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(54) Benævnelse: **Farmaceutisk formulering indeholdende curcuma**

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WO-A1-2011/101859
WO-A2-2009/061152
ZHAO YAN-GUO ET AL: "Preparation of a bis-demethoxy curcumin microemulsion based on pseudo-ternary phase diagrams and an orthogonal test analysis", JOURNAL OF PESTICIDE SCIENCE,, Bd. 36, Nr. 2, 1. Januar 2011 (2011-01-01) , Seiten 248-251, XP009173239,
WU XUEMEI ET AL: "Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability.", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY JAN 2011, Bd. 37, Nr. 1, Januar 2011 (2011-01), Seiten 15-23, XP002714380, ISSN: 1520-5762

Pharmaceutical formulation containing curcuma

The invention relates to a pharmaceutical formulation comprising curcumin or a curcumin derivative as active substance.

Curcumin can be extracted from natural sources (for example, Javanese turmeric) or produced synthetically. Curcumin has antineoplastic properties, although no blood levels required for a systemic effect can be achieved, because curcumin is insoluble in water.

WO 2011/101859 A1 describes water-soluble, curcumin-containing nanoparticles for cancer therapy. Incorporating curcumin into nanoparticles is intended here to lead to increased stability, solubility and bioavailability.

WO 2009/061152 A2 describes a composition for prevention and treatment of pain, comprising curcumin or a pharmaceutically tolerated salt thereof.

Zhao *et al.* (2011) discloses a microemulsification of bisdemethoxycurcumin with the aid of pseudoternary phase diagrams, combined with an orthogonal test in a three-phase system.

WU *et al.* (2011) describes a self-microemulsifying drug delivery system for increasing curcumin bioavailability.

Mosely *et al.* (2007) includes description of the pharmacological activity of various curcumin derivatives, such as demethoxycurcumin, bisdemethoxycurcumin and EF-24.

The task of the present invention is to create a pharmaceutical formulation of the genre mentioned above, which provides curcumin in a form that is sufficiently stable for storage and allows a simple and safe intravenous administration.

The subject matter of the invention is a pharmaceutical formulation comprising curcumin and/or a curcumin derivative, dissolved in an alcohol as well as additionally an acid and a solubilizer, wherein the curcumin derivative is selected from the group comprising demethoxycurcumin, bisdemethoxycurcumin and EF-24. The formulation according to the invention contains at most 12% by weight of water.

First, we would like to explain a few terms used within the scope of the invention. A pharmaceutical formulation is a composition, which can be used either directly as end product for pharmaceutical purposes or can be transformed as intermediate product (preferably a storable intermediate product) in a simple fashion in a clinical environment by medical personnel into a ready-to-use form. Consequently, it only comprises pharmaceutically acceptable components.

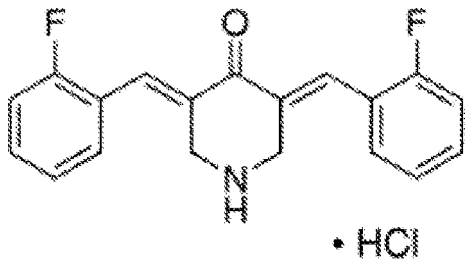
Within the scope of the invention, the term curcumin derivative means natural and synthetic curcumin derivatives. Examples include naturally occurring curcuminoids. These are plant secondary metabolites that occur in the rootstocks of different curcuma plants such as e.g. Curcuma longa. The term curcuminoids covers the three substances curcumin, demethoxycurcumin and bisdemethoxycurcumin. From a chemical point of view, curcuminoids are conjugated diarylheptanoids, i.e., polyphenols in the broader sense.

Table 1: Physical and chemical properties of curcuminoids [Govindarajan, 1980; Pedersen et al., 1985; Tønnesen et al., 1995].

Trivial name	**CUR**	**Demethoxy-CUR**	**Bisdemethoxy-CUR**
Chemical name	Diferuloylmethane	4-Hydroxycinnamoyl feruloyl methane	Bis-4-hydroxycinnamoyl methane
Total formula	$C_{21}H_{20}O_6$	$C_{20}H_{18}O_5$	$C_{19}H_{16}O_4$
Molecular	368.39	338.36	308.33

weight (g/mol)			
Appearance	Yellow, crystalline powder	Orange-yellow, amorphous product	Yellow slabs
Melting point (°C)	182-183	172-174	223-224
Max. absorption (EtOH)	427	424	418
Solubility	Insoluble in water, hexane, ether; soluble in alcohol, acetone, glacial acetic acid, organic solvents		

Furthermore, synthetically modified molecules can be produced, which have identical or similar physical and chemical properties, but can be physiologically more active. One example is EF-24:



EF-24 is an IKK inhibitor and synthetic curcumin analog. EF-24 is more potent than curcumin and has a considerably higher bioavailability; in addition, its potency in inducing cell death is 10 times greater. It has been shown to be more effective than cisplatin in anti-tumor screening, and has a significantly lower potential of inducing adverse effects.

