

(19) **DANMARK**

(10) **DK/EP 3654938 T3**



(12)

## Oversættelse af europæisk patentskrift

Patent- og  
Varemærkestyrelsen

- 
- (51) Int.Cl.: **A 61 K 9/00 (2006.01)** **A 61 K 9/14 (2006.01)** **A 61 K 9/20 (2006.01)**  
**A 61 K 9/48 (2006.01)** **A 61 K 31/352 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2022-10-03**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-08-31**
- (86) Europæisk ansøgning nr.: **18743743.9**
- (86) Europæisk indleveringsdag: **2018-07-16**
- (87) Den europæiske ansøgnings publiceringsdag: **2020-05-27**
- (86) International ansøgning nr.: **EP2018069284**
- (87) Internationalt publikationsnr.: **WO2019016146**
- (30) Prioritet: **2017-07-17 EP 17181634**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
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- (54) Benævnelse: **Faste pulverdyspersjoner omfattende quercetin, fremgangsmåde til fremstilling og formuleringer deraf**
- (56) Fremdragne publikationer:  
**CN-A- 1 813 677**  
**CN-A- 101 904 821**  
**Hong-Bo Yang ET AL: "Preparation and Characterization of the Solid Dispersion Quercetin with Phospholipid", 2017 Joint International Conference on Materials Science and Engineering Application, April 2017 (2017-04), pages 1-7, XP055438513, Retrieved from the Internet: URL: <http://dpi-proceedings.com/index.php/dtmse/article/download/10815/10368> [retrieved on 2018-01-05]**  
**SANG HYUN PARK ET AL: "Preparation and Characterization of Quercetin-Loaded Solid Dispersion by Solvent Evaporation and Freeze-Drying Method", MASS SPECTROMETRY LETTERS, vol. 7, no. 3, 30 September 2016 (2016-09-30), pages 79-83, XP055438544, ISSN: 2233-4203, DOI: 10.5478/MSL.2016.7.3.79**



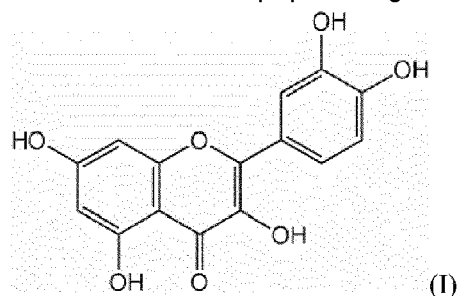
# DESCRIPTION

## FIELD OF THE INVENTION

**[0001]** The invention relates to a process for the preparation of powder solid dispersions comprising quercetin, phospholipids and a very soluble to freely soluble in water carrier and pharmaceutical, nutraceutical and cosmetic compositions comprising said powder solid dispersions. The invention also relates to powder solid dispersion comprising quercetin, phospholipids and a carrier very soluble to freely soluble in water obtainable by said process.

## BACKGROUND OF THE INVENTION

**[0002]** Quercetin (namely 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) having formula (I), belongs to the chemical family of flavonols, a sub-class of flavonoids. Quercetin is a lipophilic citron yellow powder, substantially insoluble in water, but soluble in ethanol, methanol, acetone and other lipophilic organic solvents. Quercetin has a melting point of 316°C.



**[0003]** Quercetin is present, mainly as quercetin glycosides, in many fruits and vegetables, including apples, grapes, onions, capers, berries, radish.

**[0004]** Quercetin has many potential beneficial effects on human health, including antioxidant, anti-inflammatory, anti-allergy and anti-asthmatic effects. The anti-allergy and anti-asthmatic activities of quercetin are mediated by an inhibitory effect on histamine release by mast cell and basophils. Quercetin has been also studied for its potential anticancer effect due to different mechanisms of action.

**[0005]** As a consequence of these potential beneficial effects on human health, quercetin has gained growing attention as nutraceutical and pharmaceutical ingredient. However, the potential efficacy of quercetin is limited by its low and variable bioavailability which is mainly due to its very poor water solubility. Due to the low and variable oral bioavailability, high unitary doses of quercetin are required to guarantee its pharmacological activity.

