Description

Various therapeutically active substances are not able to be administered in a pure form. It is frequently necessary to blend the active substances with other components so that a preparation is produced which is ready for use. Dependent on the chemical properties of the pharmacologically active substance it is necessary to take various considerations into account before a pharmaceutical preparation may be used for humans or animals.

When therapeutically active substances are to be administered parenterally it is usually necessary for the active substance in the form of a solid to be dissolved as a solution. Conventionally water is found to be a suitable solvent. If however the active substances are no more than sparingly soluble, it is not possible to produce any concentrated aqueous solutions for parenteral application, even though a comparatively high concentration of active substance would be desirable in order to avoid injection of an excessive volume which would not be well tolerated. In the art there has been a proposal to use cosolvents in order to bring sparingly soluble substances into solution. However, when more especially used in a highly concentrated form without or with only a small amount of added water, such cosolvents involve the disadvantage - more significantly in the case of intramuscular injections - of being poorly tolerated. There are then likely to be an induration (hardening of tissue), hemorrhage (bleeding) and/or necrosis (local death of tissue) at the injection site.

The use of tetrahydrofurfuryl alcohol polyethylene glycol as a solvent for parenteral preparations is mentioned in the Journal of Pharmaceutical Sciences, 52, page 917 ff (1963) where it is stated that undiluted application leads to irritation. This publication also describes the use of polyethylene glycols. It is stated here that the intramuscular injection of polyethylene glycol with a mean molecular weight of 300 may cause ischemic (bloodless) necroses in the muscular fascicle. These results were obtained from experiments on animals. EP-A-0,096,569 discloses the use of polyethylene glycol emulsions in preparations containing the active ingredient of the present invention.

There is further literature confirming the view that polyethylene glycol should not be used in overly high concentrations. In a catalog of pharmaceutical adjuvants, which has been compiled by a working group organized by the companies Ciba-Geigy, Hoffmann-LaRoche and Sandoz, it is pointed out that the maximum concentration of polyethylene glycol with a mean molecular weight of 300 in solutions for parenteral administration amounts to about 30%. At a concentration in excess of 40% a hemolytic effect of polyethylene glycol with a mean molecular weight of 300 (PEG 300) was found to occur.

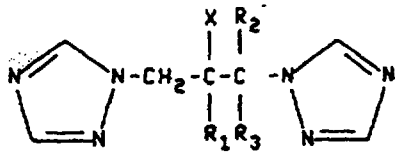
This finding has been also confirmed in Tieraerztliche Rundschau, 42, page 912 ff (1987) by O. Kern. It was found that the intramuscular injection of undiluted PEG 300 caused ischemic necrosis in rats. Furthermore it was found that an intramuscular injection of a 40% propylene glycol solution in water caused very pronounced tissue damage in various animals.

Thus it is to be seen from the prior art that different solvents may be utilized for parenteral preparations, if relatively low concentrations of these solvents are employed. The use of preparations which have a high percentage of such solvents may frequently lead to undesired side-effects.

The use of aqueous media for the pharmaceutical preparations is on the other hand not appropriate if the therapeutically active compound forms a sparingly soluble hydrate in the form of needles on contact with aqueous media. Thus in the case of therapeutically active compounds which are only sparingly soluble in water, more particularly triazole compounds, there is the danger of the hydrate crystallizing out in the form of needles. There is no need to explain that preparations intended for parenteral administration have to be in the form of a homogeneous solution without any possibility of crystallizing out from the solution.

Accordingly, one object of the present invention is to provide solvent mixtures which in the case of parenteral and more especially intramuscular administration are free of undesired side-effects while at the same time being capable of dissolving those therapeutically active substances, in a sufficient concentration and in stable manner, which are at the most only sparingly soluble in water.

The present invention relates to a pharmaceutical preparation consisting of a solvent system containing:
(a) 0 to 65% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene),
(b) 10 to 100% by weight of polyethylene glycol with a mean molecular weight of 200 to 600, and
(c) 0 to 35% by weight of water, the sum of the two components (a) and (b) amounting to at least 65% by weight, and one or more therapeutically active compounds which have a pronounced antimycotic activity.
The compounds have the following formula (I):

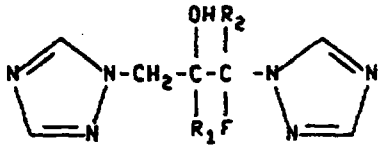


(I)

wherein R_1 denotes a phenyl radical optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Br, I, CF_3, C_1 to C_4, alkyl, and C_1, to C_4 alkoxy, or 5-chloro-pyrid-2-yl; X denotes OH, F, Cl or Br; R_2 is H, CH_3 or F; and R_3 is H or F.

