(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 2732811 B1**

(19) NO

NORGE

(51) Int Cl.

A61K 9/19 (2006.01)
A61K 9/00 (2006.01)
A61K 31/706 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2016.06.06
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2016.01.13
(86)	Europeisk søknadsnr	12193209.9
(86)	Europeisk innleveringsdag	2012.11.19
(87)	Den europeiske søknadens Publiseringsdato	2014.05.21
(30)	Prioritet	
(84)	Utpekte stater	AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
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(54) Benevnelse **Method for producing a freeze-dried compound**

(56) Anførte publikasjoner

WO-A1-2010/036702
WO-A2-2006/076620
US-A- 4 537 883
MAAS B: "Stabilität von Bendamustinhydrochlorid in Infusionsl sungen", DIE PHARMAZIE, GOVI VERLAG PHARMAZEUTISCHER VERLAG GMBH, ESCHBORN, DE, Bd. 49, Nr. 10, 1. Januar 1994 (1994-01-01), Seiten 775-777, XP008060268, ISSN: 0031-7144

The invention relates to a process for preparing a freeze-dried composition containing bendamustine or a salt thereof which, in particular within a short time, leads to products that can be easily and rapidly reconstituted.

Bendamustine is an antitumour chemotherapeutic agent from the group of alkylating agents. It is characterized above all by a very good side-effects profile. It is used in the form of aqueous injection or infusion solutions. However, such aqueous solutions have a short shelf life because bendamustine and its salts are susceptible to hydrolysis. For this reason bendamustine is regularly prepared in freeze-dried form and this lyophilisate is reconstituted with sterile solvent immediately before administration, in order to produce an injection or infusion solution.

However, the known processes for preparing freeze-dried bendamustine compositions and the products obtained therewith have a number of disadvantages.

WO 2006/076620 describes lyophilisates of bendamustine and freeze-drying processes for the preparation thereof. However, the lyophilisates described require a period of 3-5 minutes for complete reconstitution. In addition, in tests on different processes, there was found to be a problem with powder ejection during the main drying. This problem is avoided by use of a step-wise and slow main drying. Accordingly, a freeze-drying process is described, which uses a main drying in several steps at temperatures of -20°C, -15°C and -12°C and lasts in total about 89 hours. However, such a long process duration is very disadvantageous, in particular for economic reasons.

Furthermore, a process for preparing bendamustine lyophilisates is also known from WO 2011/103150. During this process, drying takes place in two steps at 25°C and 30°C, wherein the entire process duration is more than 60 hours. Furthermore, the lyophilisates must however contain cyclodextrin in order to ensure the desired stability and a rapid reconstitution to injection solutions.

Thus, the processes known from the state of the art prove to be protracted. Long process times are however very unfavourable, specifically in the case of manufacturing on an industrial scale. In addition, the lyophilisates obtained with the known processes need a very long time for complete reconstitution or require special excipients such as cyclodextrin in order to ensure rapid dissolution.

These problems are to be avoided according to the invention. The object of the invention is in particular to provide a process for preparing freeze-dried compositions containing bendamustine or a salt thereof, which is characterized by a shortened duration and which leads to compositions that can be reconstituted to solutions within a short time.

This object is achieved by the process according to claims 1 to 15. A subject-matter of the invention is also the freeze-dried composition according to claim 16.

The process for preparing a freeze-dried composition containing bendamustine or a salt thereof according to the invention is characterized in that

(a) a solution containing bendamustine or a salt thereof is frozen at a first freezing temperature,

(b) optionally

(b1) the frozen solution is tempered at a temperature of -25 to -10°C and

(b2) is frozen at a second freezing temperature, which is lower than the temperature in (b1), and

(c) the frozen solution obtained according to step (a) or (b) is dried at a first drying temperature of -5 to +5°C for a period of at least 10 hours, in order to prepare a freeze-dried composition.

In step (a) a solution is used, which contains bendamustine or a salt thereof. Bendamustine hydrochloride is preferably used. The bendamustine or the salt thereof is present in the solution in particular in a concentration of 5.65 to 5.70 mg/ml and preferably 5.67 to 5.69 mg/ml.

