride and sodium chloride, followed by ulterior drying of the obtained powder. The PXRD spectrum of the sodium salt crystals show one strong peak at about 28.6 and two additional weak peaks at about 34.2 and 19.4 ± 0.2° 2θ.

The problem of the art is to obtain a reliable synthetic process to obtain crystals of uric acid. The solution of the present invention is a process starting from ethyl (6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate that leads to pure uric acid crystals capable for therapeutical use.

Description of the invention

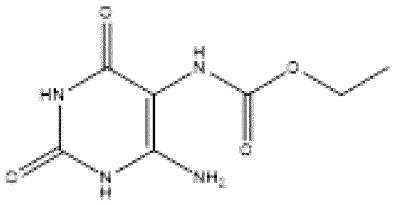
The present invention is a crystalline polymorph of uric acid (UA) with a powder X-ray diffraction pattern (PXRD) comprising at least three 2Θ angle values selected from 13.48 ± 0.2, 17.99 ± 0.2, 22.96 ± 0.2, 27,90 ± 0.2, and 28.70 ± 0.2.

In a preferable aspect, the crystalline polymorph has a PXRD comprising at least six 2Θ angle values selected from 13.48 ± 0.2, 15.69 ± 0.2, 17.99 ± 0.2, 22.96 ± 0.2, 27.17 ± 0.2, 27,90 ± 0.2, 28.70 ± 0.2, and 31.08 ± 0.2. In an even more preferable aspect, the crystalline polymorph contains all said 2Θ angle values.

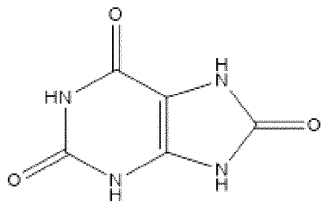
In another aspect, the invention is a crystalline polymorph of UA with a Raman spectrum comprising at least three peaks selected from 471 ± 2, 626 ± 2, 997 ± 2, 1038 ± 2, 1286 ± 2, 1406 ± 2, 1650 ± 2 cm^{-1}. In a preferable aspect the Raman spectrum comprises at least six peaks selected from at 471 ± 2, 502 ± 2, 562 ± 2, 626 ± 2, 99 ± 27, 1038 ± 2, 1120 ± 2, 1233 ± 2, 1286 ± 2, 1355 ± 2, 1406 ± 2, 1447 ± 2, 1498 ± 2, 1593 ± 2, 1650 ± 2, and 1662 ± 2 cm^{-1}. In an even more preferable aspect, the Raman spectrum comprises all these peaks.

In another aspect, the invention is a crystalline polymorph of UA with a ^{1}H-NMR spectrum of the crystalline polymorph of UA in DMSO showed peaks at: 10.6 ppm (s, 1H), 10.7 ppm (s, 1H), 11.4 ppm (s brought, 1 H), 11.8 ppm (s brought, 1 H).

As used herein, the internal code “SOL21280” is the compound Ethyl (6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate, of formula



As used herein, crude UA refers to the dry product obtained after the process of synthesis of the compound, single recrystallized UA refers to the dry product obtained after a recrystallization treatment with charcoal as explained in the provided Examples.



As used herein, inner temperature “Ti” is the internal temperature of the reaction vessel.

As used herein, a “jacket temperature of Tout” is defined as the jacket temperature of a vessel.

As used herein, "purified water" is clear and colorless liquid water according to Ph. Eur. 04/2018:0008.

Another aspect of the present invention is a process for the obtention of a UA crystal from ethyl (6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate (SOL21280), comprising:

a) Dried SOL21280 of purity ≥ 96 % area, with a water content of ≤ 5.0% w/w with respect to the total weight of the sample, is diluted in a volume of alcohol, preferably ethanol, more preferably 6 to 12 vol of ethanol. In a preferable aspect, the solution is then concentrated to about a half of said volume.

b) Adding an alcoholic ethoxide salt solution, preferably ethanolic, preferably sodium ethoxide ($NaOCH_2CH_3$), more preferably 6 to 12 eq $NaOCH_2CH_3$, even more preferably 7 eq, to obtain a suspension, and stirring for at least 15 hours, preferably 19 to 42 hours, even more preferably 20 hours. In a preferable aspect, the reaction takes place heating the vessel to maximal jacket temperature of Tout = 115°C or at about a Ti of 75 to 88°C. In a preferable aspect, the reaction takes place at reflux. In another preferable aspect, the suspension is thereafter concentrated, preferably distilling off 7.0 to 7.7 vol of the alcoholic solvent.

