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PHARMACEUTICAL COMPOSITION CONTAINING A TRYPTOPHAN DERIVATIVE

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(57) Abstract: Pharmaceutical compositions containing a compound of formula (I) wherein the radicals denote e.g.: R1 is hydrogen or C1-C6-alkyl; R2 is hydrogen or C1-C6-alkyl; R3 is hydrogen or C1-C6-alkyl; R4 is OH; R5 is hydrogen, and a pharmaceutically acceptable cyclodextrin derivative can be used for the preparation of ophthalmic formulations.
Pharmaceutical composition containing a tryptophan derivative

Field of the Invention

The present invention relates to pharmaceutical compositions containing at least one tryptophan derivative. The invention also deals with a process for the preparation of pharmaceutical compositions and to tryptophan derivatives for different medical uses.

Background of the invention

Since decades it is known that various amino acids play an important role for nutrition and treatment of human diseases. L-tryptophan is an essential heterocyclic amino acid which is part of various naturally occurring peptides. The amino acid tryptophan forms a large variety of small peptides via its carboxylic function. Many of these peptides have physiological activities. Some small peptides (such as Trp-Pro) are known to be useful for the treatment of diseases, e.g. for amyloid-associated diseases, see US 2006/0234947. However, pharmaceutical compositions containing amino acid derivatives often are not stable during storage, in particular when formulated as aqueous solutions. Furthermore, for many pharmaceutical applications, the amount of amino acid derivative needed at the specific site of action is higher than conventional pharmaceutical formulations can provide with.

The pharmaceutical compositions of this invention comprise a tryptophan derivative which often has a molecular weight between 260 and 600 g/mol. They preferably also contain an additional component in order to stabilize the active substance or compound, in particular they contain a cyclodextrin derivative (C).

For the treatment of disorders and conditions of the central nervous system (CNS), various drug compounds have been developed in recent years, however many diseases, like Alzheimer's can not be treated adequately at low cost because of complex, non reproducible chemical structures, low solubilities, limited tolerability and minimal efficacy of the compounds.

Furthermore, many compounds, when orally administered, are partly or completely
metabolized in the gastric system, without providing the expected bioavailability. This is a particular issue for small peptide structures.

Furthermore, for the treatment of disorders of the eye, such as glaucoma or cataracts, no sufficiently efficient pharmaceutical compositions are available which can be easily administered. There is a high medical need to provide with pharmaceutical compositions for treatment and prevention of diseases like glaucoma, as the disease glaucoma is widely spread in all countries and can result in loss of vision, increased eye pressure and blindness. The classification of glaucoma includes the following different types of diseases:

Primary angle-closure glaucoma, secondary open-angle glaucoma, steroid-induced glaucoma, traumatic glaucoma, pigmentary dispersion syndrome, pseudo-exfoliation syndrome, secondary angle-closure glaucoma, neovascular glaucoma, uveitis and glaucoma and other not further specified eye pathologies. In addition, age-related macular degeneration is a condition which reflects features of glaucoma and leads to a progressive loss of vision, leading finally to blindness.

The definition of glaucoma includes an elevation in the intraocular pressure (IOP) over a normal range. Currently available medications for the treatment of glaucoma belong to pharmacological classes including β-adrenergic blockers, cholinergic agonists, carbonic anhydrase inhibitors, alpha agonists. All medications operate under a mechanism whereby the IOP is lowered. These therapies are typically administered as eye drops. Hyper-osmotics may be administered intravenously for emergency treatment. In addition, laser therapy and surgical approaches are applied in special cases. There are different theories for the cause for the degeneration of the retinal ganglion cells including mechanical, vascular and excitotoxic mechanisms. The protein β-Amyloid (Aβ) was found to co-localize with dying retinal ganglion cells. A recent study demonstrated that inhibition of Aβ-aggregation reduces glaucomatous degeneration of retinal ganglion cells (see Li Guo et al, PNAS, 08/2007, Vol. 104, p. 13444-13449).

One important disadvantage of classical glaucoma treatment is that the ophthalmic compositions need to be applied by not very convenient routes and that they can not be stored at room temperature over a longer period of time (e.g. for weeks) without losing
activity. It is known in the prior art that cyclodextrins can be used in pharmaceutical compositions.

One technical problem is that cyclodextrin containing formulations are difficult to be preserved by standard classical preservatives, since the preservatives are often coordinated by the cyclodextrin. Thus, a preservative may be inactivated by the use of cyclodextrins. Additionally, the higher the cyclodextrin concentration in the formulation, the more difficult the preserving can be. Typical concentrations of cyclodextrins in prior art pharmaceutical preparations are low, meaning that they typically vary from 0.5%-5.0%. Typical uses are mentioned e.g. in US 4,596,795, describing a tablet containing progesterone and a cyclodextrin or in WO 2009/156160 describing the CNS-compound neramexane with a cyclodextrin-derivative.

In patent US 5,043,328 some indole derivates of the following general formula are disclosed, wherein \( R^7 \) is hydrogen or -COOH and \( R^8 \) is hydrogen or -NH\(_2\).

\[
\text{H} \quad \text{CH} = \text{CH} - R^7 \\
| \quad \text{N} \\
\text{CH} = \text{CH} - R^8
\]

These compounds can be used in combination with fatty acids for pharmaceutical compositions, which also can contain stabilizers such as phospholipids, sugar lipids, proteins or cyclodextrins.

In WO 2009/125246, ophthalmic compositions for treatment of glaucoma and ophthalmic hypertension are described which contain an active ingredient, such as dorzolamid, which has the following structure.

\[
\text{H}_3\text{C} \quad \text{S} \quad \text{S} \quad \text{SO}_2\text{NH}_2 \cdot \text{HCl} \\
\text{H} \quad \text{NHCH}_2\text{CH}_3
\]
This compound can be combined with further active ingredients such as a prostaglandin (see latanoprost) or timolol and can also be formulated in aqueous solutions together with a stabilizer, such as cyclodextrin.

In the document WO 2009/024346, various peptides of the structure X-Y are disclosed to be useful for the treatment of various ophthalmic diseases in which beta-amyloid plays a role. Some listings of dipeptides are provided and several diseases and types of formulations are mentioned.

In the publication of A. Frydman-Marom (Angewandte Chemie, 2009, Vol. 48, 11, 1981 - 1986), the tryptophane derivative of the following formula is described as an inhibitor of the oligomerization of beta amyloid polypeptides.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CH} & \quad \text{C} & \quad \text{N} & \quad \text{C} & \quad \text{C} & \quad \text{OH} \\
\text{CH}_2 & \quad & & & & & \\
\text{HN} & \quad \text{F} & \quad \text{H}
\end{align*}
\]

In the publication of Koji Kano (Chirality, Aug 2001, Vol. 13, 8, 474-482), several tryptophane esters are disclosed which can structurally interact with specific beta-cyclodextrins.

Summary of the invention

It is one goal of the present invention to provide new pharmaceutical compositions which can easily be prepared, based on low-cost active ingredients, which compositions are easily applicable to humans and animals, and are well tolerated and have an acceptable long-term stability. Also the long-term stabilization of pharmaceutical, and in particular ophthalmmic compositions is a goal of this invention.

The present invention in particular relates to pharmaceutical composition comprising at least one compound of formula (I)
wherein the radicals denote:

\[ 
\text{R}^1 \text{ is hydrogen, Ci-Cs-alkyl, C}_3\text{-C}_8\text{-cycloalkyl, C}_6\text{-Ci4-aryl, carboxy or C-thiocarb; in particular hydrogen or Ci-C}_3\text{-alkyl,}
\]

\[ 
\text{R}^2 \text{ is hydrogen, Ci-Cs-alkyl, C}_3\text{-C}_8\text{-cycloalkyl, C}_6\text{-Ci4-aryl, carboxy or C-thiocarb; in particular hydrogen or Ci-C}_3\text{-alkyl,}
\]

\[ 
\text{R}^3 \text{ is hydrogen or Ci-Cs-alkyl, in particular methyl,}
\]

\[ 
\text{R}^4 \text{ is OH or O-Ci-Cs-alkyl, in particular OH,}
\]

\[ 
\text{R}^5 \text{ is hydrogen or Ci-Cs-alkyl, in particular hydrogen;}
\]

and/or a pharmaceutically acceptable salt (and/or a stereoisomeric form and/or derivative) thereof. The composition can be e.g. a solid composition (e.g. powder, tablet), a semi-solid composition (e.g. gel) or a liquid composition (e.g. solution, suspension).

