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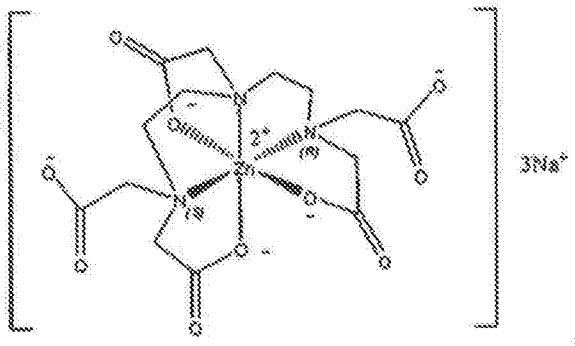
(54) **Trinátrium-cink-dietilén-triamin-pentaecetsav kristályos formái**

Description

The present invention relates to the preparation of trisodium zinc diethylenetriaminepentaacetic acid (Zn-DTPA) (Formula (I)) and to crystalline forms of this salt.



Formula (I)

The invention further relates to the use of trisodium zinc diethylenetriaminepentaacetic acid as a medicament and, in particular, a formulation orally administrable to a human and/or an animal comprising the quoted compound. Furthermore, the invention relates to the use of Zn-DTPA or an oral formulation comprising this compound for the treatment or prophylaxis of poisoning by heavy metals and/or radionuclides.

State of the art

Diethylenetriaminepentaacetic acid (DTPA) is a chelating agent. Chelating agents are in standard use in industry because they form partially selective, stable complexes with metals.

In the pharmaceutical industry, diethylenetriaminepentaacetic acid is used as a calcium or zinc complex. These complexes are able to exchange the cation with another cation if the latter cation has a larger complex formation constant, i.e. forms a more stable complex with the complex former. Solutions of this salt are used in Europe and in the USA for complexing radiouclides. (Ménétrier F, Grappin L, Raynaud P, Courtay C, Wood R, Joussineau S, List V, Stradling GN, Taylor DM, Bérard P, Morcillo MA & Rencova J (2005) Treatment of accidental intakes of plutonium and americium: Guidance notes. Appl Radiat Isot, 62: 829-846.)

Finished drugs with Zn-DTPA are approved under the trade names Pentetate Zinc Trisodium (USA, NDA August 2004, hameln pharmaceuticals) and Zinc Trisodium Pentetate (Germany, Heyl Chemisch-pharmazeutische Fabrik GmbH & Co.).

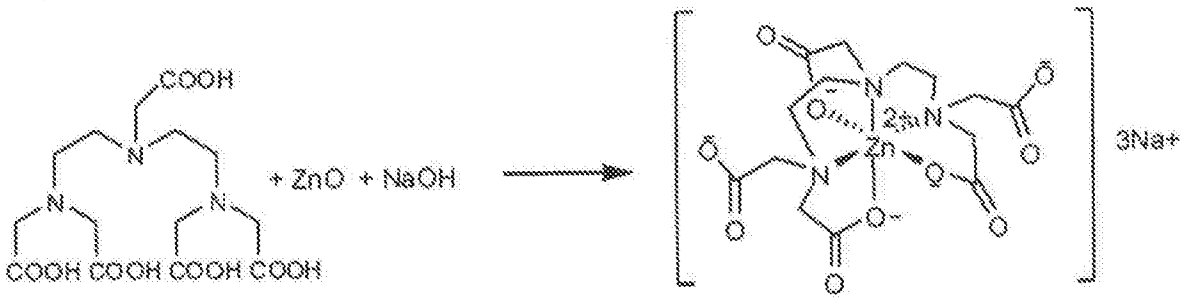
The finished drugs are administered by intravenous injection. They are indicated for a nuclear incident wherein radioactive heavy metals such as plutonium, americium and curium are released. Guilmette, R. A. et al "Effectiveness of continuously infused DTPA therapy in reducing the radiation dose from inhaled 244Cm203 aerosols" Health Physics, 1992. vol. 62, no. 4, pp. 311-318.

Efforts are currently being made to increase the oral availability of the complexes (WO 2007/145682).

The formation of the zinc complex in solution is a satisfactory synthetic method for intravenous forms of administration. The use of the peroral application, however, poses heavy demands on the physical properties of the agent. The complex has to be present in solid form. Preferably, it should have a stable nature, easy to handle.

The synthesis of the agent was first published in DE1223396 and US3480715 (example 1).

The standard method of producing Zn-DTPA consists of preparing an aqueous solution of pentasodium-diethylenetriaminepentaacetic acid and adding zinc chloride or zinc oxide as in the following diagram:



In this process, the agent is isolated by concentrating the reaction solution by removing the water by distillation and then drying the reaction product.

The synthesis method illustrated in DE1223396 results, however, in an amorphous product which is very hygroscopic and is correspondingly difficult to grind.

The hygroscopicity is illustrated, furthermore, as a disadvantageous property of Zn-DTPA in an application of nanotherapeutics (WO2007008480, example 4). It is reported that the lyophilised powder absorbed more than 10 wt % of water in less than 24 hours.