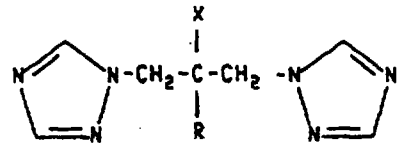
Such solvent systems containing 10 - 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene), 10 to 90% by weight of polyethylene glycol and 0 to 35% by weight of water are preferably used. A more specific and more especially preferred composition is in the form of preparations which contain 30 to 55% by weight of polyethylene glycol, 35 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and 10 to 35% by weight of water. The sum of the two components α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and polyethylene glycol amounts in every case to at least 65% by weight.

A group of compounds which may be used according to the invention are those with the formula



(II)

wherein R_1 is phenyl, optionally substituted with 1 to 3 substituents, each of them selected independently selected from the group consisting of F, Cl, Br, I, CF_3, C_1 to C_4 alkyl and C_1 to C_4, alkoxy, or 5-chloro-pyrid-2-yl, and R_2 is H, CH_3 or F. Such compounds are described in European Patent Application with the publication number 118245, Preferably triazole derivatives are used as therapeutically active substances which have a pronounced antimycotic activity. The compounds have the following formula III



(III)

wherein R denotes a phenyl radical optionally substituted with 1 to 3 substituents selected from the group consisting essentially of F, Cl, Br, I and CF_3, and X denotes OH, F, Cl or Br. These compounds are described in more detail in the European patent application with the publication number 96,569.

Compounds which are particularly preferably used in the present invention include:
1, 3-bis (1H-,12, 4-triazol-1-yl)-2-bromo-2-(2,4-dichlorophenyl)-propane,
1,3-bis(1H-1,2,4-triazol-1-yl)-2-chloro-2-(2,4-dichlorophenyl)-propane,
1,3-bis(1H-1,2,4-triazol-1-yl)-2-(4-iodophenyl)propane-2-ol and
2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol

It has been found that the triazole compounds of formula I have a good solubility in a solvent system containing 0 to 65% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene), 10 to 100% by weight of polyethylene glycol and 0 to 35% by weight of water, the sum of the components α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and polyethylene glycol being equal to at least 65% by weight of the solvent system.

It was found, surprisingly, that despite the addition of up to 35% by weight of water to a solvent system containing α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and polyethylene glycol, solvents with a content of up to 150 mg/ml of the bis-triazole derivative could be prepared. These solutions remained stable for a period of seven weeks at 4°C without the hydrate crystallizing out.

Parenteral administration involves a daily dose of 0.1 and 5 mg of the bis-triazole derivative per kg body weight of the patient to comply with individual requirements of the person to be treated.

Furthermore contrary to the views so far expressed in the literature such solutions are very well tolerated when injected intramuscularly. This was proved with the aid of tests on rabbits and dogs. The cosolvents used are thus also well tolerated physiologically, especially when used with the bis-triazole derivative.

The polyethylene glycol used was one having a mean molecular weight between 200 and 600 and preferably between 300 and 400 or, more preferably, 300.

It was further found that solvents of bis-triazole compounds in polyethylene glycol were well tolerated. Even solutions with polyethylene glycol as the sole component, were well tolerated in the case of intramuscular administration. Hemorrhage was not found to occur in the tests on animals performed and it was only in isolated instances that there was temporary induration. Owing to the risk of hemolysis solutions of bis-triazole derivatives in pure polyethylene glycol could only be administered intramuscularly and could not be used intravenously.

The use of the solvent system in accordance with the invention led to injections with a viscosity of under 1000 mPas, this ensuring good injectability.

Examples of Production.

Example 1

5 g of 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol were dissolved while stirring in a mixture of 41 g of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and 30.8 g of polyethylene glycol 300. 30.8 g of distilled water were added to this solution. The solution was aerated with nitrogen during production and after sterilization by filtration was placed in ampoules, injection vials or pre-filled syringes with preceding and subsequent aeration by nitrogen.

Example 2

10 g of 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol were dissolved while stirring in 102 g of polyethylene glycol with a mean molecular weight of 300. During production the solution was aerated with nitrogen and after sterilization by filtration was placed in ampoules, injection vials or pre-filled syringes with aeration by nitrogen before and afterwards.