As used herein, the following definitions are applicable, unless otherwise described:

The term "Ci-Cs-alkyl" represents straight or branched chain alkyl groups, such as methyl, ethyl, propyl.

The term "O-Ci-Cs-alkyl" represents straight or branched chain -O-Ci-Cs-alkyl groups.

The term "aryl" represents an aromatic group such as e.g. phenyl or naphthyl, wherein the phenyl or naphthyl group is optionally substituted by one or two substituents, which may be the same or different, selected independently from halogen or Ci-C6-alkyl.
The term "carboxy" represents a group -(C=0)-0-.

The term "thiocarb" represents a group -(C=S)-0-.  

The term "C₃-C₈-cycloalkyl" represents a 3- to 8-membered carbocyclic ring, such as cyclopropyl, cyclohexyl and others. The term "halogen" represents fluorine, chlorine, bromine and iodine.

One further important aspect of the invention is a pharmaceutical composition comprising at least one compound of formula (I)

![Chemical structure](image)

wherein the radicals denote:

1. \( R¹ \) is hydrogen, \( \text{Ci-Cs}-\text{alkyl}, \text{C₃-C₈-cycloalkyl}, \text{C₆-Ci4-aryl}, \) carboxy or \( \text{C-thiocarb} \); in particular hydrogen or \( \text{Ci-C₃-alkyl} \),
2. \( R² \) is hydrogen, \( \text{Ci-Cs}-\text{alkyl}, \text{C₃-C₈-cycloalkyl}, \text{C₆-Ci4-aryl}, \) carboxy or \( \text{C-thiocarb} \); in particular hydrogen or \( \text{Ci-C₃-alkyl} \),
3. \( R³ \) is hydrogen or \( \text{Ci-Cs}-\text{alkyl} \), in particular methyl,
4. \( R⁴ \) is OH or 0-\( \text{Ci-C₈}-\text{alkyl} \), in particular OH;
5. \( R⁵ \) is hydrogen or \( \text{Ci-Cs}-\text{alkyl} \), in particular hydrogen; and/or a pharmaceutically acceptable salt thereof,

and at least one pharmaceutically acceptable cyclodextrin derivative (C), and optionally further components (F).

The invention also relates to a pharmaceutical composition, wherein the composition contains at least one compound of formula (I) in which the radicals denote:
R<sub>1</sub> is hydrogen, Ci-Cs-alkyl, C<sub>3</sub>-Cs-cycloalkyl or C<sub>6</sub>-C<sub>14</sub>-aryl,
R<sub>2</sub> is hydrogen, Ci-Cs-alkyl, C<sub>3</sub>-Cs-cycloalkyl or C<sub>6</sub>-Ci<sub>4</sub>-aryl,
R<sub>3</sub> is hydrogen or Ci-Cs-alkyl,
R<sub>4</sub> is OH or 0-Ci-C<sub>8</sub>-alkyl,
R<sub>5</sub> is hydrogen,

and/or a pharmaceutically acceptable salt thereof,

and comprising at least one further component (F).

A pharmaceutical composition is also of interest, wherein the composition contains a compound of formula (I) wherein:

R<sub>1</sub> is hydrogen or Ci-C<sub>3</sub>-alkyl,
R<sub>2</sub> is hydrogen or Ci-C<sub>3</sub>-alkyl,
R<sub>3</sub> is hydrogen or methyl,
R<sub>4</sub> is OH,
R<sub>5</sub> is hydrogen,

and/or a pharmaceutically acceptable salt thereof,

and comprises the solvent water and optionally further components (F).

The invention also relates to a pharmaceutical composition, wherein the composition contains a compound of formula (I) wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen, R<sub>3</sub> is methyl and R<sub>4</sub> is OH, R<sub>5</sub> is hydrogen, and/or a pharmaceutically acceptable salt thereof, and comprises the solvent water and optionally further components (F).

One aspect of the invention is a pharmaceutical composition, wherein the composition contains the R-enantiomer of the compound of formula (A)
and/or a pharmaceutically acceptable salt thereof,
and at least one pharmaceutically acceptable cyclodextrin derivative (C)
and optionally a further active ingredient and/or further components (F).

Surprisingly, it was found that the solubility of compound (A) can be improved by the use of cyclodextrin derivatives (C).

The present invention also relates to a pharmaceutical composition, wherein the cyclodextrin compound (C) is selected from the group consisting of:


The invention also relates to a pharmaceutical composition, wherein the compound of formula (I) has the R-configuration and the cyclodextrin compound (C) is selected from hydroxyalkyl-substituted beta-cyclodextrins.

The invention also relates to a pharmaceutical composition, wherein the molar ratio of the compound of formula (I) and the cyclodextrin compound (C) is in the range from 0.1:1 to 1:20, preferably from 1:1 to 1:10.

One aspect of the invention relates to a pharmaceutical composition, wherein the composition is an aqueous liquid composition comprising at least 70 % by weight of water and wherein the concentration of the compound of formula (I) is in the range from 1 mg/ml to 50 mg/ml.

In particular, the invention also relates to a pharmaceutical composition further comprising a cyclodextrin compound (C), for example in a concentration of at least 5 mg/ml, for example
from 10 to 500 mg/ml, such as from 50 to 180 mg/ml.

The invention also relates to such a composition further comprising a hydrophilic pharmaceutical agent. The hydrophilicity can be determined by the octanol/water partition coefficient \((\log P)\), for example according to the standard methods mentioned herein. Generally, a pharmaceutical agent having an octanol/water partition coefficient of \(\log P < 1\) will be considered hydrophilic. Thus, hydrophilic pharmaceutical agents may for example be selected from the group of peptides, in particular dipeptides, and in particular those of formula (I), by determining their octanol/water partition coefficient.

The invention also relates to a pharmaceutical composition, such as an ophthalmic composition, wherein the composition is an aqueous liquid composition comprising as further component \((F)\) a metal containing preservative. The metal containing preservative is selected from the group consisting of mercury-, silver-, copper-, tin-containing preservatives, in particular a mercury-containing preservative.

The invention also relates to a pharmaceutical composition, such as an ophthalmic composition, wherein the composition is an aqueous liquid composition comprising as further component \((F)\) a mercury containing preservative. The mercury containing preservative may be selected from the group consisting of thiomersal, phenylmercuric borate, 2-(ethylmercurithio)-benzoic acid, thimer fonate, phenylmercuric acetate, mercurate(l-),(2,3-dihydro-2-thioxo-5-benzoxazolocarboxylato(2-)S)ethyl-, sodium. The invention also relates in general to an ophthalmic composition comprising such a mercury containing preservative, e. g. in a concentration from 0.1 to 0.0001 % by weight, for example from 0.01 to 0.001 % by weight.

The invention also relates to a pharmaceutical composition, wherein the composition is an aqueous liquid composition comprising as further component \((F)\) a metal-containing preservative, in particular the preservative thiomersal, e. g. in a concentration of 0.01 to 0.001 % by weight. The invention also relates in general to an ophthalmic composition comprising the preservative thiomersal, e. g. in a concentration of 0.01 to 0.001 % by weight.

The invention also relates to a pharmaceutical composition as described above for the treatment of a disorder or a disease of the central nervous system. One aspect of the
invention relates to a pharmaceutical composition for the treatment of an ophthalmic disorder or disease. The invention also relates to an ophthalmic composition for neurodegenerative ophthalmic disorders or diseases.

The invention also relates to a process for preparation of a pharmaceutical composition comprising the steps of mixing together at least one compound of formula (I)

\[
\begin{align*}
\text{CH}_2 & \text{-CH} \quad \text{C} \quad \text{NH} \quad \text{C} \quad \text{C} \\
\text{R}^1 & \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \quad \text{R}^5
\end{align*}
\]

wherein the radicals denote:

R\(^1\) is hydrogen, C\(_1\)-C\(_s\)-alkyl, C\(_3\)-C\(_6\)-cycloalkyl, C\(_6\)-C\(_4\)-aryl, carboxy or C-thiocarb; in particular hydrogen or C\(_i\)-C\(_3\)-alkyl,

R\(^2\) is hydrogen, C\(_i\)-C\(_s\)-alkyl, C\(_3\)-C\(_6\)-cycloalkyl, C\(_6\)-C\(_4\)-aryl, carboxy or C-thiocarb; in particular hydrogen or C\(_i\)-C\(_3\)-alkyl,

R\(^3\) is hydrogen or C\(_i\)-C\(_s\)-alkyl, in particular methyl,

R\(^4\) is OH or O-C\(_i\)-C\(_g\)-alkyl, in particular OH,

R\(^5\) is hydrogen or C\(_i\)-C\(_s\)-alkyl, in particular hydrogen;

and/or a pharmaceutically acceptable salt thereof, (and/or a stereoisomeric form or derivative thereof)

and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally further components (F).

