Scutellarin aglycone crystal forms and preparation method thereof

Abstract

Belonging to the field of pharmaceutical chemical engineering, the invention in particular relates to a variety of scutellarin aglycone crystal forms and a preparation method thereof. The invention also relates to application of the scutellarin aglycone crystal forms in preparation of drugs preventing and/or treating cardiovascular and cerebrovascular diseases, rheumatism arthritis, stroke sequelae and the like. The scutellarin aglycone crystal forms provided by the invention have good stability, and can overcome the poor oral absorption and low bioavailability problems of scutellarin.

Classifications

A61K31/352 Heterocyclic compounds having oxygen as the only ring hetero atom, e.g. fungichromin having six-membered rings with one oxygen as the only ring hetero atom condensed with carbocyclic rings, e.g. cannabinols, methantheline

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Worldwide applications

2014 • CN CN 2015 • US WO

Application CN201410764911.1A events

2014-12-15 • Application filed by 云南省药物研究所, 深圳市华力康生物医药有限公司

2014-12-15 • Priority to CN201410764911.1A

2015-05-06 • Publication of CN104592184A

2017-09-29 • Application granted

2017-09-29 • Publication of CN104592184B

Info: Patent citations (9), Non-patent citations (2), Cited by (6), Legal events, Similar documents, Priority and Related Applications

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Claims (45)

Hide Dependent

1. Scutellarein crystal form A, it is characterized in that described crystal form A is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 14.5 ± 0.2 °, 16.9 ± 0.2 °, 22.0 ± 0.2 °, 26.7 ± 0.2 ° and 27.4 ± 0.2 °.

2. the crystal form A of claim 1, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 11.2 ± 0.2 °, 13.8 ± 0.2 °, 20.4 ± 0.2 °, 24.8 ± 0.2 °, 28.7 ± 0.2 ° and 30.4 ± 0.2 ° etc.

3. the crystal form A of claim 1 or 2, it utilizes the fusing point of determine with dsc method to be about 366.1 ± 3.0 DEG C.

4. the crystal form A of any one of claim 1-3, its purity >=90%, preferably >=95%.

5. the preparation method of the crystal form A of any one of claim 1-4, it comprises the following steps:

(1) get lamp-dish flower acetic and add the organic solvent (such as propylene glycol or ethylene glycol) miscible with water that reflux temperature is 120 DEG C to 220 DEG C (such as 180 DEG C), reflux, makes lamp-dish flower acetic all dissolve;

(2) in solution, slowly acid solution is dripped; Continue backflow 6-16 hour;

(3) solution cooling, separate out precipitation, filter, filter cake is respectively with the reflux solvent (such as propylene glycol or ethylene glycol) described in step (1), water washing, and optional drying, pulverizing step, obtain Scutellarein crystal form A;

(4) optionally, also crystal form A can be obtained from scutellarin solid (comprising crystal form A, unformed or other crystal formation) by one or more in the stirring that suspends, slow cooling, anti-solvent interpolation, oppositely anti-solvent interpolation, liquid-solid gas-phase permeation, ionic liquid induced crystallization, humidity induction and wet grinding.

6. Scutellarein crystal formation D, it is characterized in that described crystal formation D is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 14.1 ± 0.2 °, 15.8 ± 0.2 °, 24.1 ± 0.2 °, 26.1 ± 0.2 °, 28.0 ± 0.2 °.

7. the crystal formation D of claim 6, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 10.0 ± 0.2 °, 11.2 ± 0.2 °, 18.0 ± 0.2 °, 24.6 ± 0.2 °, 25.6 ± 0.2 °, 29.5 ± 0.2 ° and 29.8 ± 0.2 °.

8. the crystal formation D of claim 6 or 7, it utilizes the fusing point of determine with dsc method to be about 363.2 ± 3.0 DEG C.

9. the crystal formation D of any one of claim 6-8, its purity >=90%, preferably >=95%.

