Increased water solubility of forskolin is achieved by complexing forskolin with cyclodextrins. WO2005025500A2 describes a method for complexing forskolin with cyclodextrin in an aqueous medium.

WO2017103840A1 describes water-soluble forskolin compositions by complexation with water-soluble polymers such as PVP, among others. After mixing forskolin with the polymer, a starch solution is added and the mixture is heated, then cooled and spray-dried.

WO2018127600A1 discloses a method for preparing forskolin-cyclodextrin complexes, which is based on a sintering process and allows an increased content of forskolin in the complex, as well as increased water solubility.

Another approach to increase the water solubility of forskolin is chemical derivatization. A forskolin derivative with higher water solubility compared to forskolin is 7-deacetyl forskolin, which shows a similar effect on adenylyl cyclase as forskolin (Laurenza A. et al, Molecular Pharmacology 1987, 32(1), 133-139, Pinto C. et al, Biochemical Pharmacology 2009, 78(1), 62-69). However, deacetylation of forskolin at position 7 can only increase water solubility to a limited extent (up to 1 mg/mL).

Therefore, there is a need for an improved water-soluble form of a forskolin derivative, which is characterized by both high water solubility and thus improved bioavailability, and high forskolin derivative content.

It is therefore an object of the present invention to provide a form of 7-deacetyl-forskolin having increased solubility in water and, at the same time, a high content of 7-deacetyl-forskolin.

SUMMARY ~~OF THE INVENTION~~

The object is solved by a complex of 7-deacetyl-forskolin (7-DAFSK) and polyvinylpyrrolidone (PVP), as described in the claims, aspects, examples and embodiments of the present ~~invention~~disclosure.

The present disclosure ~~invention~~ discloses a complex of 7-deacetyl-forskolin (7-DAFSK) and polyvinylpyrrolidone (PVP).

In an aspect of the present disclosure, there is provided a complex of 7-deacetyl-forskolin (7-DAFSK) and polyvinylpyrrolidone (PVP).

In another aspect of the present disclosure, there is provided a process for the preparation of a complex disclosed herein, characterized in that a mixture of 7-DAFSK

and PVP is heated to a temperature which is above the glass transition temperature of the PVP used.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a complex disclosed herein.

In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use as a medicament.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use in the treatment of cardiovascular disease, bronchial asthma, obesity, glaucoma, pulmonary disease, joint inflammation, or osteoarthritis/arthritis.

In one ~~embodiment~~example, the complex according to the ~~invention~~ present disclosure is characterized in that the average mass fraction of 7-DAFSK in the total complex is in the range of 1 to 50 wt%, preferably 5, 10, 15, 20 or 25 wt%, more preferably 30 wt%, 35 wt%, 40 wt%, 45 wt%, or higher.

In one ~~embodiment~~example, the average molar ratio of 7-DAFSK to PVP in the complex is 0.1 or higher, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60 or higher, more preferably 3 or higher.

In one ~~embodiment~~example, the complex according to the present disclosure ~~invention~~ is characterized in that PVP has an average molar mass of from 1 to 40 kD. Preferably, the PVP has an average molar mass of 1 to 25 kD, more preferably about 2 to 3 kD, most preferably about 2.5 kD.

In a further ~~embodiment~~example, the complex according to the present disclosure ~~invention~~ is characterized in that 7-DAFSK is derived from synthetic forskolin.

In one ~~embodiment~~example, the 7-DAFSK is present in a purity of at least 98.5%.

It was surprisingly found that a particularly high mass fraction of 7-DAFSK in the 7-DAFSK-PVP complex can be achieved by heating a mixture of 7-DAFSK and PVP to a temperature that is above the glass transition temperature of the PVP used. In particular, the mixture is heated to a temperature that is at least 20°C, preferably at least 25°C, 30°C, 40°C, 50°C, 60°C, 70°C, 80°C, 90°C, 100°C above the glass transition temperature of the PVP. In particular, the temperature is brought to a range of about 25 to 50°C above the glass transition temperature of the PVP.