The solution preferably contains at least one organic solvent. The organic solvent is in particular an alcohol, preferably ethanol, propanol or tert-butanol and particularly preferably ethanol. The alcohol content of the solution is preferably 1.5 to 2.5 vol.-% and particularly preferably 1.8 to 2.0 vol.-%.

The solution usually also contains water. The water content of the solution is in particular 96.5 to 97.5 vol.-% and particularly preferably 97.0 to 97.2 vol.-%.

Furthermore, it is preferred that the solution contains at least one monosaccharide, oligosaccharide or sugar alcohol, preferably sucrose, dextrose, maltose, lactose, sorbitol, mannitol or dextran, and particularly preferably mannitol. These substances

can be described as scaffolds, and they can favourably influence the freeze-drying process with respect to the mechanical stability of the freeze-dried composition. It is assumed that this positive influence takes place via the formation of partially amorphous structures. The scaffolds are present in the solution in particular in a concentration of 6.75 to 6.90 mg/ml and preferably 6.80 to 6.84 mg/ml.

As a rule the solution is poured into a suitable container, e.g. an injection bottle, and the container is placed in a conventional freeze-dryer with coolable and heatable shelves on which the solution can be exposed to the various temperatures of the freeze-drying process.

According to the invention the solution is then frozen at a first freezing temperature. It is preferred that cooling to the first freezing temperature takes place at a cooling rate of 0.6 to 1.2°C/min, preferably 0.8 to 1.0°C/min and particularly preferably about 0.9°C/min.

In addition it is preferred that the first freezing temperature is -40°C or lower, preferably -40°C to -55°C and particularly preferably -40°C to -50°C.

It has, furthermore, proved advantageous to freeze the solution for a period of 90 to 150 min, in particular 100 to 120 min at the first freezing temperature.

The subsequent step (b) is optional. However, it is preferred to carry it out as it helps to achieve short reconstitution times of the lyophilisate finally obtained. It is assumed that this takes place via activation of diffusion and crystallization processes which lead to a favourable influence on the pore size of the lyophilisate.

In step (b) the frozen solution (b1) is tempered at a temperature of -25 to -10°C and (b2) re-frozen at a second freezing temperature, which is lower than the temperature in (b1).

The temperature used for tempering in step (b1) is in particular -20 to -13°C and particularly preferably about -15°C.

It is preferred to temper the frozen solution for a period of at least 3 hours, preferably at least 4 hours and particularly preferably at least 5 hours.

A temperature of -40°C or lower, preferably -40°C to -55°C and particularly preferably -40°C to -50°C is in particular selected as second freezing temperature in step (b2).

It is preferred to expose the frozen solution to the second freezing temperature for a period of at least 2 hours and preferably at least 3 hours.

The frozen solution is heated to the temperature selected in (b1) for tempering, preferably at a heating rate of 0.9 to 1.5°C/min, preferably 1.1 to 1.3°C/min and particularly preferably about 1.2°C/min.

The subsequent re-cooling to the second freezing temperature selected in (b2) preferably takes place at a cooling rate of 0.9 to 1.5°C/min, preferably 1.1 to 1.3°C/min and particularly preferably about 1.2°C/min.

Finally in step (c) the frozen solution obtained according to step (a) or (b) is dried at a first drying temperature of -5 to +5°C for a period of at least 10 hours, in order to prepare a freeze-dried composition.

It has surprisingly been found that this particular temperature range is apparently essential for the short process duration achieved and the very favourable properties of the freeze-dried composition obtained, i.e. of the lyophilisate.

The first drying temperature is preferably -2 to +2°C and particularly preferably about 0°C.

Furthermore, it has proved advantageous to dry for a period of at least 12, in particular at least 14, preferably at least 16 and particularly preferably at least 18 hours at the first drying temperature. It is further preferred to dry for a period of up to 45 hours.

The heating of the frozen solution to the first drying temperature takes place in particular at a heating rate of 0.38 to 0.46°C/min, preferably 0.40 to 0.44°C/min and particularly preferably about 0.42°C/min.

To effect drying, the frozen solution is usually exposed to a reduced atmospheric pressure in step (c). This results in substantial sublimation of water from the solution, which precipitates e.g. on cooler areas of the freeze-dryer provided for this purpose.

According to the invention it is preferred to expose the frozen solution to a reduced pressure of 0.2 to 0.3 mbar and in particular 0.26 to 0.29 mbar during step (c).

