(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 3324936 B1**

(19) NO

NORGE

(51) Int Cl.

A61K 9/08 (2006.01)
A61K 31/69 (2006.01)

Patentstyret

(45)	Oversettelse publisert	2023.01.23
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2022.09.28
(86)	Europeisk søknadsnr	16742280.7
(86)	Europeisk innleveringsdag	2016.07.21
(87)	Den europeiske søknadens Publiseringsdato	2018.05.30
(30)	Prioritet	2015.07.22, EP, 15002164
(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 **PROCESS FOR THE PREPARATION OF A BORTEZOMIB ESTER SOLUTION**

(56) Anførte publikasjoner

WO-A1-2015/025000
WO-A2-2013/128419
CN-A- 103 070 835
EP-A1- 2 644 189
I Butler ET AL: "Removal of dissolved oxygen from water: A comparison of four common techniques", TALANTA, vol. 41, no. 2, 1 February 1994 (1994-02-01), pages 211-215, XP055449254, NL ISSN: 0039-9140, DOI: 10.1016/0039-9140(94)80110-X

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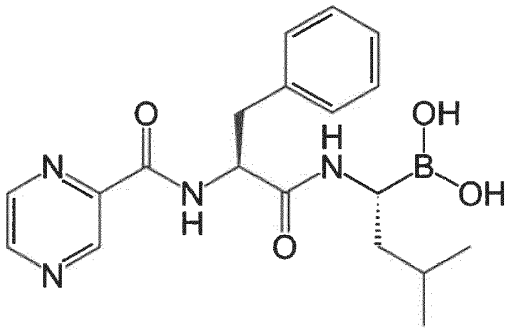
Process for the preparation of a bortezomib ester solution

The present invention relates to a process for producing a ready-to-use liquid pharmaceutical bortezomib ester solution

Bortezomib is the international nonproprietary name (INN) for (1R)-3-methyl-1-[{(2S)-3-phenyl-2-[(2-pyrazinylcarbonyl)amino]propanoyl)amino]butylboric acid, which has the following structural formula:



Bortezomib is a drug from the group of proteasome inhibitors that is licensed for monotherapy and combination therapy in the treatment of multiple myeloma and mantle cell lymphoma. The action of bortezomib is based on the selective inhibition of the chymotrypsin-like activity of the 26S proteasome (see Mutschler Arzneimittelwirkungen, Lehrbuch der Pharmakologie und Toxikologie [Drug actions: Textbook of pharmacology and toxicology], 9th edition, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2008, p. 947; ISBN 978-3-8047-1952-1).

Bortezomib is marketed under the trade name Velcade® in the form of a lyophilized powder in dose strengths of 1 mg and 3.5 mg bortezomib. Bortezomib is in Velcade® present in the form of a mannitol boronic ester that, after reconstitution, is intended to release the pharmaceutically active component bortezomib in vivo relatively readily. For intravenous administration, the sterile powder contained in a vial is reconstituted with 0.9% saline, producing a solution containing 1 mg/ml of bortezomib for intravenous administration or 2.5 mg/ml of bortezomib for subcutaneous administration. The storage stability of an unopened vial of Velcade® is stated as 3 years at a temperature of up to

30°C, but only 8 hours at 25°C in the case of a bortezomib solution obtained by reconstitution of Velcade®.

WO 2015/025000 A1 discloses a lyophilized pharmaceutical composition comprising bortezomib in a mixture with sodium gluconate, a process for the production thereof and also a liquid pharmaceutical composition comprising a solution of a composition comprising bortezomib and sodium gluconate in a diluent suitable for parenteral administration, and a process for producing the liquid composition comprising the reconstitution of the lyophilized composition with a diluent suitable for parenteral administration.

EP 2 644 189 A1 discloses a storage-stable liquid pharmaceutical composition comprising bortezomib in a therapeutically effective amount, the composition comprising the following: a single-phase liquid formulation comprising an essentially nonaqueous solvent system that is suitable for injection, an aqueous acetate buffer and bortezomib, bortezomib being present in the formulation in a therapeutically effective concentration, the predominating component of the solvent system being propylene glycol and the buffer having a pH of 3, and the solvent system, the buffer and the pH being chosen so as to effectively suppress the formation of at least one out of an amide breakdown product, a first carbinolamide breakdown product and a second carbinolamide breakdown product when the liquid formulation is stored under storage conditions.