c) Adding water, preferably 9 to 12 vol, and stirring at a jacket temperature of Tout about 40ºC for at least 30 min, preferably 90 to 105 min.

d) Adding a strong acid until a pH value ≤ 1.5, preferably with HCl, and stirring for at least 1.5 h, preferably between 1,5 and 20 hours, for a final pH < 2, preferably at a Ti of between 50ºC and 20ºC, for the obtention of a precipitate;

e) Filtrating an optionally washing with a water and ethanol said precipitate, and thermal drying to obtain a dry second cake corresponding to UA crude.

f) Charcoal treatment for the obtention of a single recrystallized UA. In a preferable aspect, said charcoal treatment comprises adding charcoal to a clear solution of crude UA and stirring at a Ti = 90 to 100ºC for 30 to 45 min, wherein said clear solution is obtained by diluting the crude UA of the previous step in purified water, preferably 12 to 18 vol water, adding a strong base solution, preferably NaOH, more preferably between 2.5 and 3.4 eq NaOH, and heating to an inner temperature of Ti = 90 to 100°C gave a clear solution, more preferably 90ºC, within at least 1 hour, preferably from 1 to 2.5 hours. In an aspect of the invention, 0.5 to 0.8 wt% of charcoal is added. The charcoal is filtered off and the filtrate collected as a clear, slightly colored solution. A strong acid is then added to the filtrate until a pH value ≤ 1.5, preferably HCl, and stirring for at least 3 hours, preferably from 3 to 20 hours, for a final pH < 2, preferably at a Ti of about 20ºC, for the obtention of a precipitate. The precipitate is filtered off and optionally washed and dried for the obtention of a dry precipitate of single recrystallized UA.

The single re-crystallized product is slightly less soluble than the crude product, probably due to a higher purity. Charcoal treatment and further recrystallization serve the purpose of decolorization and removal of inorganic content.

g) Optionally, recrystallization of the single recrystallized UA obtained in the previous step by any process known by the art.

The content of water of the final crystals measured after the Karl-Fischer titration resulted in about 0.19%.

Another aspect is a pharmaceutical composition comprising at least one crystal of the single recrystallized UA obtained by this process, and a pharmaceutically acceptable excipient. A more preferable aspect is a pharmaceutical composition comprising at least one crystal of the crystalline polymorph of the invention, and a pharmaceutically acceptable excipient. In a further aspect, the pharmaceutical composition is for oral, intradermal, intravenous, subcutaneous, or intramuscular administration, even more preferably intravenously, most preferably in the form of injection.

In a preferred aspect, a UA dose to be administrated is between 10 and 20 mg / kg patient, 16 mg / kg of patient. In a more preferred aspect, an administered dose is between 500 and 2000 mg UA, between 500 and 1000 mg, or most preferably 1000 mg UA.

In another aspect, the crystalline polymorph or the pharmaceutical composition is used in the prevention or treatment of a disease, preferably a cerebrovascular disease, more preferably of stroke. Or in another aspect, the use of the crystalline polymorph or the pharmaceutical composition in the preparation of a medicament for the prevention or treatment of a disease, preferably a cerebrovascular disease, more preferably of stroke.

A further aspect of the invention is a method of treatment of a cerebrovascular disease comprising administering an effective amount of UA in a form comprising at least one crystal of the crystalline polymorph to a subject in need thereof.

As used herein, "cerebrovascular disease" refers to any pathology or clinical disorder in an animal, preferably a human, that implies that a part of the brain is left without blood irrigation.

Brief description of the Figures

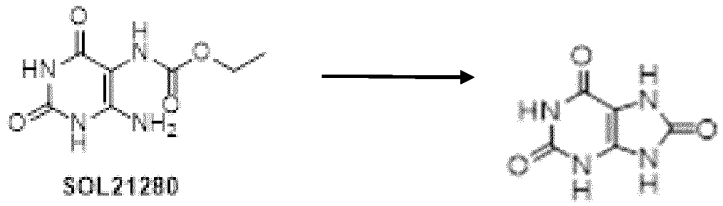
Figure 1: PXRD was carried out in a transmission geometry using a Stoe Stadi P equipped with a Mythen 1K Detector. The sample was measured between two acetate foils with no preparation other than the application of slight pressure to get a flat surface. The sample was rotated during the measurement. CuKa1 radiation (40 kV, 40 mA) was used to irradiate the sample, and the scan range was 1.5 to 50.5°2theta with a step size of 0.02°2theta. Reflection positions are generally accurate to within +/-0.1-0.2°2theta.