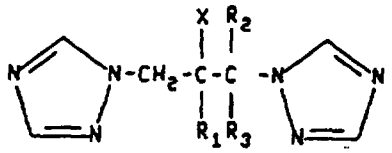
Example 3

10 g of 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol were dissolved while stirring in a mixture of 40.4 g of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene) and 60.6 g of polyethylene glycol 300. The solution was aerated with nitrogen during production and after sterilization by filtration was placed in ampoules, injection vials or pre-filled syringes with preceding and subsequent aeration by nitrogen.

Claims

Claims for the following Contracting States: DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. A pharmaceutical preparation consisting of a solvent system containing:
   (a) 0 to 65% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene);
   (b) 10 to 100% by weight of polyethylene glycol with a mean molecular weight of 200 to 600, and
   (c) 0 to 35% by weight of water, the sum of the two components (a) and (b) amounting to at least 65% by weight, and one or more therapeutically active compounds of the formula



(I)

wherein R_1 denotes a phenyl radical optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Br, I, CF_3, C_1 to C_4 alkyl, and C_1 to C_4 alkoxy, or 5-chloropyrid-2-yl; X denotes OH, F, Cl or Br; R_2 is H, CH_3 or F; and R_3 is H or F.

2. The pharmaceutical preparation as claimed in claim 1, characterized in that it contains 10 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene).

3. The pharmaceutical preparation as claimed in claim 2, characterized in that it contains 35 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene).

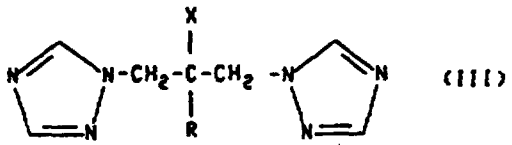
4. The pharmaceutical preparation as claimed in any one of the claims 1 through 3, characterized in that it contains 10 to 90% by weight of polyethylene glycol.

5. The pharmaceutical preparation as claimed in claim 4, characterized in that it contains 30 to 55% by weight of polyethylene glycol.

6. The pharmaceutical preparation as claimed in any one of the preceding claims, characterized in that the polyethylene glycol has a mean molecular weight of 300.

7. The pharmaceutical preparation as claimed in any one of the claims 1 through 6, characterized in that it is adapted to be parenterally administered.

8. The pharmaceutical preparation according to claim 1, characterized in that said pharmaceutically active component is a triazole derivative of the following formula III;



(III)

wherein R denotes a phenyl radical with, if desired, 1 to 3 substituents selected from the group consisting essentially of F, Cl, Br, I and CF_3, and X denotes OH, F, Cl or Br.

9. The pharmaceutical preparation as claimed in claim 8, characterized in that the said triazole derivative is 1,3, -bis(1H-1,2,4-triazol-1-yl)-2-bromo-2-(2,4-dichlorophenyl)-propane.

10. The pharmaceutical preparation as claimed in claim 8 characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-chloro-2-(2,4-dichlorophenyl)-propane.

11. The pharmaceutical preparation as claimed in claim 8, characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-(4-iodophenyl)propane-2-ol.

12. The pharmaceutical preparation as claimed in claim 8, characterized in that the said triazole derivative is 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol.

13. The pharmaceutical preparation as claimed in any one of the claims 8 through 12, characterized in that it contains 30 to 100 mg/ml of the triazole derivative.

14. The pharmaceutical preparation as claimed in any one of the claims 8 through 12, characterized in that it contains 50 to 100 mg/ml of the triazole derivative.

15. The pharmaceutical preparation as claimed in any one of the preceding claims characterized in that it is in the form of ampoules, injection vials or pre-filled syringes.

Claims for the following Contracting States: GR, ES

1. A process for the preparation of a pharmaceutical composition consisting of a solvent system containing:
   (a) 0 to 65% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly (oxyethylene),
   (b) 10 to 100% by weight of polyethylene glycol with a mean molecular weight of 200 to 600, and
   (c) 0 to 35% of weight of water, the sum of the two components (a) and (b) amounting to at least 65% by weight wherein one or more therapeutically active compounds of the formula

3. The pharmaceutical preparation as claimed in claim 2, characterized in that it contains 35 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene).