10. the preparation method of the crystal formation D of any one of claim 6-9, it is selected from the one in following seven kinds of methods:

(1) Scutellarein solid (such as crystal form A) is got, add pyridine-acetone (volume ratio is as being 3:1) or pyridine-heptane (volume ratio is as being 3:1) mixed solvent, sample is dissolved completely and obtains settled solution, slowly volatilize at ambient temperature, the solid obtained after volatilizing solvent is Scutellarein crystal formation D;

(2) get Scutellarein solid (such as crystal form A), add pyridine, solid is dissolved completely, then slowly adds ethanol, the solid obtained after the precipitation of precipitation or at ambient temperature volatilization is Scutellarein crystal formation D; Or using dimethyl formamide as solvent, tetrahydrofuran (THF) also can obtain similar results as anti-solvent.

(3) Scutellarein solid (such as crystal form A) is got, add N-Methyl pyrrolidone, solid is dissolved completely, is then slowly added in acetonitrile by this settled solution, the solid obtained after the precipitation of precipitation or at ambient temperature volatilization is Scutellarein crystal formation D; Using pyridine as solvent, ethanol as anti-solvent or using dimethyl formamide as solvent, tetrahydrofuran (THF) also can obtain similar results as anti-solvent.

(4) Scutellarein solid (such as crystal form A) is got, add DMF/MEK (volume ratio is as being 1:1) mixed solvent, obtain settled solution, add mixed polymer in settled solution, gained solution slowly volatilizees at ambient temperature, namely obtains Scutellarein crystal formation D.

(5) get Scutellarein solid (such as crystal form A), being dissolved in pyridine/ethyl acetate (volume ratio is as being 3:1), in the uncovered volatilization of room temperature, namely obtaining Scutellarein crystal formation D.

(6) Scutellarein solid (such as crystal form A) is got, add acetone or acetonitrile obtains suspension, stir 4-8 days (such as 6 days) under room temperature (RT) and 40-60 DEG C of (such as 50 DEG C) condition, centrifugation solid obtains the mixture of crystal formation D and crystal form A.

(7) Scutellarein solid (such as crystal form A) is got, add dimethyl formamide, solid is dissolved completely, then slowly adds water, the solid obtained after the precipitation of precipitation or at room temperature volatilization is the mixture of crystal formation D and crystal form A.

11. Scutellarein crystal formation E, is characterized in that described crystal formation E is in use Cu-K α radiation,

In the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 9.6 ± 0.2 °, 14.0 ± 0.2 °, 15.3 ± 0.2 °, 17.8 ± 0.2 ° and 26.6 ± 0.2 °.

The crystal formation E of 12. claims 11, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 10.2 ± 0.2 °, 10.9 ± 0.2 °, 16.1 ± 0.2 °, 19.3 ± 0.2 °, 21.2 ± 0.2 °, 28.5 ± 0.2 °, 29.8 ± 0.2 ° and 31.1 ± 0.2 ° etc.

The crystal formation E of 13. claims 11 or 12, it utilizes the fusing point of determine with dsc method to be about 364.0 ± 3.0 DEG C.

The preparation method of the crystal formation E of 14. any one of claim 11-13, it comprises the following steps:

Get Scutellarein solid (such as crystal form A) to be heated to 250-350 DEG C (such as 300 DEG C), after being then naturally down to room temperature, namely obtain Scutellarein crystal formation E.

15. Scutellarein ammonium salt crystal formations, it is characterized in that described ammonium salt crystal formation is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 9.0 ± 0.2 °, 10.5 ± 0.2 °, 14.9 ± 0.2 °, 23.6 ± 0.2 ° and 26.6 ° ± 0.2 °.

The ammonium salt crystal formation of 16. claims 15, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 6.4 ± 0.2 °, 12.8 ± 0.2 °, 13.8 ± 0.2 °, 14.9 ± 0.2 °, 15.3 ± 0.2 °, 22.7 ± 0.2 °, 25.7 ± 0.2 °, 27.7 ± 0.2 °, 29.1 ± 0.2 ° and 32.0 ± 0.2 ° etc.

The ammonium salt crystal formation of 17. claims 15 or 16, it is hydrate.