**[0006]** The high variability of quercetin in-vivo absorption is substantiated by many studies on

animals, which have shown that different dietary factors can strongly influence quercetin absorption (Nishijima, T. et al. (2009). Journal of agricultural and food chemistry, 57(6), 2583-2587; Tamura, M. et al. (2007). Journal of food science, 72(9) S648; Azuma, K. et al. (2003) Biosci. Biotechnol. Biochem. 67 12 2548. Different approaches have been applied to improve quercetin absorption, including incorporation in micro and nano-emulsions (Gao, Y. et al. (2009). Colloids and Surfaces B: Biointerfaces, 71(2), 306-314), solid lipid nanoparticles (Li, H., et al. (2009). Journal of Controlled Release, 133(3), 238-244), inclusion complexes of cyclodextrins (Aytac, Z., et al. (2016). Food chemistry, 197, 864-871), polymer nanoparticles (Patel, A. R., et al. (2012). Food Chemistry, 133(2), 423-429), but most of these approaches have many disadvantages including low encapsulation loading, complexity of manufacturing, lack of cost-effective industrial-scale production methods. Moreover most of these approaches have been applied only on laboratory scale and the potential improvement of quercetin oral bioavailability has been demonstrated only in-vitro or in-vivo animal studies.

**[0007]** CN 1 813 677 A (UNIV SICHUAN [CN], published on August 9, 2006, relates to a quercetin liposome injection powder and its preparation method. The liposome powder is made of quercetin, polyglycol-phosphatidylethanolamine, lecithin, cholesterol and an excipient (such as sorbitol, mannitol, glucose, cane sugar or trehalose) and is prepared through a process comprising dissolution of quercetin, polyglycol-phosphatidylethanolamine, lecithin and cholesterol in chloroform and methanol, evaporation of the solvents to obtain a dry residue, addition of a sterile broth and an excipient to obtain a water solution which is subjected to ultrasonic treatment and lyophilization to obtain a powder.

**[0008]** CN 102580111B (UNIV SICHUAN), published on April 9, 2014, discloses a liposome which comprises quercetin entrapped in a cyclodextrin. Specifically, the liposome is prepared through a process comprising the addition of quercetin to a solution of hydroxypropyl-beta-cyclodextrin in a solvent selected from one or more of anhydrous alcohol, n-butyl alcohol and ether to obtain a solution; the addition of egg yolk lecithin or soybean phospholipid, cholesterol, polyethylene glycol-distearyl acid, phosphatidylethanolamine to the solution, followed by addition of the resulting solution to a water solution of sucrose and removal of the solvent by lyophilization. In the liposome, lecithin or soy phospholipids are used in excess with respect to quercetin; in greater detail, the weight ratio between quercetin and lecithin or soy phospholipid is from 1:5 to 1:50.

**[0009]** CN 101 904 821 A (LINGMIN JIANG; LEI GAO), published on December 8, 2010 relates to a quercetin nano lyophilized powder having a mean diameter of less than 300 nm, preferably from 100 to 300 nm, and consisting of quercetin, a surfactant and a freeze drying protectant. The surfactant can be, *inter alia*, a phospholipid or soy lecithin, and the freeze drying protectant is a polysaccharide or a polyol. The quercetin powder is manufactured through a process carried out entirely in water; specifically, a surfactant is dispersed in water, then quercetin is added and the resulting suspension is homogenized under pressure and lyophilized. The freeze drying protectant can be added to the surfactant dispersion before addition of quercetin or before lyophilization.

**[0010]** All of CN 1 813 677 A, CN 102580111B and CN 101 904 821 A disclose liposomes, whose preparation includes the use of water.

**[0011]** Hong-Bo Yang, et al. (2017) Joint International Conference on Materials Science and Engineering Application, April 2017, pages 1-7) disclose the preparation of a solid dispersion of quercetin in a phospholipid by dissolution of quercetin and a phospholipid at a 1:2 weight ratio in tetrahydrofuran, stirring, filtration and drying under vacuum at 50°C. While X-rays suggest that quercetin as such is a crystalline solid, X-ray analysis of the solid dispersion show that in the solid dispersion quercetin is present in an amorphous form.

**[0012]** Sang Hyun Park et al. Mass Spectrometry Letters, vol. 7, no.3, 30 September 2016, pages 79-83) teach to prepare a solid dispersion of quercetin by dissolution of quercetin, a hydrophilic polymer and a carrier in ethyl alcohol, followed by evaporation to provide a residue which is taken up in HPMG, PEG 8000, PVP K40 and water, to provide a clear solution which is subjected to lyophilization to provide the solid dispersion. This document states that quercetin is thus transformed from a crystalline to an amorphous form.

**[0013]** Due to the poor and variable absorption of quercetin there is still the need to develop delivery systems able to promote its oral bioavailability and to guarantee a more constant absorption into the systemic circulation and pharmacological activity accordingly.

