(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 3651804 B1**

NORGE

(19) NO

(51) Int Cl.

A61K 9/107 (2006.01)	***A61K 47/26 (2006.01)***	***A61P 25/16 (2006.01)***
A61K 31/12 (2006.01)	***A61P 3/00 (2006.01)***	***A61P 25/28 (2006.01)***
A61K 36/185 (2006.01)	***A61P 3/04 (2006.01)***	***A61P 29/00 (2006.01)***
A61K 36/324 (2006.01)	***A61P 3/06 (2006.01)***	***A61P 35/00 (2006.01)***
A61K 36/9066 (2006.01)	***A61P 3/10 (2006.01)***	***A61P 37/00 (2006.01)***

Patentstyret

(45)	Oversettelse publisert	2023.11.20
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2023.08.23
(86)	Europeisk søknadsnr	18737623.1
(86)	Europeisk innleveringsdag	2018.07.11
(87)	Den europeiske søknadens Publiseringsdato	2020.05.20
(30)	Prioritet	2017.07.11, DE, 102017115496 2017.07.11, WO, PCT/EP17/067381 2017.07.11, WO, PCT/EP17/067382
(84)	Utpekte stater	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
(73)	Innehaver	Aquanova AG, Birkenweg 8-10, 64295 Darmstadt, Tyskland
(72)	Oppfinner	BEHNAM, Dariush, Schwalbenweg 9, 64380 Rossdorf, Tyskland
(74)	Fullmektig	Novagraaf Brevets, Bâtiment O2, 2 rue Sarah Bernhardt CS90017, 92665 ASNIÈRES-SUR-SEINE CEDEX, Frankrike

(54) Benevnelse **SOLUBILISATE WITH CURCUMIN, BOSWELLIA, AND XANTHOHUMOL**

(56) Anførte publikasjoner

EP-A1- 0 755 940, EP-A1- 1 431 385, WO-A2-2007/006497, DE-A1-102006 024 911, DE-U1-202012 012 130, US-A1- 2016 081 975

REJI KIZHAKKEDATH: "Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis", MOLECULAR MEDICINE REPORTS, Bd. 8, Nr. 5, 1. November 2013 (2013-11-01), Seiten 1542-1548, XP055462856, GR ISSN: 1791-2997, DOI: 10.3892/mmr.2013.1661

DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1. September 2017 (2017-09-01), KHAYYAL M T: "Novel formulations of Curcumin, Boswellia and Xanthohumol extracts markedly enhance their individual and combined anti-inflammatory activity", XP002783955, Database accession no. EMB-621379886 & ZEITSCHRIFT FUR PHYTOTHERAPIE 20170901 HIPPOKRATES VERLAG GMBH NLD, Bd. 38, Nr. Supplement 1, 1. September 2017 (2017-09-01), ISSN: 1438-9584

ALEXA KOCHER ET AL: "The oral bioavailability of curcuminoids in healthy humans is markedly enhanced by micellar solubilisation but not further improved by simultaneous ingestion of sesamin, ferulic acid, naringenin and xanthohumol", JOURNAL OF FUNCTIONAL FOODS, Bd. 14, 1. April 2015 (2015-04-01), Seiten 183-191, XP055435032, NL ISSN: 1756-4646, DOI: 10.1016/j.jff.2015.01.045
ZAMZOW DANIEL R ET AL: "Xanthohumol improved cognitive flexibility in young mice", BEHAVIOURAL BRAIN RESEARCH, Bd. 275, 1. September 2014 (2014-09-01), Seiten 1-10, XP029077816, ISSN: 0166-4328, DOI: 10.1016/J.BBR.2014.08.045

SOLUBILISATE WITH CURCUMIN, BOSWELLIA, AND XANTHOHUMOL

Description

The invention relates to a solubilizate comprising curcumin and boswellia and xanthohumol according to claim 1. Furthermore, the invention relates to a fluid containing such a solubilizate, to a capsule filled with such a solubilizate or fluid, and to a dietary supplement and/or pharmaceutical drug containing such a solubilizate.

Curcumin is discussed as an active substance based on various potential pharmacological properties. For example, there is evidence of the antioxidant and the anti-inflammatory effect of curcumin as well as for the effectiveness against viruses and bacteria and against cancer. Indications could therefore be, for example, Parkinson's, Alzheimer's, diabetes, colorectal tumors, pancreatic cancer and liver dysfunctions.

In order to be able to enter the bloodstream after oral intake, the active substance must pass through the small intestinal blood barrier, is then metabolized in the liver and enters the hepatic vein as a bioavailable fraction. The rest of the total active substance ingested and released in the body is either degraded microbially in the intestine or eliminated with feces or bile.

A level of toxicity due to the micellization of the active substance according to the invention in comparison to the native form could be ruled out on the basis of studies using MTT assays for cell viability. The verification of cell vitality by MTT testing is based on the reduction of the yellow water-soluble dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into a blue-violet water-insoluble formazan.

The extract from the resin of the frankincense tree, *Boswellia serrata* extract, contains several pentacyclic triterpenes which are collectively often referred to as total boswellic acids ("total BAs"). The term "boswellic acids" refers to a group of chemical compounds naturally occurring in said resin of the frankincense trees. The two basic structures are α-boswellic acid and β-boswellic acid. Also, some derivatives of the boswellic acids are known, in particular compounds which carry

a keto group at position 11 and/or which are acetylated at position 3. The boswellic acids that are currently considered to be significant in terms of pharmacological effects in particular include “αBA” α-boswellic acid and “βBA” β-boswellic acid and their derivatives “KBA” 11-keto-β-boswellic acid (CAS 17019-92-0) and “AKBA” 3-O-acetyl-11-keto-β-boswellic acid (CAS 67416-16-9) and “AαBA” 3-O-acetyl-α-boswellic acid and “AβBA” 3-O-acetyl-β-boswellic acid. In particular, the derivative AKBA is considered to have an anti-inflammatory effect.

In the context of the present application, the term "boswellia", in particular in the term "boswellia solubilizate" is used in the sense that the term "boswellia" refers to the active substances from the resin of the frankincense tree, i.e. to at least one boswellic acid and/or at least one derivative of a boswellic acid. The term "boswellic acid solubilizate" refers to a micellar formulation of at least one boswellic acid. This may also contain at least one boswellic acid derivative.

Xanthohumol is a flavonoid naturally occurring in hops. It is a prenylated plant polyphenol which is assigned to the chalcones and has only been identified in hops thus far. The bitter hop varieties have a significantly higher content of xanthohumol than aroma varieties. In tests, xanthohumol was found to be effective against the emergence and development of cancer cells. In laboratory experiments, it was also found that xanthohumol is capable of protecting the nerve cells of the brain and thus could possibly help to slow down the course of diseases like Alzheimer's or Parkinson's.