The preparation method of the ammonium salt crystal formation of 18. any one of claim 15-17, it is method (1) or (2):

(1) Scutellarein solid (such as crystal form A) is got, add the ammoniacal liquor of certain volume, stir at ambient temperature, add ammoniacal liquor to original volume when ammoniacal liquor volume reduces to continue to stir, after 13-17 days (such as 15 days), namely obtain Scutellarein ammonium salt crystal formation;

(2) Scutellarein solid (such as crystal form A) is got, add ammoniacal liquor, and add acetone and obtain suspension, stir 4-8 days (such as 6 days) at ambient temperature, centrifugation solid obtains the mixture of Scutellarein ammonium salt crystal formation and Scutellarein crystal form A.

19. Scutellarein crystal form Bs, it is characterized in that described crystal form B is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 7.2 ± 0.2 °, 9.9 ± 0.2 °, 14.6 ± 0.2 °, 15.7 ± 0.2 ° and 26.2 ± 0.2 °.

The crystal form B of 20. claims 19, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 11.2 ± 0.2 °, 14.1 ± 0.2 °, 18.9 ± 0.2 °, 20.8 ± 0.2 °, 25.0 ± 0.2 ° and 28.0 ± 0.2 ° etc.

The crystal form B of 21. claims 19 or 20, it utilizes the fusing point of determine with dsc method to be about 361.6 ± 3.0 DEG C.

The preparation method of the crystal form B of 22. any one of claim 19-21, it is method (1) or (2) or (3):

(1) Scutellarein solid (such as crystal form A) is got, add in pyridine-water (volume ratio is as being 3:1) mixed solvent, sample is dissolved completely and obtains settled solution, gained solution slowly volatilizees at ambient temperature, namely obtains Scutellarein crystal form B after volatilizing solvent;

(2) Scutellarein solid (such as crystal form A) is got, add in pyridine-acetonitrile (volume ratio is as being 3:1) mixed solvent, sample is dissolved completely and obtains settled solution, gained solution slowly volatilizees at ambient temperature, namely obtains Scutellarein crystal form B after volatilizing solvent.

(3) Scutellarein solid (such as crystal form A) is got, add in pyridine-heptane (volume ratio is as being 3:1) mixed solvent, sample is dissolved completely and obtains settled solution, gained solution slowly volatilizees at ambient temperature, namely obtains Scutellarein crystal form B after volatilizing solvent.

23. Scutellarein crystal Cs, it is characterized in that described crystal C is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 7.2 ± 0.2 °, 14.6 ± 0.2 °, 19.5 ± 0.2 °, 20.7 ± 0.2 ° and 25.0 ± 0.2 °.

The crystal C of 24. claims 23, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 9.2 ± 0.2 °, 16.4 ± 0.2 °, 16.9 ± 0.2 °, 17.7 ± 0.2 °, 18.2 ± 0.2 °, 18.9 ± 0.2 °, 21.5 ± 0.2 °, 22.0 ± 0.2 °, 22.8 ± 0.2 °, 25.7 ± 0.2 °, 27.0 ± 0.2 °, 27.7 ± 0.2 °, 28.7 ± 0.2 °, 29.3 ± 0.2 ° and 32.4 ± 0.2 ° etc.

The crystal C of 25. claims 23 or 24, it utilizes the fusing point of determine with dsc method to be about 363.2 ± 3.0 DEG C.

The preparation method of the crystal C of 26. any one of claim 23-25, it is method (1) or (2):

(1) get Scutellarein solid (such as crystal form A), add pyridine, solid is dissolved completely, then slowly adds heptane, the solid obtained after the precipitation of precipitation or at room temperature volatilization is Scutellarein crystal C;

(2) get Scutellarein solid (such as crystal form A), add pyridine, solid is dissolved completely, then slowly join in heptane, the solid obtained after the precipitation of precipitation or at room temperature volatilization is Scutellarein crystal C.

27. Scutellarein crystal formation F, it is characterized in that described crystal formation F is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the charateristic avsorption band being about following position: 18.1 ± 0.2 °, 31.7 ± 0.2 ° and 37.3 ± 0.2 °.

The crystal formation F of 28. claims 27, it utilizes the fusing point of determine with dsc method to be about 328.4 ± 3.0 DEG C.

The preparation method of the crystal formation F of 29. claims 27 or 28, it comprises the following steps:

Get Scutellarein solid (such as crystal form A), add normal hexane or toluene obtains suspension, stir 4-8 days (such as 6 days) under room temperature (RT) and 40-60 DEG C of (such as 50 DEG C) condition, centrifugation solid obtains the mixture of crystal formation F and crystal form A.