WO 2013/128419 A2 discloses pharmaceutical compositions comprising bortezomib, tromethamine and an organic carboxylic acid, the composition having a pH of about 3 to 6.

With a view to safer handling of the cytostatic agent bortezomib, it would be desirable if bortezomib could be offered on the market in the form of a ready-to-use solution. Although bortezomib mannitol ester is relatively stable in a solid formulation, this is not the case in aqueous formulation, since free bortezomib in aqueous solution is very sensitive to oxidation and bortezomib mannitol ester in solution is present in equilibrium with its hydrolysis products bortezomib and mannitol.

WO 2011/116286 A2 accordingly proposes a ready-to-use bortezomib solution based on the organic solvent propylene glycol. It is claimed that a solution produced in this way meets the stability and thus storage stability demands placed on a ready-to-use solution. However, a disadvantage of said produced solution is that propylene glycol causes severe irritation and can also lead to liver abnormalities and kidney damage.

An object of the present invention is therefore to provide a process for producing a ready-to-use liquid pharmaceutical bortezomib ester solution in which the bortezomib ester solution has improved physiological tolerance.

This object is achieved by a process for producing a ready-to-use liquid pharmaceutical bortezomib ester solution, comprising the steps of

a) providing an aqueous solvent;
b) dissolving a component for forming a bortezomib ester in the solvent, the component used for forming a bortezomib ester being mannitol;
c) dissolving bortezomib or a pharmaceutically acceptable salt thereof in the solvent;
d) reducing the oxygen content of the solvent to a value of less than 0.5 mg/l.

It was surprisingly found that a ready-to-use liquid pharmaceutical bortezomib ester solution based on an aqueous solvent can be produced by i) dissolving a component for forming a bortezomib ester in the solvent, the component used for forming a bortezomib ester being mannitol, ii) dissolving bortezomib or a pharmaceutically acceptable salt thereof in the solvent, and iii) reducing the oxygen content of the solvent to a value of less than 0.5 mg/l. The water content of the solution produced according to the invention means it has improved physiological tolerance.

As an alternative to steps b) and c) of the process according to the invention, it is of course also possible to dissolve the prepared bortezomib ester, for example in solid or liquid form, in the solvent in a single process step. Bortezomib esters and processes for the production thereof are disclosed for example in WO 96/13266 and EP 1 355 910.

The solution produced according to the invention has the further advantage that it is stable.

The term “stability” is in this context understood as meaning the definition developed by the Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik (APV) [Working Group for Pharmaceutical Process Engineering], according to which “stability” means the within-specification quality of the medicament up to the end of the shelf life specified by the manufacturer. The quality of the medicament is here determined by the active substance content, the purity and the organoleptic, physicochemical and microbiological properties, wherein the active substance content should not by the end of the shelf life have fallen below 90% of the declared value.

The solution produced according to the invention has at a temperature of 2 to 8°C a stability (or in other words storage stability or shelf life) of at least 3 months, preferably of at least 6 months, more preferably of at least 12 months, even more preferably of at least 24 months and most preferably of at least 36 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 90%, preferably below 95%, of the amount of bortezomib originally used.

It is according to the invention additionally preferable that the solution produced according to the invention has at a temperature of 2 to 8°C a stability (or in other words storage stability or shelf life) of 3 months, more preferably a stability of 6 months, more preferably a stability of 9 months, more preferably a stability of 12 months, more preferably a stability of 15 months, more preferably a stability of 18 months, more preferably a stability of 21 months, more preferably a stability of 24 months, more preferably a stability of 27 months, more preferably a stability of 30 months, more preferably a stability of 33 months and even more preferably a stability of 36 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 90% of the amount of bortezomib originally used.