According to the invention, the curcumin derivatives are therefore preferably selected from the group comprising demethoxycurcumin, bisdemethoxycurcumin and EF-24.

Curcumin is available in various tautomeric forms; a keto-enol tautomerism exists between a keto form and two equivalent enol forms. The keto-enol structure represents the unstable position of the curcumin molecule.

The chemical stability of curcumin in aqueous solutions is pH dependent. Under neutral to basic conditions, curcumin in aqueous solution is not stable. In alkaline solution, the dissociation of the enol takes place first (pKa 7.8), as a result of which the negative charge above the aromatic compounds is stabilized and the conjugated diene structure is destroyed. The successive dissociation of the phenols subsequently follows in the alkaline environment (pKa 8.5 and 9.0).

Since the hydroxyl groups are present in undissociated form when the pH is acidic, the curcuminoids' stability is greater in this environment. The invention has recognized that curcumin does not disintegrate because of the higher physiological pH when it enters the blood stream, but binds to plasma protein and thus remains in the blood circulation. One attempt at explaining this phenomenon, which does not commit the applicant and limit the scope of protection, is that curcumin represents a lipophilic and polyphenolic compound and is therefore capable of interacting with macromolecules.

The formulation according to the invention preferably contains at most 5% by weight, more preferably at most 3% by weight, of water, and more preferably it is free from water. Free from water means that no water is added or at the very most is added in such quantities that the keto-enol balance described above is not impaired.

The invention provides curcumin or a curcumin derivative as a storable and relatively concentrated solution; an infusion solution can be produced in a simple fashion and in a clinical environment using the formulation according to the invention, in which curcumin is dissolved in an aqueous environment and can therefore easily be administered intravenously. The invention has realized that curcumin can be brought into a relatively concentrated alcoholic solution, which allows the stable storage; according to the invention, the shelf life of said concentrate can be 2 years or longer.

A physiologically acceptable pH is achieved in the aqueous environment because of the acid present in the alcoholic concentrate when an infusion solution is

produced with the formulation according to the invention. The resulting infusion solution preferably has a pH in the range of a weak acid. For example, the addition of citric acid to the concentrate achieves a pH from 5.5 to 6.0 in the aqueous infusion solution, which remains stable for the entire duration of the infusion. The solubilizer according to the invention helps to ensure that curcumin remains in solution and does not precipitate in the aqueous environment after an aqueous infusion solution has been prepared using the pharmaceutical formulation.

Ethanol is the particularly preferable type of alcohol used as solvent. The alcohol content preferably amounts to 40 to 90% by weight, more preferably to 40 to 70% by weight.

Inorganic acids such as e.g. phosphoric acid or hydrochloric acid can in principle be considered as acids. Organic acids are preferable. Suitable organic acids should preferably be provided in pure crystalline form, advantageously however at least in anhydrous form. Preferably, they should be soluble by at least 1% by weight in the used alcohol. The acid anion may not be a toxic substance, because it must be tolerable when administered intravenously. Preferable organic acids are tartaric acid, succinic acid, ethanoic acid, particularly preferably citric acid and ascorbic acid.

Ascorbic acid slows the degradation of curcumin in aqueous medium and thus also stabilizes an aqueous infusion solution produced with the concentrate according to the invention. Ascorbic acid is physiologically active and is also used therapeutically as infusion solution.

The solubilizers are preferably selected from the group comprising surfactants and solubilizing polymers. Polyvinylpyrrolidones, adducts of ethylene oxide to castor oil, polyethylene glycols and polysorbates are particularly preferable among the solubilizing polymers. Suitable solubilizers can be obtained for example from the company BASF and are described in the brochure entitled

"Solubility Enhancement with BASF Pharma Polymers" (Solubilizer Compendium, October 2011, editor: Thomas Reintjes).

A suitable ethylene oxide adduct of castor oil can be obtained for example from BASF under the name Kolliphor ELP.

As an example, Polysorbate 80 (also known as Tween 80) is suitable among the polysorbates.

The pharmaceutical formulation according to the invention can preferably contain 0.2 to 3% by weight, preferably 0.5 to 2% by weight, more preferably 0.5 to 1.5% by weight, of curcumin or curcumin derivative. The citric acid content (if applicable) preferably amounts to 0.2 to 1% by weight, more preferably to 0.3 to 0.5% by weight. The ascorbic acid content (if applicable) preferably amounts to 0.05 to 0.4% by weight, preferably to 0.07 to 0.15% by weight.