DE1223396 gives no indication of the existence of a crystalline form, or different polymorphic forms of Zn-DTPA.

Table 1 shows the hygroscopicity of the solid substance when the product is obtained from the method known in the state of the art by concentration from the reaction mixture (cf. also example 1).

Table 1

Time [hrs] **No.**	**Average increase in mass [%]**						
	1	**2**	**4**	**6**	**8**	**24**	**48**
Batch 1	0.51	0.89	1.56	2.35	2.95	7.38	11.92
Batch 2	0.56	0.97	1.73	2.61	3.26	7.82	12.02

After 12 hours, due to hygroscopicity the increase in mass is about 7-8 %, and after 48 hours, the increase in mass of the sample is approximately 12 %. This is about the order of magnitude known for Zn-DTPA in the state of the art. Here, the hygroscopicity of common Zn-DTPA is so strong that, if it is exposed to atmospheric humidity for a sufficiently long period, it even dissolves due to its hygroscopicity.

Because of the comparable electron configuration of calcium (Ca:[Ar]4s2; Zn:[Ar] 3d10 4s2) Ca-DTPA forms a similar complex. However, due to the different atomic radii, the complex is significantly less stable. Thus, it is difficult to compare the two complexes in terms of their chemical and physical properties.

A method is described for producing Ca-DTPA wherein an alcohol is added to a cold aqueous solution

of the product to create precipitation (GB944020). However, a crystalline form of this complex is not described here.

Up to now, it has not been possible to present Zn-DTPA in a form which results in a stable product which can be processed under atmospheric conditions to create a pharmaceutical form for administration orally.

Against his background, the objective of the present invention was to produce Zn-DTPA in a form which is more stable under atmospheric conditions than the form known and available up to now. In particular, it was a task for the invention to slow down and/or to decrease the hygroscopicity of Zn-DTPA. Also, the intention was that the inventive DTPA should be preferably suitable for pharmaceutical forms for administration orally.

This task is resolved by trisodium zinc diethylenetriaminepentaacetic acid (Zn-DTPA) in a crystalline form.

If there should be any doubt in the definition of the word "crystalline", as far as this text is concerned, the meaning of "crystalline" is that ions or molecules are not randomly positioned in the particular substance, but, instead, are arranged in a regular fashion in a crystalline structure. This is shown in the x-ray diffractogram as a clearly identifiable diffraction pattern. Examples of this kind of diffraction pattern are provided in the Figures. The reflexions shown there, as illustrated, for example, in Tables 1 and 2, are arranged to be reproducible for each crystal form at the same 2 theta angle. As already described above, up to now crystalline forms of Zn- DTPA have not been available. Surprisingly, it has turned out that these types of crystalline forms can be produced by methods described below. In particular, it has been proved, surprisingly, that the hygroscopicity is slowed down and generally restricted in the case of the crystalline forms. Also, reference will be made in this regard to embodiments produced below.

Preferably, the trisodium zinc diethylenetriaminepentaacetic acid according to the invention is present in a crystalline form wherein its powder x-ray diffractogram is assigned to a powder x-ray diffractogram having at least the following characteristic peaks (Form I, Fig. 1):

Table 2

Pos. [°2th.]	d-spacing [Å]	Rel. Int. [%]
6.8836	14.90	48
8.1807	12.54	100
14.477	7.10	52
17.725	5.81	43

or has at least the following characteristic peaks (Form II, Fig. 2):

Table 3

Pos. [°2th.]	d-spacing [Å]	Rel. Int. [%]
11.302	9.08	21
14.892	6.90	32
16.699	6.16	100
21.721	4.75	41

The x-ray diffractograms in Figure 1 and Figure 2 show the two crystalline forms I and II. Unless otherwise stated, the x-ray diffractogram data in this text refer to recordings that were made with Co K-alpha radiation. A detailed description of the x-ray diffractogram recordings can be found in example 7.

In this case, it will be obvious to an expert that, depending on the quite specific measurement conditions, deviations can occur concerning both the peak position as well as the relative intensity of the peaks. Accordingly, within the context of this text, a "powder x-ray diffractogram is assigned to a powder x-ray diffractogram with a certain peak position and peak intensity" means that the expert is able to establish that the measured test sample corresponds to the particular peak sample and the corresponding peak intensity taking account of the special measurement situation. This means that the diffraction pattern is substantially consistent with the Figures of the preferred crystal form, preferably the peaks of the powder x-ray diffractogram of the preferred inventive crystal forms are each displaced by a maximum of ± 0.5, particularly preferably ± 0.3, with regard to their position, preferably with regard to their d-value compared with the statements made in this text. In particular, the intensities provided in the Tables are to be regarded in this connection purely as information and not limited to the crystal form according to the invention.

Form I occurs, if methanol is used, for example, to extract Zn-DTPA from a hot, aqueous solution. The same applies to example 2 also.