It is according to the invention additionally preferable that the solution produced according to the invention has at a temperature of 2 to 8°C a stability (or in other words

storage stability or shelf life) of 3 months to 6 months, more preferably a stability of 3 to 9 months, more preferably a stability of 3 to 12 months, more preferably a stability of 3 to 15 months, more preferably a stability of 3 to 18 months, more preferably a stability of 3 to 21 months, more preferably a stability of 3 to 24 months, more preferably a stability of 3 to 27 months, more preferably a stability of 3 to 30 months, more preferably a stability of 3 to 33 months and even more preferably a stability of 3 to 36 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 90% of the amount of bortezomib originally used.

It is according to the invention additionally preferable that the solution produced according to the invention has at a temperature of 2 to 8°C a stability (or in other words storage stability or shelf life) of 3 months, more preferably a stability of 6 months, more preferably a stability of 9 months, more preferably a stability of 12 months, more preferably a stability of 15 months, more preferably a stability of 18 months, more preferably a stability of 21 months, more preferably a stability of 24 months, more preferably a stability of 27 months, more preferably a stability of 30 months, more preferably a stability of 33 months and even more preferably a stability of 36 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 95% of the amount of bortezomib originally used.

It is according to the invention additionally preferable that the solution produced according to the invention has at a temperature of 2 to 8°C a stability (or in other words storage stability or shelf life) of 3 months to 6 months, more preferably a stability of 3 to 9 months, more preferably a stability of 3 to 12 months, more preferably a stability of 3 to 15 months, more preferably a stability of 3 to 18 months, more preferably a stability of 3 to 21 months, more preferably a stability of 3 to 24 months, more preferably a stability of 3 to 27 months, more preferably a stability of 3 to 30 months, more preferably a stability of 3 to 33 months and even more preferably a stability of 3 to 36 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 95% of the amount of bortezomib originally used.

It is according to the invention additionally preferable that the solution produced according to the invention has at a temperature of 25°C a stability (or in other words

storage stability or shelf life) of at least 3 months, preferably of at least 6 months, more preferably of at least 12 months and even more preferably of at least 24 months, wherein the bortezomib content should not by the end of the shelf life have fallen below 90%, preferably below 95%, of the amount of bortezomib originally used.

The present invention relates to a process for producing a ready-to-use liquid pharmaceutical bortezomib ester solution. Ready-to-use solutions containing active substances are known in the prior art and also referred to there as RTU solutions. Whereas solid active substance formulations to be administered in solution form are marketed for example in the form of powders or lyophilizates and are converted into a solution by reconstitution only shortly before their administration, ready-to-use solutions are marketed in the form of prepared solutions.

The solution produced according to the invention may for example be administered immediately, i.e. without further preparation, or else only after further preparation, such as dilution to a desired active substance concentration.

In the context of the process according to the invention, the ready-to-use solution is produced using, and based on, an aqueous solvent. An aqueous solvent is here understood as meaning a solvent or a solvent mixture of individual components that are liquid at a temperature of 20°C and a pressure of 1013 mbar, this consisting to an extent of at least 50% by weight of water, preferably to an extent of at least 70% by weight of water, more preferably to an extent of at least 90% by weight of water and even more preferably to an extent of at least 95% by weight of water. In this context, it is according to the invention particularly preferable when the solvent consists to an extent of at least 99% by weight of water and even more preferably to an extent of at least 100% by weight of water.

Besides water, the solvent may additionally contain a certain proportion of one or more liquid organic components miscible with water. Examples of such organic components are ethanol and isopropanol.

In the solution produced according to the invention, a bortezomib ester is present in dissolved form. Bortezomib is what is known as a boronic acid and contains the functional group $-B(OH)_2$, which can undergo esterification with a bortezomib ester-forming component containing one or more alcohol groups with elimination of water and optionally acid.

In the process according to the invention, the component for forming a bortezomib ester is dissolved in the solvent according to step b). In principle, step b) can be carried out both before step c) and after step c). However, according to a preferred embodiment of the process according to the invention, step b) is carried out before step c). This ensures that bortezomib, which is only relatively poorly soluble in water, has easier and improved solubility in the solvent.

In the context of the process according to the invention, the oxygen content of the solvent is reduced according to step d). In step d), the oxygen content is reduced by a measure that is specifically aimed at reducing the oxygen content in the solvent and not, for example, at an uncontrolled reduction in oxygen, such as occurs for example in the case of undesirable oxidative breakdown of bortezomib.