In a preferred embodiment of the process according to the invention the freeze-dried composition obtained according to step (c) is further dried at a second drying temperature of +20°C to +40°C, preferably +30°C to +40°C and particularly preferably at about +40°C in step (d).

This subsequent drying serves in particular to remove more strongly bound water from the obtained lyophilisate.

It is preferred to dry for a period of at least 6, preferably at least 8 and particularly preferably at least 12 hours at the second drying temperature. Furthermore, it is preferred to dry for a period of up to 15 hours.

The heating of the freeze-dried composition to the second drying temperature takes place in particular at a heating rate of 0.10 to 0.25°C/min, preferably 0.15 to 0.20°C/min and particularly preferably about 0.17°C/min.

Also during the drying at the second drying temperature, the obtained composition is usually exposed to reduced atmospheric pressure. This increases the efficiency of the drying. The pressure is usually 0.03 to 0.09 mbar and in particular 0.04 to 0.06 mbar.

After completion of the process according to the invention the freeze-dried composition is usually allowed to come to room temperature and the containers containing it, such as e.g. injection bottles, are sealed under sterile conditions.

The process according to the invention can be carried out in freeze-dryers as used for the preparation of lyophilisates for pharmaceutical purposes. These have heatable and coolable shelves, on which a suitable vessel with the solution to be dried is placed. Suitable freeze-dryers are e.g. Klee freeze-drying systems (Optima Group pharma GmbH, Gladenbach) with a shelf capacity of 0.5 to 1 m^2 and 14 to 15 m^2.

It was surprisingly shown that the process according to the invention differs from conventional processes by a clearly

shortened process duration. This represents an essential advantage in the case of industrial manufacture.

The process according to the invention can be completed e.g. within a period of about 41 hours whereas the process duration of conventional processes is more than 60 hours.

Despite the short process duration the freeze-dried composition obtained according to the invention has only a low residual moisture content. With the process according to the invention a residual moisture of only about 0.25% can be achieved. This is particularly advantageous for the stability of the composition during storage, as a high residual water content would promote the hydrolysis of bendamustine or a salt thereof and thus the reduction of the active-ingredient content as well as the formation of undesired degradation products.

The residual moisture of the composition obtained according to the invention is in particular less than 1.0%, preferably less than 0.7% and particularly preferably less than 0.3%.

It was also surprisingly found that with the process according to the invention, the achieved residual moisture within a batch scarcely fluctuates. By contrast, with conventional processes there are frequently significant fluctuations in residual moisture which, in the case of an unacceptably high level, can even make a further drying of corresponding products necessary.

The composition obtained according to the invention also apparently has a special and advantageous structure as only a very short period of time, in particular of less than 20 seconds, is sufficient for the reconstitution thereof to a solution. This represents a further significant advantage, because it allows the clinical staff to freshly prepare injection solutions immediately before the intended

administration to the patients, without having to put up with long waiting times for complete dissolution. Likewise, such short reconstitution times reduce the risk of an undesired degradation reaction of the active ingredient.

For the reconstitution of the composition usually water for injection purposes is employed.

Because of the advantageous properties described, the invention also relates to a freeze-dried composition containing bendamustine or a salt thereof, wherein the composition is obtainable by the process according to the invention.

This composition is available in particular in the form of a container containing it, preferably an injection bottle.

The invention is explained in more detail below with reference to examples.

Examples

Example 1 – Composition with 25 mg bendamustine

(a) Preparation of the solution

Firstly a solution was prepared by weighing 2.84 g bendamustine hydrochloride into a container and, after the addition of 7.6 g ethanol, dissolving it under stirring. 485.9 g water for injection purposes was weighed into a separate container and 3.41 g mannitol was dissolved therein under stirring. The bendamustine-ethanol mixture was transferred into the mannitol solution and stirred until all the constituents were dissolved.

4.5 ml of this solution was then poured into an injection bottle with a volume of 20 ml.