#### **DESCRIPTION OF THE FIGURE**

**[0014]** Figure: X-ray diffraction pattern of a solid dispersion of the invention (quercetin:phospholipids:carrier weight ratio = 3:3:2), quercetin dihydrate and a physical mixture of quercetin dihydrate (quercetin:phospholipids:carrier weight ratio = 3:3:2),

#### **SUMMARY OF THE INVENTION**

**[0015]** The invention concerns a process for preparing a powder solid dispersion comprising quercetin, phospholipids and a carrier that is very soluble to freely soluble in water and that is selected from the group consisting of mono- and di-saccharides; polyalcohols; soluble oligo- and poly-saccharides, said process comprising dissolving or suspending in an anhydrous organic solvent and under heating quercetin, phospholipids and the carrier and then removing the solvent to obtain the powder solid dispersion, wherein the process is carried out using solvents containing less than 5% wt. of water and it does not comprise any steps of dissolution in water.

**[0016]** The present invention relates to powder solid dispersions comprising quercetin, phospholipids and a carrier very soluble to freely soluble in water obtainable by said process.

**[0017]** Further object of the invention are formulations for oral administration comprising the powder solid dispersion and one or more pharmaceutically and food acceptable excipients.

#### **DESCRIPTION OF THE INVENTION**

**[0018]** The present invention is directed to a process for preparing a powder solid dispersion comprising quercetin, phospholipids and a carrier that is very soluble to freely soluble in water and that is selected from the group consisting of mono- and di-saccharides; polyalcohols; soluble oligo- and poly-saccharides, said process comprising dissolving or suspending in an anhydrous organic solvent and under heating quercetin, phospholipids and the carrier and then removing the solvent to obtain the powder solid dispersion, wherein the process is carried out using solvents containing less than 5% wt. of water and it does not comprise any steps of dissolution in water.

**[0019]** It has been surprisingly found that powder solid dispersions comprising, preferably consisting of, quercetin, phospholipids and a carrier very soluble to freely soluble in water obtainable by said process are characterized by an improved solubility and oral bioavailability of quercetin in humans.

**[0020]** According to a preferred embodiment, quercetin is quercetin dihydrate.

**[0021]** The phospholipids may be selected from the group consisting of lecithins from soy, sunflower or egg, phosphatidyl choline, phosphatidyl serine, phosphatidyl ethanolamine, or their mixtures, wherein the acyl groups, which may be the same or different, are mostly derived from palmitic, stearic, oleic, linoleic, linolenic acids. In a preferred embodiment, the lecithin is soy or sunflower lecithin; in a more preferred embodiment, the lecithin is sunflower lecithin.

**[0022]** The quercetin to phospholipids weight ratio may range from 5:1 to 1:1, preferably from 2:1 to 1:1.

**[0023]** According to the invention, the term "very soluble" and the term "freely soluble" have the meaning, as defined in the European Pharmacopeia 5.0, reported in the following scheme:

**Scheme**

<b>Descriptive term</b>	<b>Approximate volume of solvent in milliliters per gram of solute</b>
Very soluble	less than 1
Freely soluble	from 1 to 10

**[0024]** The terms used have the defined significance referred to a temperature between 15°C and 25°C.

**[0025]** The term "carrier" is used hereinafter to indicate "a carrier very soluble to freely soluble in water". The carrier is selected from the group consisting of mono- and di-saccharides (such as sucrose, fructose, maltodextrins); polyalcohols (such as mannitol, sorbitol, xylitol); soluble oligo- and poly-saccharides (such as dextran, pullulan). In a preferred embodiment, the carrier is a maltodextrin.

**[0026]** The quercetin to carrier weight ratio may range from 1:5 to 5:1, preferably from 1:2 to 3:1. For the avoidance of doubt, throughout the present application, when ranges are indicated, range ends are included.

**[0027]** Preferably, the solid dispersion of the invention has an average particle size distribution ranging from 100  $\mu\text{m}$  to 300  $\mu\text{m}$ .

**[0028]** Preferably, the solid dispersion of the invention consists only of quercetin, phospholipids and a carrier as defined above. In a preferred embodiment, the solid dispersion of the invention consists of quercetin, sunflower lecithin and maltodextrin; in another preferred embodiment, the solid dispersion of the invention consists of quercetin, sunflower lecithin and fructose.

**[0029]** Without being bound to theory, it is believed that the carrier plays a fundamental role for the performance of the powder solid dispersion, promoting the fast dissolution rate of quercetin and contributing to promote its oral bioavailability. It is also believed that the soluble carrier also plays a relevant role in optimizing the physical properties of the final product.