For example, http://www.besserlaengerleben.at/gesund-und-fit/hopfen-hilft-gegen-cholesterin-und-blutzucker.html reports about studies according to which xanthohumol seems to lower plasma levels of PCSK9, a protein that plays an important role in cholesterol levels. A reduction in PCSK9 levels could improve the decomposition of LDL cholesterol from the blood. Scientists at Oregon State University have shown in laboratory animals that the intake of large amounts of xanthohumol can lead to improvements in metabolic syndrome and reduced weight gain. These research results could lead to new approaches in treating obesity, high cholesterol and high blood sugar. The combination of these health problems, known as metabolic syndrome, is nowadays one of the leading causes

of death in industrialized countries besides cardiovascular diseases and type 2 diabetes.

Xanthohumol occurs naturally in hops and therefore in beer. The highest levels used in the study would be equivalent to a human dose of 350 milligrams per day for one person. However, this value clearly exceeds what can be achieved by normal intake of food. However, intake through a dietary supplement would theoretically be possible without problems.

Hop extracts are currently commercially available as dietary supplements. However, it has been found that the bioavailability of xanthohumol is low when hops extracts are taken orally.

For the purposes of this application, the term "active substance" refers to a substance that is provided in a pharmaceutically effective concentration and is preferably added for the purpose of having a pharmaceutical effect. Here, the name of the corresponding active substance can also be understood to mean substances that are converted in the body into the active substance and/or into its biologically active form.

US 2016/0081975 A1 discloses a non-aqueous pre-gel concentrate containing curcumin, Boswellia extract, hop extract, TPGS (D-alpha-tocopheryl polyethylene glycol succinate), lecithin and other components.

The problem faced by the inventor is therefore to provide a formulation which makes the health-promoting to curative properties of curcumin and boswellia and xanthohumol available for human or animal organisms. In particular, one object of the invention is to provide for the highest possible bioavailability of curcumin and boswellia and xanthohumol.

These problems are solved in a surprisingly simple manner by a solubilizate according to claim 1. This solubilizate contains curcumin in a content of less than or equal to 10 wt.%, preferably less than or equal to 8 wt.%, particularly preferably from 3 wt.% to 7 wt.%, one or more boswellic acids and/or one or more boswellic acid derivatives, which are selected from the group comprising "KBA" 11-keto-β-boswellic acid (CAS 17019-92-0), "AKBA" 3-O-acetyl-11-keto-β-boswellic acid

(CAS 67416-16-9), "AαBA" 3-O-acetyl-α-boswellic acid and "AßBA" 3-O-acetyl-β-boswellic acid in a total content of less than or equal to 10 wt.%, preferably less than or equal to 8 wt.%, particularly preferably from 4.7 wt.% to 6.6 wt.%, xanthohumol in a content of less than or equal to 10 wt.%, preferably less than or equal to 5 wt.%, particularly preferably from 1 wt.% to 3 wt.%, and at least one emulsifier, specifically polysorbate 80 or polysorbate 20 or a mixture of polysorbate 20 and polysorbate 80, the emulsifier content, in particular the polysorbate content, being at least 70 wt.%, preferably being in the range of from 75 wt.% to 95 wt.%, particularly preferably being in the range of from 79 wt.% to 88 wt.%.

In a preferred embodiment of the invention, the solubilizate consists of curcumin in a content of less than or equal to 10 wt.%, preferably less than or equal to 8 wt.%, particularly preferably from 3 wt.% to 7 wt.%, one or more boswellic acids and/or one or more boswellic acid derivatives, which are selected from the group comprising "KBA" 11-keto-β-boswellic acid (CAS 17019-92-0), "AKBA" 3-O-acetyl-11-keto-β-boswellic acid (CAS 67416-16-9), "AαBA" 3-O-acetyl-α-boswellic acid and "AßBA" 3-O-acetyl-β-boswellic acid in a total content of less than or equal to 10 wt.%, preferably less than or equal to 8 wt.%, particularly preferably from 4.7 wt.% to 6.6 wt.%, xanthohumol in a content of less than or equal to 10 wt.%, preferably less than or equal to 5 wt.%, particularly preferably from 1 wt.% to 3 wt.%, and at least one emulsifier, specifically polysorbate 80 or polysorbate 20 or a mixture of polysorbate 20 and polysorbate 80, the emulsifier content, in particular the polysorbate content, being at least 70 wt.%, preferably being in the range of from 75 wt.% to 95 wt.%, particularly preferably being in the range of from 79 wt.% to 88 wt.%..

Due to the high proportion of boswellia,, in an advantageous embodiment the invention provides that the solubilizate contains an extract obtained from the resin of the *Boswellia serrata* plant by extraction using ethyl acetate as a source of the one or more boswellic acids and/or one or more boswellic acid derivatives, wherein boswellic acids are contained in a concentration of at least 85 wt.% in this extract.

It has been found that, depending on how much boswellia is to be solubilized and in particular also depending on the question of whether further active substances are to be micellated in addition to boswellia, the mass ratio of emulsifier to boswellic acids and/or to boswellic acids and at least one of their derivatives is in the range of between 20:1 and 3:1, preferably in the range of between 16:1 and 4:1, preferably in the range of between 14:1 to 5:1.

Due to the high proportion of xanthohumol, in an advantageous embodiment the invention provides that the solubilizate contains an ethanolic extract of hard resins from hops as the source of xanthohumol, with a xanthohumol concentration in this extract in the range between 65 wt.% and 95 wt.%, preferably in the range of from 80 wt.% to 92 wt.%. In particular, the product "Xantho-Flav Pure" that will be discussed in more detail below can be used as a xanthohumol source within the context of the invention.

It has been found that, depending on how much xanthohumol is to be solubilized and in particular also depending on the question of whether further active substances are to be micellated in addition to xanthohumol, the mass ratio of emulsifier, in particular polysorbate 80, to xanthohumol can be adjusted to in the range between 30:1 and 3:1, preferably in the range between 25:1 and 5:1, preferably in the range between 9.8:1 and 6.6:1.

Depending on how much curcumin is to be provided in micellated form in addition to boswellia and xanthohumol in the solubilizate comprising curcumin and boswellia and xanthohumol, within the context of the invention, the ratio of emulsifier to curcumin may be chosen in the range between 30:1 and 3:1, preferably in the range between 25:1 and 9:1, preferably in the range between 23:1 and 12:1. Accordingly, the ratio of emulsifier to boswellic acids and/or to boswellic acids and at least one of their derivatives may be in the range between 20:1 and 3:1, preferably in the range between 16:1 and 4:1, preferably in the range between 14:1 to 5:1, and the ratio of emulsifier, in particular of polysorbate 80, to xanthohumol may be in the range between 30:1 and 3:1, preferably in the range between 25:1 and 5:1, preferably in the range between 9.8:1 and 6.6:1.