The invention also relates to the use of a cyclodextrin compound (C) (or the compound (C) for use), in particular of a beta-cyclodextrin, for the preparation of a pharmaceutical composition for the treatment of ophthalmic diseases and to the use of a cyclodextrin
compound (C), in particular of a beta-cyclodextrin, for the treatment of ophthalmic diseases. The invention also relates to the use of a hydroxyalkyl-substituted beta-cyclodextrin for the preparation of a pharmaceutical composition for the treatment of glaucoma and to the use of a hydroxyalkyl-substituted beta-cyclodextrin for the treatment of glaucoma.

The invention further relates to such a use, wherein the composition is an aqueous liquid composition comprising as further component (F) a metal containing preservative. The metal containing preservative can be selected from the group consisting of mercury-, silver-, copper-, tin-containing preservatives. For example, the preservative may be silver nitrate, silver chloride, silver sulfadiazine, chitosan-copper-complexes, zinc oxide. Often the preservative is a mercury containing preservative. The mercury containing preservative may for example be selected from the group consisting of thiomersal, phenylmercuric borate, 2-(ethylmercurithio)-benzoic acid, thimer, phenylmercuric acetate, Mercurate(1-), (2,3-dihydro-2-thioxo-5-benzoxazolecarboxylato(2–)-S)ethyl-, sodium.

The mercury containing preservative may be present in a concentration from 0.1 to 0.0001 % by weight, often in a concentration from 0.01 to 0.001 % by weight. For example, the preservative may be thiomersal in a concentration from 0.01 to 0.001 % by weight (of the total composition).

The invention also relates to such a use wherein the concentration of the cyclodextrin-compound (C) is at least 5 mg/ml, for example 10 to 500 mg/ml, such as 50 to 180 mg/ml.

The invention also relates to the use of a cyclodextrin compound (C) for the preparation of a pharmaceutical composition for the treatment of ophthalmic diseases in the posterior segment of the eye (including the anterior hyaloids membrane and all optical structures behind it, such as vitreous humor, retina, choroid and optic nerve).

The invention also relates to the use of a hydroxyalkyl-substituted beta-cyclodextrin for the preparation of a pharmaceutical composition for the treatment of glaucoma.

The invention also relates to the use of metal-containing preservatives for the preservation of cyclodextrin containing formulations, in particular of pharmaceutical compositions. The invention also relates to the use of metal-containing preservatives for the preservation of cyclodextrin containing formulations, in particular pharmaceutical formulations (such as
ophthalmic formulations) containing a hydrophilic pharmaceutical agent. The invention also relates to the metal-containing preservative belonging to the group of silver, mercury, tin-containing preservatives.

5 The hydrophilic pharmaceutical agent typically exhibits an octanol/water partition coefficient of log P < 1 inhibition, as outlined later.

The invention also relates to the use of metal-containing preservatives for the preservation of cyclodextrin containing formulations, in particular of pharmaceutical compositions, further comprising the use of at least one metal-containing preservative, in particular of thiomersal, wherein the pharmaceutical composition comprises a hydrophilic pharmaceutical agent, and wherein the concentration of the cyclodextrin compound (C) in the pharmaceutical composition is at least 10 mg/ml.

15 The compounds of the invention are usually named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours, and "rt" for room temperature).

20 The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense referring to a molecule that structurally resembles a reference molecule, but has been modified in a controlled manner to replace one or more specific substituent(s) of the molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs to identify slightly modified versions of a known compound which may have improved or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type) is a drug design approach that is known in pharmaceutical chemistry.

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to ingredients of the compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g a, human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency or listed in a recognized pharmacopeia for use in mammals.
The compounds of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

The compounds of the invention having a chiral center may exist in and be isolated in optically active (such as R- or S-isomers) and racemic forms. Some compounds may exhibit polymorphism. The present invention encompasses any racemic, optically active, polymorphic, tautomeric or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

The compounds of formula (I) are dipeptide derivatives, which often contain at least one acidic and one basic group. As a result, the solubility in solvents like water depends on the pH-values of the composition. Often, the solubility at neutral pH is rather limited, but in acidic or alkaline compositions, the solubility is much higher. However, for many purposes, such as ophthalmic formulations, acidic or alkaline compositions are in general less desirable, e.g. due to limited tolerability.

The composition according to the invention may comprise the compound of formula (I) and/or a "pharmaceutically acceptable salt" and/or a "derivative" and/or a "polymorphic form" and/or one or several "stereoisomeric forms" of a compound of formula (I).

The composition preferably comprises at least one compound of formula (I) and/or a pharmaceutically acceptable salt thereof and also comprises at least one pharmaceutically acceptable cyclodextrin derivative (C), and optionally one or several further components (F).

The pharmaceutically acceptable salts of the compound (I) can be prepared by known methods. These salts include e.g. acid addition salts, such as salts made with hydrochloric, methylsulfonic, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, tartaric, citric, benzoic, carbonic, cinnamic, mandelic, methanesulfonic, ethane-sulfonic, hydroxyl-ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexane-sulfamic, salicylic, p-amino salicylic, 2-
phenoxybenzoic or 2-acetoxybenzoic acid. Pharmaceutically acceptable salts also include base addition salts, e.g. using rations such as Na, K, Mg, Ca, alkyl-ammonium or choline. All of these salts may be prepared by conventional means. The nature of the salt is not particularly critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

The invention in particular relates to aqueous liquid compositions containing compound (I). These are liquid preparations wherein the major liquid component is water. The compositions often contain at least 70% by weight, often at least 80% by weight (w/w of the total composition) of water, but these aqueous liquid compositions may further comprise other liquid components, such as pharmaceutically acceptable organic co-solvents.

These co-solvents and other auxiliaries (such as preservatives, pH-regulators, sweeteners, polymers) are also named further components (F) of the composition. Examples of co-solvents are e.g. ethanol or glycerol. Such water-miscible organic co-solvents may be incorporated e.g. in order to solubilise a poorly water-soluble ingredient, such as a lipophilic substance. The term liquid composition or formulation includes liquid solutions and dispersions, such as emulsions and suspensions. Often, aqueous liquid solutions of a compound of formula (I) are preferred.

The invention also relates to semi-solid compositions. This term means a composition with low viscosity whose major liquid component is water. The semi-solid composition may comprise further components (F), such as pharmaceutically acceptable organic co-solvents, viscosity regulation polymers, pH-regulators, preservatives and emulsifiers. Examples of such liquid components are ethanol, glycerol, propylene glycol, and polyethylene glycol. Such water-miscible organic solvents (such as glycerol) may be incorporated for example in order to solubilise an insufficiently water-soluble ingredient, such as a lipophilic substance. The term semi-solid composition includes in particular gels, but also creams and ointments. In comparison to a liquid composition these formulations have an increased viscosity, compared to aqueous solutions.

The viscosity of semi-solid compositions can be controlled by using one or several polymeric components or a combination of polymers. Typical examples are acacia gum and derivatives, alginic acid and derivatives, carbomer and derivatives (e.g. carboxymethyl-

The term "polymorphic form" of a compound of formula (I) means a particular crystalline or non-crystalline form of a particular compound (I) which has particular physical properties (such as particular X-ray structure) with differ from the properties of a compound having the same chemical formula.

The term "stereoisomeric form" of compound (I) is used herein in the conventional chemical sense to refer to a molecule that has the same summarizing chemical formula but differs in the structure. Typical examples are enantiomers, diastereoisomers, racemates etc.

The compositions according to the present invention contain a compound of formula (I) and in one embodiment they comprise one or several cyclodextrin-derivatives (C). Cyclodextrin-derivatives (C) generally are oligo-saccharides composed of glucopyranose units. The unsubstituted or native cyclodextrins are usually prepared by the enzymatic degradation of starch. They are cone-like, toroidal molecules with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type.