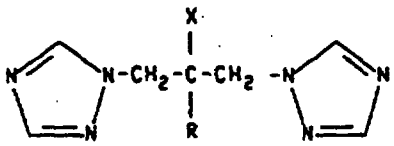
4. The pharmaceutical preparation as claimed in any one of the claims 1 through 3, characterized in that it contains 10 to 90% by weight of polyethylene glycol.

5. The pharmaceutical preparation as claimed in claim 4, characterized in that it contains 30 to 55% by weight of polyethylene glycol.

6. The pharmaceutical preparation as claimed in any one of the preceding claims, characterized in that the polyethylene glycol has a mean molecular weight of 300.

7. The pharmaceutical preparation as claimed in any one of the claims 1 through 6, characterized in that it is adapted to be parenterally administered.

8. The pharmaceutical preparation according to claim 1, characterized in that said pharmaceutically active component is a triazole derivative of the following formula III;



(III)

wherein R denotes a phenyl radical with, if desired, 1 to 3 substituents selected from the group consisting essentially of F, Cl, Br, I and CF_3, and X denotes OH, F, Cl or Br.

9. The pharmaceutical preparation as claimed in claim 8, characterized in that the said triazole derivative is 1,3, -bis(1H-1,2,4-triazol-1-yl)-2-bromo-2-(2,4-dichlorophenyl)-propane.

10. The pharmaceutical preparation as claimed in claim 8 characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-chloro-2-(2,4-dichlorophenyl)-propane.

11. The pharmaceutical preparation as claimed in claim 8, characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-(4-iodophenyl)propane-2-ol.

12. The pharmaceutical preparation as claimed in claim 8, characterized in that the said triazole derivative is 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol.

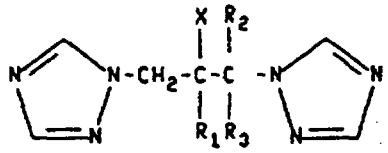
13. The pharmaceutical preparation as claimed in any one of the claims 8 through 12, characterized in that it contains 30 to 100 mg/ml of the triazole derivative.

14. The pharmaceutical preparation as claimed in any one of the claims 8 through 12, characterized in that it contains 50 to 100 mg/ml of the triazole derivative.

15. The pharmaceutical preparation as claimed in any one of the preceding claims characterized in that it is in the form of ampoules, injection vials or pre-filled syringes.

Claims for the following Contracting States: GR, ES

1. A process for the preparation of a pharmaceutical composition consisting of a solvent system containing:
   (a) 0 to 65% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly (oxyethylene),
   (b) 10 to 100% by weight of polyethylene glycol with a mean molecular weight of 200 to 600, and
   (c) 0 to 35% of weight of water, the sum of the two components (a) and (b) amounting to at least 65% by weight wherein one or more therapeutically active compounds of the formula



(I)

wherein R_1 denotes a phenyl radical optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Br, I, CF_3, C_1 to C_4 alkyl, and C_1 to C_4 alkoxy, or 5-chloropyrid-2-yl; X denotes OH, F, Cl or Br; R_2 is H, CH_3 or F; and R_3 is H or F are dissolved in the solvent system containing component (b) and optionally (a) and wherein component (c) is optionally added to this solution.

2. The process according to claim 1 wherein the solution is aerated with nitrogen during production and after sterilization by filtration and is placed in suitable receptacles such as ampoules, injection vials or pre-filled syringes with presiding and subsequent aeration by nitrogen.

3. The process according to claim 1 characterized in that component (a) of the solvent system contains 10 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene).

4. The process according to claim 1 characterized in that component (a) of the solvent system contains 35 to 45% by weight of α-tetrahydrofurfuryl-ω-hydroxypoly(oxyethylene).

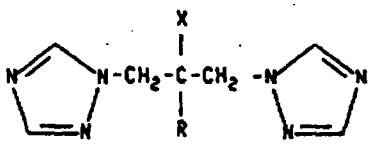
5. The process according to claim 1 characterized in that component (b) of the solvent system contains 10 to 90% by weight of polyethylene glycol.

6. The process according to claim 1 characterized in that component (b) of the solvent system contains 30 to 55% by weight of polyethylene glycol.

7. The process according to claim 5 characterized in that the polyethylene glycol has a mean molecular weight of 300.

8. The process according to claim 2 characterized in that the pharmaceutical preparation is adapted to be parenterally administered.