For a stable micellization of curcumin and boswellia in the solubilizate according to the invention, it has proven to be advantageous if the ratio of emulsifier to the total mass of curcumin and boswellic acids and/or of curcumin and boswellic acids and at least one of their derivatives is in the range between 15:1 and 3:1, preferably in the range between 10:1 and 4:1, preferably in the range between 8.8:1 and 5.7:1.

Depending on how much emulsifier can be used for a specific intended use of the solubilizate, the invention offers the possibility for the solubilizate to contain up to 20 wt.%, preferably up to 15 wt.% of ethanol. The addition of ethanol can reduce the content of polysorbate, which is advantageous with regard to the ADI value of polysorbate.

Depending on which active substances are to be solubilized and in what quantity, it may be helpful for the formation of stable micelles if the solubilizate contains up to 25 wt.%, preferably up to 10 wt.% of glycerol. The addition of glycerol can also reduce the content of polysorbate.

The solubilizates according to the invention exhibit a narrow particle size distribution with small mean particle sizes, even under the physiological conditions of a gastric passage; the distribution of the diameter of the micelles in a dilution of the solubilizate with distilled water in a ratio of 1:500 under physiological conditions (pH 1.1 and 37 °C) preferably ranges from about d_{10} = 6 nm to about d_{90} = 16 nm. These values were determined from a volume distribution. Details regarding the analysis of the particle size of the micelles of the solubilizates will be explained below.

The invention advantageously provides solubilizates having very good anti-inflammatory properties. The anti-inflammatory activity, measured as a concentration of C-reactive protein (CRP) in the blood serum of arthritic rats after a single administration of the solubilizate in a dose of 5 mg/kg bodyweight of curcumin and 10 mg/kg bodyweight of boswellic acids, is in the range from about 1200 pg/mL to about 1500 pg/mL, compared to between about 3200 pg/mL and about 3500 pg/mL after administration of the same dose of native curcumin and boswellia.

The anti-inflammatory effect of a solubilizate according to the invention comprising curcumin and boswellia, measured as the concentration of myeloperoxidase (MPO) in the blood serum of arthritic rats after a single administration of the solubilizate in a dose of 5 mg/kg bodyweight of curcumin and 10 mg/kg bodyweight of boswellic acids, is in the range from about 750 mU/mL to about 815 mU/mL and thus is significantly lower than the approximately 1150 mU/mL to about 1250 mU/mL after administration of the same dose of native curcumin and boswellia.

The enzyme unit (U) is a unit which has since been replaced by the katal (kat) to indicate enzymatic activity. Since the numerical values change when the katal is used, the enzyme unit (U) continues to be used in medicine and clinical chemistry. One enzyme unit U corresponds to the conversion of one micro-mole of substrate per minute.

An indication of the improved bioavailability compared to compositions comprising boswellia and curcumin which have not been micellated according to the invention is obtained by a measurement of turbidity of the solubilizate, the measurement of which is considerably more accessible. As a result of the formulation according to the invention, the turbidity of the solubilizate is preferably less than 25 FNU, preferably less than 3 FNU, measured by scattered light measurement using infrared light according to the specifications of the ISO 7027 standard at a dilution of the solubilizate in a ratio of 1:500 in water and under physiological conditions (pH 1.1 and 37 °C).

In the context of the invention, the solubilizate may contain the xanthohumol in non-solubilized form, in particular in native form. Such a product is obtained when adding a xanthohumol-containing powder, for example a hop extract, to a solubilizate as described above. As a result, the solubilizate contains active substances such as boswellia and curcumin in solubilized form, that is to say in the form of micelles, and additionally xanthohumol in non-solubilized form, that is to say not contained in micelles. In this case, xanthohumol as a dispersed phase may be surrounded by an emulsifier envelope, for example in the form of emulsion drops or particles of a suspoemulsion with the other solubilizate as a continuous phase.

In order to facilitate oral application of the solubilizate according to the invention in a more simple and convenient way for the consumer or patient, the invention also provides a capsule filled with a solubilizate as described above or with a corresponding solubilizate consisting of or comprising curcumin, boswellic acid and xanthohumol, wherein the capsule is in the form of a soft gelatin capsule or a hard gelatin capsule or a soft gelatin-free capsule or a hard gelatin-free capsule, for example a cellulose capsule.

Moreover, within the scope of the invention, the solubilizate according to the invention may be incorporated into other fluids, in particular liquids. The active substance-filled small micelles will be retained in this case. Thus, the invention also provides a fluid containing the solubilizate as described above, wherein the fluid is selected from the group consisting of foods, beverages, cosmetics and pharmaceutical products. In the context of the invention, the fluid may in particular include an aqueous dilution of the solubilizate.

The invention thus also provides a solubilizate or fluid as described above in a particularly simple manner, in particular for oral use as a dietary supplement and/or as a pharmaceutical drug in a method for treating and/or preventing diseases involving inflammation, cancer, Alzheimer's, Parkinson's, obesity, high cholesterol, high blood sugar, metabolic syndrome and/or autoimmune diseases.

In a preferred embodiment of the solubilizate according to the invention, the solubilizate is designed for use as a dietary supplement and/or as a pharmaceutical drug in a curcumin dose ranging from 0.5 mg/kg bodyweight to 1 mg/kg bodyweight, preferably in a dose of 0.81 mg/kg bodyweight, and in a boswellia dose ranging from 1 mg/kg bodyweight to 2 mg/kg bodyweight, preferably in a dose of 1.62 mg/kg bodyweight, in particular once daily, and in a xanthohumol dose ranging from 0.5 mg/kg bodyweight to 1 mg/kg bodyweight, preferably in a dose of 0.81 mg/kg bodyweight.

For producing a solubilizate according to the invention comprising curcumin and boswellia and xanthohumol as the active substances, it is possible to either mix together individually prepared solubilizates, or to directly prepare a solubilizate containing curcumin and boswellia and xanthohumol.

The invention furthermore provides methods for producing a solubilizate as described above. If co-micellization of boswellia with curcumin and xanthohumol is desired, the invention provides the following variant of a preparation method, comprising the steps of

a) providing polysorbate 80 and/or polysorbate 20 and/or a mixture of polysorbate 20 and polysorbate 80

b) adding *Boswellia serrata* extract powder and an ethanolic extract of hard resins from hops, in particular Xantho-Flav Pure powder and/or Xantho-Flav powder,

c) adding curcumin powder

wherein step a) comprises heating to a temperature in the range of from 40 °C to 62 °C, preferably to a temperature in the range of from 45 °C to 57 °C, particularly preferably to a temperature in the range of from 48 °C to 52 °C, and wherein step b) comprises heating to a temperature in the range of from 60 °C to 75 °C, preferably to a temperature in the range of from 61 °C to 70 °C, particularly preferably to a temperature in the range of from 63 °C to 67 °C, and

wherein step c) comprises heating to a temperature in the range of from 82 °C to 97 °C, preferably to a temperature in the range of from 83 °C to 92 °C, particularly preferably to a temperature in the range of from 85 °C to 89 °C.