30. Scutellarein crystal formation G, it is characterized in that described crystal formation G is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 8.3 ± 0.2 °, 14.3 ± 0.2 °, 18.2 ± 0.2 °, 20.7 ± 0.2 ° and 23.6 ± 0.2 °.

The crystal formation G of 31. claims 23, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 7.2 ± 0.2 °, 10.9 ± 0.2 °, 15.8 ± 0.2 °, 16.7 ± 0.2 °, 22.4 ± 0.2 °, 24.8 ± 0.2 °, 25.7 ± 0.2 ° and 27.7 ± 0.2 ° etc.

The crystal formation G of 32. claims 30 or 31, it utilizes the fusing point of determine with dsc method to be about 358.8 ± 3.0 DEG C.

The preparation method of the crystal formation G of 33. any one of claim 30-32, it is method (1) or (2):

(1) Scutellarein solid (such as crystal form A) is got, add pyridine/heptane mixed solvent, obtain settled solution, add mixed polymer in settled solution, gained solution slowly volatilizees at ambient temperature, obtains Scutellarein crystal formation G.

(2) Scutellarein solid (such as crystal form A) is got, add pyridine or pyridine/methyl alcohol or pyridine/1,4-dioxane or pyridine/methyl tertiary butyl ether or pyridine/2-methyltetrahydrofuran or pyridine/toluene (volume ratio is as being 3:1) mixed solvent, sample is dissolved completely and obtains settled solution, slowly volatilize at ambient temperature, the solid obtained after volatilizing solvent is Scutellarein crystal formation G.

34. Scutellarein crystal formation H, it is characterized in that described crystal formation H is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 7.4 ± 0.2 °, 14.8 ± 0.2 °, 19.1 ± 0.2 °, 21.0 ± 0.2 ° and 25.0 ± 0.2 °.

The crystal formation H of 35. claims 34, it is characterized in that in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 10.1 ± 0.2 °, 10.9 ± 0.2 °, 11.5 ± 0.2 °, 16.2 ± 0.2 °, 19.8 ± 0.2 °, 22.2 ± 0.2 °, 23.2 ± 0.2 °, 27.7 ± 0.2 ° and 29.0 ± 0.2 ° etc.

The crystal formation H of 36. claims 34 or 35, it utilizes the fusing point of determine with dsc method to be about 364.4 ± 3.0 DEG C.

The preparation method of the crystal formation H of 37. any one of claim 34-36, it comprises the following steps:

Get Scutellarein solid (such as crystal form A), be dissolved in pyridine/ethyl acetate mixed solvent, room temperature is volatilized, and obtains crystal formation D; Be dissolved in pyridine/ethyl acetate by the crystal formation D obtained, room temperature is volatilized, and obtains crystal formation H.

38. Scutellarein crystal formation I, it is characterized in that described crystal formation I is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 6.9 ± 0.2 °, 15.6 ± 0.2 °, 19.9 ± 0.2 °, 22.3 ± 0.2 ° and 26.8 ± 0.2 °.

The crystal formation I of 39. claims 38, it is characterized in that described crystal formation I is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 21.0 ± 0.2 °, 25.8 ± 0.2 ° and 26.3 ± 0.2 ° etc.

The crystal formation I of 40. claims 38 or 39, it utilizes the fusing point of determine with dsc method to be about 362.1 ± 3.0 DEG C.

The preparation method of the crystal formation I of 41. any one of claim 38-40, it comprises the following steps:

Get Scutellarein solid (such as crystal form A), be dissolved in pyridine/ethyl acetate mixed solvent, room temperature is volatilized, and obtains crystal formation I.

The crystal formation E of the crystal form A of 42. any one of claim 1-4, the crystal formation D of any one of claim 6-9, any one of claim 11-13, the crystal formation F of claim 27 or 28, it is anhydride.

The crystal formation G of the crystal form B of 43. any one of claim 19-21, the crystal C of any one of claim 23-25, any one of claim 30-32, the crystal formation H of any one of claim 34-36, the crystal formation I of any one of claim 38-40, it is solvate, such as, be pyrroles's compound.