**[0030]** It has been found that in the solid dispersions of the invention the physicochemical properties of quercetin are significantly modified, so much so that quercetin's pharmacological performances are improved even if the quercetin/phospholipids weight ratio is low. Surprisingly, it has been observed that quercetin, in particular quercetin dihydrate, can be incorporated in the phospholipids in high amount and that dissolution in water is fast even though X-rays of the solid dispersions of the invention show that a significant amount of crystalline is still present. Indeed, on the basis of the teaching of the aforementioned publications of Hong-Bo Yang, ET AL and of Sang Hyun Park ET AL one would expect that fast dissolution would be due to absence of quercetin in the crystalline form.

**[0031]** The solid dispersions of the invention can be advantageously prepared with a process (or method) which avoids the use of chlorinated solvents and does not comprise any lyophilization steps and which can be easily scaled-up on pilot and industrial equipment.

**[0032]** In one embodiment, the process comprises the following steps:

1. a) preparing a solution of quercetin in an organic solvent comprising less than 5% wt. water [solution (S1)];
2. b) preparing a solution/suspension of phospholipids in the same solvent used in step a) [solution or suspension (S2)];

3. c) contacting the solution of quercetin obtained in step a) with the solution/suspension of phospholipids obtained in step b) to provide a further solution or suspension [suspension or solution (S3)];
4. d) adding a carrier very soluble to freely soluble in water carrier to the solution or suspension obtained in step c) and
5. e) removing the solvent under vacuum or under spray-drying, to form a powder solid dispersion.

**[0033]** In another embodiment, the process comprises the following steps:

a-1) preparing a solution of quercetin in an organic solvent comprising less than 5% wt. water[solution (S1)];

b-1) adding phospholipids and a carrier very soluble to freely soluble in water carrier to solution (S1) to provide a solution or suspension of quercetin, phospholipids and carrier in the solvent [solution or suspension (S3)] and

c-1) removing the solvent under vacuum or under spray-drying to form a powder solid dispersion.

**[0034]** The organic solvent is a food grade solvent having a boiling point at atmospheric pressure not higher than 80°C; preferably, the solvent is a C<sub>1</sub>-C<sub>4</sub> straight or branched alcohol, ethyl acetate or acetone, More preferably, the solvent is selected from the group comprising ethyl alcohol, isopropyl alcohol, n-propyl alcohol, n-butanol, ethyl acetate, acetone. Even more preferably, the solvent is selected from ethanol and ethyl acetate.

**[0035]** The process of the invention is carried out using solvents containing less than 5% wt. of water and it does not comprise any steps of dissolution in water.

**[0036]** The dissolution or suspension of quercetin, phospholipids and carrier is carried out under heating; in particular, steps a) to d) and a-1) and b-1) of the preferred embodiments are carried out under heating; typically, heating is carried out at a temperature ranging from 30°C to the solvent boiling temperature, preferably from 40°C to 80°C, more preferably from 50°C to 60°C, until partial or complete solubilization (i.e. suspension) of quercetin, phospholipids and carrier. A person skilled in the art shall be able to determine the time necessary to obtain complete or partial solubilization (i.e. suspension) of quercetin, phospholipids and carrier.

**[0037]** For the avoidance of doubt, within the present application, the term "solution" denotes a liquid composition which, upon visual inspection, is clear at the selected temperature; the term, "suspension" denotes a liquid composition which, upon visual inspection, is opaque but nonetheless homogeneous.



**[0038]** After steps e) or c1), the powder solid dispersion may be calibrated to obtain the desired particle size distribution within the aforementioned range of 100  $\mu\text{m}$  to 300  $\mu\text{m}$  and may be eventually mixed with pharmaceutically and food acceptable excipients, such as silicon dioxide, talc, magnesium stearate, to further improve its physical and technological properties.

**[0039]** The fast dissolution of the very to freely water soluble carrier, on which the quercetin and phospholipids are loaded, contributes to enhance quercetin wettability and fast dissolution. As a consequence, a high quercetin concentration in the absorption site is created, determining a high concentration gradient which is the driving force for the passive diffusion of quercetin through the absorption membranes of the gastro-intestinal tract.

**[0040]** Without being bound to theory, it is believed that the complete or at least partial co-solubilization of quercetin and phospholipids in the selected organic solvent during the process of the invention contributes to improve quercetin's solubility and oral bioavailability.