Figure 2: The Raman spectrum was recorded with a Bruker MultiRAM FT-Raman spectrometer, which is operated with a Nd:YAG laser (1064 nm wavelength) and a liquid-nitrogen cooled germanium detector. A nominal laser power of 100 mW was used to accumulate 64 scans with a resolution of 2 cm^{-1}. Peak positions are generally accurate to within +/- 2 cm^{-1}

Figure 3: ^{1}H-NMR spectrum of the UA crystals in DMSO, ppm. 600 MHz, number of scans: 8, temperature: 298 K, 10.6 ppm (s, 1H), 10.7 ppm (s, 1H), 11.4 ppm (s brought, 1 H), 11.8 ppm (s brought, 1 H), 3.34 (H2O), 2.51 (DMSO), 0.00 (TMS)

Examples

Example 1: Method of obtention of UA from SOL21280.



A 10 L double jacketed glass vessel was rendered inert by three times evacuation to 25 KPa and backfilling with nitrogen. 3.0 L ethanol (10 vol) was added into vessel. The jacket temperature was set to Tout =25°C.

Starting 300 g SOL21280 (98.2% w/w by H NMR assay, 99.5% area by HPLC,0.7% w/w water content) was added as a solid. Further 0.3 L Ethanol (2 vol) were added.

At a jacket temperature of Tout = 80°C and a pressure of p = 40 to 50 KPa, 2.02 L (6.7 vol) of solvent were distilled off (azeotropic drying). The vessel was pressurized with nitrogen and 222 ml ethanol (1.1 vol) of ethanol were added. The suspension was heated to reflux with a jacket temperature of Tout(max) = 106°C.

7.0 eq of 20% sodium ethoxide solution was added within 65 minutes at reflux at a maximum jacket temperature of Tout(max) = 106°C and an inner temperature of Ti = 78° to 86°C. After addition of 27% of the solution, the reaction mixture turned into a viscous suspension and mixing got ineffective. Addition was continued. Towards the end of the addition, a steerable suspension was obtained.

The reaction mixture was stirred at reflux overnight for 20 h.

An In-Process Control (IPC) was collected at this stage to ascertain a ≥ 95% conversion as analyzed by HPLC.

At a jacket temperature of Tout = 80°C and a pressure of p = 40 to 50 KPa, 2.26 L (7.5 vol) of solvent were distilled off.

2.7 L (9.0 vol) of water were added at a jacket temperature of Tout = 80°C and an inner temperature of Ti = 70° to 58°C within 17 minutes. The resulting suspension heated to an inner temperature of Ti = 70°C within 25 minutes and kept at this temperature for 17 minutes, after which, the inner temperature was reduced to Ti = 49°C within 36 min.

At an inner temperature of Ti = 59° to 57°C, 1.67 L (7.2 eq) 20% HCl was added (4.0 vol) within 33 min to obtain a pH = 0.2.

The obtained suspension was cooled to an inner temperature Ti = 20°C overnight. The pH is checked to be pH = 1.0.

The product was filtered off to remove solids over a filter nutsche.

The vessel and the filter cake were rinsed with water twice (2 x 1.2 L, 2 x 3 vol), followed by ethanol twice (2 x 1.2 L, 2 x 3 vol). The filter cake was pre-dried by perching with air for 30 min. The product was then dried on a rotary evaporator in vacuum at a final pressure < 2 KPa and a maximal water bath temperature of 55°C until constant weight (+/- 1.0 g within 30 min drying).

201.6 g product were obtained (86% yield, crude, not corrected). The product had a HPLC purity of 99.8% area and a content by H NMR assay of 92% w/w.

The dried crude product was analyzed for HPLC purity and HPLC assay.

Charcoal treatment and single recrystallization:

A stock solution of 12 vol water plus 0.01 wt. 50% NaOH-solution was prepared in a stirring tank, resulting a 0.01 N NaOH-solution.

In a conical flask, 35.0 g obtained crude UA (corresponds to 32.2 g corrected for assay) were added to 451 ml (14 vol) water.