Particularly preferably, the inventive trisodium zinc diethylenetriaminepentaacetic acid occurs in a crystalline form wherein its powder x-ray diffractogram is assigned to a powder x-ray diffractogram that shows one or even all of the peaks provided in the following Table, additional to those given in Table 3 in the powder x-ray diffractogram of the inventive crystalline form of Zn-DTPA (Form I, Fig. 1):

Table 4 Peak list (Form I)

Pos. [°2th.]	d-spacing [Å]	Rel. Int. [%]
6.8836	14.90	48
8.1807	12.54	100
13.781	7.46	7
14.477	7.10	52
17.725	5.81	43
20.567	5.01	4

Form II occurs, for example, when the water is removed from the reaction mixture by azeotropic distillation with n-butanol (cf. e.g. example 5, below), and crystallises the product out of the reaction mixture. A comprehensive peak list for form II is provided below (**Table 5** Table 6), wherein it is preferable that, from amongst the peaks provided above, at least one, two, three or even all of the peaks provided also in the following table are found in the powder x-ray diffractogram of the inventive crystalline form of Zn-DTPA.

Table 5 Peak list (Form II)

Pos. [°2th.]	d-spacing [Å]	Rel. Int. [%]

11.302	9.08	21
11.384	9.02	86
14.892	6.90	32
16.699	6.16	100
20.038	5.14	6
20.962	4.92	8
21.721	4.75	41
22.840	4.52	6
26.436	3.91	3
27.139	3.81	4
27.291	3.79	5
28.494	3.63	1
32.168	3.23	5
33.734	3.08	10
34.426	3.02	1
36.161	2.88	8
36.777	2.84	2
42.811	2.45	6
43.183	2.43	5

The inventive (in particular preferred) crystalline forms of Zn-DTPA are also noted for having high chemical stability and a low hygroscopicity. At the same time, the Zn-DTPA according to the invention is worth considering not only in view of its absolute hygroscopicity compared with products from the state of the art, but also because of the rate at which it absorbs water.

Accordingly, an inventive trisodium zinc diethylenetriaminepentaacetic acid is preferable wherein the trisodium zinc diethylenetriaminepentaacetic acid, starting from a water content of 8 wt % takes up ≤ 10 wt % water when stored at 65 % humidity and 25 °C for 48 h.

Preferably in this case, an inventive trisodium zinc diethylenetriaminepentaacetic acid is used which, starting from a water content of 8 wt % takes up ≤ 7 wt % water when stored at 65 % humidity and 25 °C for 48 h.

The particular advantage of a slow absorption of water is that, when processing the inventive crystalline form of Zn-DTPA, less rigid measures are needed regarding lowering the atmospheric humidity, and, in the ideal case, the inventive forms can be processed actually further without any special measures, for example going on th process pharmaceutical formulations.

The following Table 1 shows a comparison between conventionally produced amorphous Zn-DTPA and two crystalline forms according to the invention. In this case, each of the samples used were subjected to the same pre-drying process (cf. examples 3 and 4). The samples were each exposed for the time stated in the Table at 25 °C and a relative atmospheric humidity of 65 %.

Table 6 shows the comparison between conventionally produced amorphous Zn-DTPA and the two crystalline forms.

Table 6

Time [hrs] No.	Average increase in mass [%]						
	1	2	4	6	8	24	48
Form I (from example 2)	0.32	0.54	0.92	1.34	1.64	3.91	6.81
Form II, A (from example 3)	0.34	0.57	1.00	1.49	1.84	4.42	5.07
Form II, B (from example 4)	0.41	0.72	1.29	1.97	2.43	5.18	5.25
Amorphous (from example 1)	0.51	0.89	1.56	2.35	2.95	7.38	11.92
Amorph II (from example 1)	0.56	0.97	1.73	2.61	3.26	7.82	12.02

The inventive crystalline forms therefore exhibit an increase in mass of less than 10 %, preferably less than 7 %, particularly preferably less than 6 % after 48 hours under the stated conditions.

Also, compared with the amorphous forms known from the state of the art, the absolute absorption of water of the inventive crystalline forms is improved significantly. As a result, if the amorphous forms are exposed sufficiently to atmospheric humidity, they have a tendency to dissolve. Thus, it is preferable according to the invention to use trisodium zinc diethylenetriaminepentaacetic acid wherein it remains in the solid state after storage at 65 % humidity and 25 °C for 200 h.

Furthermore, an inventive trisodium zinc diethylenetriaminepentaacetic acid is preferred which comprises a total content of ≤ 16 wt %, preferably ≤ 15 wt %, further preferably ≤ 14 wt % of water after storage at 65 % humidity and 25 °C for 200 h.

The advantage of the low hygroscopicity (absolute) lies particularly in the fact that the inventive crystalline forms remain stable as solid bodies whereas the amorphous forms of Zn-DTPA known from the state of the art actually tend to dissolve. As a result, a whole series of applications are opened up as a result of the inventive forms.

Accordingly, a part of the invention is an inventive trisodium zinc diethylenetriaminepentaacetic acid for use as a medicament. As described above already, up to now the crystalline forms have not been available and, as a result, have not been able to be used even in the medical field, even though there has been a demand for this.