The internal cavity of cyclodextrins is more hydrophobic and capable of accommodating both lipophilic and hydrophilic molecules in the form of inclusion complexes, thus enabling, for example, the solubilisation of poorly soluble drugs in aqueous media. Other types of complexes involving cyclodextrins have recently been identified. As used herein, a complex means an association of molecules by non-covalent interactions.

The formation of complexes takes, e.g. place in solution and typically is an equilibrium process. Complexes may also occur in solid state. An inclusion complex is a structure
wherein a guest molecule is either partially or completely contained within a cavity of a larger host molecule.

The three major types of pharmaceutically acceptable cyclodextrins (C) are alpha-, beta- and gamma-cyclodextrins, comprising 6, 7 and 8 glucopyranose units, respectively. In addition, a number of chemically modified cyclodextrins have been developed, often motivated by the desire to increase the water solubility and extend their usefulness as solubilising excipients. The beta-cyclodextrin-derivatives are of particular interest for the compositions according to the invention. Typical examples of such pharmaceutically acceptable cyclodextrin derivatives include the following products:

alpha-cyclodextrin (ACD), beta-cyclodextrin, randomly methylated betacyclodextrin, 2-O-methyl-beta-cyclodextrin (e.g. MBCD), heptakis-(2,6-di-0-methyl)-beta-cyclodextrin (dimethyl-beta-cyclodextrin), acetylated dimethyl-beta-cyclodextrin, heptakis-(2,3,6-tri-0-methyl)-beta-cyclodextrin (trimethyl-beta-cyclodextrin, sulfoalkylether-beta-cyclodextrin, sulfobutylether-beta-cyclodextrin, O-carboxymethyl-O-ethyl-beta-cyclodextrin, glucuronyl-glucosyl-beta-cyclodextrin, glucosyl-beta-cyclodextrin, maltosyl-beta-cyclodextrin, beta-cyclodextrin sulphate, beta-cyclodextrin phosphate, gamma-cyclodextrin, sulfoalkylether-beta-cyclodextrin, and sulfobutylether-beta-cyclodextrin (SBEBCD), and hydroxyalkyl-modified cyclo-dextrins (including hydroxypropyl-beta-cyclodextrin, e.g., 2-hydroxypropyl-beta-cyclodextrin (HPBCD), or hydroxypropyl-gamma-cyclodextrin, e.g. 2-hydroxy-propylgamma-cyclodextrin (HPGCD)).

The term "cyclodextrins" includes such modified versions of the native cyclodextrins. A typical example of a suitable grade of hydroxyalkyl-beta-cyclodextrin is amorphous, (often randomly substituted) hydroxypropyl-beta-cyclodextrin.

This often has a "Degree of Substitution" (DS) in the range of about 4.5, i.e. between approx. 4 and 5, such as the product marketed as Kleptose7i HPB (by Roquette). It is noted that the DS value, as used herein, defines the average number of substituted hydroxyl groups per anhydroglucose unit, not per cyclodextrin molecule.
Other examples of useful grades are (e.g. randomly substituted) hydroxypropyl-beta-cyclodextrin with a degree of Substitution DS in the range of about 5.6, or in the range of 2 to 4, or in the range of 5, or in the range of 6.5, respectively. An example of a suitable grade of hydroxypropyl-gamma-cyclodextrin is the product marketed as Cavasol 7i W8 HP (by Wacker Chemie, Germany).

A particularly interesting group of cyclodextrins is the group of beta-cyclodextrins, in particular the hydroxypropyl-beta-cyclodextrins. An often used cyclodextrin (C) is the product Kleptose as described in the experimental part.

The amount of the compound of formula (I) in the pharmaceutical composition may be decided taking into account the desired pharmaceutical use (e.g. oral or parenteral CNS-formulations or topic ophthalmic formulations), the type of the active ingredient of formula (I) and the concentrations of the other ingredients. The concentration of the active ingredient of formula (I) may be e. g. at least 0.1 mg/ml. If the active ingredient is a compound of formula (I), the concentration in a (liquid) formulation often is in the range from 0.1 to 100 mg/ml, for example 5 to 50 mg/ml, and often from 15 to 35 mg/ml.

The amount of cyclodextrin-derivative (C) in the composition may be selected taking into account the type of cyclodextrin (C) and the concentration of the active compound (I) and the pharmaceutical use. The concentration of the cyclodextrin-derivative (C) in the composition often is at least 5 mg/ml, for example 10 to 500 mg/ml, often from 50 to 180 mg/ml. If the only active ingredient is a compound of formula (I), the concentration of the cyclodextrin-derivative (C) in the composition may be in the range from about 1 to about 1000 mg/ml, for example from 10 to 500 mg/ml, often from 50 to 180 mg/ml.

Alternatively, the pharmaceutical composition may comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the range of 1 to 50 mg/ml. For example, a concentration of 5-50 mg/ml (or often from 15 to 35 mg/ml) of a compound of formula (I), or a pharmaceutically acceptable salt thereof, may be formulated in such a composition. According to the present invention, for example liquid or semi solid compositions may be prepared with a molar ratio of a compound of formula (I) to cyclodextrin-derivative (C) of from 0.1 : 1 to 10 : 1.
Another embodiment of the invention may comprise a molar ratio of a compound of
formula (I) to cyclodextrin-derivative (C) of from 0.3 : 1 to 3 : 1. Other embodiments may
comprise a molar ratio of about 0.6 : 1 to 2 : 1.

5 It was found that such molar ratios lead to a remarkably high degree of taste masking, which
may be associated with the spontaneous formation of a soluble complex between the
cyclodextrin molecule and the drug of formula (I).

Moreover, the potentially unpleasant smell of the active compound of formula (I) can
substantially be reduced. The degree of taste-masking is surprising in view of the high
water-solubility of the compounds of formula (I). It is surprising that apparently a
complexation achieves effective taste/smell-masking for a peptide compound without
eliminating other properties of the drug substance.

15 After oral or topical (e.g. into the eye) administration, the compound of formula (I) is rapidly
absorbed from the composition and becomes bioavailable.

The addition of one or more further components (F) which improve the character of the
pharmaceutical composition is also possible. For example, for oral compositions, one or
more sweeteners may be incorporated into the composition. Furthermore, one or more
excipients selected from the group of flavours, flavour enhancers, and taste masking agents
may be added. Typical sweeteners are natural or synthetic compounds which have a sweet
taste and are physiologically acceptable. Examples of natural sweeteners include common
sugars and sugar alcohols such as sucrose, glucose, fructose, maltose, maltitol, xylitol,
lactitol, mannitol, and sorbitol. A sugar alcohol may be used to improve the flavour of the
composition of the invention, for example sorbitol. A useful concentration range for sorbitol
or other sugars and sugar alcohols is from about 5 % (w/v) to about 25 % (w/v), a 10 %
(w/v) may also be used. Useful artificial sweeteners include saccharin-sodium, Saccharin,
sodium cyclamate, acesulfame K, neohesperidine dihydrochalcone, and aspartame, as well
as any other sweeteners whose safety in human use is established.

Appropriate concentrations depend on the individual sweetener which is selected, but also
on the specific cyclodextrin which is chosen. For example, hydroxypropyl-beta-cyclodextrin
already provides for a rather sweet taste so that the addition of a sweetening agent may not
increase the palatability of the formulation any further.
Suitable flavors which may further improve the taste of cyclodextrin-containing aqueous compositions of compounds of formula (I) (including compound (A) and pharmaceutically acceptable salts thereof) include grape, orange, peppermint, spearmint, cherry, liquorice, and aniseed. In particular, peppermint flavours are physicochemically and organoleptically well-compatible with the key components of the composition of the invention and may lead to palatable formulations.

For liquid compositions, the preservation of the active compound of formula (I) is very important. It is possible to formulate the composition without any additional preservative. In one embodiment, the composition of the invention is substantially free of preservatives. In this context, the term "substantially" means that preservatives are not detectable in the composition, or only in concentrations which are generally considered irrelevant with regard to any preservation effects. The pharmaceutical composition may optionally comprise as further component (F) at least one preservative. Whether a composition is effectively preserved may be determined according to tests known in the art.