9. The process according to claim 1, characterized in that said pharmaceutically active component is a triazole derivative of the following formula III:



(III)

wherein R denotes a phenyl radical with, if desired, 1 to 3 substituents selected from the group consisting essentially of F, C1, Br, I and CF_3 and X denotes OH, F, C1 or Br.

10. The process according to claim 9 characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl-)2-bromo-2-(2,4-dichlorophenyl)-propane.

11. The process according to claim 9 characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-chloro-2-(2,4-dichlorophenyl)-propane.

12. The process according to claim 9 characterized in that the triazole derivative is 1,3-bis(1H-1,2,4-triazol-1-yl)-2-(4-iodophenyl)propane-2-ol.

13. The process according to claim 9 characterized in that said triazole derivative is 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol.

14. The process according to claims 1 and 9 to 13 characterized in that the pharmaceutical preparation con-

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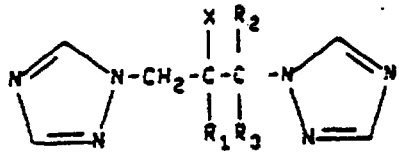
tains 30 to 100 mg/ml of the triazole derivative.

15. The process according to claim 14 characterized in that the pharmaceutical preparation contains 50 to 100 mg/ml of the triazole derivative.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. Pharmazeutische Zubereitung bestehend aus einem Lösungsmittelsystem enthaltend
   (a) 0-65 Gew.-% α-Tetrahydrofurfuryl-ω-hydroxypoly-(oxyethylen)
   (b) 10-100 Gew.-% Polyethylenglykol mit einem mittleren Molekulargewicht von 200-600 und
   (c) 0-35 Gew.-% Wasser,
   wobei die Summe der zwei Komponenten (a) und (b) wenigstens 65 Gew.-% ausmacht, und eine oder mehrere therapeutisch wirksame Verbindungen der Formel



(I)

worin R_1 ein Phenylrest ist, der gegebenenfalls mit 1 bis 3 Substituenten, unabhängig voneinander ausgewählt aus der Gruppe bestehend aus F, Cl, Br, I, CF_3, C_1-C_4-Alkyl und C_1-C_4-Alkoxy oder 5-Chlor-pyrid-2-yl, substituiert ist; X die Bedeutung von OH, F, Cl oder Br hat; R_2 H, CH_3 oder F ist und R_3 H oder F ist.

2. Pharmazeutische Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß sie 10-45 Gew.-% α-Tetrahydrofurfuryl-ω-hydroxypoly(oxyethylen) enthält.

3. Pharmazeutische Zubereitung nach Anspruch 2, dadurch gekennzeichnet, daß sie 35-45 Gew.-% α-Tetrahydrofurfuryl-ω-hydroxypoly(oxyethylen) enthält.

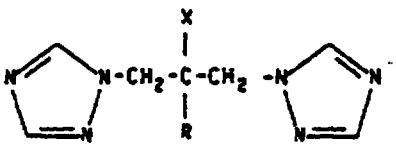
4. Pharmazeutische Zubereitung nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß sie 10-90 Gew.-% Polyethylenglykol enthält.

5. Pharmazeutische Zubereitung nach Anspruch 4, dadurch gekennzeichnet, daß sie 30-55 Gew.-% Polyethylenglykol enthält.

6. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das Polyethylenglykol ein mittleres Molekulargewicht von 300 aufweist.

7. Pharmazeutische Zubereitung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß sie parenteral verabreichbar ist.

8. Pharmazeutische Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß besagter pharmazeutisch aktiver Bestandteil ein Triazolderivat der folgenden Formel (III) ist:



(III)

worin R ein Phenylrest ist mit, falls gewünscht, 1 bis 3 Substituenten, ausgewählt aus der Gruppe bestehend aus im wesentlichen F, Cl, Br, I und CF_3, und X die Bedeutung von OH, F, Cl oder Br hat.

* C L M S *

9. Pharmazeutische Zubereitung nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei besagtem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-brom-2-(2,4-dichlorphenyl) propan handelt.

10. Pharmazeutische Zubereitung nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei dem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-chlor-2-(2,4-dichlorphenyl)-propan handelt.

11. Pharmazeutische Zubereitung nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei dem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(4-iodphenyl)propan-2-ol handelt.

12. Pharmazeutische Zubereitung nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei besagtem Triazolderivat um 2,4-Difluor-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzylalkohol handelt.