Against this background and, in particular, in the light of the improved properties (especially with respect to the hygroscopicity), a part of the invention is an, in particular, pharmaceutical formulation orally administrable to a human and/or an animal comprising inventive Zn-DTPA.

A large number of useful formulations, in particular, for oral and quite particularly pharmaceutical administration, are feasible due to the improved stability of the inventive Zn-DTPA. An orally administrable formulation is, in this case, a formulation which can be administered to an animal or to a

human, in particular to a human, due to its ingredients and preferably also due to its consistency. In this context, a pharmaceutical formulation is one which preferably fulfils prerequisites applied to pharmaceutical products, in particular, in Germany.

Preferably the orally administrable, in particular orally administrable pharmaceutical formulation is a solid formulation comprising suitable carriers. The solid formulation can be realised as a direct compression of the agent or can comprise other auxiliary agents selected from the group consisting, in particular, of starch (corn, potato or wheat starch), lactose, glucose, mannitol or sorbitol; binding agents, in particular, MCC (microcrystalline cellulose) or starch; moist binding agents/adhesives for granulation, in particular, starch pastes, cellulose ethers, Kollidon or gelatine; explosives, in particular, potato starch, corn starch, PVP, carbopol or magnesium peroxide and lubricants.

Another part of the invention is the use of inventive Zn-DTPA or an orally administrable formulation, comprising inventive Zn-DTPA for the treatment or prophylaxis of intoxication with heavy metals and/or radionuclides. In this case radionuclides are, in particular, the preferred type of application. Here, the inventive Zn-DTPA or, respectively the formulation comprising this, is particularly effective against the heavy metals and/or radionuclides selected from the group consisting of uranium, curium, plutonium and americium, wherein the last two listed are particularly preferable.

A part of the invention is a method for the preparation of inventive trisodium zinc diethylenetriaminepentaacetic acid comprising the steps:

a) reaction of pentetic acid with zinc oxide or other zinc salt in the presence of water,

b) twice the concentration of the reaction solution to ≤ 15 % of the initial volume and subsequent addition of an organic solvent and

c) isolating the crystalline reaction product.

This inventive method represents an excellent way of preparing the form I described above.

A part of the invention is also a method for the preparation of inventive trisodium zinc diethylenetriaminepentaacetic acid, comprising the steps

a) reaction of pentetic acid with zinc oxide or other zinc salt in the presence of water,

b) removal of 90 - 99 wt %, preferably 94 to 96 wt % of the water from the reaction mixture, wherein 15 - 100 wt %, preferably 20 - 60 wt %, particularly preferably 20 to 45 wt % of organic solvent is added in relation to the water content before the start of the removal of the water parallel to or before the start of the removal of water,

c) optionally adding further organic solvent according to step b),

d) further removing water and preferably also organic solvent until the steam temperature is within the range of ± 5°C of the boiling temperature of the organic solvent and/or until crystallisation occurs and

e) isolating the crystalline reaction product.

This inventive method is particularly suitable for preparing the crystalline form II.

In general, the inventive Zn-DTPA can be prepared by neutralising diethylenetriaminepentaacetic acid in an aqueous solution with sodium hydroxide and then adding zinc oxide. Zinc salts other than zinc oxide are also possible.

In this case, it is advantageous for the inventive method if the (organic) solvent is selected such that the solubility of Zn-DTPA in the solvent is less than 1 g/ml.

Because the inventive product can be dissolved very easily in water, during the preparation of the inventive product, the water must be removed from the reaction mixture (see above).

In principle, it is possible to remove water by vacuum distillation, for example, wherein a suitable solvent has to be added beforehand or during in order to replace a part of the water. As described above, it is preferable in this process to add 15 - 100 wt %, preferably 20 - 45 wt % of an organic solvent in relation to the water content before the start of the removal of the water.

The inventive products are obtained particularly reliably if the volume of water removed from the reaction solution is controlled. This is possible by, for example, collecting the water, but, alternatively, the distillation temperature is also a good indication of the water content remaining in the reaction mixture.

In this connection, azeotropic distillation is a particularly suitable method of removing water, wherein the water is removed in stages and the remaining proportion of water in the reaction mixture is inversely proportional to the temperature.

Azeotropic distillation is a common method of removing water from an oily reaction product (see also EP1413575, example 5). Toluene is used as the agent of choice. Another example of the removal of water from a reaction product by azeotropic distillation is described in EP0449445.

Accordingly, it is advantageous if the (organic) solvent used forms an azeotrope with water. In this case, the removal of the water is facilitated by the azeotropic distillation, wherein preferably water is removed from the reaction mixture until the product in the mixture can begin to crystallise in the heat. In this process, it is also possible, after reaching the desired water content of just about 1 - 10 wt %, preferably 4-6 wt % of the original water content or, respectively, particularly preferably of about 5 wt % of the original water content, to add organic solvent once again.

Furthermore, according to the invention it can be preferable, during the azeotropic distillation, to return the organic solvent back into the reaction solution. Also, in this connection it can be preferable, after removal of the water, to also distil organic solvent out as part of the azeotropic distillation.