**[0041]** A calorimetric analysis by Differential Scanning Calorimetry (DSC) was performed to determine, on the basis of the reduction of the enthalpy of fusion (J/g), the degree of amorphization of quercetin in the powder solid dispersion compared to the totally crystalline unformulated quercetin, in particular compared to quercetin dihydrate. X-ray analysis was also performed. The X-ray diffraction pattern of the powder solid dispersions of the invention showed characteristic peaks at  $8.9\pm 0.2$ ,  $13.5\pm 0.2$ ,  $26.0\pm 0.2$  and  $27.8\pm 0.2$   $2\theta$  angle (CuK $\alpha$   $\lambda=1.5419\text{\AA}$ )

**[0042]** Therefore, a further object of the invention is a powder solid dispersion comprising, preferably consisting of, quercetin, phospholipids and a carrier very soluble to freely soluble in water obtainable by the process of the invention, wherein the quercetin to phospholipids weight ratio ranges from 5:1 to 1:1 and characterized by an X-ray diffraction pattern characteristic peaks at  $8.9\pm 0.2$ ,  $13.5\pm 0.2$ ,  $26.0\pm 0.2$  and  $27.8\pm 0.2$   $2\theta$  angle (CuK $\alpha$   $\lambda=1.5419\text{\AA}$ ). For the avoidance of doubt, all preferred definitions and embodiment concerning quercetin, phospholipids, the carrier, weigh ratio and particle size apply to this object of the invention.

**[0043]** The powder solid dispersion of the invention is easy to incorporate in conventional solid dosage forms, like tablets and capsules, but also in ready-to-use or extemporaneous liquid formulations, that are particularly useful and appealing in the sport nutrition sector, which represents one of the most important field of application of quercetin.

**[0044]** Another object of the invention are formulations for oral administration containing the powder solid dispersions of the invention and one or more pharmaceutically and food acceptable excipients, such as disintegrants, lubricants, binders, coating agents, colorants, absorption promoters, solubilizing agents, stabilizers, flavors, sweeteners, antiseptics, preservatives, antioxidants and the like.

**[0045]** The formulations according to the invention may be prepared according to conventional techniques as described for example in Remington's Pharmaceutical Handbook, Mack

Publishing Co., NY USA.

**[0046]** Examples of dosage forms of the formulations of the invention include coated or uncoated tablets, chewable tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, extemporary and ready-to-use liquid formulation and combinations thereof.

**[0047]** The improved solubility of quercetin contained in the powder solid dispersion of the invention was evaluated in simulated gastric and intestinal fluids.

**[0048]** The oral bioavailability of the powder solid dispersions of quercetin was evaluated in humans compared to (unformulated, in free form) quercetin. The results show a significant improvement of oral bioavailability of quercetin in a powder solid dispersion according to the invention compared to (unformulated, in free form) quercetin dihydrate.

**[0049]** A pharmacokinetic study on human subjects confirmed the improvement of oral bioavailability of about 50-times for quercetin of the powder solid dispersions of the invention in comparison with quercetin as such.

**[0050]** The obtained powder solid dispersions of the invention are characterized by a high content of quercetin, by an improvement of quercetin solubility and dissolution rate, by an improvement of the oral bioavailability of quercetin in humans (AUC and  $C_{max}$ ), if compared to the quercetin as such. All this is surprising; indeed, while the DSC analysis of the powder solid dispersions of the invention seemed to indicate an almost quantitative amorphization of quercetin, which was thought to be necessary to increase solubilization in body fluids and bioavailability, the X-ray analysis showed significant peaks of quercetin in a crystalline form different from the dihydrate form.

**[0051]** The following examples further describe the invention.

## **EXAMPLES**

### **Example 1: Preparation of a powder solid dispersion**

**[0052]** 375 g of quercetin dihydrate are added to 13 L of ethyl alcohol, then heating at 60°C and mixing for about 15 minutes until complete dissolution.

**[0053]** 375 g of sunflower lecithin and 250 g of maltodextrin are added to the quercetin solution. The obtained suspension is stirred at 50°C for about 60 minutes. The solvent is removed under reduced pressure until a soft mass is obtained. The remaining solvent is removed under vacuum at 50°C for about 12 hours, up to a ethyl alcohol residue lower than

10000 ppm.

**Example 2: Preparation of a powder solid dispersion**

**[0054]** 350 g of quercetin dihydrate to 12 L of ethyl acetate is added, then heating at 60°C and mixing for about 15 minutes until complete dissolution.

**[0055]** 300 g of sunflower lecithin and 350 g of fine fructose are added to the quercetin solution. The obtained suspension is stirred at 50°C for about 60 minutes. The solvent is removed under reduced pressure until a soft mass is obtained. The remaining solvent is removed under vacuum at 50°C for about 16 hours, up to a ethyl acetate residue lower than 5000 ppm.