46.0 g (3.0 eq) 50% NaOH-solution was added to obtain a brown suspension.

The suspension was heated to an inner temperature of Ti = 90°C to obtain a clear red-brown solution.

0.5 wt. charcoal (Norit Supra A) was added to the clear solution at Ti = 91°C. The obtained suspension was stirred at Ti = 90°C for 45 min to create a slurry.

The charcoal was filtered off using a preheated (90°C) P3 glass sinter nutsch loaded with Hyflo (11 g0.34 wt). The filter nutsche was rinsed with preheated (60°C) 3 x 96 ml 0.01N NaOH-soln. (3 x 3 vol).

The clear, slightly yellow filtrate cooled to 20°C during filtration and further handling. The solution was heated to an inner Temperature of Ti = 47°C again and 85 ml (2.64 vol) 20% HCl solution was added within 28 minutes at Ti = 47°C to obtain a pH = 1.0. The pH was re-checked after 15 min to be stable (pH = 1.1). The product precipitated during the addition.

The suspension was cooled to ambient temperature overnight.

The product was filtered off over a glass sintered filter nutsche (P 3) so that no product remained in the flask. The flask and the filter cake were rinsed with water three times (3 x 32 ml, 3 x 1 vol) and ethanol twice (2 x 32 ml, 2 x 1 vol).

The product was dried on a rotary evaporator in vacuum at a final pressure < 2 KPa and a maximum water bath temperature of 50°C. 30.1 g recrystallized UA was obtained (88%).

The dried material is a recrystallized UA that was stored in a glass flasks.

The obtained recrystallized UA is a white to yellow solid, and characterization by HPLC purity > 99.95% area.

Example 2: Obtention of single recrystallized crystals of UA from SOL21280.

The process of obtention of UA of Example 1 was screened for different amounts of base sodium ethoxide (4 to 12 eq) and volume of ethanol as solvent (6 to 12 vol) screened (**¡Error! No se encuentra el origen de la referencia.**). Also, the mode of addition was changed from adding the base to the suspension of starting SOL21280 in ethanol (standard addition) at reflux and addition of the solid SOL21280 to a mixture of the solidum ethoxide solution and ethanol at 60°C (inverse addition).

IPC: After about 19 to 24 hours reaction time a conversion to crude UA of ≥95% area could be obtained. With said conversion of 95%, the isolated product contained only ≤ 0.9% area residual starting material SOL21280 after work-up. This level of remaining SOL21280 was reproducibly removed in the following charcoal treatment and single

recrystallization to be undetectable. One reaction already worked-up with a conversion of 93%, residual SOL21280 was 0.8% area in the crude UA product and completely removed at the charcoal treatment and final crystallization. In terms of purity of the final UA crystal product, conversions to crude UA < 93% would be acceptable, preferably starting with SOL21280 with a HPLC purity of ≥96.0% a/a seemed to give the final crystals of UA with a HPLC purity within specifications, based on the documented examples. However, due to the stronger absorption of UA compared to the carbamate, isolated yield will drop with lower conversion. Specifying a minimum conversion to crude UA of ≥95% area is more for economic reasons than for quality reasons. On the other side, reaction with long reaction time (about 40 h) tend to a lower chemical yield. Therefore, in terms of yield, it would be better to reduce the specification of conversion to ≥93% for reaction times >28 hours to avoid refluxing for a second night (Table 2).