In principle, step d) can be carried out after step(s) a), b) and/or c). However, according to a preferred embodiment of the process according to the invention, step d) is carried out after step b) and before step c). This measure allows a comparatively stable bortezomib ester solution to be provided in a relatively inexpensive manner by means of the process according to the invention.

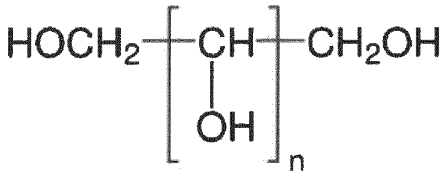
In principle, the reduction in the oxygen content of the solvent can be carried out by any means that appears to those skilled in the relevant art to be suitable for carrying out the process according to the invention, for example by subjecting the solvent to reduced pressure. However, according to a preferred embodiment of the process of the invention, step d) is carried out by passing an inert gas through the solvent. This allows the process according to the invention to be carried out in a technically simple and thus cost-effective manner. Suitable inert gases are according to the invention preferably noble gases and nitrogen, nitrogen being particularly preferred on cost grounds.

According to another preferred embodiment of the process according to the invention, the oxygen content of the solvent is according to step d) reduced to a value of less than 0.5 mg/l to 0.01 mg/ml. This ensures that the bortezomib ester solution obtainable by means of the process according to the invention has extensive stability. The oxygen content in the solvent is according to the invention to be determined using an oxygen sensor based on the Clark electrode (US 2 913 386) as described in Allen J., Lab Medicine 2003(34), 544-547).

In the solution produced according to the invention, a bortezomib ester is present in dissolved form. As already stated above, bortezomib is what is known as a boronic acid and contains the functional group $-B(OH)_2$, which can undergo esterification with a bortezomib ester-forming component containing one or more alcohol groups with elimination of water. According to the disclosure of the present invention, it is possible to use all bortezomib esters of bortezomib with a bortezomib ester-forming component that are suitable for the pharmaceutical purpose according to the invention. However, it is preferable when the bortezomib ester is an ester of bortezomib with a polyol as the bortezomib ester-forming component. This ensures that the ready-to-use bortezomib ester solution obtainable by means of the disclosed process has relatively high stability. Particularly preferred here are those bortezomib polyol esters in which the two OH groups of the $-B(OH)_2$ group of a molecule of bortezomib have undergone esterification with two OH groups of a molecule of polyol with elimination of water and formation of a ring structure, as demonstrated for example in EP 1 355 910 with reference to structural formulas.

According to another preferred embodiment of the disclosed process, the component for forming a bortezomib ester is an alditol. A bortezomib alditol ester solution produced by means of the disclosed process is characterized by relatively high stability. Particularly preferred here are those bortezomib alditol esters in which the two OH groups of the $-B(OH)_2$ group of a molecule of bortezomib have undergone esterification with two OH groups of a molecule of alditol with elimination of water and formation of a ring structure, as demonstrated for example in EP 1 355 910 with reference to structural formulas.

Alditols are known in the prior art and correspond to the general structural formula shown below, where n is selected from natural numbers and is equal to or greater than 1.



According to another preferred embodiment of the disclosed process, the component for forming a bortezomib ester is an alditol of the above structural formula where n = 1 to 10, preferably an alditol where n = 2 to 4. Solutions comprising a bortezomib alditol ester of said selection obtainable by means of the disclosed process are characterized by relatively high stability and high solubility.

According to another preferred embodiment of the disclosed process, the component for forming a bortezomib ester is selected from the group consisting of arabitol, dulcitol, erythritol, mannitol, ribitol, sorbitol and xylitol, and especially from the group consisting of mannitol, sorbitol and xylitol, particular preference according to the invention being given to mannitol and especially D-mannitol. Solutions comprising a bortezomib alditol ester of said alditols obtainable through the performance of the disclosed process are characterized by particularly high stability.