**Example 3: Characterization of the powder solid dispersion by DSC (Differential Scanning Calorimetry) and by X-ray analysis**

**[0056]** The powder solid dispersion obtained in Example 1 was analyzed by DSC compared to (unformulated, in free form) quercetin dihydrate. The analysis was performed using a Mettler DSC1 System. Heat flow was recorded from 30 to 300°C with linear heating rate (10°C/min), using closed aluminum crucibles (40 µl volume) with a pinhole, under a 50 ml/min nitrogen flow. About 5-10 mg of powder were used for each measurement. The thermal profiles were acquired and elaborated by a dedicate software. The disappearance of the endothermic peak of quercetin in the solid dispersion DSC curve seemed to indicate almost quantitative amorphization. Instead, the XRDP (X-Ray Diffraction Pattern) of the powder solid dispersion obtained in Example 1 compared to that of quercetin dihydrate and of a physical mixture having the same quali-quantitative composition of the solid dispersion obtained in Example 1 (Physical Mixture) (see figure) showed that the solid dispersion of the invention still contains a significant amount of crystalline form that is, however, different from quercetin dihydrate as such or from quercetin dihydrate present in the physical mixture.

**[0057]** The XRDP of quercetin dihydrate of this example is characterized by the most intense diffraction peak at 12.5 2θ angle with relative intensity of 100% (net intensity 7096 counts). In the physical mixture the same peak at 12.5 2θ angle remains the most intense (relative intensity 100%, net intensity 2577 counts), while in the solid dispersion at 12.5 2θ angle only noise baseline is detectable.

**[0058]** On the contrary, in the XRDP of the solid dispersion of this example the most intense diffraction peak is at 13.5 2θ angle with relative intensity of 100% (net intensity 501 counts) while both in quercetin dihydrate and in the physical mixture XRDPs, at 13.5 2θ only noise baseline is detectable.

[0059] As far as crystallinity is concerned, according to Bruker software Diffrac EVA v. 3.1 and its algorithm "Crystallinity" the degree of crystallinity calculated from the XRDP for the three materials of the example are: quercetin dihydrate = 85%; physical mixture = 47%; solid dispersion = 37%.

**Example 4: Characterization of the powder solid dispersion - solubility studies in simulated gastro-intestinal fluids**

[0060] Quercetin dihydrate, quercetin powder solid dispersion obtained in Example 1 and a mechanical (physical) mixture of the component of the said solid dispersion were subjected to comparative solubility experiments, in the presence of high excess of analyte, using the following simulated gastro-intestinal fluids:

- fasted state simulated gastric fluid;
- fasted state simulated intestinal fluid;
- fed state simulated intestinal fluid.

[0061] Equivalent amounts of quercetin were used during the experiments. Quercetin dihydrate, quercetin powder solid dispersion of Example 1 and the mechanical (physical) mixture were kept under magnetic stirring for 2 hours. The supernatant was filtered and the quercetin concentration was calculated by HPLC analysis. The results of these solubility studies are reported in the following table 1:

**Table 1**

<b><i>Fasted state simulated gastric fluid (pH 1.6)</i></b>	
<b>Material</b>	<b>Quercetin (µg/mL)</b>
Quercetin powder solid dispersion (Example 1)	8.2
Mechanical mixture	0.1
Quercetin dihydrate	< LOD
<b><i>Fasted state simulated intestinal fluid (pH 6.5)</i></b>	
<b>Material</b>	<b>Quercetin (µg/mL)</b>
Quercetin powder solid dispersion (Example 1)	83.8
Mechanical mixture	19.9
Quercetin dihydrate	7.5
<b><i>Fed state simulated intestinal fluid (pH 5.0)</i></b>	
<b>Material</b>	<b>Quercetin (µg/mL)</b>
Quercetin powder solid dispersion (Example 1)	216.6
Mechanical mixture	29.1
Quercetin dihydrate	19.1

<i>Fed state simulated intestinal fluid (pH 5.0)</i>	
Material	Quercetin ( $\mu\text{g/mL}$ )

[0062] The results of the solubility studies show that, despite the presence of a significant amount of quercetin in crystalline form, the powder solid dispersion of the invention is much more soluble than quercetin dihydrate as such or as a mechanical mixture with phospholipids.

**Example 5: Pharmacokinetic study on humans**

[0063] A single dose randomized, crossover pharmacokinetic study in healthy volunteers under fasting conditions was performed using film-coated tablets containing 500 mg of (unformulated) quercetin dihydrate, 500 mg of quercetin (40%) powder solid dispersion (corresponding to 200 mg of quercetin dihydrate) and 250 mg of quercetin (40%) powder solid dispersion (corresponding to 100 mg of quercetin dihydrate). The mean pharmacokinetic parameters ( $\text{AUC}_{0-\infty}$ ;  $C_{\text{max}}$ ) are reported in the following table 2:

**Table 2**

Pharmacokinetic parameters	Quercetin dihydrate 500 mg tablets	Quercetin solid dispersion 500 mg tablets	Quercetin solid dispersion 250 mg tablets
$\text{AUC}_{0-\infty}$ ( $\text{min} \cdot \text{ng/mL}$ )	5405.0	96163.9	50747.1
$C_{\text{max}}$ ( $\text{ng/mL}$ )	10.93	223.10	126.35

[0064] The results show that, despite the presence of a significant amount of quercetin in crystalline form, the solid dispersions of the invention have a much more higher AUC and  $C_{\text{max}}$  than quercetin dihydrate as such.