As a general rule, the distillation of water and, possibly, organic solvent takes place until a honey-like liquid develops which preferably precipitates on the reactor surface and thickens as water continues to be removed.

In the case of preferred embodiments of the inventive method, the product begins to solidify at 97 - 98 °C vapour temperature.

Preferably, when a vapour temperature of 110 °C is reached (particularly during an azeotropic distillation with n-butanol as the organic solvent), the inventive crystalline product precipitates.

Preferably this is now isolated by a filtration step.

The organic solvents used for the inventive method are selected preferably from the group consisting of acetone, n-butanol, 2-methyl-1-propanol, methanol, ethanol, n-propanol, 2-propanol, 2-methyl-2-propanol, toluene and ethyl acetate.

In this process, it is particularly preferably for the preparation of the crystal form I that methanol is the organic solvent, whereas, for the crystalline form II, toluene in particular is preferable and, most preferably, n-butanol is the organic solvent to use.

This does not mean, on the other hand, that other solvents that form an azeotrope with water cannot be used for the preparation according to the inventive method. As indicated above already, the removal of the water in the inventive method by azeotropic distillation is advantageous, but it is not necessary for every solvent. Similar results can be achieved also if the reaction solution is sufficiently restricted by (optional) distillation, followed by adding a (organic) solvent to the aqueous reaction solution.

The preferred steps for the inventive method are the neutralising of the pentetic acid used by means of a sodium hydroxide solution and/or the cooling of the reaction mixture, in particular, before filtering.

However, since it is possible in principle to obtain the filtrate out of the hot suspension also, it is possible to isolate the inventive reaction product relatively quickly wherein impurities remain in the filtered liquid.

Thus, during the course of the preferred inventive method, it is possible to make use of two effects in particular: firstly, in this process, there is the low solubility of Zn-DTPA in certain organic solvents and, secondly, the capability of certain solvents to form an azeotrope with water in order that water removal conditions and the water removal progress are controlled optimally. While these properties have been used already to remove water from reaction mixtures, it is surprising, however, that it is possible, by means of the inventive and, in particular, the preferred inventive methods, to obtain Zn-DTPA in defined crystalline form with reproducible product properties and with a reduced hygroscopicity and, therefore, with improved stability.

The preferred inventive method in the form of the azeotropic distillation has, in particular, the following advantages:

- It is comparatively easy to determine the quantity of the water remaining in the reaction mixture (due to the temperature relationship), in particular when compared with other methods of removing water, such as by vacuum distillation. Naturally the same applies also for the quantity of water removed from the reaction mixture.

- When using the preferred solvent, in particular, using n-butanol in conjunction with an azeotropic distillation, the advantage lies in the low solubility of the product in the solvent and, what is more, in a high reaction yield.

- Furthermore, it is possible to recover the organic solvent, in particular, n-butanol, which reduces the preparation costs.

- It is a particular advantage of the inventive method that only one polymorphic form is obtained.

Examples

Example 1: Preparation of amorphic Zn-DTPA

152.5 g NaOH were dissolved in 1.7 l of water and the solution cooled to 30 °C. Next, 500 g of DTPA were added while stirring, and then stirred until the solution was clear (about 20 min). 103.4 g of zinc oxide were added to the solution and the solution was stirred overnight until a clear solution emerged.

The pH value was adjusted to 7.0 with a 10 % NaOH solution and the solution was filtered. Then, the solution was reduced under vacuum at 40 °C while being stirred vigorously and dried for 17 hours at 90 °C at 2.5 KPa.

641.1 g were produced corresponding to 96.5 % of the theoretical. Purity by HPLC: 99.6 %; water content: 7.16 %.

Example 2: Preparation of crystalline Zn-DTPA form I

296 g of NaOH were dissolved in 3.4 l of water and the solution cooled to 30 °C. Next, 1 kg of DTPA was added while stirring, then stirred until the solution was clear (about 20 min). 207 g of zinc oxide were added to the solution and the solution was stirred overnight until a clear solution emerged.

The pH value was adjusted to 7.01 with a 10 % NaOH solution and the solution was filtered. Then, the solution was reduced under vacuum at 40 °C while stirring and 3.2 l of methanol were added. The solution was again reduced so that 3 litres of liquid were distilled out. 2 litres of methanol were again added so that a solid substance crystallised out. The crystals were filtered out and dried for 17 hours at 90 °C at 2.5 KPa.

812.4g were produced, i.e. 61.14% of the theoretical. Purity by HPLC: 99.6 %; water per Karl Fischer: 5.49 %.

Example 3: Preparation of crystalline Zn-DTPA form II

296 g of NaOH were dissolved in 3.4 l of water and 1 kg of DTPA added while stirring in an apparatus with a water separator. 207 g of zinc oxide were added, and the pH value adjusted to 7.0. 1 litre of n-butanol was added to the suspension and the solution heated while water was being removed (azeotropic distillation) until crystallisation occurred. After cooling, the crystalline product was filtered out of the reaction solution.