In the solution obtainable by means of the process according to the invention, the bortezomib ester is present in equilibrium with its hydrolysis products free bortezomib and free component for forming a bortezomib ester. In order to further enhance the stability of the solution obtainable by means of the process according to the invention, according to another preferred embodiment of the invention the component for forming a bortezomib ester is used in an at least 10 times molar excess based on bortezomib, preferably in a 10 to 400 times molar excess, particularly preferably in a 10 to 100 times molar excess and very particularly preferably in a 15 to 30 times molar excess.

According to another preferred embodiment of the process according to the invention, at least 90% of the bortezomib present in the resulting solution is in the form of an ester, more preferably at least 95% and even more preferably at least 99%. This ensures that the solutions obtainable by means of the process according to the invention have relatively high stability. The degree of esterification of bortezomib in the resulting solution can be adjusted by measures known to those skilled in the art, for example through the pH of the solution or via the content in the solution of the free component for forming a bortezomib ester. The degree of esterification of bortezomib is according to the invention preferably determined by titration and of the determined apparent pK_a of bortezomib or by ^{11}B NMR (see W. Marinaro, Physical and chemical properties of boronic acids: Formulation implications, Dissertation University Kansas, ProQuest, UMI Dissertations Publishing 2007, ISBN-13: 978-0-549-13739-9).

According to another preferred embodiment of the process according to the invention, bortezomib is dissolved in the solvent in an amount of 0.5 mg to 10 mg per millilitre of solvent, preferably in an amount of 1.0 mg/ml to 5 mg/ml.

According to another preferred embodiment of the process according to the invention, NaCl is additionally dissolved in the solvent. NaCl has been shown to further improve the stability of the bortezomib ester solution obtainable by the process according to the invention.

According to another preferred embodiment of the process according to the invention, the solvent is adjusted to a pH (measured at a temperature of 20°C) within a range from 3 to 6, preferably to a pH within a range from 3 to 5 and more preferably to a pH within a range from 3.5 to 4.5. A solution in the stated pH ranges obtainable by means of the process according to the invention has been shown to be characterized by particularly high stability.

According to another preferred embodiment of the process according to the invention, the adjustment of the pH takes place after step c).

In another preferred embodiment of the process according to the invention, the adjustment of the pH of the solution obtainable by means of the process according to the invention is carried out using hydrochloric acid or sodium hydroxide, depending on what pH the solution is to be adjusted to.

In order to keep the pH of the solution obtainable by means of the process according to the invention as constant as possible within a pH range from 3.7 to 5.7 and thus to ensure the solution has lasting increased stability, according to another preferred embodiment of the invention an acetic acid/acetate buffer system is dissolved in the solvent.

In order to keep the pH of the solution obtainable by means of the process according to the invention as constant as possible within a pH range from 2.8 to 4.8 and thus to ensure the solution has lasting increased stability, according to another preferred embodiment of the invention a lactic acid/lactate buffer system is dissolved in the solution.

According to another preferred embodiment of the process according to the invention, the resulting bortezomib ester solution is formed in such a way that it is suitable for parenteral administration, preferably for intravenous and/or subcutaneous administration.

According to another preferred embodiment of the process according to the invention, the resulting bortezomib ester solution is free of stabilizers, in particular free of chelators and antioxidants. The resulting solution has surprisingly been found to be adequately stable despite the absence of chelators such as ethylenediaminetetraacetic acid (EDTA) and antioxidants.

In order to improve further the physiological tolerance of the solution obtainable by means of the process according to the invention, according to another preferred embodiment of the invention the solvent is free of organic solvents. Consequently, the bortezomib ester solution resulting from the process according to the invention is free of organic solvents too.

According to another preferred embodiment of the process according to the invention, the resulting bortezomib ester solution is free of liposomes and/or free of detergents. This measure likewise contributes to improving the physiological tolerance of the solution obtainable by means of the process according to the invention.

According to another preferred embodiment of the process according to the invention, the bortezomib ester solution obtainable by means of the process according to the invention is sterile.

According to another preferred embodiment of the process according to the invention, after step d) of passing the inert gas through the solvent, the bortezomib ester solution is exposed to a reduced pressure.

According to another preferred embodiment of the process according to the invention, the process additionally includes the step of transferring the bortezomib ester solution to a container and closing the filled container in an airtight manner.