According to the invention, the ratio of citric acid (if applicable) to curcumin or curcumin derivative preferably amounts to 10 to 100 parts by weight, preferably to 15 to 50 parts by weight of citric acid per 100 parts by weight of curcumin or curcumin derivative. If ascorbic acid is added, 3 to 30 parts by weight, preferably 4 to 20 parts by weight of ascorbic acid are used per 100 parts by weight of curcumin or curcumin derivative.

The weight ratio of alcohol to solubilizer preferably amounts to 2:1 to 1:4, more preferably to 1:1 to 1:3.

Moreover, the subject matter of the invention is a method for producing a pharmaceutical formulation according to the invention. The method comprises the following steps:

a. dissolving the curcumin or curcumin derivative in alcohol,

b. adding the acid,

c. mixing the solubilizer with alcohol,

d. mixing the components contained in b) and c).

A curcumin solution in alcohol (preferably ethanol) is produced first; in so doing, heating it up can be preferable (for example, to about 70°C) to accelerate the dissolution process. The acid can already be present in the alcohol in dissolved form or it can be dissolved in the warm alcoholic curcumin solution.

A single-phase mixture of the solubilizer with alcohol is produced in a further step; said solution produced in step c) is added to the curcumin solution until the desired volume of the pharmaceutical formulation is obtained.

An infusion solution comprising a carrier solution and a pharmaceutical formulation according to the invention dissolved in said carrier solution is another subject matter of the invention. According to the invention, the carrier solution can in particular be isotonic saline solution, a glucose solution (for example 5% aqueous glucose solution) or another solution acceptable for infusion purposes.

The infusion solution according to the invention is a single-phase solution, in which curcumin or the curcumin derivative is present in dissolved form. The solubilizers contained in the pharmaceutical formulation according to the invention help ensure that the curcumin or the curcumin derivative does not precipitate but remains in solution when the infusion solution according to the invention is produced with the pharmaceutical formulation according to the invention and the carrier solution. The acid contained in the pharmaceutical formulation sets the desired physiological pH in the aqueous environment of the infusion solution.

When an isotonic saline solution is used as carrier solution, a citric acid/citrate buffer develops in the infusion solution according to the infusion, which sets and buffers the desired pH value (preferably 5 to 7, more preferably 5.5 to 6.5).

An infusion solution according to the invention can preferably contain 0.2 to 4 mg, more preferably 0.5 to 1 mg of curcumin or curcumin derivative per ml of infusion solution.

For example, 500 ml of infusion solution can comprise between 250 and 450 mg of curcumin within the scope of the invention. A curcumin quantity required for a systemic therapy can be administered with the intravenous administration of the infusion solution over a period of, for example, 90 min.

Furthermore, the subject matter of the invention is a pharmaceutical formulation according to the invention or an infusion solution for use as a medication, in particular an antineoplastic drug.

Exemplary embodiments of the invention are described below.

Example 1

100 mg of curcumin are dissolved in 3.8 ml of absolute ethanol while stirring and heating to approximately 70°C. A clear, dark yellow solution has formed after 15 min.

40.7 mg of citric acid are dissolved without water in this solution.

25.88 g of Kalliphor ELP are mixed with 12.37 g of absolute ethanol. The mixture produced in this fashion is used to top up the previously produced curcumin solution to 10 ml.

The obtained solution is sterile filtered and autoclaved at 121°C.

A storable pharmaceutical formulation comprising curcumin in dissolved form is obtained in this fashion.

Example 2

To produce an infusion solution, the pharmaceutical formulation according to example 1 is poured into a carrier solution (preferably isotonic saline solution or 5% glucose solution), such that a curcumin concentration of 0.5 to 1 mg/mL is achieved in said infusion solution.

Example 3

An alcohol with a proportion of water is used as solvent in this example.

100 mg of curcumin are dissolved in 3.8 ml of 70% ethanol (the remainder is water) while stirring and heating to approximately 70°C. A clear, dark yellow solution has formed after 15 min.

10 mg of ascorbic acid are dissolved without water in said solution.

25.88 g of Kalliphor ELP are mixed with 12.37 g of absolute ethanol. The mixture produced in this fashion is used to top up the previously produced curcumin solution to 10 ml.

The obtained solution is sterile filtered and autoclaved at 121°C.

A storable pharmaceutical formulation comprising curcumin in dissolved form is obtained in this fashion. The proportion of water is approximately 12% by weight.

A higher curcumin concentration is dissolved in the pharmaceutical formulation in examples 4 and 5 below.

Example 4

150 mg of curcumin are dissolved in 4 ml of absolute ethanol while stirring and heating to approximately 70°C. A clear, dark yellow solution has formed after 15 min.