Drying of the product at 90 °C at 2.5 KPa for 17 hours produced 1.3 kg, corresponding to 100 % of the theoretical; Contents per HPLC 101.6 %, water content: 8 %.

Example 4: Preparation of crystalline Zn-DTPA form II

296 g NaOH were dissolved in 3.4 l of water and 1 kg of DTPA added while stirring in an apparatus with a water separator. 207 g of zinc oxide were added, and the pH value adjusted to 7.0. About 2.5 litres of water were distilled off. Then, 1 litre of n-butanol was added to the solution and heated while water was being removed until crystallisation occurred. After cooling, the crystalline product was filtered out of the reaction solution.

Drying of the product at 90 °C at 2.5 KPa for 17 hours produced 1.2 kg, corresponding to 92 % of the theoretical; Contents per HPLC 100.0 %, water content: 7.6 %.

Example 5:

5 kg of diethylenetriaminepentaacetic acid were added to a solution of 1.48 kg of sodium hydroxide in water (17 kg). Then 1.04 kg of zinc oxide was added and the reaction mixture stirred.

In the next step, diatomite (1.0 kg) was added and the suspension was filtered through a suitable filter and then rinsed with water. Next, 22 kg of butanol were added to the filtrate and this mixture distilled azeotropically at atmospheric pressure.

The water was separated during the distillation and the volume of the separated water as well as the distillation temperatures were checked regularly. The n-butanol phase was reintroduced into the reaction vessel and, during the azeotropic distillation, 6 kg of more n-butanol were added gradually to the reaction mixture to partially replace the removed water.

When a temperature of 101 - 102 °C was reached, more n-butanol (12 kg) was added and the distillation continued until a temperature of 110 °C was reached in the reaction mixture. At this stage, no more n-butanol was introduced into the reaction mixture and all n-butanol was separated.

The boiling suspension was stirred and the reaction product separated by filtration. In doing so, it is possible in principle to cool the reaction mixture or to filter it while hot.

Finally, the end product was dried in a vacuum dryer at 90 °C and the desired product (crystal form II) was obtained.

The remaining liquid and the butanol phase were distilled and the recovered butanol was used for the next batch.

Example 6: Determination of the hygroscopicity
The hygroscopicity of Zn-DTPA was checked by measuring the increase in weight in a controlled environment. At (25 ± 2) °C air temperature and (60 ± 5) % atmospheric humidity, the weights of each of two test samples (5.000g) were checked (analytical scale, XS 205, Mettler Toledo) in a stability chamber (Thermo TEC). The weight was recorded after 1, 2, 4, 6, 8, 24 and 48 hours.

Example 7: Determination of powder x-ray diffractogram
The powder x-ray diffractogram samples of the solid forms of Zn-DTPA were determined within the 2-theta range 2° to 51° using a Bragg-Brentano focusing powder diffractometer, Philips, Model 1730/10 (Philips, Holland), wherein the diffractometer was connected to a PC for further analysis.

The instrument was equipped with an x-ray tube, which provided Co Kα radiation, wave length 0.179021 nm. The conditions during measurement were as follows:

Excitation voltage: 40 kV, anode current strength: 35 mA, step size: 0.02°, step time 2.4 seconds.

Test sample: smooth surface, inserted in a nickel sample holder. The test sample was measured at room temperature and retained. In the measurements, the test samples were used as lightly pressed powder discs. Before the measurements, the material samples were very gently crushed using an agate mortar and an agate bowl.

The qualitative characteristics of the diffraction pattern, that is, the peak positions and relative intensities of the measured test samples are given (in the whole text) in a Table (D-values and intensity and ° 2th.).

The results of the measurements of the respective test samples are given in Figures 1 and 2 and in the Tables above.

TRINÁTRIUM-CINK-DIETILÉN-TRIAMIN-PENTAECETSAV KRISTÁLYOS FORMÁI

Szabadalmi igénypontok

1. Trinátrium-cink-dietilén-triamin-pentaecetsav (Zn-DTPA) kristályos formában.

2. Trinátrium-cink-dietilén-triamin-pentaecetsav az 1. igénypont szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsavnak a por-röntgendiffraktogramja (angolul: „powder X-ray diffractogram") egy olyan por-röntgendiffraktogram körébe tartozik, amely legalább a következő jellemző csúcsokkal rendelkezik (I Forma):

Pozíció [2-Théta fok] Pos. [°2Th.]	Rétegek közti távolság d-spacing [Å]	Relatív intenzitás Rel. Int. [%]
6,8836	14,90	48
8.1807	12,54	100
14.477	7,10	52
17.725	5,81	43

vagy egy olyan por-röntgendiffraktogram körébe tartozik, amely legalább a következő jellemző csúcsokkal rendelkezik (II Forma):

Pozíció [2-Théta fok] Pos. [°2Th.]	Rétegek közti távolság d-spacing [Å]	Relatív intenzitás Rel. Int. [%]
11.302	9,08	21
14.892	6,90	32
16.699	6,16	100
21.721	4,75	41

3. Trinátrium-cink-dietilén-triamin-pentaecetsav az 1. vagy 2. igénypont szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsav egy 8 tömeg%-os (wt%) víztartalomból kiindulva ≤ 10 tömeg% (legfeljebb 10 tömeg%) (wt%) vizet vesz fel, amikor 65%-os nedvesség (páratartalom) mellett és 25°C-on van tárolva 48 h-ig (óráig).