According to another preferred embodiment of the process according to the invention, the transfer of the bortezomib ester solution to the container takes place in an inert gas atmosphere. As a result, contact between the solution obtainable by means of the process according to the invention and the atmospheric oxygen is largely avoided, which has a beneficial effect on the stability of the bortezomib ester solution.

According to another preferred embodiment of the process according to the invention, step d) is carried out after step b) and before step c) and also one more time after step c) and before transfer of the bortezomib ester solution to the container, which likewise has a beneficial effect on the stability of the bortezomib ester solution.

According to another preferred embodiment of the process according to the invention, the container is made of a material that is impermeable to oxygen.

According to another preferred embodiment of the process according to the invention, the container is made of glass.

According to another preferred embodiment of the process according to the invention, the container is a vial.

According to another preferred embodiment of the process according to the invention, the headspace of the containers is filled with an inert gas. The headspace of the container is the part of the internal space of the container that is not taken up by the bortezomib ester solution. Suitable inert gases are for example noble gases and nitrogen, nitrogen being particularly preferred on cost grounds.

According to another preferred embodiment of the process according to the invention, the headspace of the container is adjusted to a pressure of 870 mbar to 1085 mbar, wherein a pressure of 950 mbar to 1050 mbar, a pressure of 1010 mbar to 1050 mbar or a pressure of 1020 mbar to 1030 mbar is particularly preferable.

According to another preferred embodiment of the process according to the invention, the headspace of the airtight-sealed container is adjusted to an oxygen content of max. 0.15% by volume, preferably an oxygen content of 0.15% by volume to 0.005% by volume. The oxygen content in the headspace is according to the invention preferably to be determined by gas chromatography using a flame-ionization detector or by near-infrared diode laser measurement according to Posset et al., Pharm Ind. 77(5), 739-747 (2015).

According to another preferred embodiment of the process according to the invention, the ratio of headspace to internal space of the sealed container has a value of less than 0.95, preferably to a value of 0.75 to 0.95. In another preferred embodiment, the headspace to internal space of the sealed container has a value of 0.75, preferably a value of 0.5 to 0.75.

The active substance present in the solution to be produced according to the invention has been shown to be subject to degradation due to exposure to light. According to another preferred embodiment of the process according to the invention, the process is

as far as possible, and particularly preferably completely, carried out with exclusion of exposure to light.

A typical bortezomib ester solution obtainable by means of the process according to the invention contains 65% by weight to 99.85% by weight of water, 0.05% by weight to 1% by weight of bortezomib (in the free and unesterified form calculated as free bortezomib), 0.1% by weight to 20% by weight of mannitol (in the free and unesterified form calculated as free mannitol) and also 0% by weight to 14% by weight of pharmaceutical excipients, for example NaCl and/or an organic solvent.

A further typical solution obtainable by means of the process according to the invention contains 80% by weight to 99.85% by weight of water, 0.05% by weight to 1% by weight of bortezomib (in the free and unesterified form calculated as free bortezomib), 0.1% by weight to 5% by weight of mannitol (in the free and unesterified form calculated as free mannitol) and also 0% by weight to 14% by weight of pharmaceutical excipients, for example NaCl and/or an organic solvent.

Additionally disclosed in the present case is a ready-to-use liquid pharmaceutical bortezomib ester solution obtainable according to the process of the invention.

The active substance present in the solution has been shown to be subject to degradation due to exposure to light. The solution obtainable with the process according to the invention is therefore preferably stored in a container, where the container protects the solution from exposure to light or reduces the exposure to light of the solution. The container may for example be a primary packaging container – such as an amber glass ampoule – or a secondary packaging container – such as a folding box as outer packaging.

The bortezomib ester solution obtainable by means of the process according to the invention can be used for the treatment of multiple myeloma and/or mantle cell lymphoma.

The description of some preferred embodiments of the invention that follows serves for the elucidation thereof.

The process according to the invention can be carried out for example with the aid of the disclosure of US 6 274 169, in particular with the aid of the devices illustrated and described therein.