Therefore, the present ~~invention~~ disclosure also provides a method for preparing the 7-DAFSK-PVP complex according to the present disclosure~~invention~~, which is characterized in that a mixture of 7-DAFSK and PVP is heated to a temperature higher than the glass transition temperature of the PVP used.

In one ~~embodiment~~example, the process according to the present disclosure ~~invention~~ is characterized in that a solvent, preferably water, ethanol, methanol, acetone, ethyl methyl ketone, dichloromethane and/or ethyl acetate, even more preferably water, ethanol, methanol, propanol and/or dichloromethane, is added to the mixture of 7-DAFSK and PVP. Particularly preferably, water and/or ethanol, or a mixture thereof, is added to the mixture of 7-DAFSK and PVP.

In a particular ~~embodiment~~example, the mixture according to the present disclosure ~~invention~~ is kept at a temperature higher than the glass transition temperature of the PVP used for at least 5 minutes.

In one ~~embodiment~~example, the method according to the present disclosure ~~invention~~ includes the following steps:

a) Preparing a mixture of 7-DAFSK and PVP and adding a solvent, preferably an alcohol, preferably ethanol, to the mixture,

b) Addition of water,

c) Heating the mixture, above the glass transition temperature of the PVP for at least 5 minutes,

d) Cooling of the mixture and dissolving in water,

e) Removal of the undissolved components, optionally by filtering.

In one particular application form, the mixture is heated at least 20, 25, 30, 35, 40, 45, 50, 55, 60°C, 70°C, 80°C, 90°C, 100°C above the glass transition temperature of the PVP.

The application of the method according to the present disclosure ~~invention~~ allows the efficient and straightforward preparation of 7-DAFSK-PVP complexes, which significantly increase the water solubility of 7-DAFSK and may also contain a high mass fraction of 7-DAFSK, enabling beneficial applications of 7-DAFSK in diagnosis and/or therapy.

With the complexes of 7-DAFSK with PVP according to the present disclosure~~invention~~, the water solubility of 7-DAFSK can be increased. By using a high mass fraction of 7-DAFSK in the complex according to the present disclosure~~invention~~, the water solubility of 7-DAFSK can be increased without thus requiring an unfavorably large amount of PVP. Formulations with forskolin derivatives can thus also be assembled in a more material-saving manner than before. By avoiding large amounts of PVP and associated side effects, the present ~~invention~~ disclosure facilitates and improves the use of 7-DAFSK in diagnosis and/or therapy.

Therefore, the present ~~invention~~ disclosure also provides a pharmaceutical composition containing a 7-DAFSK-PVP complex according to the present disclosure~~invention~~.

In one ~~embodiment~~example, said pharmaceutical composition is characterized in that the composition comprises 7-DAFSK at a concentration of at least 25 mg/L, 50 mg/L, 75 mg/L, 100 mg/L, 200 mg/L, 300 mg/L, 400 mg/L, 500 mg/L, 600 mg/L, 800 mg/L, 1000 mg/L, 2000 mg/L, 3000 mg/L, or 4000 mg/L, preferably 4000 mg/L.

One ~~aspect~~example of the present ~~invention~~ disclosure relates to a pharmaceutical composition for oral, intravenous or inhalation administration.

In a particular ~~embodiment~~example, the pharmaceutical composition according to the present disclosure ~~invention~~ is used in a therapeutic method.

In another particular ~~embodiment~~example, the pharmaceutical composition according to the present disclosure ~~invention~~ is used for the treatment of cardiovascular diseases, bronchial asthma, obesity, glaucoma, pulmonary diseases, joint inflammation, or osteoarthritis/arthritis.

One ~~aspect~~example of the present ~~invention~~ disclosure relates to a pharmaceutical composition according to the present disclosure ~~invention~~ for use as a medicament.