This preparation method makes it possible to produce a solubilizate which is able to form micelles loaded with curcumin as well as with boswellic acids and with xanthohumol in an aqueous dilution. For this purpose, it is also possible to mix the two active substances with one another in a preparatory step under appropriately adapted temperature control, and then to add them in combined form, as a mixture.

However, it is also possible within the scope of the invention to provide native xanthohumol in a solubilizate comprising curcumin and boswellic acids. For this purpose, the invention provides the following variant of a preparation method, comprising the steps of

a) providing polysorbate 80 and/or polysorbate 20 and/or a mixture of polysorbate 20 and polysorbate 80

b) adding *Boswellia serrata* extract powder

c) adding curcumin powder

wherein step a) comprises heating to a temperature in the range of from 40 °C to 62 °C, preferably to a temperature in the range of from 45 °C to 57 °C, particularly preferably to a temperature in the range of from 48 °C to 52 °C, and wherein step b) comprises heating to a temperature in the range of from 60 °C to 75 °C, preferably to a temperature in the range of from 61 °C to 70 °C, particularly preferably to a temperature in the range of from 63 °C to 67 °C, and

wherein step c) comprises heating to a temperature in the range of from 82 °C to 97 °C, preferably to a temperature in the range of from 83 °C to 92 °C, particularly preferably to a temperature in the range of from 85 °C to 89 °C,

comprising a subsequent step of

d) adding an ethanolic extract of hard resins from hops, in particular Xantho-Flav Pure powder and/or Xantho-Flav powder at a temperature in the range of from 26 °C to 30 °C.

In particular it is possible, prior to step b), to perform a step

b1) comprising adding water at a temperature in the range of from 40 °C to 62 °C, preferably at a temperature in the range of from 45 °C to 57 °C, particularly preferably at a temperature in the range of from 48 °C to 52 °C.

The invention also relates to solubilizates which exhibit micelles in aqueous dilution loaded with curcumin alone as well as with boswellic acids alone as well as with xanthohumol alone, at least immediately after their preparation. Therefore, the invention also provides a method for producing a solubilizate as described above by mixing a curcumin solubilizate and a boswellia solubilizate and a xanthohumol solubilizate, in particular in a quantitative ratio of 1:1:1.

The invention will be explained in more detail in the following by way of embodiments. The following components were used:

Boswellia

In the context of the present application, the term "boswellia" in particular refers to an extract from the resin of the frankincense plant. Specifically, an extract of the *Boswellia serrata* species was used, which was an extract obtained by extraction with ethyl acetate from the resin of the plant, which extract has the botanical name *Boswellia serrata* and the product code "HC22519", manufactured by Frutarom Belgium N.V., Londerzeel, Belgium. A solubilizate containing this extract is also referred to as "boswellic acid solubilizate" because of its content of boswellic acids.

Besides extracts from the resin of the frankincense plant, it is also possible to use boswellic acids and/or derivatives of boswellic acids for the purposes of the solubilizates according to the invention. In particular, the following may be considered: alpha-boswellic acid (CAS number 471-66-9), beta-boswellic acid (CAS number 631-69-6) and their derivatives, 3-O-acetyl-alpha-boswellic acid (CAS number 89913-60-0), 3-O-acetyl-beta-boswellic acid (CAS number 5968-70-7), 11-keto-beta-boswellic acid (KBA, CAS number 17019-92-0) and

3-O-acetyl-11-keto-beta-boswellic acid (AKBA, CAS number 67416-61-9).

Curcumin

The product named "Turmeric Oleoresin Curcumin Powder 95 %" with the product code EP-5001 from Green Leaf Extractions Pvt Limited., Kerala, India, was used as the curcumin. The CAS number for curcumin powder is 458-37-7. It is a natural product obtained by solvent extraction of the rhizomes of *Curcuma Longa*. The curcumin content of the powder is at least 95 %, according to manufacturer specifications. This curcumin content is determined by ASTA method 18.0.

As an alternative to the "oleoresin turmeric 95 %" curcumin powder from Green Leaf mentioned above, it is also possible for the embodiments described below to use, as the curcumin, 95 % curcumin extract by Neelam Phyto-Extracts, Mumbai, India, or curcumin BCM-95-SG or curcumin BCM-95-CG from eurochem GmbH,

Gröbenzell, Germany, or Curcuma Oleoresin 95 % from Henry Lamotte OILS GmbH, Bremen, Germany, for example.

Xanthohumol

The products "Xantho-Flav" or "Xantho-Flav Pure" of the "Hopsteiner" brand by Simon H. Steiner, Hopfen, GmbH, Mainburg, Germany were used as the xanthohumol source. Both are natural products produced from hops. The active substance is the hop polyphenol xanthohumol. This is a yellow-colored powder with a xanthohumol content between 65 % and 85 % in "Xantho-Flav" and at least 85 % in "Xantho-Flav Pure", according to manufacturer specifications. The concentrations of xanthohumol and isoxanthohumol in "Xantho-Flav Pure" are quantified by the manufacturer according to UV spectrophotometric analysis or HPLC EBC 7.8 using external calibration standard pure XN (370 nm) or IX (290 nm). "Xantho-Flav Pure" contains the prenylated flavonoid xanthohumol in a very high concentration. For the embodiments in the context of the present application, "Xantho-Flav Pure" of batch number 9432 was used.

Polysorbate 80

The source of polysorbate 80 was the material "TEGO SMO 80 V FOOD" with the specification code "K04 EU-FOOD" from Evonik Nutrition & Care GmbH, Essen, Germany. The product complies with the EU requirements for food additive E 433. As an alternative to the TEGO SMO 80 V from Evonik mentioned above, it is also possible to use TEGO SMO 80 V from InCoPA Gmbh, Illertissen, Germany, or Crillet 4/Tween 80-LQ-(SG) from CRODA GmbH, Nettetal, Germany, or Lamesorb SMO 20 and Kotilen-O/1 VL from Univar or from Kolb Distributions AG, Hedingen, Switzerland, as the polysorbate 80 in the embodiments described below.