**Example 6: Formulation containing quercetin powder solid dispersion (film-coated tablets)**

[0065]

Quali-quantitative composition	(mg/tablets)
Quercetin solid dispersion (Example 1)	250.0 mg
Dicalcium phosphate dihydrate	270.0 mg
Mannitol	180.0 mg
Sodium croscarmellose	40.0 mg

Quali-quantitative composition	(mg/tablets)
Silicon dioxide	15.0 mg
Talc	15.0 mg
Magnesium stearate	10.0 mg
Film-coating	20.0 mg

**Example 7: Formulation containing quercetin powder solid dispersion (soft gelatin capsules)**

[0066]

Quali-quantitative composition	(mg/capsule)
Quercetin solid dispersion (Example 2)	300.0 mg
Flaxseed oil	345.0 mg
Beeswax	10.0 mg
Fluid lecithin	5.0 mg

**Example 8: Formulation containing quercetin powder solid dispersion (granules for dispersion)**

[0067]

Quali-quantitative composition	(mg/tablets)
Quercetin solid dispersion (Example 1)	500.0 mg
Maltodextrin	2330.0 mg
Guar gum	300.0 mg
Flavours	200.0 mg
Citric acid	155.0 mg
Sucralose	15.0 mg

## REFERENCES CITED IN THE DESCRIPTION

Cited references

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**P a t e n t k r a v**

5 1. Fremgangsmåde til fremstilling af en fast pulverdyspersion omfattende quercetin, phospholipider og en bærer, der er meget opløselig til frit opløselig i vand, og som er udvalgt fra gruppen bestående af mono- og disaccharider; polyalkoholer; opløselige oligo- og polysaccharider, hvilken proces omfatter opløsning eller suspension i et vandfrit organisk opløsningsmiddel og under opvarmning af quercetin, phospholipider og bæreren og derefter fjernelse af opløsningsmidlet for at opnå den faste pulverdyspersion, hvor processen udføres under anvendelse af opløsningsmidler indeholdende mindre end 5 vægt-% vand, og det omfatter ikke nogen trin til opløsning i vand.

15 2. Fremgangsmåde ifølge krav 1, som omfatter følgende trin med:  
a) fremstilling af en opløsning af quercetin i et organisk opløsningsmiddel omfattende mindre end 5 vægt-% vand;  
b) fremstilling af en opløsning/suspension af phospholipider i det samme opløsningsmiddel som anvendt i trin a);  
c) omsætning af en opløsning af quercetin opnået i trin a) med en opløsning/suspension af phospholipider opnået i trin b);  
20 d) tilsætning af bæreren til blandingen opnået i trin c) og  
e) fjernelse af opløsningsmidlet under vakuum eller under sprøjtetørring for at danne en fast pulverdyspersion.

25 3. Fremgangsmåde ifølge krav 2, hvor trin a) til d) udføres ved en temperatur fra 40°C til 80°C.

4. Fremgangsmåde ifølge krav 1, som omfatter følgende trin med:  
a-1) fremstilling af en opløsning af quercetin i et organisk opløsningsmiddel omfattende mindre end 5 vægt-% vand [opløsning (S1)];



b-1) tilsætning af phospholipider og bæreren til opløsning (S1) for at tilvejebringe en opløsning eller suspension af quercetin, phospholipider og bærer i opløsningsmidlet [opløsning eller suspension (S3)], og c-1) fjernelse af opløsningsmidlet under vakuum eller under spøjtetørring til dannelse af en fast pulverdispersion.

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**5.** Fremgangsmåde ifølge krav 4, hvor trin a1) og b1) udføres ved en temperatur i området fra 40°C til 80°C.

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**6.** Fremgangsmåde ifølge krav 1 til 5, hvor vægtforholdet mellem quercetin og phospholipider ligger i området fra 5:1 til 1:1.

**7.** Fremgangsmåde ifølge krav 6, hvor vægtforholdet mellem quercetin og phospholipider ligger i området fra 2:1 til 1:1.