The pharmaceutical composition can also contain as further component (F) a preservative such as benzalkonium chloride, cetalkylpyridinium chloride, cetrimide, cetyl trimethylammonium bromide, benzethonium chloride, chlorhexidine gluconate, ethanol, isotopropanol, propyl glycol, butylparaben, ethylparaben, methylparaben, propylparaben, sorbic acid, benzoic acid, thiomersal, organomercury components, chlorobutanol and/or benzyl alcohol. As further component (F) and preservative the compound thiomersal and combinations of thiomersal with a second preservative are of particular use for the pharmaceutical compositions.

It was surprisingly found, that certain further components (F) are particularly useful for the preservation of ophthalmic formulations (such as solutions of gels), which comprise a compound of general formula (I). It can be particularly difficult to preserve formulations against microorganisms (e.g. bacteria and fungi), if the formulation contains a cyclodextrin derivative.

From different tests it can be seen that a sufficient microbial preservation of ophthalmic formulations is not possible with benzalkonium chloride, cetrimide and chlorhexidine
according to the European standards (Pharmacopeia 7.0) and US standards (US-Pharmacopeia).

It can be shown that in particular the aromatic Hg-containing compounds, such as thiomersal exhibit a sufficient activity against Candida albicans, Aspergillus niger, Pseudomonas aeruginosa and Staphylococcus aureus, which meet the compendia requirements.

Even in a low concentration of 0.001 to 0.01 % by weight of thiomersal in the aqueous formulation, a preservation against the organisms Candida albicans, Aspergillus niger, Pseudomonas aeruginosa and Staphylococcus aureus for 28 days (and more) can be achieved.

Also the combination of thiomersal with a second preservative, such as benzalkonium chloride, was found to be applicable for the preservation of ophthalmic formulations, and in particular those formulations comprising a tryptophane derivative of formula (I), in particular compound (A), and a cyclodextrin-component (in particular Kleptose).

The invention also relates to the use of thiomersal for the preservation of a pharmaceutical composition, in particular an ophthalmic formulation, e.g. as those described above.

The pharmaceutical composition can as further component (F) also contain a pH-regulator, e.g. to improve the stability. Typical examples are selected from the group consisting of physiologically acceptable acids, bases, and acidic and alkaline salts. For example, the combination of citric acid and sodium citrate may be used for buffering the pH of the composition at a value selected in the range from about pH 4 to about pH 8. In one embodiment, the pH of the pharmaceutical composition may be adjusted to a value from pH 2 to pH 12 (e.g. for injection solutions) or to a value from pH 3 to pH 9 (e.g. for oral or ophthalmic solutions), using pharmaceutically acceptable buffering agents or mixtures (such as citric acid/sodium citrate buffer, phosphate buffer, tromethanol buffer, boric acid buffer, amino acid buffer or acetate buffer).

A very useful pH of the pharmaceutical composition for ophthalmic applications is a value from pH 5 to pH 6.5, often from 5 to 6.
Further components (F) which are routinely used in pharmaceutical formulations may be incorporated as appropriate to adjust the composition to the specific requirements of a particular drug compound, or to a specific use or target population. Typical examples of further components (F) are thickeners such as soluble gums, including carrageenan, alginate, xanthan, and soluble cellulose esters; colouring agents; stabilizers, such as antioxidants, or crystallization inhibitors, such as glycerol, propylene glycol, or polyvinylpyrrolidone.

The compounds of formula (I) can be used for the prevention and/or treatment of neurodegenerative conditions or diseases, among these ophthalmic conditions or diseases associated with neurodegeneration.

They can be used e.g. for the following diseases:

- Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), diseases involving β-amyloid and/or tauopathy, motor neuron diseases, amyotrophic lateral sclerosis (ALS), olivopontocerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, tinnitus, L-dopa-induced dyskinesias, dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders,
social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, major depressive disorder, depression, bipolar manic-depressive disorder, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, schizophrenia, spasticity, Tourette's syndrome, sleep disorders, anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders and schizophreniform disorder.

Also age related macular degeneration can be treated by the compounds of formula (I).

Optionally, the composition may further comprise another active ingredient which is not a compound of formula (I). The invention also relates to a combination to be co-administered to the living human or animal a therapeutically effective amount of a compound (I) as described above in combination with at least one additional pharmaceutical agent which is effective in treating e. g. the ophthalmic condition, wherein the combination of the compound (I) and the at least one additional pharmaceutical agent is effective in treating the condition.

The additional pharmaceutical agent is e. g. selected from medications administered to treat eye diseases containing anti-glaucoma drugs, antibiotics, anti-inflammatory drugs, steroids, anti-allergic drugs and artificial tear fluid. As anti-glaucoma drugs, IOP-lowering drugs are of particular interest.

Such an additional pharmaceutical agent is e. g. selected from:

acetazolamide, diclofenamide, carteolol, timolol, metipranolol, betaxolol, pindolol, levobunolol, brimonidine, clonidine, pilocarpine, carbachol, dipivefrine, apraclonidine, brinzolamide, dorzolamide, bimatropro, travaprost, latanoprost, chlortetracycline, ciprofloxacin, ofloxacin, fusidin acid, gentamicine, kanamycine, levofloxacin, lomefloxacin, oxytetracycline, natamycine, azidamfenicole, chloramphenicole, tobramycine, erythromycin, polymyxin-B, acaclovir, trifluridine, betamethasone, dexamethasone, fluorometholone,
hydrocortisone, prednisolone, rimexolone, cromoglicate, azelastine, lodoxamide, emedastine, nedocromile, levocabstine, olopatadine, ketoifene, hypromellose, carbo门前, hyaluronate, carmellose, hypromellose, povidone, hyetellose, polivinylalcohol, dexamethasone, tetryzoline, troxerutine, tramazoline, naphazoline, xylometazoline, phenylephrine and antazoline.

The compound of formula (I) or the combination product is e.g. administered once a day, twice a day or three times a day. Often it is administered chronically. In one embodiment, the composition is administered in the form of eye drops, eye creams, and intraophthalmic depot formulations. The composition can also be administered in an immediate or modified release formulation. The compound of formula (I) and the additional pharmaceutical agent can be administered separately or conjointly.

Often, the pharmaceutical compositions disclosed herein may be administered in addition to one or more pressure lowering (IOP-lowering) drugs, for example IOP lowering drugs as used in conventional glaucoma treatment.

It has been surprisingly found that the combination of a compound of formula (I) and/or its pharmaceutical acceptable salts and at least one cyclodextrin derivative (C) is particularly useful in aqueous media.

A complex formation may take place with several types of native cyclodextrins or synthetic cyclodextrins, including beta- and gamma-cyclodextrin, in particular hydroxyalkyl-beta- or hydroxypropyl-beta-cyclodextrin. The complex formation takes place spontaneously in aqueous solutions at normal room temperature, which is in contrast to many other known cyclodextrin complexes whose preparation requires the application of heat and/or long stirring times.

The preparation of the composition according to the invention is technically easy, quick and cost-efficient. For the preparation of the compositions, the components are e.g. weighed and the compound of formula (I) is combined (mixed) with measured amounts of the cyclodextrin-derivative (C) and water and optionally further components (F), optionally followed by stirring until dissolution occurs. The mixture may be agitated and/or heated. The solution may be further processed by filtration or centrifugation to remove residual
particles. If a solid formulation is desired, the solution may be dried, such as by spray drying or freeze drying.

The following experiments were carried out in order to further illustrate the invention.

Example 1

Five pharmaceutical compositions were prepared using the compound (A), which has the chemical name 2-[2-Amino-3-(1H-indol-3-yl)-propionylamino]-2-methyl-propionic acid

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH} \quad \text{C} \quad \text{NH} \quad \text{C} \quad \text{COOH} \\
\text{NNH}_2 & \quad \text{C} \quad \text{C} \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \quad \text{CH}_3
\end{align*}
\]

(A)

This compound (A) and its two enantiomers (R and S) were all prepared by classical chemical synthesis. The compound, and in particular its R-enantiomer, was tested in various compositions for CNS-applications and for ophthalmic uses.

In the following tests, the R-enantiomer of compound (A) was used.

The compound (A) showed an aqueous solubility, at pH 7.2, of about 14 mg/ml.

The compound (A) showed an aqueous solubility, at pH 7, of about 10 mg/ml.

The compound (A) showed an aqueous solubility, at pH 6, of about 10 mg/ml.

The compound (A) showed an aqueous solubility, at pH 4.6, of about 14 mg/ml.