Polysorbate 20

The source of polysorbate 20 was the material "TEGO SML 20 V FOOD" with the specification code "K09 EU-FOOD" from Evonik Nutrition & Care GmbH, Essen, Germany. The product complies with the EU requirements for food additive E 432. As an alternative to the TEGO SML 20 from Evonik mentioned above, it is also

possible to use Crillet 1/Tween 20-LQ-(SG) from CRODA GmbH, Nettetal, Germany as the polysorbate 20 within the context of the invention.

If is added in the preparation of a solubilizate, distilled water is used.

Ethanol

In the context of the present application, ethanol was purchased from Berkel Pfälzische Spritfabrik GmbH & Co. KG. According to the specification for "undenatured neutral alcohol" 1411U taxed", the content of ethanol of this product is about 92.6 to 95.2 wt.%.

The particle size analyses of the micelles in aqueous dilutions of solubilizates according to the invention were measured according to the principle of dynamic light scattering using laser light of 780 nm wavelength. The particle size measurements were performed using the ParticleMetrix NANO-flex backscatter particle analyzer. The measuring principle is based on dynamic light scattering (DLS) in a 180° heterodyne backscattering setup. With this geometry, part of the laser beam is mixed into the scattered light (heterodyne technique). Because of the short light path of 200 micrometers to 300 micrometers within the sample, backscattering is an advantage for absorbent and highly concentrated samples. The heterodyne technique has an enhancing effect on the signal-to-noise ratio and on the sensitivity of the sub-100 nm range.

The laser light is coupled into the Y fork of an optical fiber. What returns in the same fiber is the laser light partially reflected at the sapphire window of the sample chamber and the light backscattered from the sample. The detector in the second leg of the Y fork captures the interfering signals. Fast Fourier transform evaluation analyzes the fluctuating stray light components to give a frequency-dependent power spectrum. Each frequency component represents a Brownian diffusion constant and can therefore be assigned to a particle size. For conversion into a particle size distribution, the Stokes-Einstein relation is used:

$$D = k\frac{T}{3\pi\eta d_p}$$

This equation includes the diffusion constant D, the Boltzmann constant k, temperature T, dynamic viscosity η of the medium and the diameter d_p of the particles. A temperature sensor is arranged near the sapphire window close to the sample in the measurement device.

For the experimental determination of turbidity of the solubilizates according to the invention, the turbidity meters are calibrated using a standard suspension. Thus, instead of measured light intensity, the concentration of the calibration suspension is indicated. So, when any suspension is measured, the indication means that the relevant liquid causes the same light scattering as the standard suspension at the indicated concentration. The internationally defined turbidity standard is formazin. The most common units include the indication FNU, i.e. Formazin Nephelometric Units. This is the unit used in water treatment, for example, for measuring at 90° in compliance with the requirements of the ISO 7072 standard.

For preparing a solubilizate according to the invention having the active substances curcumin and Boswellia, it is possible to either mix individually prepared solubilizates with one another or to directly prepare a solubilizate containing curcumin and boswellia. First, a preparation example using two solubilizates that were previously prepared individually will be described below.

Embodiment 1

Solubilizate of curcumin / boswellic acid / xanthohumol

First, a 7 % curcumin solubilizate is prepared. The following were used for this purpose:

925 g polysorbate 80,

75 g 95 % curcumin powder (= 71.2 g of curcumin).

The polysorbate 80 is heated to 48 to 52 °C. The curcumin powder is added to the polysorbate while stirring, while continuing to heat to a temperature in the range of from 95 to 97 °C. The powder is added at an appropriate rate so as to be evenly drawn into the emulsifier during stirring. After cooling to a temperature below a

maximum of 60 °C, the curcumin solubilizate is bottled. This solubilizate was used for the preparation of a solubilizate comprising curcumin and boswellia.

However, it should be noted that the curcumin content can be further increased without incurring adverse consequences, for example in terms of stability of the micelles. A composition consisting of 100 g of 95 % curcumin powder and 900 g of polysorbate 80 results in a stable product just like a composition consisting of 120 g of 95 % curcumin powder and 880 g of polysorbate 80. The preparation of these two variants corresponds to that described above. Thus, besides a 7 % solubilizate, anything up to 11 % solubilizates can be prepared.

At a dilution ratio of 1:500 in water at pH 1.1 and a temperature of 37 °C, the 7 % curcumin solubilizate exhibits an average turbidity of 0.9 FNU.

Next, a 6 % boswellic acid solubilizate was prepared. The following were used for this purpose:

76 g 80 % *Boswellia serrata* extract (= 60.8 g of boswellic acid),

24 g water,

400 g polysorbate 20.

The water is mixed with the boswellia powder while heating up to a temperature in the range from 87 to 93 °C. Polysorbate 20 is incorporated while maintaining the temperature. The emulsifier is added at an appropriate rate so that the fluids are homogenized stably to form a solubilizate while stirring. Heavy foaming may occur during the preparation. This can be ignored if a clear solubilizate can be seen on the bottom of the collection vessel when bottled.

This clarity, which indicates complete micellization, is checked by laser beam measurements. Such a laser beam measurement may be performed, for example, by illuminating the sample using a commercially available laser pointer, in particular with a wavelength in the range between 650 nm and 1700 nm (spectral color red), and subsequent visual inspection of the illuminated or irradiated solubilizate. The check is not made by sampling and thus outside the reaction vessel, but in the reaction vessel. The laser beam is directed through a sight glass,

which is located on the front of the reaction vessel, perpendicularly to the reaction vessel. If merely a point of light appears on the rear inner surface of the reaction vessel, completely free of scattering, the resulting particle structures in the reaction vessel are smaller than the wavelength of the visible light, which is thus a visual confirmation that the process of micellization has been completed.

The product is bottled at approximately 50 °C.

Finally, a 10 % Xantho-Flav solubilizate (≙9.2 % xanthohumol) is prepared from

100 g Xantho-Flav Pure (≙ 92 g of xanthohumol), and

900 g polysorbate 80.

For this purpose, the Xantho-Flav Pure powder is incorporated into Polysorbate 80 by stirring. The powder is added at an appropriate rate so as to be evenly drawn into the emulsifier. Homogenization is continued under heating to 83 to 87 °C. Once a homogeneous solubilizate is obtained, it is cooled to a temperature below 60 °C. The Xantho-Flav solubilizate is then bottled and stored in a dark and cool place, i.e. below 25 °C.

The solubilizates of curcumin, boswellia and xanthohumol are mixed together to obtain a solubilizate that includes all three active substances.

Embodiment 2

Instead of the xanthohumol solubilizate mentioned above, it is also possible within the scope of the invention to use the following solubilizate, which additionally contains ethanol, in the solubilizate containing curcumin, Boswellia and xanthohumol:

10 % Xantho-Flav solubilizate (≙ 8 % of xanthohumol) with ethanol

For this variant of a xanthohumol solubilizate, the following are used:

100 g Xantho-Flav (≙ 80 g of xanthohumol),

150 g ethanol (96 %) neutral alcohol grade 1411U, and

750 g polysorbate 80.