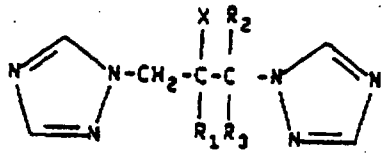
13. Pharmazeutische Zubereitung nach einem der Ansprüche 8 bis 12, dadurch gekennzeichnet, daß sie 30-100 mg/ml des Triazolderivates enthält.

14. Pharmazeutische Zubereitung nach einem der Ansprüche 8 bis 12, dadurch gekennzeichnet, daß sie 50-100 mg/ml des Triazolderivates enthält.

15. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß sie in Form von Ampullen, Injektionsfläschchen oder Fertigspritzen vorliegt.

Patentansprüche für folgende Vertragsstaaten: GR, ES

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung bestehend aus einem Lösungsmittelsystem enthaltend
   (a) 0-65 Gew.-% α-Tetrahydrofurfuryl- ω -hydroxypoly (oxyethylen)
   (b) 10-100 Gew.-% Polyethylenglykol mit einem mittleren Molekulargewicht von 200-600 und
   (c) 0-35 Gew.-% Wasser
   wobei die Summe der zwei Komponenten (a) und (b) wenigstens 65 Gew.-% ausmacht, worin eine oder mehrere therapeutisch wirksame Verbindungen der Formel



(I)

worin R_1 ein Phenylrest ist, der gegebenenfalls mit 1 bis 3 Substituenten, unabhängig voneinander ausgewählt aus der Gruppe bestehend aus F, Cl, Br, I, CF_3, C_1-C_4-Alkyl und C_1-C_4-Alkoxy oder 5-Chlor-pyrid-2-yl, substituiert ist; X die Bedeutung von OH, F, Cl oder Br hat, R_2 H, CH_3 oder F ist und R_3 H oder F ist, in dem Lösungsmittelsystem enthaltend Komponente (b) und gegebenenfalls (a) gelöst wird und worin Komponente (c) gegebenenfalls zu dieser Lösung hinzugefügt wird.

2. Verfahren nach Anspruch 1, worin die Lösung während der Herstellung und nach der Sterilisierung durch Filtration mit Stickstoff belüftet wird und in geeignete Gefäße gefüllt wird wie Ampullen, Injektionsfläschchen oder Fertigspritzen unter vorausgehender und anschließender Belüftung mit Stickstoff.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Komponente (a) des Lösungsmittelsystems 10-45 Gew.-% α-Tetrahydrofurfuryl-ω-hydroxypoly(oxyethylen) enthält.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Komponente (a) des Lösungsmittelsystems 35-45 Gew.-% α-Tetrahydrofurfuryl-ω-hydroxypoly(oxyethylen) enthält.

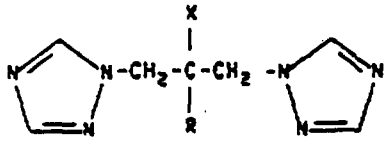
5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Komponente (b) des Lösungsmittelsystems 10-90 Gew.-% Polyethylenglykol enthält.

6. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Komponente (b) des Lösungsmittelsystems 30-55 Gew.-% Polyethylenglykol enthält.

7. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das Polyethylenglykol ein mittleres Molekulargewicht von 300 aufweist.

8. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die pharmazeutische Zubereitung parenteral verabreichbar ist.

9. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß besagter pharmazeutisch aktiver Bestandteil ein Triazolderivat der folgenden Formel III ist:



(III)

worin R ein Phenylrest ist mit, falls gewünscht, 1 bis 3 Substituenten, ausgewählt aus der Gruppe bestehend aus im wesentlichen F, Cl, Br, I und CF_3, und X die Bedeutung von OH, F, Cl oder Br hat.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß es sich bei dem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-brom-2-(2,4-dichlorphenyl)propan handelt.

11. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß es sich bei dem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-chlor-2-(2,4-dichlorphenyl)propan handelt.

12. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß es sich bei dem Triazolderivat um 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(4-iodphenyl)propan-2-ol handelt.

13. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß es sich bei besagtem Triazolderivat um 2,4-Difluor-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzylalkohol handelt.

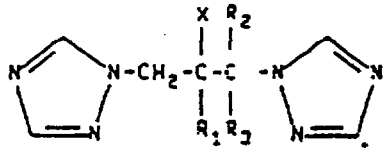
14. Verfahren nach den Ansprüchen 1 und 9 bis 13, dadurch gekennzeichnet, daß die pharmazeutische Zubereitung 30-100 mg/ml des Triazolderivates enthält.

