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.

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.

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 ultra-sonic treatment and lyophilization to obtain a powder.

CN 102580111B (UNIV SICHUAN), published on April 9, 2014, discloses a

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 dissolution or 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.

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.

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 µm to 300 µm 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.

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.

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.

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±0.2, 13.5±0.2, 26.0±0.2 and 27.8±0.2

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

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.

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

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

Quercetin powder solid dispersion (Example 1)	216.6
Mechanical mixture	29.1
Quercetin dihydrate	19.1

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

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 ($AUC_{0-\infty}$; C_{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**
$AUC_{0-\infty}$ *(min*ng/mL)*	5405.0	96163.9	50747.1
C_{max} *(ng/mL)*	10.93	223.10	126.35

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_{max} than quercetin dihydrate as such.

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

Quali-quantitative composition	(mg/tablets)
Quercetin solid dispersion (Example 1)	250.0 mg
Dicalcium phosphate dihydrate	270.0 mg