44. pharmaceutical compositions, it contains the crystal form A being selected from any one of claim 1-4, the crystal formation D of any one of claim 6-9, the crystal formation E of any one of claim 11-13, the ammonium salt hydrate crystal forms of any one of claim 15-17, the crystal form B of any one of claim 19-21, the crystal C of

any one of claim 23-25, the crystal formation F of claim 27 or 28, the crystal formation G of any one of claim 30-32, at least one in the crystal formation H of any one of claim 34-36 or the crystal formation I of any one of claim 38-40, and pharmaceutically acceptable carrier or vehicle.

The crystal form A of 45. any one of claim 1-4, the crystal formation D of any one of claim 6-9, the crystal formation E of any one of claim 11-13, the ammonium salt hydrate crystal forms of any one of claim 15-17, the crystal form B of any one of claim 19-21, the crystal C of any one of claim 23-25, the crystal formation F of claim 27 or 28, the crystal formation G of any one of claim 30-32, the crystal formation H of any one of claim 34-36 or the crystal formation I of any one of claim 38-40 prevents and/or treats cardiovascular and cerebrovascular diseases in preparation and (loses paralysis after caused by the such as occlusive cerebrovascular, coronary heart disease, stenocardia), rheumatic arthritis, apoplexy sequela, nephrotic syndrome, diabetic nephropathy, the kidney diseases such as chronic glomerulonephritis, the liver injury of antitubercular agent physical property, acute icterohepatitisshock, chronic hepatitis, the hepatic diseases such as Refractory ascites resulted from hepatocirrhosis, acute exacerbation of chronic obstructive pulmonary disease merges hypoxemia, diabetic peripheral neuropathy, the chronic complicating diseases of diabetes such as diabetic foot, retina flowmetry, ischemic optic neuropathy, the ophthalmic diseasess such as eye central serous retinopathy, purposes in the medicine of the disease such as sudden deafness or FGR.

Description

Scutellarein crystal formation and preparation method thereof

Technical field

The invention belongs to field of medicine and chemical technology, be specifically related to multiple Scutellarein crystal formation and preparation method thereof.The invention still further relates to Scutellarein crystal formation and prepare the purposes prevented and/or treated in the medicine of cardiovascular and cerebrovascular diseases, rheumatic arthritis or apoplexy sequela etc.

Background technology

Scutellarin (also claiming scutellarin, English Scutellarin by name) has and improves brain circulation of blood, increases cerebral blood flow (CBF), reduces the effect such as blood viscosity and anti-platelet aggregation.Scutellarin clinical application is extensive, is mainly used in cardiovascular and cerebrovascular diseases, loses paralysis, coronary heart diseases and angina pectoris etc. after caused by the occlusive cerebrovascular.Scutellarin has significant curative effect (Tang Yuping in treatment cardiovascular and cerebrovascular diseases, rheumatic arthritis and apoplexy sequela etc., Li Nianguang, the golden storehouse for grain, etc. of section. scutellarin aglycone derivative and preparation method thereof and its application [P]. Jiangsu: CN101891728A, 2010-11-24.).In addition, Breviscarpine also can be used for treating nephrotic syndrome clinically, diabetic nephropathy, the kidney diseases such as chronic glomerulonephritis, the liver injury of antitubercular agent physical property, acute icterohepatitisshock, chronic hepatitis, the hepatic diseases such as Refractory ascites resulted from hepatocirrhosis and acute exacerbation of chronic obstructive pulmonary disease merge hypoxemia, diabetic peripheral neuropathy, the chronic complicating diseases of diabetes such as diabetic foot, retina flowmetry, ischemic optic neuropathy, the ophthalmic diseasess such as eye central serous retinopathy, and (the Sun Hua such as sudden deafness and FGR, Song Yi. the clinical expansive approach [J] of Breviscarpine. Asia-Pacific traditional medicine, 2013, 05:63-64.).

Due to purifying process imperfection in the early time, the treatment adopting Breviscarpines to carry out clinical disease as bulk drug more.Breviscarpine administration Problems existing is, Breviscarpine is originally as scutellarin, scutellarin isomers-different scutellarin and other mixture thereof, and complicated component, exists some problems in quality control.And scutellarin is the principal constituent in Breviscarpine, be the result that technology advances, but scutellarin oral absorption is poor, Oral availability is not high.