15. Verfahren nach Anspruch 14, dadurch gekennzeichnet, daß die pharmazeutische Zubereitung 50-100 mg/ml des Triazolderivates enthält.

Revendications

Revendications pour les Etats contractants suivants:DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. Préparation pharmaceutique consistant en un mélange de solvants contenant :
   (a) 0 à 65 % en poids d'α-tétrahydrofurfuryl-ω-hydroxypoly(oxyéthylène),
   (b) 10 à 100 % en poids d'un polyéthylèneglycol ayant un poids moléculaire moyen de 200 à 600, et
   (c) 0 à 35 % en poids d'eau, la somme des quantités des deux constituants (a) et (b) s'élevant à au moins 65 % en poids, et un ou plusieurs composés thérapeutiquement actifs, de formule



(I)

dans laquelle R_1 représente un radical phényle portant facultativement 1 à 3 substituants choisis indépendamment dans le groupe consistant en F, Cl, Br, I, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou 5-chloro-pyrid-2-yle ; X représente un groupe OH, F, Cl ou Br ; R_2 représente H, un groupe CH_3 ou F ;

* C L M S *

et R_3 représente H ou F.

2. Préparation pharmaceutique suivant la revendication 1, caractérisée en ce qu'elle contient 10 à 45 % en poids d'α-tétrahydrofurfuryl-ω-hydroxypoly(oxyéthylène).

3. Préparation pharmaceutique suivant la revendication 2, caractérisée en ce qu'elle contient 35 à 45 % en poids d'α-tétrahydrofurfuryl-ω-hydroxypoly(oxyéthylène).

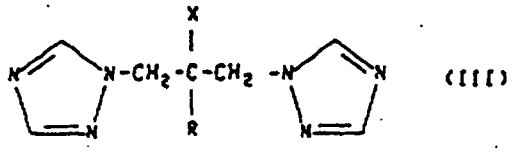
4. Préparation pharmaceutique suivant l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle contient 10 à 90 % en poids de polyéthylèneglycol.

5. Préparation pharmaceutique suivant la revendication 4, caractérisée en ce qu'elle contient 30 à 55 % en poids de polyéthylèneglycol.

6. Préparation pharmaceutique suivant l'une quelconque des revendications précédentes, caractérisée en ce que le polyéthylèneglycol possède un poids moléculaire moyen égal à 300.

7. Préparation pharmaceutique suivant l'une quelconque des revendications 1 à 6, caractérisée en ce qu'elle est apte à une administration parentérale.

8. Préparation pharmaceutique suivant la revendication 1, caractérisée en ce que le constituant pharmaceutiquement actif est un dérivé de triazole répondant à la formule III suivante :



(III)

dans laquelle R représente un radical phényle portant, si cela est désiré, 1 à 3 substituants choisis dans le groupe consistant essentiellement en F, Cl, Br, I et un groupe CF_3, et X représente un groupe OH, F, Cl ou Br.

9. Préparation pharmaceutique suivant la revendication 8, caractérisée en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-1-yl)-2-bromo-2-(2,4-dichlorophényl)-propane.

10. Préparation pharmaceutique suivant la revendication 8, caractérisée en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-1-yl)-2-chloro-2-(2,4 dichlorophényl)-propane.

11. Préparation pharmaceutique suivant la revendication 8, caractérisée en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-1-yl)-2-(4-iodophényl)-propane-2-ol.

12. Préparation pharmaceutique suivant la revendication 8, caractérisée en ce que le dérivé de triazole est l'alcool 2,4-difluoro-α,α-bis(1H-1,2,4-triazole-1-yl-méthyl)benzylique.

13. Préparation pharmaceutique suivant l'une quelconque des revendications 8 à 12, caractérisée en ce qu'elle contient 30 à 100 mg/ml du dérivé de triazole.

14. Préparation pharmaceutique suivant l'une quelconque des revendications 8 à 12, caractérisée en ce qu'elle contient 50 à 100 mg/ml du dérivé de triazole.