First, the Xantho-Flav powder is dissolved in ethanol while being heated to a temperature in the range between 48 and 52 °C. A homogeneous solution is created. Polysorbate 80 is then added to the solution of Xantho-Flav in ethanol while heating to between 83 and 87 °C. The addition thereof is done at a rate such that the two fluids homogenize effectively while stirring. The resulting solubilizate is cooled to below 60 °C and is bottled and stored in a dark and cool place, i.e. at temperatures below 25 °C.

Embodiment 3

Alternatively, it would also be possible to use a 7 % boswellic acid solubilizate. For this purpose

82 g 80 % *Boswellia serrata* extract (= 65.6 g boswellic acid),

70 g water,

350 g polysorbate 20,

441 g polysorbate 80

are used, which corresponds to a total amount of 943 g.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other and thereby dissolved in one another while stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water while stirring intensely enough so that the water is evenly dissolved in the emulsifier solution. Without changing the temperature, the *Boswellia serrata* extract is incorporated into the water-diluted emulsifier mixture while stirring. The *Boswellia serrata* extract is added at a rate slow enough to be evenly drawn into the diluted emulsifier solution while stirring.

Mixing with the curcumin solubilizate described above and with one of the xanthohumol solubilizates mentioned gives a solubilizate according to the invention that comprises curcumin, xanthohumol and boswellia as the active substances.

Embodiment 4

For preparing a solubilizate of 2.9 % curcumin / 2.5 % boswellic acid / 3.7 % xanthohumol according to Example 1,

500 g 3 % curcumin solubilizate,

500 g 6 % boswellia solubilizate, and

500 g 10 % xanthohumol solubilizate

are used according to Embodiment 1.

The three solubilizates are optionally heated to a temperature in the range from 50 to 60 °C to lower their viscosity, i.e. enhance flowability. The three solubilizates are homogenized by stirring to form a mixed solubilizate comprising curcumin and boswellia and xanthohumol. The product is cooled to a maximum temperature of 60 °C and bottled. This product is particularly suitable for use as a capsule filling.

Embodiment 5

Solubilizate of 3.3 % Curcumin / 3.6 % boswellic acid with 1.8 % of xanthohumol

The following are used:

45 g 80 % *Boswellia serrata* extract (36 g boswellic acid),

35 g 95 % curcumin powder (33.25 g of curcumin),

23 g Xantho-Flav with at least 80 % xanthohumol (18.4 g xanthohumol),

60 g water,

50 g ethanol (96 %) neutral alcohol grade 1411U,

350 g polysorbate 20,

437 g polysorbate 80.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other while being dissolved in one

another, while stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water and ethanol. Stirring is performed intensely enough so that the water and the ethanol are dissolved evenly in the emulsifier solution. Without changing the temperature, the *Boswellia serrata* extract and the xanthohumol powder are incorporated into the emulsifier mixture diluted with water and ethanol while stirring. The *Boswellia serrata* extract and the hop extract are added at a rate slow enough so as to be evenly drawn into the dilute emulsifier solution while stirring. Subsequently, the temperature is increased to a range between 63 °C and 67 °C while stirring vigorously. Then, the curcumin powder is incorporated while stirring. The temperature is further increased to a value in the range between 85 °C and 89 °C while stirring intensely enough so that the curcumin is evenly distributed in the sample and homogenized.

This is followed by cooling to a temperature of less than or equal to 45 °C.

The dark-yellow viscous preparation comprising a solubilizate of curcumin and boswellic acid and xanthohumol is then bottled and stored in a dark and cool place, i.e. below 25 °C.

For a particle size analysis of this solubilizate described under embodiment 5, this solubilizate was first diluted with distilled water in a ratio of 1:500 and heated to 37 °C under constant stirring using a magnetic stirrer and with the aid of a hotplate. Subsequently, the pH was adjusted to 1.1 using 32 % hydrochloric acid. The samples were then measured immediately. The results are summarized in the table below. Here, the data from two measurements were averaged.

	d_{10} (nm)	d_{50} (nm)	d_{90} (nm)	d_{99} (nm)
Intensity distribution	10.18	15.70	533.0	3080
Volume distribution	7.90	10.96	15.21	20.37

After dilution in water at a ratio of 1:500 and at pH 1.1 and a temperature of 37 °C, a measurement of turbidity gave a value of 1.9 FNU.

Embodiment 6 below illustrates the direct preparation of a solubilizate comprising curcumin and boswellia, which contains xanthohumol in non-solubilized form, according to a further embodiment of the invention.

Embodiment 6

Solubilizate of 3.3 % curcumin / 3.6 % boswellic acid with 1.8 % of xanthohumol

The following are used:

45 g 80 % *Boswellia serrata* extract (36 g boswellic acid),

35 g 95 % curcumin powder (33.25 g of curcumin),

23 g Xantho-Flav with at least 80 % xanthohumol (18.4 g xanthohumol),

60 g water,

50 g ethanol (96 %) neutral alcohol grade 1411U,

350 g polysorbate 20,

437 g polysorbate 80.

While heating to a temperature in the range from 48 to 52 °C, polysorbate 20 and polysorbate 80 are homogenized with each other while being dissolved in one another, while stirring. While maintaining the temperature, the emulsifier mixture is mixed with the water and ethanol. Stirring is performed intensely enough so that the water and the ethanol are dissolved evenly in the emulsifier solution. Without changing the temperature, the *Boswellia serrata* extract is incorporated into the water-diluted emulsifier mixture while stirring. The *Boswellia serrata* extract is added at a rate slow enough so as to be evenly drawn into the diluted emulsifier solution, while stirring. Subsequently, the temperature is increased to a range between 63 °C and 67 °C while stirring vigorously. The curcumin powder is incorporated while stirring. The temperature is further increased to a value in the range between 85 °C and 89 °C while stirring intensely enough so that the curcumin is evenly distributed in the sample and homogenized.

This is followed by cooling to a temperature of less than or equal to 30 °C. Then, Xantho-Flav powder is incorporated while stirring. The native xanthohumol is added at a rate slow enough so as to be evenly drawn into the sample while stirring. In this case, the temperature is maintained in a range between 26 °C and 30 °C.

Thus, in this embodiment, in contrast to curcumin and boswellic acid, xanthohumol is contained in non-micellated form, but rather exclusively in its native form, because at low temperatures micelles cannot form from powdery raw materials. This has been found and verified by corresponding particle measurements (two clearly different fractions).

The dark-yellow viscous preparation comprising a solubilizate of curcumin and boswellic acid with native xanthohumol is then bottled and stored in a dark and cool place, i.e. below 25 °C.