Table 1: Summary of isolated purities and yields of the crude UA

Amount SOL21280	Pre-treatment/ Additives	Vol EtOH (reaction)	Eq NaOEt	Vol. NaOEt-solution	Total volume	Reaction time	IPC analytic by HPLC		
							Conv.	% area Crude UA	%area SOL21280
6.0 g	--	6 vol	7.0 eq	12.2 vol	18.2 vol	21 h	95.9%	86.0%	3.7%
6.0 g	--	6 vol	12.0 eq	18.7 vol	24.7 vol	21 h	96.4%	89.7%	3.3%
25 g	--	6 vol	8.5 vol	14.8 vol	20.8 vol	16.5 h	94.6%	91.0%	5.2%
29 g	1 eq water added	6 vol	10 eq	17.4 vol	23.4 vol	15 h	12.9%	11.4%	77.4%
29 g	2 eq water added	6 vol	10 eq	17.4 vol	23.4 vol	15 h	10.7%	9.6%	80-0%
6.5 g	0.25 eq water added	6 vol	10 eq	17.4 vol	23.4 vol	24 h 40 h	73.4% 95.6%	58.7% 76.0%	20.9% 3.5%
7.0 g	--	12 vol	10 eq	17.4 vol	23.4 vol	41.5 h	97.4%	81.1%	2.2%
7.0 g	--	6 vol	10 eq	17.4 vol	23.4 vol	41.5 h	96.7%	67.8%	2.4%
10.0 g	Inverse addition	13 vol	6.0 eq	10.5 vol	23.5 vol	22 h	100%	89.9%	0.0%
2.0 g	Inverse addition	17 vol	4.0 eq	7.0 vol	24.0 vol	21 h	90.0%	79.4%	8.6%
10.0 g	--	12 vol	7.0 eq	12.2 vol	24.2 vol	22 h	95.1%	85.7%	4.4%
10.0 g	Azeotropic dried	12 vol	7.0 eq	12.2 vol	24.2 vol	22 h	98.7%	89.3%	1.2%
10.0 g	--	6 vol	10 eq	17.4 vol	23.4 vol	39 h	49.7%	44.5%	45.0%
10.0 g	Azeotropic dried	6 vol	10 eq	17.4 vol	23.4 vol	15 h	93.2%	88.4%	6.5%
45 g	Azeotropic dried	6 vol	7 eq	12.2 vol	24.2 vol	15 h			

Table 2: Summary of isolated purities and yields of the crude and single recrystallized UA

Amount SOL21280	Pre-treatment/ Additives	Vol EtOH reaction	Eq NaOEt	React. time	IPC analytic by HPLC			Crude yield	Crude purity	Single Crystal purity
					Conv.	%area Crude UA	%area SOL 21280			
25 g	--	6 vol	8.5 vol	16.5 h	94.6%	91.0%	5.2%	17.4 g (90%)	98.9% (SOL21280: 0.62%)	99.87%
10 g	--	12 vol	7.0 eq	22 h	95.1%	85.7%	4.4%	5.3 g (67%)	98.4% (SOL21280: <0.05%)	99.80%
10 g	Azeotropic dried	12 vol	7.0 eq	22 h	98.7%	89.3%	1.2%	5.6 g (71%)	98.9% (SOL21280: 0.07%)	99.84%
10 g	Azeotropic dried	6 vol	10 eq	15 h	93.2%	88.4%	6.5%	6.10 g (77%)	98.6% (SOL21280: 0.77%)	99.95%
45 g	Azeotropic dried	6 vol	7 eq	24 h	95.5%	93.9%	4.4%	30.7 g (68%)	99.0% (SOL21280: 0.93%)	100%
300 g	Azeotropic dried	6 vol	7 eq	19 h	95.3%	89.1	4.3%	202 g (86%)	99.0% (SOL21280: 0.72%)	100% 99.94%

Example 3: Process parameters of the charcoal treatment

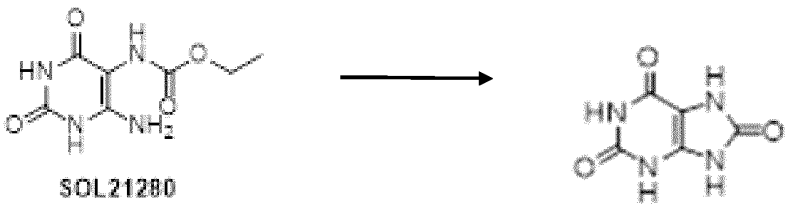
During the process development, different parameters of the charcoal treatment were screened.

The solubility depending on amount of base was evaluated (Table 3). This screening showed that between 2.5 and 3.0 eq of base are necessary to dissolve all crude UA at 90°C. In order to have a lower salt content for precipitation and therewith less risk of a high salt content in the product, only a maximum of 3.0 eq of base should be used.
This screening showed that 12 vol of water were sufficient to dissolve the crude UA with ≥ 3.0 eq sodium hydroxide. In some experiments, the solution remained cloudy using 12 vol water. In order to obtain more reproducible results, the standard amount of water was increased to 14 vol water.