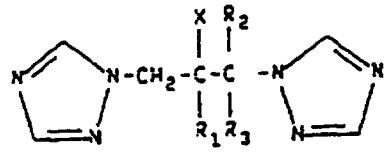
15. Préparation pharmaceutique suivant l'une quelconque des revendications précédentes, caractérisée en ce qu'elle est sous forme d'ampoules, de flacons pour injections ou de seringues prédosées.

Revendications pour les Etats contractants suivants: GR, ES

1. Procédé de préparation d'une composition pharmaceutique consistant en un mélange de solvants contenant :
   (a) 0 à 65 % en poids d'α-tétrahydrofurfuryl-ω-hydroxypoly(oxyéthylène),
   (b) 10 à 100 % en poids d'un polyéthylèneglycol ayant un poids moléculaire moyen de 200 à 600, et

(c) 0 à 35 % en poids d'eau,

la somme des quantités des deux constituants (a) et (b) s'élevant à au moins 65 % en poids, dans lequel un ou plusieurs composés thérapeutiquement actifs, de formule



(I)

dans laquelle R_1 représente un radical phényle portant facultativement 1 à 3 substituants choisis indépendamment dans le groupe consistant en F, Cl, Br, I, CF_3, alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou 5-chloro-pyrid-2-yle ; X représente un groupe OH, F, Cl ou Br ; R_2 représente H, un groupe CH_3 ou F ; et R_3 représente H ou F, sont dissous dans le mélange de solvants contenant le constituant (b) et, facultativement, le constituant (a), et dans lequel le constituant (c) est ajouté facultativement à cette solution.

2. Procédé suivant la revendication 1, dans lequel la solution est aérée avec de l'azote au cours de la production et après stérilisation par filtration et est introduite dans des récipients convenables tels que des ampoules, des flacons pour injections ou des seringues prédosées, avec aération par de l'azote avant et après introduction.

3. Procédé suivant la revendication 1, caractérisé en ce que le constituant (a) du mélange de solvants contient 10 à 45 % en poids d'α-tétrahydrofurfuryl-ω-hydroxy-poly(oxyéthylène).

4. Procédé suivant la revendication 1, caractérisé en ce que le constituant (a) du mélange de solvants contient 35 à 45 % en poids d'α-tétrahydrofurfuryl-ω-hydroxy-poly(oxyéthylène).

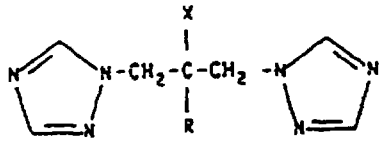
5. Procédé suivant la revendication 1, caractérisé en ce que le constituant (b) du mélange de solvants contient 10 à 90 % en poids de polyéthylèneglycol.

6. Procédé suivant la revendication 1, caractérisé en ce que le constituant (b) du mélange de solvants contient 30 à 55 % en poids de polyéthylèneglycol.

7. Procédé suivant la revendication 5, caractérisé en ce que le polyéthylèneglycol possède un poids moléculaire moyen égal à 300.

8. Procédé suivant la revendication 2, caractérisé en ce que la préparation pharmaceutique est apte à une administration parentérale.

9. Procédé suivant la revendication 1, caractérisé en ce que le constituant pharmaceutiquement actif est un dérivé de triazole répondant à la formule III suivante :



(III)

dans laquelle R représente un radical phényle portant, si cela est désiré, 1 à 3 substituants choisis dans le groupe consistant essentiellement en F, Cl, Br, I et un groupe CF_3, et X représente un groupe OH, F, Cl ou Br.

10. Procédé suivant la revendication 9, caractérisé en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-l-yl)-2-bromo-2-(2,4-dichlorophényl)-propane.

11. Procédé suivant la revendication 9, caractérisé en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-l-yl)-2-chloro-2-(2,4-dichlorophényl)-propane.

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12. Procédé suivant la revendication 9, caractérisé en ce que le dérivé de triazole est le 1,3-bis(1H-1,2,4-triazole-l-yl)-2-(4-iodophényl)propane-2-ol.

13. Procédé suivant la revendication 9, caractérisé en ce que le dérivé de triazole est l'alcool 2,4-difluoro-α,α-bis(1H,-1,2,4-triazole-1-ylméthyl)benzylique.

14. Procédé suivant les revendications 1 et 9 à 13, caractérisé en ce que la préparation pharmaceutique contient 30 à 100 mg/ml du dérivé de triazole.

15. Procédé suivant la revendication 14, caractérisé en ce que la préparation pharmaceutique contient 50 à 100 mg/ml du dérivé de triazole.