The following solubilizate of curcumin and boswellic acid may likewise be used as a basis for adding xanthohumol in native form, in the same way as in Embodiment 6.

The weight percentages of curcumin and boswellic acids and of xanthohumol in the final product are then obtained by adjusting the amount of xanthohumol added.

Embodiment 7

Solubilizate of 5.4 % curcumin / 6.6 % boswellic acid as a basis for a product comprising native xanthohumol

This further embodiment of the solubilizate according to the invention with native xanthohumol was also prepared directly. As with the curcumin-boswellic acid solubilizate described above, the active substances were co-micellated here as well. The following were used for this purpose:

82 g 80 % *boswellia serrata* extract (= 65.6 g boswellic acid),

57 g 95 % curcumin powder (= 54.1 g of curcumin),

70 g water,

350 g polysorbate 20,

441 g polysorbate 80.

The solubilizate of 5.4 % curcumin / 6.6 % boswellic acid was prepared in the same way as the preparation of the curcumin-boswellic acid solubilizate in Embodiment 6 described above.

After cooling to a temperature of less than or equal to 30 °C, Xantho-Flav powder is incorporated in the desired amount while stirring. The native xanthohumol is added at a rate slow enough so as to be evenly drawn into the sample while stirring. The temperature is thereby maintained in a range between 26 °C and 30 °C.

At low temperatures, no product micelle can form. Xanthohumol is therefore only present in native and not in micellated form in this embodiment. This is demonstrated and verified in the corresponding particle measurement by two clearly different fractions.

The dark-yellow viscous preparation comprising a solubilizate of curcumin and boswellic acid with native xanthohumol is then bottled and stored in a dark and cool place, i.e. below 25 °C.

Depending on the intended use, it is also possible within the scope of the invention for the contents of curcumin and boswellia extract and xanthohumol in the individual solubilizates to be adjusted so as to be significantly higher than in the example discussed.

If higher loads of active substances are adjusted in the solubilizate prior to or without the addition of native xanthohumol, this is limited by the fact that an emulsion will be produced instead of a solubilizate when a content of active substances specific for the respective composition is exceeded. When the content of active substances is increased, the corresponding contents of the other components (in wt.%) have to be reduced.

Above a specific limit, a disperse system is obtained which, however, is not irreversibly soluble in water like the solubilizates according to the invention, and

which exhibits the very low turbidity measured for these solubilizates under physiological conditions of the gastric passage, i.e. under physiological conditions (pH 1.1 and 37 °C). This is the case for the xanthohumol within the scope of the variant according to the invention whereby native xanthohumol is added without solubilizing it. However, curcumin and boswellia are again solubilized in the form of micelles in this variant.

If too high a content of curcumin or boswellia and/or optionally xanthohumol is chosen, dispersions will be formed. These might be (nano)emulsions, however, in terms of the relevant active substance(s), these are not solubilizates in which the active substance(s) are contained in the very small micelles. However, according to the inventor's experience, it is only the solubilizates that allow for the significantly increased bioavailability of the active substance(s) according to the invention, even if an emulsion allowed for a higher active substance load. Surprisingly, though, it has also proven to be advantageous to administer non-solubilized xanthohumol together with curcumin and boswellic acid in a solubilizate.

The transparent and completely stably water-soluble formulation according to the invention exhibits, without additives as is the case in soft and hard gelatin capsules, steady transparency in gelatin-free capsules (hard and/or soft) and in water-based liquid end products, regardless of pH. Products exhibiting such transparency and water solubility are urgently sought by the relevant industry for innovative products as a capsule filling. To the best of the inventor's knowledge, there has not yet been a formulation of curcumin with boswellia, i.e. with at least one boswellic acid and/or at least one boswellic acid derivative, and with xanthohumol, which meets these requirements.

As a result of the formulation according to the invention in a solubilizate with very small, stable and gastric acid-resistant micelles, the invention provides a solubilizate of curcumin with boswellia and xanthohumol for use as a dietary supplement and/or as a pharmaceutical drug, in particular for use as a dietary supplement and/or as a pharmaceutical drug having an anti-inflammatory effect.

It will be apparent to a person skilled in the art that the invention is not limited to the examples described above, but rather can be modified in multiple ways. It is in particular possible for the features of the individually illustrated examples to be combined or swapped.

5

_____

PATENTKRAV

1. Solubilisat, som inneholder og spesielt består av

kurkumin i et innhold på mindre enn eller lik 10 vekt-%, fortrinnsvis mindre enn eller lik 8 vekt-%, mest foretrukket 3 vekt-%til 7 vekt-%;

én eller flere boswellinsyrer og/eller ett eller flere boswellinsyrederivater, spesielt 11 keto-β-boswellinsyre, KBA, (CAS 17019-92-0), 3-O-acetyl-11-keto-β-boswellinsyre, AKBA, (CAS 67416-16-9), 3-O-acetyl-α-boswellinsyre, AaBA, og/eller 3-O-acetyl-β-boswellinsyre, AβBA, i et totalt innhold på mindre enn eller lik 10 vekt-%, fortrinnsvis mindre enn eller lik 8 vekt-%, mest foretrukket 3 vekt-%til 6,6 vekt-%; og

xanthohumol i et innhold på mindre enn eller lik 10 vekt-%, fortrinnsvis mindre enn eller lik 5 vekt-%, mest foretrukket 1 vekt-%til 3 vekt-%; og

minst én emulgator, nemlig polysorbat 80 eller polysorbat 20 eller en blanding av polysorbat 20 og polysorbat 80;

karakterisert ved at emulgatorinnholdet, spesielt polysorbatinnholdet, er minst 70 vekt-%, fortrinnsvis i et område mellom 75 vekt-% og 95 vekt-%, mest foretrukket i et område mellom 79 vekt-%og 88 vekt-%.

2. Solubilisatet ifølge krav 1,

karakterisert ved at

solubilisatet inneholder et ekstrakt fra harpiksen til *boswellia serrata*-planten oppnådd ved ekstraksjon med etylacetat, som en kilde for den ene eller flere boswellinsyrene og/eller ett eller flere boswellinsyrederivater, hvori dette ekstraktet inneholder boswellinsyrer i en konsentrasjon på minst 85 vekt-%.