For each injection bottle the solution had the following composition:
25.56 mg bendamustine hydrochloride
30.69 mg mannitol
68.4 mg ethanol
4.373 g water for injection purposes

(b) Freeze-drying

The solution was then freeze-dried by carrying out the following steps successively in a Klee freeze-dryer with a shelf capacity of 0.6 m^2:

1. Arranging the filled injection bottles on the shelf of the freeze-dryer pre-cooled to +3°C

2. Cooling to -50°C at a cooling rate of 0.9°C/min

3. Maintaining at -50°C for 1 hour

4. Heating to -15°C at a heating rate of 1.2°C/min

5. Maintaining at -15°C for 3 hours

6. Cooling to -50°C at a cooling rate of 1.2°C/min

7. Maintaining at -50°C for 2 hours

8. Reducing the atmospheric pressure to 0.28 mbar

9. Heating to 0°C at a heating rate of 0.42°C/min

10. Maintaining at 0°C for 18 hours

11. Reducing the atmospheric pressure to 0.05 mbar

12. Heating to +40°C at a heating rate of 0.17°C/min

13. Maintaining at +40°C for 8 hours

14. Ventilating the drying chamber of the freeze-dryer and cooling to room temperature

15. Sealing the injection bottle at a low vacuum of 950 mbar

The temperatures indicated above, to which the solution is subjected during the freeze-drying cycle, relate to the respective temperature of the shelf.

The whole process thus lasted only about 41 hours. A white, powdery lyophilisate was obtained, the essential properties of which are listed below.

(c) Essential properties

Firstly, the time required for reconstitution of the obtained lyophilisate was ascertained (reconstitution time). To this end, 10 ml water for injection purposes was added to the

lyophilisate. The mixture was shaken until a clear solution was obtained. The time required for this was measured.

Furthermore, the remaining water content (residual moisture) was determined. To this end, 5 ml dried methanol was added first to the lyophilisate. The obtained suspension was transferred into a Mettler Toledo titrator and the residual moisture in % was determined by means of Karl Fischer titration.

The properties of the lyophilisate ascertained, as well as the freeze-drying process duration required for its preparation were as follows:

Parameter	**Result**
reconstitution time	18 seconds
residual moisture	0.66%
process duration	about 41 hours

These properties show that according to the invention, despite the process duration which is shortened compared with conventional processes, it is possible to prepare a freeze-dried composition which can be reconstituted in less than 20 seconds and, in addition, has only low residual moisture. An injection or infusion solution can thus be rapidly prepared from the composition according to the invention, and the low residual moisture promotes the stability of the composition according to the invention vis-à-vis hydrolytic degradation processes.

Example 2 – Composition with 100 mg bendamustine

(a) Preparation of the solution

17.9 ml of the solution prepared according to Example 1 was poured into an injection bottle with a volume of 50 ml.

For each injection bottle the solution had the following composition:
101.67 mg bendamustine hydrochloride
122.08 mg mannitol
272.08 mg ethanol
17.395 g water for injection purposes

(b) Freeze-drying

The solution was then freeze-dried by carrying out the following steps successively in a Klee freeze-dryer with a shelf capacity of 0.6 m^2:

1. Arranging the filled injection bottles on the shelf of the freeze-dryer pre-cooled to +3°C

2. Cooling to -50°C at a cooling rate of 0.9°C/min

3. Maintaining at -50°C for 1 hour

4. Heating to -15°C at a heating rate of 1.2°C/min

5. Maintaining at -15°C for 3 hours

6. Cooling to -50°C at a cooling rate of 1.2°C/min

7. Maintaining at -50°C for 3 hours

8. Reducing the atmospheric pressure to 0.28 mbar

9. Heating to 0°C at a heating rate of 0.42°C/min

10. Maintaining at 0°C for 32 hours

11. Reducing the atmospheric pressure to 0.05 mbar

12. Heating to +40°C at a heating rate of 0.17°C/min

13. Maintaining at +40°C for 4 hours

14. Ventilating the drying chamber of the freeze-dryer and cooling to room temperature

15. Sealing the injection bottle at a low vacuum of 950 mbar

The whole process thus lasted only about 52 hours. A white, powdery lyophilisate was obtained, the essential properties of which are listed below.

(c) Essential properties

Firstly, the time required for reconstitution of the obtained lyophilisate was ascertained (reconstitution time). To this end, the process was carried out analogously to Example 1. Furthermore, the remaining water content (residual moisture) was determined analogously to Example 1.

