perpendicular to the water planes and parallel to the axis of the columns. The chloride ions are coordinated with three hydrogen bonds from 3/2 water molecules.

Presumably the same structure was earlier attributed to a tetrahydrate [W.H. Taylor, *Z. Krist.* *91* (1935) 450]. A phase transition between the pentahydrate and a second polymorphic form was described to occur near 30°C in aqueous suspension [S.W. Bodman, S.P. Kodama, P.C. Pfeil, R.E. Stevens, *J. Chem. Eng. Data 12* (1967) 500]. The second form was also obtained by vacuum drying of the pentahydrate at room temperature, and its water content was indicated to amount to approximately 1 mol/mol.

The solid state form of a compound is of great importance for pharmaceutical applications. It may influence the chemical and physical stability of the compound itself and of its formulations, may have an impact on pharmacokinetics and bioavailability. In the case of hydrates, the composition has also an influence on the correct dosage of the active pharmaceutical ingredient.

Methylthioninium chloride used in pharmaceutical compositions is described as a trihydrate (USP Material Safety Data Sheet for Methylene Blue (Catalogue Number 1428008), 2005), which is thought to be methylthioninium chloride pentahydrate admixed with other components. The mixture or components in the mixture are stable under different conditions, they may convert to other polymorphic or pseudopolymorphic species and hence change their composition, so that correct dosage is a problem and storage stability may be considered to be insufficient.

SUMMARY

In an aspect, there is provided crystalline methylthioninium chloride monohydrate as Form E, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 9.0 |
| 2 | 12.5 |
| 3 | 14.1 |
| 4 | 14.4 |
| 5 | 18.1 |
| 6 | 23.2 |
| 7 | 24.1 |
| 8 | 26.0 |

In another aspect, there is provided crystalline methylthioninium chloride dihydrate as Form D, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 7.0 |
| 2 | 8.5 |
| 3 | 12.0 |
| 4 | 14.4 |
| 5 | 25.3 |
| 6 | 25.7 |
| 7 | 27.5 |

In another aspect, there is provided a process for the preparation of methylthioninium chloride dihydrate in form D as disclosed herein, comprising: dissolving methylthioninium chloride pentahydrate in acetic acid and combining the solution with toluene, either by adding toluene to the acetic acid solution or by adding the acetic acid solution to toluene; isolating the solid by filtration shortly after precipitation; and removing the solvent by vacuum drying or in an inert gas flow, whereby the relative air humidity in all process steps is less than 50%.

In another aspect, there is provided crystalline methylthioninium chloride dihydrate as Form B, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 5.8 |
| 2 | 11.2 |
| 3 | 25.3 |
| 4 | 26.8 |

In another aspect, there is provided a process for the preparation of methylthioninium chloride monohydrate in form E as disclosed herein, wherein: water-containing methylthioninium chloride; a mixture of methylthioninium chloride pentahydrate and at least one of Form B as disclosed herein and Form D as disclosed herein; or methylthioninium chloride pentahydrate is suspended and stirred at ambient temperature in a dry solvent, preferably isopropanol, for a time sufficient to generate form E; the solid is isolated by filtration; and residual solvent is removed from the solid by either vacuum drying or purging with dry gas.

In another aspect, there is provided a process for the preparation of methylthioninium chloride dihydrate in form B as disclosed herein, which comprises exposing solid methylthioninium chloride pentahydrate at about room temperature to an inert gas flow having a relative humidity from 8 to 15% for a time sufficient to generate pure form B.

In another aspect, there is provided a pharmaceutical composition comprising methylthioninium chloride dihydrate form B as disclosed herein or methylthioninium chloride dihydrate Form D as disclosed herein, or methylthioninium chloride monohydrate form E as disclosed herein.

In another aspect, there is provided a pharmaceutical composition comprising methylthioninium chloride dihydrate form B as disclosed herein or methylthioninium chloride dihydrate Form D as disclosed herein, or methylthioninium chloride monohydrate form E as disclosed herein and a pharmaceutically acceptable carrier, excipient or diluent.

In another aspect, there is provided methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E as disclosed herein for use in therapy.

In another aspect, there is provided the use of methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E as disclosed herein in the manufacture of a medicament for the treatment of a disease condition.

In another aspect, there is provided the use of methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E as disclosed herein in the manufacture of a medicament for the treatment of a tauopathy, Alzheimer's disease (AD), skin cancer, melanoma, Hepatitis C, HIV or West Nile virus.

DETAILED DESCRIPTION

The present invention provides specific polymorphic forms of methylthioninium chloride hydrates, as well as safe and reproducible processes for their preparation. The present invention also provides specific polymorphic forms of methylthioninium chloride hydrates, which are stable under defined conditions, and which have good solubility and bioavailability. The present invention provides specific polymorphic forms of methylthioninium chloride hydrates, which can be easily metered to arrive at defined contents in pharmaceutical compositions in order to administer exact amounts of the active compound.

A first aspect of the present invention is MTC substantially in crystalline Form B of methylthioninium chloride dihydrate.

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**Claims**

1. Crystalline methylthioninium chloride monohydrate as Form E, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 9.0 |
| 2 | 12.5 |
| 3 | 14.1 |
| 4 | 14.4 |
| 5 | 18.1 |
| 6 | 23.2 |
| 7 | 24.1 |
| 8 | 26.0 |

2. The compound of claim 1 having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 9.0 |
| 2 | 12.5 |
| 3 | 14.1 |
| 4 | 14.4 |
| 5 | 18.1 |
| 6 | 23.2 |
| 7 | 24.1 |
| 8 | 26.0 |
| 9 | 24.5 |
| 10 | 27.2 |

3. The compound of any one of claims 1 to 2, which shows no thermal event up to the decomposition temperature near 220°C when heated at a rate of 100°C per minute in Differential Scanning Calorimetry.