34 mg of citric acid are dissolved without water in said solution.

25.88 g of Kalliphor ELP are mixed with 12.37 g of absolute ethanol. The mixture produced in this fashion is used to top up the previously produced curcumin solution to 10 ml.

The obtained solution is sterile filtered and autoclaved at 121°C.

A storable pharmaceutical formulation comprising curcumin in dissolved form is obtained in this fashion.

Example 5

150 mg of curcumin are dissolved in 4 ml of absolute ethanol while stirring and heating to approximately 70°C. A clear, dark yellow solution has formed after 15 min.

10 mg of ascorbic acid are dissolved without water in said solution.

25.88 g of Kalliphor ELP are mixed with 12.37 g of absolute ethanol. The mixture produced in this fashion is used to top up the previously produced curcumin solution to 10 ml.

The obtained solution is sterile filtered and autoclaved at 121°C.

A storable pharmaceutical formulation comprising curcumin in dissolved form is obtained in this fashion.

PATENTKRAV

1. Farmaceutisk formulering, **kendetegnet ved at** den indeholder curcuma og/eller et curcumaderivat, en alkohol, en syre og et opløsningsmiddel og højst indeholder 12 vægt-% vand, hvor curcumaderivatet er udvalgt blandt gruppen bestående af demethoxycurcuma, bisdemethoxycurcuma og EF-24.

2. Farmaceutisk formulering ifølge krav 1**, kendetegnet ved at** alkoholen er ethanol og/eller hvor alkoholindholdet kan være 40 til 90 vægt-%, foretrukket 40 til 70 vægt-%.

3. Farmaceutisk formulering ifølge krav 1 eller 2, **kendetegnet ved at** den indeholder højst 5 vægt-% vand, mere foretrukket højst 3 vægt-% vand er mere foretrukket vandfri.

4. Farmaceutisk formulering ifølge et af kravene 1 til 3, **kendetegnet ved at** syren er ascorbinsyre eller en fødevaresyre, foretrukket citronsyre.

5. Farmaceutisk formulering ifølge et af kravene 1 til 4, **kendetegnet ved at** opløsningsmidlerne er udvalgt blandt gruppen bestående af overfladeaktive stoffer og opløsende polymerer, hvor de opløsende polymerer kan udvælges blandt gruppen bestående af polyvinylpyrrolidoner, addukter af ethylenoxid på ricinusolie og polysorbater.

6. Farmaceutisk formulering ifølge et af kravene 1 til 5, **kendetegnet ved at** den indeholder 0,2 til 3 vægt-%, foretrukket 0,5 til 2 vægt-%, mere foretrukket 0,5 til 1,5 vægt-% curcuma eller curcumaderivat.

7. Farmaceutisk formulering ifølge et af kravene 1 til 6, **kendetegnet ved at** den indeholder 0,2 til 1 vægt-%, foretrukket 0,3 til 0,5 vægt-% citronsyre, eller at de er 0,05 til 0,4 vægt-%, foretrukket 0,07 til 0,15 vægt-% ascorbinsyre.

8. Farmaceutisk formulering ifølge et af kravene 1 til 7, **kendetegnet ved at** den inde-

holder 10 til 100 vægtdele, foretrukket 15 til 50 vægtdele citronsyre pr. 100 vægtdele curcuma eller curcumaderivat eller de 3 til 30 vægtdele, foretrukket 4 til 20 vægtdele ascorbinsyre pr. 100 vægtdele curcuma eller curcumaderivat.

9. Farmaceutisk formulering ifølge et af kravene 1 til 8, **kendetegnet ved at** vægtforholdet mellem alkohol og opløsningsmiddel er 2:1 til 1:4, foretrukket 1:1 til 1:3.

10. Fremgangsmåde til fremstilling af en farmaceutisk formulering ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved** følgende trin:

a) opløsning af curcuma eller curcumaderivatet i alkohol,
b) tilsætning af syren,
c) blanding af opløsningsmidlet med alkohol,
d) blanding af komponenterne opnået i b) og c).

11. Infusionsopløsning, **kendetegnet ved at** den indeholder en bæreropløsning og en farmaceutisk formulering opløst deri ifølge et hvilket som helst af kravene 1 til 9, hvor bæreropløsningen kan udvælges blandt gruppen isotonisk saltopløsning og glukoseopløsning.

12. Infusionsopløsning ifølge krav 11, **kendetegnet ved at** den indeholder 0,2 til 4 mg/ml, foretrukket 0,5 til 1 mg/ml curcuma eller curcumaderivat.

13. Farmaceutisk formulering ifølge et hvilket som helst af kravene 1 til 9 til anvendelse som et medikament.

14. Infusionsopløsning ifølge krav 11 eller 12 til anvendelse som medikament.