Table 3: Solubility of crude UA in water with different equivalents of bases

	1.5 eq NaOH	2.0 eq NaOH	2.5 eq NaOH	3.0 eq NaOH	3.5 eq NaOH	4.0 eq NaOH
12 vol water, Tout = 100°C	thick susp.	thick susp.	Susp.	Solution	Solution	solution
12 vol water, Tout = 55°C	thick susp.	thick susp.	--	Fine susp.	Fine susp.	Susp.
14 vol water, Tout = 55°C	--	--	--	Fine susp.	Fine susp.	Susp.

Example 4: Method of obtention of single crystallized UA from SOL21280.



Based on the guidelines disclosed in Example 1 as a base, a screening of reaction conditions was performed. The results are shown in **¡Error! No se encuentra el origen de la referencia.**, below. In general, the reaction conditions as disclosed seems to be quite robust. Longer slurry times at the charcoal treatment (up to 90 min), increase of base to 3.4 eq NaOH

or variation of the amount of water (12 to 16 vol) does have big impact on the purification effect. Increasing the amount of charcoal seems to have a slightly effect on the recovery (0.5 wt 85% to 88% recovery, 0.7 wt. 84%, 0.8 wt. 82%).

Table 4: Summary of isolated purities and yields of the single recrystallized UA:

Amount SOL21280	HPLC purity SOL21280	KF Fresh	Pre-treatment/ Additives	Vol EtOH (reaction)	Eq NaOEt	Crude yield	Crude purity	Recovery charcoal	Single Crystal Purity
7.0 g	98.31%	n.d.	--	6 vol	10 eq	9.8g* (>100%)		1.41 g (26%)	99.90%
27.0g	98.74%	1.9%	--	6 vol	10 eq		99.30%	11.52 (74%)	99.32% - 100%
25 g	99.02%	2.9%	--	6 vol	8.5 eq	17.4 g (90%)	98.9% (SOL21280: 0.62%)	13.4 g (84%)	99.87% - 100%
10 g	98.85%	1.8%	--	12 vol	7.0 eq	5.3 g (67%)	98.4% (SOL21280: <0.05%)	3.9 g (85%)	99.80% - 100%
10 g	98.85%	1.8%	Azeotropic dried	12 vol	7.0 eq	5.6 g (71%)	98.9% (SOL21280: 0.07%)	4.2 g (86%)	99.84% - 100%
10 g	99.75%	1.3%	Azeotropic dried	6 vol	10 eq	6.10 g (77%)	98.6% (SOL21280: 0.77%)	4.7 g (86%)	99.95% - 100%
45 g			Azeotropic dried	6 vol	7 eq	30.7 g (68%)	99.0% (SOL21280: 0.93%)	4.3 g (91%)	100%
300 g			Azeotropic dried	6 vol	7 eq	202 g (86%)	99.0% (SOL21280: 0.72%)	30.7 g (93%)	100%
								128 g (96%)	99.94% - 100%

KF Fresh corresponds to the content of water measured after the measured after the Karl-Fischer titration.

Comments: * contains salts, precipitation of crude without addition of water.

Example 5: HPLC method used for assessing all stages of the process

Table 5: Instrument	**Model**
HPLC	Agilent 1200 series, quaternary with DAD detector or equivalent
HPLC Column	YMC-Pack ODS-AQ, 3.0 µ, 250 x 4.6, 120A Part No. AQ12S03-2546WT

Mobile Phase A: Acetate buffer solution pH 4.7

Dissolve 1.0 g of Ammonium acetate in 1 L Milli-Q Water. Adjust the pH to 4.7 with Acetic acid and stir well.

Mobile Phase B: Acetonitrile 100%.

Parameter	**Settings**		
Gradient	Time [min]	Eluent A [%]	Eluent B [%]
	0.0	100.0	0.0
	14.0	100.0	0.0
	24.0	80.0	20.0
	29.0	50.0	50.0
	31.0	50.0	50.0
	31.1	100.0	0.0
	45	100.0	0.0
Flow	0.5 mL/min		
Temperature	Column: 30 °C Auto-sampler: 20 °C		
Injection volume:	10 µL		
Detection:	UV (λ = 275 nm) Bandwidth: 4 nm		
Acquisition time	45 min		

The HPLC purities of the starting material SOL212180, and the crude and single crystallized UA product after charcoal treatment in different experiments performed similar as the Examples above is shown in the following Table 5:

SOL21280	Crude UA	Single Crystallized UA
97.6% 97.9%	n.d.	100%
98.2% 98.4%	n.d.	
98.8%	99.06%	100%
99.8%	98.98%	100%
99.65%	98.97%	100%
100%		
99.4%	98.95%	99.87%

The Table is read as follows: Each line represents the sequence of a synthesis of one batch of final product, e.g. in the last line, the starting material **SOL21280** had a HPLC purity of 99.38% a/a. This material was used to obtain the crude UA with a HPLC purity of 98.95% area, which gave a single crystalized UA with a HPLC purity of 99.87% a/a.