At acidic conditions, the solubility of the compound (A) is higher.

At alkaline pH-values, the solubility of the compound (A) is also better.
The solubility of the R-enantiomer of compound (A) was determined as a function of the pH-value by using UV-spectroscopy to quantify the concentration of the compound in a series of aqueous media. It was found that from pH 4.5 to 7 the solubility is particularly low.


The logP value may be determined according to the draft OECD guideline OECD (2000), OECD Draft guideline for the Testing of Chemicals: 122 Partition Coefficient (n-Octanol/Water): pH-Metric Method for Ionisable Substances. For Example, logP of compound (A) was investigated using OECD (2000) OECD Draft guideline for the Testing of Chemicals: 122. The sample was titrated in two triple titrations from pH 1.9 to pH 10.9 at concentrations of 1.3 to 1.9mM in various ratios of octanol / water. The apparent sample pKas in octanol / water were found to have no measurable shift from their aqueous values, hence the sample logP is lower than -1.

Example 2

The following compositions I to V were prepared as solutions with a pH-value of about 7:

<table>
<thead>
<tr>
<th>Composition I [mg/g]</th>
<th>Composition II [mg/g]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (A)</td>
<td>8.0</td>
</tr>
<tr>
<td>Glycerol</td>
<td>28</td>
</tr>
<tr>
<td>Carbopol 974 P</td>
<td>1.3</td>
</tr>
<tr>
<td>Trometamol</td>
<td>1.0</td>
</tr>
<tr>
<td>Water</td>
<td>ad 1000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composition III [mg/ml]</th>
<th>Composition IV [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound (A)</td>
<td>30</td>
</tr>
<tr>
<td>Kleptose</td>
<td>160</td>
</tr>
<tr>
<td>Disodium hydrogen phosphate</td>
<td>4.15</td>
</tr>
<tr>
<td>Sodium dihydrogen phosphate</td>
<td>0.29</td>
</tr>
</tbody>
</table>

- 25 -
Sodium chloride 2.0 2.0
Methocel E4M - 5.0
Water Qsp qsp

Composition V [mg/g]

<table>
<thead>
<tr>
<th>Compound (A)</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleptose</td>
<td>160</td>
</tr>
<tr>
<td>Glycerol (99%)</td>
<td>5.0</td>
</tr>
<tr>
<td>Gelrite</td>
<td>2.0</td>
</tr>
<tr>
<td>1M NaOH</td>
<td>0.015 mL ; water qsp</td>
</tr>
<tr>
<td>Water</td>
<td>ad 1000</td>
</tr>
</tbody>
</table>

As it easily can be seen, compositions I and II (gel) contain 8.0 mg of compound (A) per ml of the composition. Composition I and II do not contain a cyclodextrin derivative (C).

The compositions III, IV and V contain 30 mg of compound (A) per ml of the composition. All three compositions III (solution), IV (gel) and V (in situ gel) also contain a considerable amount of a cyclodextrin derivative (C). Various ratios of compound of formula (I) to cyclodextrine derivative (C) were tested.

Example 3

In the following table the major components of the pharmaceutical compositions tested are described in more detail:

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Manufacturer/Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleptose HPB</td>
<td>Roquette; Hydroxypropyl-beta-cyclodextrin</td>
</tr>
<tr>
<td>Glycerol 99%</td>
<td>Merck KGaA</td>
</tr>
<tr>
<td>Gelzan CM</td>
<td>Sigma Inc. (USA), Gellan Gum</td>
</tr>
<tr>
<td>Carbomer 974 P</td>
<td>Noveon, Carboxymethyl cellulose-Na</td>
</tr>
<tr>
<td>Methocel E4M</td>
<td>Colorcon, Methylhydroxy-propyl-cellulose</td>
</tr>
</tbody>
</table>
Benzalkonium chloride solution 50% Euro OTC
Kollidon 90 F BASF, Polyvinylpyrrolidone
Trometamol Merck KGaA, Tris(hydroxymethyl)-aminomethan

The water used was water for injection.
The following properties were found for the pharmaceutical compositions I to V:

<table>
<thead>
<tr>
<th>Composition</th>
<th>Compound A [mg/mL]</th>
<th>pH</th>
<th>Osmolality [mosmol/kg]</th>
<th>Viscosity [mPa*s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition I</td>
<td>8.0</td>
<td>6.4</td>
<td>315</td>
<td>40.8</td>
</tr>
<tr>
<td>Composition II</td>
<td>8.0</td>
<td>6.4</td>
<td>310</td>
<td>192.3</td>
</tr>
<tr>
<td>Composition III</td>
<td>30.0</td>
<td>6.9</td>
<td>305</td>
<td>1.5</td>
</tr>
<tr>
<td>Composition IV</td>
<td>30.0</td>
<td>6.9</td>
<td>320</td>
<td>18.1</td>
</tr>
<tr>
<td>Composition V</td>
<td>30.0</td>
<td>7.1</td>
<td>215</td>
<td>71.3</td>
</tr>
</tbody>
</table>

The five pharmaceutical compositions I to V, all containing the active ingredient (A), were applied to the eyes of test animals (dark agouti rats (pigmented) and to albino rats). At different points of time after the administration of the compositions into the eye a micro-dissection of the eye of the animal was performed. Tissue samples were collected and a chemical dissolution and analysis was made for different compartments of the eye of the test animals.

With all five pharmaceutical compositions I to V, a significant amount of compound of formula (A) was delivered to the retina of the test animals. The evaluation of the results obtained from the Retina, the Vitreous, the Choroid and the Plasma of the test animals showed that the amounts of the compound (A) in the various compartments of the eye were significantly higher, when the compositions III, IV and V were used than when the pharmaceutical compositions I and II were applied.

For example, the amounts of compound (A) in the Retina of dark agouti rats was more than three times higher when composition III was applied (or when composition V was applied) than by applying compositions I or II to the eye of the test animal.
Therefore, a much better treatment of glaucoma can be achieved with compositions III to V than with compositions I and II.

Example 4

For further pharmacological testing, three additional pharmaceutical compositions VI, VII and VIII were prepared by using the following components:

<table>
<thead>
<tr>
<th>Compound (A)</th>
<th>Composition VI [mg/ml]</th>
<th>Composition VII [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleptose</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Citric acid anhydrous</td>
<td>1.30</td>
<td>1.30</td>
</tr>
<tr>
<td>Sodium citrate dehydrate</td>
<td>7.70</td>
<td>7.70</td>
</tr>
<tr>
<td>Methocel E4M</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>Water</td>
<td>qsp</td>
<td>qsp</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound (A)</th>
<th>Composition VIII [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleptose</td>
<td>160</td>
</tr>
<tr>
<td>Glycerol</td>
<td>5.0</td>
</tr>
<tr>
<td>Gelrite</td>
<td>2.0</td>
</tr>
<tr>
<td>1 M NaOH</td>
<td>-</td>
</tr>
<tr>
<td>Water</td>
<td>qsp</td>
</tr>
</tbody>
</table>

The pharmaceutical compositions VI (solution), VII (gel) and VIII (in situ gel) can be characterized by the following characteristics:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Compound A [mg/mL]</th>
<th>pH</th>
<th>Osmolality [mosmol/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition VI</td>
<td>20.0</td>
<td>5.7</td>
<td>288</td>
</tr>
<tr>
<td>Composition VII</td>
<td>20.0</td>
<td>5.7</td>
<td>266</td>
</tr>
<tr>
<td>Composition VIII</td>
<td>20.0</td>
<td>5.7</td>
<td>245</td>
</tr>
</tbody>
</table>
All three compositions VI, VII and VIII were tested in test animals (rats as described above). For all three compositions, significant amounts of compound (A) were delivered to the retina of the animals. The ratio of compound of formula (I) to cyclodextrine derivative (C) was 1:8. Even by using smaller concentrations of the active ingredient (A) in compositions VI, VII and VIII, and by using the preferred pH-value range of 5.6 to 6.2, very good test data were obtained.

Example 5
For application to the human eye, the following ophthalmic composition IX was prepared:

<table>
<thead>
<tr>
<th>Composition IX [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound (A)</strong></td>
</tr>
<tr>
<td><strong>Kleptose</strong></td>
</tr>
<tr>
<td><strong>Citric acid anhydrous</strong></td>
</tr>
<tr>
<td><strong>Sodium citrate dehydrate</strong></td>
</tr>
<tr>
<td><strong>Methocel E4M</strong></td>
</tr>
<tr>
<td><strong>Sodium chloride</strong></td>
</tr>
<tr>
<td><strong>Water</strong></td>
</tr>
</tbody>
</table>

This composition had a viscosity of 32 mPas (using a cone-plate rheometer, C60/l°).