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**8.** Fremgangsmåde ifølge krav 1 til 7, hvor quercetin er quercetin-dihydrat.

**9.** Fremgangsmåde ifølge krav 1 til 8, hvor phospholipiderne er udvalgt fra gruppen bestående af lecithiner fra soya, solsikke eller æg, phosphatidylcholin, phosphatidylserin, phosphatidylethanolamin eller blandinger deraf, hvor acylgrupperne, som er de samme eller forskellige, hovedsageligt er afledt fra palmitin-, stearin-, olie-, linol-, linolsyrer.

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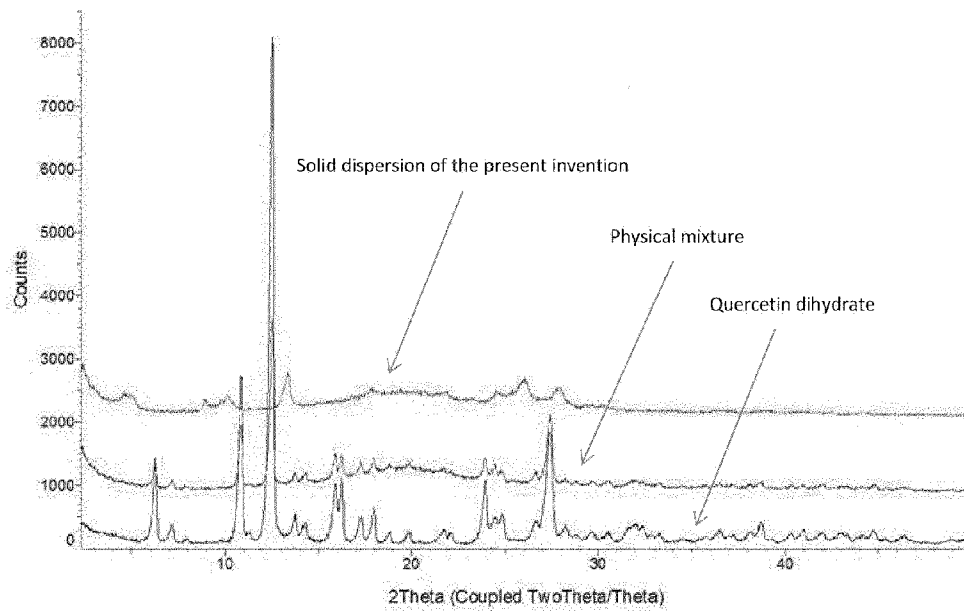
**10.** Fremgangsmåde ifølge krav 1 til 9, hvor mono- og disacchariderne er udvalgt fra gruppen bestående af saccharose, fructose, maltodextriner.

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**11.** Fremgangsmåde ifølge krav 1 til 10, hvor polyalkoholerne er udvalgt fra gruppen bestående af mannitol, sorbitol, xylitol.

12. Fremgangsmåde ifølge krav 1 til 11, hvor de opløselige oligo- og polysaccharider er dextran eller pullulan.
- 5 13. Fremgangsmåde ifølge krav 1 til 12, hvor vægtforholdet mellem quercetin og bærer ligger i området fra 1:5 til 5:1.
14. Fremgangsmåde ifølge krav 13, hvor vægtforholdet mellem quercetin og bærer ligger i området fra 1:2 til 3:1.
- 10 15. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 14, hvor det organiske opløsningsmiddel er udvalgt fra gruppen bestående af ethylalkohol, isopropylalkohol, n-propylalkohol, n-butanol, ethylacetat, acetone.
- 15 16. Pulverfast dispersion omfattende quercetin, phospholipider og en bærer, der er meget opløselig til frit opløselig i vand, opnåelig ved en fremgangsmåde ifølge et hvilket som helst af kravene 1 til 15.
17. Pulverfast dispersion ifølge krav 16, med en gennemsnitlig partikelstørrelsesfordeling i området fra 100  $\mu\text{m}$  til 300  $\mu\text{m}$ .
- 20 18. Pulverfast dispersion ifølge krav 16 eller 17, **kendetegnet ved** et røntgen-diffraktionsmønster med peaks ved  $8,9\pm 0,2$ ,  $13,5\pm 0,2$ ,  $26,0\pm 0,2$  og  $27,8\pm 0,2$   $2\theta$ -vinkel ( $\text{CuK}\alpha$   $\lambda=1,5419\text{\AA}$ ).
- 25 19. Formulering til oral administration, indeholdende en fast pulverdispersion ifølge krav 16-18 og en eller flere farmaceutisk og fødevaremæssigt acceptable excipienser.

# DRAWINGS



Figure