The properties of the lyophilisate ascertained, as well as the freeze-drying process duration required for its preparation were as follows:

Parameter	**Result**
reconstitution time	17 seconds
residual moisture	0.25%
process duration	about 52 hours

These properties show that, despite a shorter process duration, this composition according to the invention could also be reconstituted within less than 20 seconds and had only low residual moisture.

Patentkrav

1. Fremgangsmåte for fremstilling av en frysetørket sammensetning med et innhold av bendamustin eller et salt derav, der
(a) en løsning med et innhold av bendamustin eller et salt derav fryses ved en første frysetemperatur,
(b) eventuelt
(b1) tempres den fryste løsningen ved en temperatur på -25 til -10 °C og
(b2) fryses ved en andre frysetemperatur som er lavere enn temperaturen i (b1), og
(c) den fryste løsningen oppnådd etter trinn (a) eller (b) tørkes ved en første tørketemperatur på -5 til +5 °C over et tidsrom på minst 10 timer for å frembringe en frysetørket sammensetning.

2. Fremgangsmåte ifølge krav 1, der nedkjølingen til den første frysetemperaturen i trinn (a) skjer med en kjølerate på 0,6 til 1,2 °C/min.

3. Fremgangsmåte ifølge krav 1 eller 2, der den første frysetemperaturen i trinn (a) er på -40 °C eller lavere, foretrukket -40 °C til -55 °C og spesielt foretrukket -40 °C til -50 °C.

4. Fremgangsmåte ifølge et av kravene 1 til 3, der trinn (b) gjennomføres.

5. Fremgangsmåte ifølge krav 4, der den fryste løsningen tempres i trinn (b1) over et tidsrom på minst 3 timer, foretrukket minst 4 timer og spesielt foretrukket minst 5 timer.

6. Fremgangsmåte ifølge krav 4 eller 5, der oppvarmingen til temperaturen for tempring i trinn (b1) skjer med en oppvarmingsrate på 0,9 bis 1,5 °C/min.

7. Fremgangsmåte ifølge et av kravene 4 til 6, der nedkjølingen til den andre frysetemperaturen i trinn (b2) skjer med en kjølerate på 0,9 til 1,5 °C/min.

8. Fremgangsmåte ifølge et av kravene 1 til 7, der den første tørketemperaturen i trinn (c) er på -2 °C til +2 °C og fortrinnsvis omtrent 0 °C.

9. Fremgangsmåte ifølge et av kravene 1 til 8, der tørkingen i trinn (c) skjer over et tidsrom på minst 12, spesielt minst 14, foretrukket minst 16 og spesielt foretrukket minst 18 timer.

10. Fremgangsmåte ifølge et av kravene 1 til 9, der oppvarmingen til den første tørketemperaturen i trinn (c) skjer med en oppvarmingsrate på 0,38 bis 0,46 °C/min.

11. Fremgangsmåte ifølge et av kravene 1 til 10, der
(d) den frysetørkede sammensetningen oppnådd etter trinn (c) tørkes videre ved en andre tørketemperatur på +20 til +40 °C, foretrukket +30 °C til +40 °C og spesielt foretrukket omtrent +40 °C.

12. Fremgangsmåte ifølge krav 11, der den videre tørkingen i trinn (d) skjer i minst 6, foretrukket minst 8 og spesielt foretrukket minst 12 timer.

13. Fremgangsmåte ifølge krav 11 eller 12, der oppvarmingen til den andre tørketemperaturen i trinn (d) skjer med en oppvarmingsrate på 0,10 bis 0,25 °C/min.

14. Fremgangsmåte ifølge et av kravene 1 til 13, der løsningen som anvendes i trinn (a), inneholder minst en alkohol, foretrukket etanol, propanol eller tert.-butanol, og spesielt foretrukket etanol.

15. Fremgangsmåte ifølge et av kravene 1 til 14, der løsningen som anvendes i trinn (a), inneholder minst et monosakkarid, oligosakkarid eller sukkeralkohol, foretrukket sukrose, dekstrose, maltose, laktose, sorbitol, glycin, mannitol eller dekstran, og spesielt foretrukket mannitol.

16. Frysetørket sammensetning med et innhold av bendamustin eller et salt derav, der sammensetningen kan oppnås ved hjelp av fremgangsmåten ifølge et av kravene 1 til 15.