The release rate of compound (A) from this composition was tested in a Franz cell study (Supor-200 membrane). After 60 minutes, already 60 % of the active compound were released.

An additional Composition IXa was prepared and tested comprising:

<table>
<thead>
<tr>
<th>Composition IXa [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound (A)</strong></td>
</tr>
<tr>
<td><strong>Kleptose</strong></td>
</tr>
<tr>
<td><strong>Citric acid anhydrous</strong></td>
</tr>
<tr>
<td><strong>Sodium citrate dehydrate</strong></td>
</tr>
</tbody>
</table>
Example 6

In addition, the stability of the aqueous compositions VI to VIII at various temperatures (5°C, 25°C and 40°C) was investigated. Even after four weeks of storage, the compositions VI to VIII containing compound (A) only showed moderate degradation.

Example 7

For further stability testing, the following compositions were prepared:

a) 10 mg compound (A) per ml, with 0.1 mg sodium benzoate per ml;
b) 10 mg compound (A) per ml, with 0.2 mg sodium benzoate per ml;
c) 100 mg compound (A) per ml, with 0.1 mg sodium benzoate per ml;
d) 100 mg compound (A) per ml, with 0.2 mg sodium benzoate per ml;
e) 10 mg compound (A) per ml, with 0.1 mg sodium benzoate per ml and 10% (v/v) of propylene glycol;
f) 10 mg compound (A) per ml, with 0.2 mg sodium benzoate per ml and 10% (v/v) of propylene glycol.

For all compositions, the compound (A) was dissolved in citric acid solution and completed to the required volume with citric buffer to a pH-value of 3.

Then, the preservatives were added. The six solutions were first tested for one week at room temperature.

None of the formulations showed any change after one week at room temperature, the optical appearance, the pH-value and the odor remained unchanged. Then they were stored for several weeks at temperatures of 25°C with 60% humidity and at 5°C. The compositions with 10 mg compound (A) were stable for several months.
Example 8

In the further series of tests, the compatibility of the compound (A) with other typical ophthalmic excipients was investigated. It was found that compound (A) in aqueous solutions at pH 5.5 showed no incompatibilities with many further components (F), such as hypromellose, carbomer, Gellan gum and various preservatives.

Example 9

In a male Dark Aguti rat model, glaucoma is produced by injection of hypertonic saline into episcleral veins of one eye to induce increased ophthalmic pressure (chronic ophthalmic hypertension), while the opposite eye serves as a control. In treatment groups, various doses of compound (A) of the instant invention are injected intravitreally (in 50 μl volume) at the time of glaucoma induction and in some groups the administration continues for following 7 days to see whether such extended treatment results in increased efficacy.

The extent of retinal ganglion cell (RGC) apoptosis at 3 weeks and 6 weeks after chronic ophthalmic hypertension (OHT) induction is assessed in each animal by dynamic confocal scanning laser ophthalmoscopy and fluorescent-labeled Annexin V.

Animals are sacrificed after 3 and 6 weeks and their eyes are enucleated and fixed in 4% para-formaldehyde overnight. Afterwards, retinas are separated for assessing apoptosis related changes, for example visualized with FITC Annexin V kit (BD Biosciences, Franklin Laker (USA)).

In animals treated with low doses of compound (A), there is a strong decrease in RGC apoptosis compared to animals treated with the vehicle only. This shows that compound (A) is useful for the treatment of glaucoma.

The equilibrium solubility of compound (A) was tested in a citrate buffer saline at pH6 in presence of different cyclodextrins by the shake flask method. The beta-cyclodextrins HPBCD and MBCD showed the best solubility improvement of the tested cyclodextrin derivatives.
<table>
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<tr>
<th>Composition</th>
<th>Solubility of compound (A) [mg/mL]</th>
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<tbody>
<tr>
<td>110 mg/ml HPB (Kleptose HPB, Roquette)</td>
<td>27.9</td>
</tr>
<tr>
<td>110 mg/ml HPG (Cavasol W8 HP Pharma, ISP)</td>
<td>16.2</td>
</tr>
<tr>
<td>110 mg/ml MBC (Kleptose Crystebe, Roquette)</td>
<td>28.7</td>
</tr>
<tr>
<td>100 mg/ml ACD (a-Cyclodextrin, Fluka)</td>
<td>12.7</td>
</tr>
</tbody>
</table>

All these compositions can advantageously be used for the treatment of the various ophthalmic diseases described above.

Example 10

In male Dark Aguti rats, an aqueous formulation comprising 20 mg/mL of Compound (A) and 160 mg/mL Kleptose was applied (one time) to one eye, while the opposite eye served as a control.

In other male Dark Aguti rats, an aqueous formulation comprising 8 mg/mL of Compound (A) but containing no Kleptose (cyclodextrin) was applied (one time) to one eye, while the opposite eye served as a control. In the treatment groups, the formulations comprising compound (A) were injected intra-vitreally (in 10 µL volume instillation) and the concentrations of compound (A) were measured in the retina of the animals (after 5 minutes). The mean concentrations of compound (A) are as follows:

- Formulation with Compound A: 0.005% of dose applied,
- Formulation with Compound A + Cyclodextrin: 0.2% of dose applied.

This shows the surprising effect of the combined use of compound (A) with a cyclodextrin, that a 40-fold better permeation can be achieved, even by applying only a 2.5-fold dose of the drug compound.

Example 11

For testing of the long term preservation of the ophthalmic formulations with metal-containing preservatives, the pharmaceutical compositions VI of example 4 was modified by adding thiomersal in a concentration of 0.01% by weight in the aqueous formulation.
A long-time preservation against the organisms Candida albicans, Aspergillus niger, Pseudomonas aeruginosa and Staphylococcus aureus after 28 days was observed with a reduction of all for organisms of at least log 5.

By using the preservative sorbic acid (0.3 % by weight) instead of thiomersal in the above mentioned ophthalmic formulation, already after 14 days an insufficient preservation against Candida albicans can be observed.

Example 12

For testing the influence of the cyclodextrin content in ophthalmic formulations, the solubility of Compound (A) was tested. The equilibrium solubility (at 20°C) of compound (A) in water without cyclodextrin was measured as 11.6 mg/ml.

The equilibrium solubility (at 20°C) of compound (A) in water containing 65 mg/ml cyclodextrin (HPBCD) was measured as 20.2 mg/ml. The equilibrium solubility (at 20°C) of compound (A) in water containing 165 mg/ml cyclodextrin was measured as 41.2 mg/ml.
Patent Claims

1. Pharmaceutical composition comprising at least one compound of formula (I)

\[
\begin{align*}
  & \text{CH}_2 \text{CH} \text{CH} \text{C} \text{NH} \text{C} \text{C} \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^4 \\
  & \text{R}^5 \text{R}^5
\end{align*}
\]

wherein the radicals denote:

- \( R^1 \) is hydrogen, Ci-Cs-alkyl, Cs-Cs-cycloalkyl, C6-Ci4-aryl, carboxy or C-thiocarb; in particular hydrogen or Ci-C3-alkyl,
- \( R^2 \) is hydrogen, Ci-Cs-alkyl, Cs-Cs-cycloalkyl, C6-Ci4-aryl, carboxy or C-thiocarb; in particular hydrogen or Ci-C3-alkyl,
- \( R^3 \) is hydrogen or Ci-Cs-alkyl, in particular methyl,
- \( R^4 \) is OH or O-Ci-Cs-alkyl, in particular OH;
- \( R^5 \) is hydrogen or Ci-Cs-alkyl, in particular hydrogen; and/or a pharmaceutically acceptable salt thereof, and/or a stereoisomeric form or derivative thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally further components (F).