3. Solubilisatet ifølge et hvilket som helst av de foregående kravene,

karakterisert ved at

forholdet mellom emulgator og boswellinsyrer og/eller boswellinsyrer og minst ett av deres derivater er i et område mellom 20:1 og 3:1, fortrinnsvis i et område mellom 16:1 og 4:1, fortrinnsvis i et område mellom 14:1 og 5:1,

og/eller **ved at**

forholdet mellom emulgator og kurkumin er i et område mellom 30:1 og 3:1, fortrinnsvis i et område mellom 25:1 og 9:1, fortrinnsvis i et område mellom 23:1 og 12:1,

og/eller **ved at**

forholdet mellom emulgator, spesielt polysorbat 80, og xanthohumol er i et område mellom 30:1 og 3:1, fortrinnsvis i et område mellom 25:1 og 5:1, fortrinnsvis i et område mellom 9,8:1 og 6,6:1,

og/eller **ved at**

solubilisatet inneholder opptil 20 vekt-%, fortrinnsvis opptil 15 vekt-%etanol, og/eller **ved at**

en diameterfordeling av micellene i en fortynning av solubilisatet med destillert vann i et forhold på 1:500 ved pH 1,1 og 37 °C er i et område fra ca. d_{10} = 6 nm til ca. d_{90} = 16 nm,

og/eller **ved at**

solubilisatet viser en turbiditet på mindre enn 25 FNU, fortrinnsvis mindre enn 3 FNU, målt ved måling av spredt lys ved anvendelse av infrarødt lys i henhold til spesifikasjonene til ISO 7027-standarden ved en fortynning av solubilisatet i et forhold på 1:50 i vann under fysiologiske forhold (pH 1,1 og 37 °C).

4. Solubilisatet ifølge et hvilket som helst av de foregående kravene,

karakterisert ved at

solubilisatet inneholder xanthohumol i ikke-solubilisert form, spesielt i naturlig form.

5. Kapsel fylt med et solubilisat ifølge et hvilket som helst av de foregående kravene,

karakterisert ved at

kapselen er i form av en myk gelatinkapsel eller en hard gelatinkapsel eller en myk gelatinfri kapsel eller en hard gelatinfri kapsel, for eksempel en cellulosekapsel.

6. Fluid, som inneholder et solubilisat ifølge et hvilket som helst av kravene 1 til 4,

karakterisert ved at

fluidet velges fra gruppen som består av matvarer, kosttilskudd, drikkevarer, kosmetikk og farmasøytiske produkter.

7. Fluidet ifølge krav 6,

karakterisert ved at

fluidet omfatter en vandig fortynning av solubilisatet.

8. Solubilisatet ifølge et hvilket som helst av kravene 1 til 4 eller fluidet ifølge et hvilket som helst av kravene 6 eller 7 for, spesielt oralt, anvendelse som et kosttilskudd og/eller som et farmasøytisk legemiddel i en fremgangsmåte for behandling og/eller forebygging av sykdommer som involverer betennelse, kreft, Alzheimers, Parkinsons, fedme, høyt kolesterol, høyt blodsukker, metabolsk syndrom og/eller autoimmune sykdommer.

9. Solubilisatet for anvendelse ifølge krav 8 for anvendelse som et kosttilskudd og/eller som et farmasøytisk legemiddel

i en kurkumindose som varierer fra 0,5 mg/kg kroppsvekt til 1 mg/kg kroppsvekt, fortrinnsvis i en dose på 0,81 mg/kg kroppsvekt;

og i en boswelliadose som varierer fra 1 mg/kg kroppsvekt til 2 mg/kg kroppsvekt, fortrinnsvis i en dose på 1,62 mg/kg kroppsvekt;

og i en xanthohumoldose som varierer fra 0,5 mg/kg kroppsvekt til 1 mg/kg kroppsvekt, fortrinnsvis i en dose på 0,81 mg/kg kroppsvekt;

spesielt én gang daglig.

10. Fremgangsmåte for fremstilling av et solubilisat ifølge et hvilket som helst av kravene 1 til 4, omfattende trinnene

(a) å tilveiebringe polysorbat 80 og/eller polysorbat 20 og/eller en blanding av polysorbat 20 og polysorbat 80;

(b) å tilsette *boswellia serrata*-ekstraktpulver og et etanolekstrakt av harde harpikser fra humle,

(c) å tilsette kurkuminpulver;

hvori trinn (a) omfatter oppvarming til en temperatur i et område fra 40 °C til 62 °C, fortrinnsvis til en temperatur i et område fra 45 °C til 57 °C, mest foretrukket til en temperatur i et område fra 48 °C til 52 °C; og

hvori trinn (b) omfatter oppvarming til en temperatur i et område fra 60 °C til 75 °C, fortrinnsvis til en temperatur i et område fra 61 °C til 70 °C, mest foretrukket til en temperatur i et område fra 63 °C til 67 °C; og

hvori trinn (c) omfatter oppvarming til en temperatur i et område fra 82 °C til 97 °C, fortrinnsvis til en temperatur i et område fra 83 °C til 92 °C, mest foretrukket til en temperatur i et område fra 85 °C til 89 °C.

11. Fremgangsmåte for fremstilling av et solubilisat ifølge et hvilket som helst av kravene 1 til 4, omfattende trinnene

(a) å tilveiebringe polysorbat 80 og/eller polysorbat 20 og/eller en blanding av polysorbat 20 og polysorbat 80;

(b) å tilsette *boswellia serrata*-ekstraktpulver;

(c) å tilsette kurkuminpulver;

hvori trinn (a) omfatter oppvarming til en temperatur i et område fra 40 °C til 62 °C, fortrinnsvis til en temperatur i et område fra 45 °C til 57 °C, mest foretrukket til en temperatur i et område fra 48 °C til 52 °C; og

hvori trinn (b) omfatter oppvarming til en temperatur i et område fra 60 °C til 75 °C, fortrinnsvis til en temperatur i et område fra 61 °C til 70 °C, mest foretrukket til en temperatur i et område fra 63 °C til 67 °C; og

hvori trinn (c) omfatter oppvarming til en temperatur i et område fra 82 °C til 97 °C, fortrinnsvis til en temperatur i et område fra 83 °C til 92 °C, mest foretrukket til en temperatur i et område fra 85 °C til 89 °C;

og omfattende et etterfølgende trinn av

d) å tilsette et etanolisk ekstrakt av harde harpikser fra humle ved en temperatur i et område fra 26 °C til 30 °C.

12. Fremgangsmåten ifølge krav 10 eller 11, hvori før trinn (b), utføres et trinn

(b1) omfattende tilsetning av vann ved en temperatur i et område fra 40 °C til 62 °C, fortrinnsvis ved en temperatur i et område fra 45 °C til 57 °C, mest foretrukket ved en temperatur i et område fra 48 °C til 52 °C.

13. Fremgangsmåte for fremstilling av et solubilisat ifølge et hvilket som helst av kravene 1 til 4, omfattende blanding av et kurkuminsolubilisat og et boswelliasolubilisat og et xanthohumolsolubilisat, spesielt i et kvantitativt forhold på 1:1:1.