~~4. A process for the preparation of methylthioninium chloride monohydrate substantially in form E according to any one of claims 1 to 3, wherein:~~
~~water-containing methylthioninium chloride or a mixture of various hydrates or a specific hydrate of methylthioninium chloride is suspended and stirred at ambient temperature in a dry solvent, preferably isopropanol, for a time sufficient to generate form E; the solid is~~

~~isolated by filtration; and residual solvent is removed from the solid by either vacuum drying or purging with dry gas.~~

~~54~~. Crystalline methylthioninium chloride dihydrate as Form D, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 7.0 |
| 2 | 8.5 |
| 3 | 12.0 |
| 4 | 14.4 |
| 5 | 25.3 |
| 6 | 25.7 |
| 7 | 27.5 |

~~65~~. The compound of claim ~~5~~ 4 having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 7.0 |
| 2 | 8.5 |
| 3 | 12.0 |
| 4 | 14.4 |
| 5 | 25.3 |
| 6 | 25.7 |
| 7 | 27.5 |
| 8 | 6.0 |
| 9 | 10.4 |
| 10 | 20.9 |
| 11 | 21.1 |
| 12 | 21.7 |
| 13 | 22.3 |
| 14 | 23.7 |
| 15 | 24.5 |
| 16 | 26.9 |
| 17 | 28.5 |
| 18 | 29.0 |

| | |
|---|---|
| 19 | 30.4 |
| 20 | 31.8 |

~~7~~6. The compound of any one of claims ~~5~~ 4 to ~~6~~5, which has two endothermic peak maxima at 164°C and 185°C and a step in the baseline near 63°C when heated at a rate of 100°C per minute in Differential Scanning Calorimetry.

~~8~~7. A process for the preparation of methylthioninium chloride dihydrate ~~substantially~~ in form D according to any one of claims ~~5~~ 4 to ~~7~~6, comprising: dissolving methylthioninium chloride pentahydrate in acetic acid and combining the solution with toluene, either by adding toluene to the acetic acid solution or by adding the acetic acid solution to toluene; isolating the solid by filtration shortly after precipitation; and removing the solvent by vacuum drying or in an inert gas flow, whereby the relative air humidity in all process steps is less than 50%.

~~9~~8. Crystalline methylthioninium chloride dihydrate ~~substantially~~ as Form B, having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 5.8 |
| 2 | 11.2 |
| 3 | 25.3 |
| 4 | 26.8 |

~~10~~9. The compound of claim ~~9~~ 8 having the following characteristic peaks in a powder X-ray diffraction pattern:

| Peak | 2θ values (± 0.1°) |
|---|---|
| 1 | 5.8 |
| 2 | 11.2 |
| 3 | 25.3 |
| 4 | 26.8 |
| 5 | 15.6 |
| 6 | 16.9 |
| 7 | 20.3 |
| 8 | 28.3 |

~~11~~10. The compound of any one of claims ~~9~~ 8 to ~~10~~9, which has a melting peak at 186°C with a shoulder towards lower temperature when heated at a rate of 100°C per minute in Differential Scanning Calorimetry.

11. A process for the preparation of methylthioninium chloride monohydrate in form E according to any one of claims 1 to 3, wherein:

water-containing methylthioninium chloride; a mixture of methylthioninium chloride pentahydrate and at least one of Form B according to any one of claims 8 to 10 and Form D according to any one of claims 4 to 6; or methylthioninium chloride pentahydrate is suspended and stirred at ambient temperature in a dry solvent, preferably isopropanol, for a time sufficient to generate form E;

the solid is isolated by filtration; and

residual solvent is removed from the solid by either vacuum drying or purging with dry gas.

12. A process for the preparation of methylthioninium chloride dihydrate ~~substantially~~ in form B according to any one of claims 8 to 10, which comprises exposing solid methylthioninium chloride pentahydrate at about room temperature to an inert gas flow having a relative humidity from 8 to 15% for a time sufficient to generate ~~essentially~~ pure form B.

13. A pharmaceutical composition comprising methylthioninium chloride dihydrate form B according to any one of claims ~~1~~ 8 to ~~3~~ 10 or methylthioninium chloride dihydrate Form D according to any one of claims ~~5~~ 4 to ~~8~~6, or methylthioninium chloride monohydrate form E according to any one of claims ~~9~~ 1 to ~~11~~3.

14. A pharmaceutical composition comprising methylthioninium chloride dihydrate form B according to any one of claims ~~1~~ 8 to ~~3~~ 10 or methylthioninium chloride dihydrate Form D according to any one of claims ~~5~~ 4 to ~~8~~6, or methylthioninium chloride monohydrate form E according to any one of claims ~~9~~ 1 to ~~11~~ 3 and a pharmaceutically acceptable carrier, excipient or diluent.

15. Methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E according to any one of claims 1 to 3, ~~5~~ 4 to ~~8~~6, or ~~9~~ 8 to ~~11~~ 10 for use in therapy.

16. Use of methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E according to any one of claims 1 to 3, ~~5~~ 4 to ~~8~~6, or ~~9~~ 8 to ~~11~~ 10 in the manufacture of a medicament for the treatment of a disease condition.

17. Use of methylthioninium chloride dihydrate form B or D or methylthioninium chloride monohydrate form E according to any one of claims 1 to 3, ~~5~~ 4 to ~~8~~6, or ~~9~~ 8 to ~~11~~ 10 in the manufacture of a medicament for the treatment of a tauopathy, Alzheimer's disease (AD), skin cancer, melanoma, Hepatitis C, HIV or West Nile virus.