CLAIMS

1. A crystalline polymorph of uric acid, characterized by a powder X-ray diffraction pattern comprising at least three 2Θ angle values selected from the group consisting of: 13.48 ± 0.2, 17.99 ± 0.2, 22.96 ± 0.2, 27,90 ± 0.2, and 28.70 ± 0.2.

2. The crystalline polymorph according to claim 1, characterized by a powder X-ray diffraction pattern comprising at least six 2Θ angle values selected from the group consisting of: 13.48 ± 0.2, 15.69 ± 0.2, 17.99 ± 0.2, 22.96 ± 0.2, 27.17 ± 0.2, 27,90 ± 0.2, 28.70 ± 0.2, and 31.08 ± 0.2.

3. A crystalline polymorph of uric acid, characterized by a Raman spectrum comprising at least three peaks at 471 ±2, 626 ±2, 997 ±2, 1038 ±2, 1286 ±2, 1406 ±2, 1650 ±2 cm^{-1}.

4. A crystalline polymorph of uric acid, characterized by an ^{1}H-NMR spectrum in DMSO comprising the following peaks: 10.6 (s, 1H), 10.7 (s, 1H), 11.4 (s brought, 1 H), and 11.8 ppm (s brought, 1 H).

5. Process for the obtention of the crystalline polymorph of Uric acid as defined in any one of claims 1 to 4, comprising:

    a) diluting ethyl (6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate of purity ≥ 96 % area with a water content of ≤ 3.0% w/w with respect to the total weight of material in an alcohol, in a vessel;
    b) adding an ethoxide salt and stirring for at least 19 hours at a Ti of about 75 to 88ºC, to obtain a suspension;
    c) concentrating the suspension obtained in the previous step, adding water and stirring at a jacket temperature of Tout about 40ºC for at least 90 min;
    d) adding a strong acid to a pH value < 1.5 and stirring for at least 1.5 h for a final pH < 2, to obtain a precipitate;
    e) filtration of the precipitate obtained in the previous step to obtain a dry cake of uric acid crude; and
    f) charcoal treatment for the obtention of a second precipitate of single recrystallized Uric acid;

6. The process according to claim 5, wherein said charcoal treatment comprises:
    - diluting the crude Uric acid obtained in step e) in purified water;
    - adding charcoal and stirring at a Ti = 90 to 100ºC for 30 to 45 min;

- adding up to 3 eq of a strong base solution until complete dissolution, and heating to an inner temperature of Ti = 90 to 100°C within at least 1 hour;
- filter off the charcoal and collecting the filtrate as a clear colored solution;
- adding a strong acid to said filtrate until a pH value ≤ 1.5 and stirring for at least 3 hours for the obtention of the precipitate.

7. The process according to claims 5 or 6, in which said strong base is NaOH.

8. The process according to any one of claims 5 to 7, in which said strong acid is HCl.

9. The process according to any one of claims 5 to 8, in which said alcohol is ethanol.

10. The process according to any one of claims 5 to 9, in which said ethoxide salt is sodium ethoxide.

11. A pharmaceutical composition comprising at least one crystal of the crystalline polymorph as defined in any one of claims 1 to 4, and a pharmaceutically acceptable excipient.

12. The pharmaceutical composition according to claim 11, wherein said composition is administered orally, intradermally, intravenously, subcutaneously, or intramuscularly.

13. The pharmaceutical composition according to claim 12, wherein said composition is administered intravenously.

14. The pharmaceutical composition according to claim 13, wherein said pharmaceutical composition is in the form of an injection.

15. The crystalline polymorph according to any one of claims 1 to 4, or the pharmaceutical composition according to any one of claims 11 to 14, for use in the prevention or treatment of a cerebrovascular disease.

16. The crystalline polymorph or the pharmaceutical composition for use according to claim 15, in which said cerebrovascular disease is stroke.