2. Pharmaceutical composition according to claim 1, wherein the composition contains at least one compound of formula (I) in which the radicals denote:

- \( R^1 \) is hydrogen, Ci-Cs-alkyl, Cs-Cs-cycloalkyl or C6-Ci4-aryl,
- \( R^2 \) is hydrogen, Ci-Cs-alkyl, Cs-Cs-cycloalkyl or C6-Ci4-aryl,
- \( R^3 \) is hydrogen or Ci-Cs-alkyl,
- \( R^4 \) is OH or 0-Ci-C5-alkyl,
- \( R^5 \) is hydrogen or Ci-Cs-alkyl, in particular hydrogen,
and/or a pharmaceutically acceptable salt thereof,
and comprises at least one further component (F).

3. Pharmaceutical composition according to claim 1 or 2, wherein the composition contains a compound of formula (I) wherein

\[ R^1 \text{ is hydrogen or } C_1-C_3\text{-alkyl,} \]
\[ R^2 \text{ is hydrogen or } C_1-C_3\text{-alkyl,} \]
\[ R^3 \text{ is hydrogen or methyl,} \]
\[ R^4 \text{ is OH,} \]
\[ R^5 \text{ is hydrogen or } C_1-C_5\text{-alkyl, in particular hydrogen,} \]

and/or a pharmaceutically acceptable salt thereof,
and comprises the solvent water and optionally further components (F).

4. Pharmaceutical composition according to any of claims 1 to 3, wherein the composition contains a compound of formula (I) wherein \( R^1 \) and \( R^2 \) are hydrogen, \( R^3 \) is methyl, \( R^4 \) is OH and \( R^5 \) is hydrogen, and/or a pharmaceutically acceptable salt thereof, and comprises the solvent water and optionally further components (F).

5. Pharmaceutical composition according to any of claim 1 to 4, wherein the composition contains the R-enantiomer of the compound of formula (A)

\[
\begin{array}{cccccc}
\text{CH}_2 & \text{CH} & \text{C} & \text{NH} & \text{C} & \text{COOH} \\
\text{NH}_2 & & & & & \\
\text{H} & & & & & \\
\end{array}
\]

(A)

and/or a pharmaceutically acceptable salt thereof,
and at least one pharmaceutically acceptable cyclodextrin derivative (C)
and optionally a further active ingredient and/or further components (F).

6. Pharmaceutical composition according to any of claim 1 to 5, wherein the cyclodextrin compound (C) is selected from the group consisting of:
alpha-cyclodextrin, beta-cyclodextrin, randomly alkylated beta-cyclodextrin, 2-O-
methyl-beta-cyclodextrin, heptakis-(2,6-di-O-methyl)-beta-cyclodextrin (dimethyl-beta-
cyclo-dextrin), acetylated dimethyl-beta-cyclodextrin, heptakis-(2,3,6-tri-O-methyl)-
beta-cyclodextrin(trimethyl-beta-cyclodextrin, 2-hydroxypropyl-beta-cyclo-dextrin,
sulfo-alkylether-beta-cyclodextrin, sulfoalkylether-beta-cyclodextrin, O-carboxymethyl-O-ethyl-beta-cyclodextrin, glucuronyl-glucosyl-beta-cyclodextrin,
glucosyl-beta-cyclo-dextrin, maltosyl-beta-cyclodextrin, beta-cyclodextrin sulphate,
beta-cyclodextrin phosphate, gamma-cyclodextrin, 2-hydroxypropyl-gamma-cyclo-
dextrin, sulfoalkylether-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin.

7. Pharmaceutical composition according to any of Claims 1 to 6, wherein the compound of formula (I) has the R-configuration and the cyclodextrin compound (C) is selected from hydroxyalkyl-substituted beta-cyclodextrins.

8. Pharmaceutical composition according to any of claims 1 to 7, wherein the molar ratio of the compound of formula (I) and the cyclodextrin compound (C) is in the range from 0.1:1 to 1:20.

9. Pharmaceutical composition according to any of claims 1 to 8, wherein the composition is an aqueous liquid composition comprising at least 70 % by weight of water and wherein the concentration of the compound of formula (I) is in the range from 1 mg/ml to 50 mg/ml.

10. Pharmaceutical composition according to any of claims 1 to 9, wherein the composition is an aqueous liquid composition comprising as further component (F) a metal-containing preservative, in particular the preservative thiomersal.

11. Pharmaceutical composition according to any of claims 1 to 10 for the treatment of a disorder or a disease of the central nervous system.

12. Pharmaceutical composition according to any of claims 1 to 10 for the treatment of an ophthalmic disorder or disease.

13. Process for preparation of a pharmaceutical composition comprising the steps of mixing together at least one compound of formula (I)
wherein the radicals denote:

R\textsuperscript{1} is hydrogen, Ci-Cs-alkyl, C\textsubscript{5}-C\textsubscript{8}-cycloalkyl, C\textsubscript{6}-Ci4-aryl, carboxy or C-thiocarb;
in particular hydrogen or Ci-C\textsubscript{3}-alkyl,

R\textsuperscript{2} is hydrogen, Ci-Cs-alkyl, C\textsubscript{5}-C\textsubscript{8}-cycloalkyl, C\textsubscript{6}-Ci4-aryl, carboxy or C-thiocarb;
in particular hydrogen or Ci-C\textsubscript{3}-alkyl,

R\textsuperscript{3} is hydrogen or Ci-Cs-alkyl,
in particular methyl,

R\textsuperscript{4} is OH or O-Ci-Cg-alkyl, in particular OH,

R\textsuperscript{5} is hydrogen or Ci-Cs-alkyl, in particular hydrogen;

and/or a pharmaceutically acceptable salt thereof, and/or a stereoisomeric form or derivative thereof,

and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally further components (F).

14. Use of a cyclodextrin compound (C), in particular a hydroxyalkyl-substituted beta-cyclodextrin, for the preparation of a pharmaceutical composition for the treatment of ophthalmic diseases.

15. Use according to claim 14, further comprising the use of a metal-containing preservative, in particular of thiomersal, wherein the pharmaceutical composition comprises a hydrophilic pharmaceutical agent, and wherein the concentration of the cyclodextrin compound (C) in the pharmaceutical composition is at least 10 mg/ml.
# INTERNATIONAL SEARCH REPORT

**International application No**

PCT/EP2011/061356

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/405 A61K45/06 ...

**P.B. 5818 Patentlaan 2**

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**B. MINIMUM DOCUMENTATION SEARCHED**

- (classification system followed by classification symbols)
- A61K

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2009/125246 A1 (TECHNOPHARMA SA [CH]; ALEO DAN LO [IT]; MANGIAFICO SERGIO [IT]; SAITA) 15 October 2009 (2009-10-15) abstract claims 1-7</td>
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**See patent family annex.**

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**Date of the actual completion of the international search**

2 September 2011

**Date of mailing of the international search report**

13/09/2011

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2**

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**Authorized officer**

Dami ani, Federica

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<td>KAN0 K ET AL: &quot;Chiral recognition of dipeptide methyl esters by an anionic beta-cyclodextrin ..&quot;. August 2001 (2001-08), CHIRALITY AUG 2001 LNKD- PUBMED: 11466771, VOL. 13, NR. 8, PAGE(S) 474 - 482, XP002601659, ISSN : 0899-0042 the whole document ----</td>
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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**International application No**

PCT/EP2011/061356

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<th>Patent family member(s)</th>
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<tr>
<td></td>
<td></td>
<td>AU 7264187 A</td>
<td>12-11-1987</td>
</tr>
<tr>
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<td></td>
<td>CA 1302266 C</td>
<td>02-06-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3615710 Al</td>
<td>26-11-1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 235687 A</td>
<td>10-11-1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0244832 A2</td>
<td>11-11-1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2051705 T3</td>
<td>01-07-1994</td>
</tr>
<tr>
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<td></td>
<td>GR 3005768 T3</td>
<td>07-06-1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 201671 B</td>
<td>28-12-1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IE 60273 Bl</td>
<td>29-06-1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 82459 A</td>
<td>31-07-1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 62267222 A</td>
<td>19-11-1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 84841 A</td>
<td>01-06-1987</td>
</tr>
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<td>ZA 8703299 A</td>
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<td>CN 102046149 A</td>
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<td>EP 2280689 Al</td>
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<td>US 2011028477 Al</td>
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<td>26-02-2009</td>
<td>AR 069729 Al</td>
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<td></td>
<td></td>
<td>AU 2008290825 Al</td>
<td>26-02-2009</td>
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<td></td>
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<td>CA 2688215 Al</td>
<td>26-02-2009</td>
</tr>
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<td>CN 101743015 A</td>
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<td>EP 2180898 A2</td>
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