Exemplary embodiment 1

1250.0 g of mannitol was dissolved in 48.88 kg of water while stirring. Sterile-filtered nitrogen was then passed through the solution thus obtained while stirring, until the oxygen content of the solution was 0.5 mg/l (measured using a Clark electrode, Mettler Toledo InPro 6800). The mannitol solution thus produced was then heated to a temperature of 45°C. First 125.0 g of bortezomib and then 450.0 g of NaCl were then dissolved in the heated mannitol solution while stirring.

Once the NaCl had dissolved, the bortezomib-mannitol solution obtained as described above was first made up to a final volume of 50 l with water thermally equilibrated at room temperature and was then cooled to 20°C. The pH of the cooled solution was then adjusted to a value of 4.3 with 1% aqueous NaOH solution or 1% aqueous HCl solution. After the pH adjustment, sterile-filtered nitrogen was again passed through the bortezomib-mannitol solution while stirring, until the oxygen content of the solution was 0.5 mg/l (measured using a Clark electrode, Mettler Toledo InPro 6800). The bortezomib-mannitol solution then underwent a sterilizing filtration using a sterilizing filtration capsule with application of a nitrogen pressure of 1.5 bar.

1.4 ml portions of the abovementioned sterile-filtered solution were transferred under a nitrogen atmosphere to vials (10R DIN, 13 mm neck) having a volume of (12.15 ml) that had been flushed with nitrogen several times. The filled open vials were then transferred to a lyophilization chamber. The chamber was evacuated at a temperature of 20°C down to a pressure of 50 mbar ± 10 mbar and then flushed with sterile-filtered nitrogen, with the nitrogen pressure adjusted to 950 ± 25 mbar. Said evacuation/flushing process was then repeated two more times, with the nitrogen pressure in the chamber adjusted to a value of 1013 mbar when flushing with nitrogen in the second repetition.

The vials were closed with a rubber stopper under a nitrogen atmosphere while in the chamber, then taken out of the chamber and crimped with an aluminium cap. The oxygen content in the headspace of the vials immediately after closure and crimping was 0.15% by volume (measured by gas chromatography and flame-ionization detector: sampling: displacement of the gas in the vial headspace by injecting water with concomitant withdrawal via a three-way valve; the valve was for this purpose fixed in a clamp and immersed bottom up under water; determination of oxygen alongside nitrogen; column: molecular sieve 5A, 50 m, 0.53 µm, carrier gas: helium (approx. 80 kPa); injection: manual; NB: Since the oxygen content in the sample is well below the limit of quantitation (ref. std. 0.50% vol./vol. oxygen), evaluation can be via a single-point calibration limit test at the LOQ (0.1% vol./vol.)).

Stability study

Filled vials according to exemplary embodiment 1 were placed in storage for 6 months at temperatures of 2-8°C, 15°C and 25°C. After one, two and six months, the bortezomib content of the solutions was determined by high-performance liquid chromatography (HPLC) as described hereinbelow. In the tables below, the relative bortezomib contents of the solutions placed in storage, based on the amount of bortezomib originally used, are stated in percent.

Time	2-8°C	15°C	25°C
1 month	-	-	101.4
2 months	101.8	101.5	100.9
3 months	102.3	102.1	100.7
6 months	101.1	100.2	97. 9

Exemplary embodiment 2

Vials were prepared in analogous manner to exemplary embodiment 1, with the sole difference that the pH of the solution was adjusted to a value of 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5 with 1 N hydrochloric acid and 1 N sodium hydroxide solution.

Stability study

Filled vials according to exemplary embodiment 2 were placed in storage for 4 weeks at a temperature of 40°C. After one, two, three and four weeks of storage, the bortezomib content of the solutions was determined by HPLC as described hereinbelow.

The evaluation of the bortezomib contents of the solutions showed that a solution had the highest stability when the pH of the solution was adjusted to a value of 3.5 to 4.5.