Scutellarein is the hydrolysate (Liu Jianming of scutellarin, Xiong Yuqing. the progress [J] of scutellarin and aglycon Pharmacokinetic Characteristics thereof. CHINA JOURNAL OF CHINESE MATERIA MEDICA, 2009,24:3165-3168.), have another name called scutellarin, English Scutellarein, CAS NO.529-53-3 by name, molecular formula is $C_{15}h_{10}o_6$, molecular weight is 286.2.

Along with the development of purifies and separates technology and detection technique, in conjunction with finding the research of scutellarin and aglycon at present, Scutellarein has higher perviousness compared with B prime at gi tract, and oral absorption is about 3 times of scutellarin.Che Qingming etc. study rat oral gavage and give equivalent Scutellarein and scutellarin, show that oral being easy to of Scutellarein absorbs, compared with scutellarin, internal metabolism is stablized, and its relative bioavailability is 301.8% (Che Qingming, Chen Ying, Pan Liyi, He Hong. the rat pharmacokinetics of breviscapine B aglycone different dosing dosage compares [J]. Chinese Journal of New Drugs, 2006,18:1557-1561.).Che Qingming etc. also find, the effective constituent scutellarin of Herba Erigerontis injection is converted mainly in vivo after Scutellarein oral administration, the situation of the distribution of its blood medicine and Herba Erigerontis injection is comparatively close to (Che Qingming, Pan Liyi, Chen Ying, He Hong. the pharmacokinetic studies [J] of breviscapine B aglycone. Chinese Pharmaceutical Journal, 2007,18:1418-1421.).In other words, Scutellarein has the pharmacologically active being almost equal to scutellarin.Lu etc. utilize cerebral tissue to carry out the dynamics research of scutellarin liposome, show scutellarin by hemato encephalic barrier at cerebral tissue distribution (Int J Pharm.2005Dec8 in conjunction with existing result of study; 306 (1-2): 99-106.Distribution of liposomal breviscapine in brain following intravenous injection in rats.Lv W1, Guo J, Li J, Huang L, Ping Q.).Aglycon oral administration, when dosage is 200mg/kg, Scutellarein and scutellarin can be measured in rat plasma, and when dosage is 20mg/kg, scutellarin can only be measured, can't detect original shape medicine (Che Qingming, Chen Ying, Pan Liyi, He Hong. bile excretion research [J] of breviscapine B aglycone. CHINA JOURNAL OF CHINESE MATERIA MEDICA, 2006,20:1710-1712.).Occupy Wen Zheng etc. and determine scutellarin Plasma Concentration and Clinical pharmacokinetics, experimenter's oral administration 360mg scutellarin, hematometry scutellarin concentration is got at 1,3,5,8 hour, only littlely measure 20ng/ml constantly 5, and in blood plasma and urine, record a large amount of aglycons, prompting scutellarin may be hydrolyzed to aglycon at colon and absorb and (occupy civilian political affairs, Chu Jihong, Tan Renxiang, the peaceful .UPLC-MS/MS of bear joins usage analysis lamp-dish flower acetic at GI metabolite [J]. Chinese Clinical pharmacology and therapeutics, 2006,03:292-295.).

Because scutellarin oral absorption is poor, Oral availability is not high, and Scutellarein can be converted into scutellarin in vivo, and its oral absorption is better than scutellarin, if the crystal formation that Scutellarein has certain stability can be obtained, will more be conducive to drug development and suitability for industrialized production.

Summary of the invention

The present invention prepares the polymorphic of Scutellarein and the ammonium salt hydrate crystal forms of aglycon by the method such as crystallization of slowly volatilizing, the stirring that suspends, slow cooling, anti-solvent interpolation, oppositely anti-solvent interpolation, liquid-solid gas-phase permeation, liquid-liquid-vapor infiltration, ionic liquid induced crystallization, polymkeric substance induced crystallization, humidity induction, wet grinding, heating induction, this completes the present invention.

First aspect present invention relates to Scutellarein crystal form A, it is characterized in that described crystal form A is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the principal character absorption peak being about following position: 14.5 ± 0.2 °, 16.9 ± 0.2 °, 22.0 ± 0.2 °, 26.7 ± 0.2 ° and 27.4 ± 0.2 °.