4. Trinátrium-cink-dietilén-triamin-pentaecetsav az előző igénypontok egyike szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsav egy 8 tömeg%-os (wt%) víztartalomból kiindulva ≤ 7 tömeg% (legfeljebb 7 tömeg%) (wt%) vizet vesz fel, amikor 65%-os nedvesség (páratartalom) mellett és 25°C-on van tárolva 48 h-ig (óráig).

5. Trinátrium-cink-dietilén-triamin-pentaecetsav az előző igénypontok egyike szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsav az után, hogy 65%-os nedvesség (páratartalom) mellett és 25°C-on van tárolva 200 h-ig (óráig), szilárd halmazállapotban marad.

6. Trinátrium-cink-dietilén-triamin-pentaecetsav az előző igénypontok egyike szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsav az után, hogy 65%-os nedvesség (páratartalom) mellett és 25°C-on van tárolva 200 h-ig (óráig), ≤ 16 tömeg% (legfeljebb 16 tömeg%) (wt%) vizet tartalmaz.

7. Trinátrium-cink-dietilén-triamin-pentaecetsav az előző igénypontok egyike szerint, ahol a trinátrium-cink-dietilén-triamin-pentaecetsav az után, hogy 65%-os nedvesség (páratartalom) mellett és 25°C-on van tárolva 200 h-ig (óráig), ≤ 14 tömeg% (legfeljebb 14 tömeg%) (wt%) vizet tartalmaz.

8. Trinátrium-cink-dietilén-triamin-pentaecetsav az előző igénypontok egyike szerint, gyógyszerként történő alkalmazásra.

9. Egy embernek és/vagy állatnak orálisan adagolható készítmény (formuláció), amely tartalmazza az előző igénypontok bármelyike szerinti trinátrium-cink-dietilén-triamin-pentaecetsavat.

10. Trinátrium-cink-dietilén-triamin-pentaecetsav az 1.-től 8.-ig igénypontok egyike szerint vagy embernek és/vagy állatnak orálisan adagolható készítmény (formuláció) a 9. igénypont szerint, amely nehézfémek és/vagy radionuklidek általi mérgezésnek a kezelésére vagy megelőzésére szolgál.

11. Eljárás az 1.-től 8.-ig igénypontok egyike szerinti trinátrium-cink-dietilén-triamin-pentaecetsavnak az előállítására, ahol az magában foglalja a következő lépéseket:

    a) dietilén-triamin-pentaecetsav (pentetasav, angolul: „pentetic acid") reakciója cink-oxiddal vagy más cinksóval víz jelenlétében,

    b) a reakcióoldat kétszeres koncentrálása a kiindulási térfogat legfeljebb 15%-ára (≤ 15%-ra a kiindulási térfogatból) és azt követően egy szerves oldószer hozzáadása és

    c) a kristályos reakcióterméknek izolálása.

12. Eljárás az 1.-től 8.-ig igénypontok egyike szerinti trinátrium-cink-dietilén-triamin-pentaecetsavnak az előállítására, ahol az magában foglalja a következő lépéseket:

    a) dietilén-triamin-pentaecetsav (pentetasav, angolul: „pentetic acid") reakciója cink-oxiddal vagy más cinksóval víz jelenlétében,

    b) a víz 90 tömeg%-tól 99 tömeg%-ig történő eltávolítása a reakcióelegyből, ahol 15 tömeg%-tól 100 tömeg%-ig szerves oldószer van hozzáadva a víztartalomhoz viszonyítva a víz eltávolításának a megkezdése előtt, a víz eltávolításának a megkezdésével párhuzamosan vagy az előtt,

    c) opcionálisan további szerves oldószer hozzáadása a b) lépés után,

    d) a víz további eltávolítása, amíg a gőz hőmérséklete a következő tartományban van: a szerves oldószernek a forrási hőmérséklete (forráspontja) ± 5°C, és/vagy amíg a kristályosodás megtörténik és

    e) a kristályos reakcióterméknek izolálása.

13. Eljárás a 11. vagy 12. igénypont szerint, ahol a szerves oldószer a következőkből álló csoportból van választva: aceton, n-butanol, 2-metil-1-propanol, metanol, etanol, n-propanol, 2-propanol, 2-metil-2-propanol, toluol és etil-acetát.

14. Eljárás a 11. igénypont szerint, ahol a szerves oldószer a metanol, vagy eljárás a 12. igénypont szerint, ahol a szerves oldószer az n-butanol.

15. Eljárás a 11.-től 14.-ig igénypontok egyike szerint, ahol a víz koncentrálása, illetve eltávolítása a b) lépésben azeotróp desztilláció révén van megvalósítva.