HPLC

The relative bortezomib content of the solutions based on the original sample weight was determined by HPLC according to the European Pharmacopoeia, 8th edition, Chapter 2.2.29, pages 60 to 62 with the following system parameters:

- Instrument: HPLC SpectraSYSTEM from Thermo Electron Corp. equipped with diode-field detector and a column oven;
- Column: SymmetryShield RP 18, 5 µm, 250 x 4.6 mm, Waters article number 186000112;
- Mobile phase A: Degassed mixture of 715 ml of water, 285 ml of acetonitrile and 1 ml of formic acid;
- Mobile phase B: Degassed mixture of 200 ml of water, 800 ml of methanol and 1 ml of formic acid;
- Flow rate: 1.0 ml/min;
- Injected volume: 20 µl;
- Detection: Diode-field spectrophotometer with a wavelength set at 270 nm and spectral scanning from 200 to 420 nm;
- Temperature: 35°C;
- External standard: 10 mg of bortezomib dissolved in 20 ml of diluent
- Sample preparation: 1 ml of a bortezomib solution having a concentration of 2.5 mg/ml is diluted with diluent to a volume of 5 ml.
- Diluent: Water/acetonitrile 70:30 (vol.-%/ vol.-%)

– Gradient:

Time [min]	Mobile phase A [vol.-%]	Mobile phase A [vol.-%]
0-20	100	0
20-35	100 → 0	0 → 100
35-50	0	100
50-52	0 →100	100 → 0
52-57	100	0

Patentkrav

1. Fremgangsmåte for fremstilling av en flytende farmasøytisk bortezomibesteroppløsning som er klar til bruk, omfattende trinnene å

a) tilveiebringe et vandig løsningsmiddel;
b) løse opp en komponent for å danne en bortezomibester i løsningsmidlet, hvor komponenten som brukes for å danne en bortezomibester er mannitol;
c) løse opp bortezomib eller et farmasøytisk akseptabelt salt derav i løsningsmidlet;
d) redusere oksygeninnholdet i løsningsmidlet til en verdi som er lavere enn 0,5 mg/l.

2. Fremgangsmåte ifølge krav 1, **karakterisert ved at** trinn b) utføres før trinn c).

3. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** trinn d) utføres etter trinn b) og før trinn c).

4. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** trinn d) utføres ved å føre en inert gass gjennom løsningsmidlet.

5. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** oksygeninnholdet i løsningsmidlet reduseres i henhold til trinn d) til en verdi som er lavere enn 0,5 mg/l til 0,01 mg/ml.

6. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** komponenten for å danne en bortezomibester, beregnet på bortezomib, brukes i et minst 10 gangers molart overskudd, i et minst 10 gangers molart overskudd, fortrinnsvis i et 10 til 400 gangers molart overskudd, spesielt foretrukket i et 10 til 100 gangers molart overskudd og helt spesielt foretrukket i et 15 til 30 gangers molart overskudd.

7. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** bortezomib løses opp i løsningsmidlet i en mengde fra 0,5 mg til 10 mg per milliliter løsningsmiddel, fortrinnsvis i en mengde fra 1,0 mg/ml til 5 mg/ml.

8. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** løsningsmidlet justeres til en pH-verdi i et område fra 3 til 6, fortrinnsvis til en pH-verdi i et område fra 3 til 5 og mer foretrukket til en pH-verdi i et område fra 3,5 til 4,5.

9. Fremgangsmåte ifølge krav 8, **karakterisert ved at** justeringen av pH-verdien finner sted etter trinn c).

10. Fremgangsmåte ifølge krav 4, **karakterisert ved at** etter trinn d) hvor den inerte gass føres gjennom løsningsmidlet, eksponeres bortezomibesteroppløsningen for et redusert trykk.

11. Fremgangsmåte ifølge et hvilket som helst av de forutgående krav, **karakterisert ved at** fremgangsmåten i tillegg omfatter trinnet å overføre bortezomibesteroppløsningen til en beholder og lukke den fylte beholder på en lufttett måte.

12. Fremgangsmåte ifølge krav 11, **karakterisert ved at** overføringen av bortezomibesteroppløsningen til beholderen finner sted i en atmosfære av inert gass.

13. Fremgangsmåte ifølge krav 11 eller 12, **karakterisert ved at** trinn d) utføres etter trinn b) og før trinn c) og også en gang til trinn c) og før overføringen av bortezomibesteroppløsningen til beholderen.