In one embodiment of the invention, described crystal form A is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 11.2 ± 0.2 °, 13.8 ± 0.2 °, 20.4 ± 0.2 °, 24.8 ± 0.2 °, 28.7 ± 0.2 ° and 30.4 ± 0.2 ° etc.

In a specific embodiments of the present invention, described crystal form A is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, there is the charateristic avsorption band being about following position: 7.2 ± 0.2 °, 11.2 ± 0.2 °, 13.8 ± 0.2 °, 14.5 ± 0.2 °, 16.9 ± 0.2 °, 20.4 ± 0.2 °, 21.3 ± 0.2 °, 22.0 ± 0.2 °, 23.0 ± 0.2 °, 24.4 ± 0.2 °, 24.8 ± 0.2 °, 26.7 ± 0.2 °, 27.4 ± 0.2 °, 28.7 ± 0.2 °, 30.4 ± 0.2 °, 31.1 ± 0.2 °, 32.3 ± 0.2 °, 33.1 ± 0.2 °, 33.8 ± 0.2 °, 34.8 ± 0.2 ° and 37.3 ± 0.2 °.

In specific embodiment of the invention scheme, its typical X-ray powder diffraction pattern as shown in Figure 1.

According to the crystal form A of any one of the present invention, it utilizes the fusing point of determine with dsc method (onset temperature) scope to be 366.1 ± 3.0 DEG C.

In specific embodiment of the invention scheme, it utilizes the fusing point of determine with dsc method to be about 366.1 DEG C.

In specific embodiment of the invention scheme, its typical DSC figure as shown in Figure 2.

According to the crystal form A of any one of the present invention, its purity >=90%, preferably >=95%.

The invention still further relates to the preparation method of the crystal form A of any one of the present invention, it comprises the following steps:

(1) get scutellarin and add the organic solvent (such as propylene glycol or ethylene glycol) miscible with water that reflux temperature is 120 DEG C to 220 DEG C (such as 180 DEG C), reflux, makes lamp-dish flower acetic all dissolve;

(2) in solution, slowly drip acid (such as dilute hydrochloric acid or dilute sulphuric acid) solution; Continue backflow 6-16 hour;

(3) solution cooling, separate out precipitation, filter, filter cake is respectively with the reflux solvent (such as propylene glycol or ethylene glycol) described in step (1), water washing, and optional drying, pulverizing step, obtain Scutellarein crystal form A;

(4) optionally, also crystal form A can be obtained from scutellarin solid (comprising crystal form A, unformed or other crystal formation) by one or more in the stirring that suspends, slow cooling, anti-solvent interpolation, oppositely anti-solvent interpolation, liquid-solid gas-phase permeation, ionic liquid induced crystallization, humidity induction and wet grinding.

In embodiments of the invention, the method in above-mentioned steps (4) is selected from one or more in following eight kinds of methods:

(1) Scutellarein solid (such as crystal form A) is got, add water or ethanol or or acetic acid or acetonitrile or acetone or methyl iso-butyl ketone (MIBK) or tetrahydrofuran (THF) or Iso Butyl Acetate or methyl tertiary butyl ether or 1, 4-dioxane or normal hexane or toluene or glycol/water mixed solvent or propylene glycol/water mixed solvent or PEG400/ heptane mixed solvent or N-Methyl pyrrolidone/water mixed solvent or methyl-sulphoxide/water mixed solvent or dimethyl formamide/water mixed solvent obtain suspension, stir 4-8 days (such as 6 days) under room temperature (RT) or 40-60 DEG C of (such as 50 DEG C) condition, centrifugation solid obtains crystal form A,

(2) Scutellarein solid (such as crystal form A) is got, add methyl-sulphoxide/alcohol mixed solvent or methyl-sulphoxide/tetrahydrofuran (THF) mixed solvent or N-Methyl pyrrolidone/methyl tertiary butyl ether mixed solvent or N-Methyl pyrrolidone/ethyl acetate mixed solvent or dimethyl formamide/acetone mixed solvent or or dimethyl formamide/acetonitrile mixed solvent, 40-60 DEG C (such as 50 DEG C) balance for some time (such as 30min) lower the temperature afterwards 2-5 days (such as 3 days) be down to 3-10 DEG C (such as 5 DEG C), suspend at such a temperature stir 1-4 days (such as 2 days) afterwards centrifugation solid obtain crystal form A,