Drawings

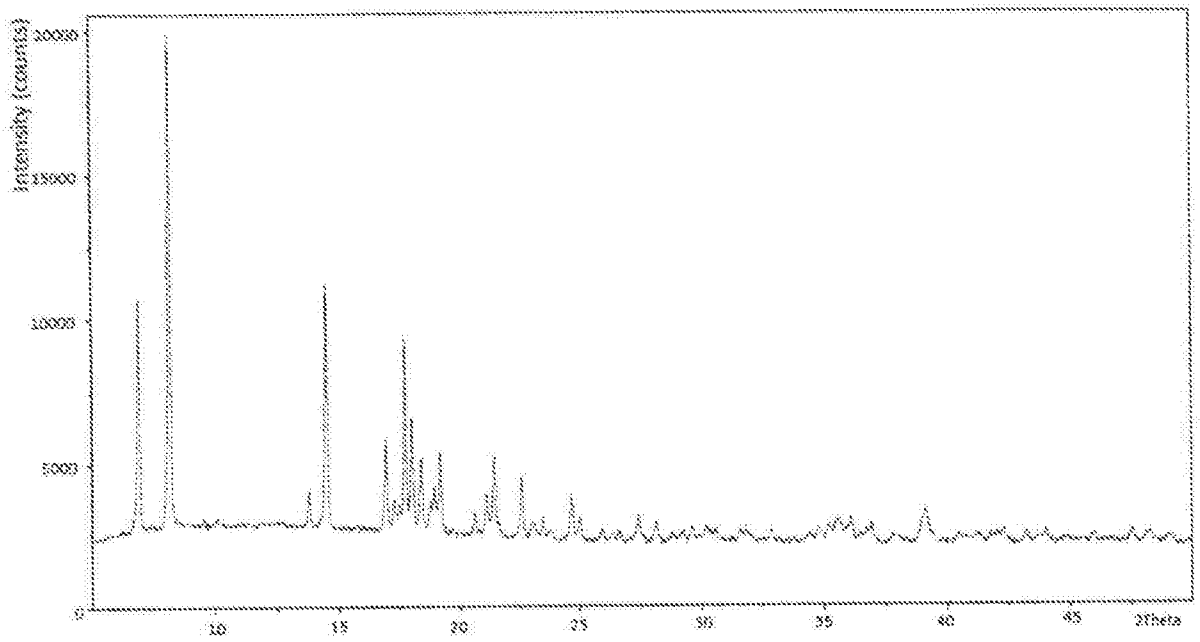


Fig. 1

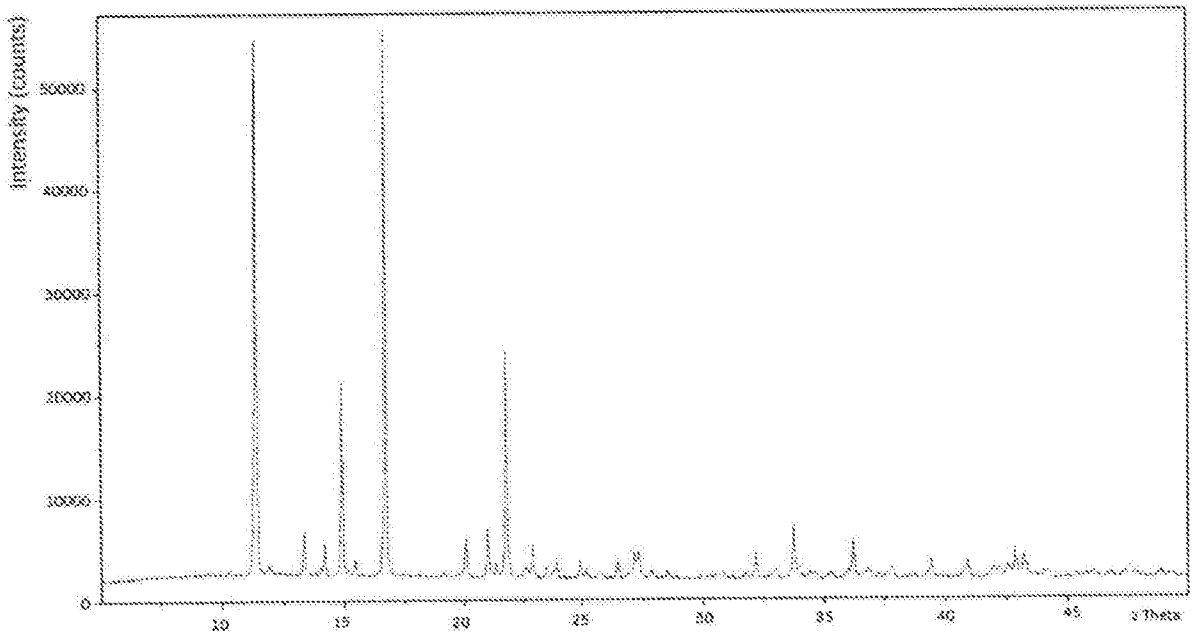


Fig. 2