(3) Scutellarein solid (such as crystal form A) is got, add positive solvent, solid is dissolved completely, then this settled solution is slowly added anti-solvent, the solid obtained after the precipitation of precipitation or at ambient temperature volatilization is Scutellarein crystal form A; The combination of positive solvent and anti-solvent can be N-Methyl pyrrolidone/water or methyl-sulphoxide/methyl alcohol or methyl-sulphoxide/acetone or dimethyl formamide/water;

(4) Scutellarein solid (such as crystal form A) is got, add positive solvent, solid is dissolved completely, is then slowly joined in anti-solvent by this settled solution, the solid obtained after the precipitation of precipitation or at ambient temperature volatilization is Scutellarein crystal form A; The combination of positive solvent and anti-solvent can be N-Methyl pyrrolidone/water or methyl-sulphoxide/methyl alcohol or methyl-sulphoxide/acetone or dimethyl formamide/water;

(5) Scutellarein solid (such as crystal form A) is got in bottle, the closed glass jar that methylene dichloride or ethanol or methyl alcohol or toluene or acetonitrile or tetrahydrofuran (THF) or dimethyl formamide or acetone are housed is placed in by uncovered for bottle, under room temperature condition, lucifuge is placed for some time (such as 13 days) and is taken out solid afterwards, obtains crystal form A;

(6) Scutellarein solid (such as crystal form A) is got in bottle, add methyl-sulphoxide/tetrahydrofuran (THF) mixed solvent or dimethyl formamide/acetonitrile mixed solvent or methyl-sulphoxide/alcohol mixed solvent, obtain settled solution, add ionic liquid in settled solution.Gained solution slowly volatilizees at ambient temperature, obtains crystal form A; Described ionic liquid such as refers to 1-butyl-3-methyl imidazolium cation salts solution;

(7) Scutellarein solid (such as crystal form A) is got in bottle, be positioned over constant humidity (such as 30%-99%, such as, in container 32.8% or 57.6% or 75.3% or 97.3%), room temperature storage for some time (such as 11 days), obtain crystal form A;

(8) get Scutellarein solid (such as crystal form A) in mortar, add Virahol or acetic acid or acetonitrile or acetone or Iso Butyl Acetate, grinding (such as 15min), obtains crystal form A.

The invention still further relates to Scutellarein crystal formation D, it is characterized in that described crystal formation D is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, at least there is the charateristic avsorption band being about following position: 14.1 ± 0.2 °, 15.8 ± 0.2 °, 24.1 ± 0.2 °, 26.1 ± 0.2 °, 28.0 ± 0.2 °.

In one embodiment of the invention, described crystal formation D is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, what also have in the charateristic avsorption band being selected from and being about following position is one or more: 10.0 ± 0.2 °, 11.2 ± 0.2 °, 18.0 ± 0.2 °, 24.6 ± 0.2 °, 25.6 ± 0.2 °, 29.5 ± 0.2 ° and 29.8 ± 0.2 ° etc.

In a specific embodiments of the present invention, described crystal formation D is in use Cu-K α radiation, in the X-ray powder diffraction pattern represented with 2 θ angles, there is the charateristic avsorption band being about following position: 7.0 ± 0.2 °, 9.9 ± 0.2 °, 11.1 ± 0.2 °, 14.1 ± 0.2 °, 15.7 ± 0.2 °, 18.0 ± 0.2 °, 19.9 ± 0.2 °, 21.2 ± 0.2 °, 22.4 ± 0.2 °, 24.1 ± 0.2 °, 24.6 ± 0.2 °, 25.2 ± 0.2 °, 25.5 ± 0.2 °, 26.0 ± 0.2 °, 27.9 ± 0.2 °, 29.4 ± 0.2 °, 29.8 ± 0.2 °, 30.9 ± 0.2 °, 31.8 ± 0.2 °, 35.0 ± 0.2 °, 36.8 ° ± 0.2 ° and 38.6 ± 0.2 °.

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