narrow edge. Cyclodextrins are relatively large with a number of hydrogen donors and acceptors and do not permeate lipophilic membranes.

In pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability (Loftsson T., et al., 2005, Expert.Opin.Drug Deliv., 335-351).

The most common natural cyclodextrins consist of six (α-cyclodextrin), seven (ß-cyclodextrin) and eight (ɣ-cyclodextrin) glucopyranose units. Further known natural cyclodextrins are δ cyclodextrins. Random substitution of the hydroxyl groups can result in increased solubility. The main reason for solubility enhancement is that random substitution transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives. Cyclodextrin derivatives include hydroxypropyl derivatives of ß- and ɣ-cyclodextrin, the randomly methylated ß-cyclodextrin, sulfoburylether ß-cyclodextrin and branched cyclodextrins such as glucosyl-ß-cyclodextrin (Loftsson T. et al., 2005). On reacting cyclodextrin in alkaline solution with propylene oxide a 2-hydroxypropyl group will be connected to one or more hydroxyls of the cyclodextrin (HP-cyclodextrin). A higher substitution of the hydroxyls with 2-hydroxypropyl also results in the formation of oligomeric hydroxypropylene oxide side chain formation.

Various methods for preparing drug-cyclodextrin complexes are already known, such as for example, co-precipitation, slurrying, kneading or grinding. In US20050051483, a forskolin ß-cyclodextrin complex is produced by adding forskolin to water containing dissolved hydroxypropyl-ß-cyclodextrin, agitating the mixture and filtering it.

Saettone M. F. et al. describe topical solutions containing forskolin. It is specifically stated that ß- and ɣ-cyclodextrins were not effective solubilizers of forskolin (Journal of Ocular Pharmacol, vol. 5, no. 2, 1989, pp. 111-118)

However, there is still a need for providing improved methods for complexing forskolin with cyclodextrin leading to cyclodextrin-complexes with high content of forskolin.

The object of the present invention is to provide a method for improved complexing of cyclodextrin and forskolin and to provide a forskolin complex with improved solubility but preserved structure.

SUMMARY

In one aspect, the present disclosure refers to a method for preparing a forskolin cyclodextrin inclusion complex comprising the steps:

a) mixing forskolin and cyclodextrin in a weight ratio of 1:0.5 to 1:4,

b) adding water and solvent to form a mixture,

c) heating said mixture at a temperature ranging from 180°C to 230°C,

specifically ranging from 200 to 230°C, ranging from 210 to 220°C, specifically at about 220°C,

d) adding water to said mixture followed by mixing and allowing the mixture to precipitate,

e) isolating the precipitate from the mixture and optionally drying the precipitate.

In another aspect, the present disclosure refers to an inclusion complex comprising ɣ-cyclodextrin and forskolin in a weight ratio of 1:0.2 to 1:4 (w/w).

In yet another aspect, the present disclosure refers to a pharmaceutical composition containing an inclusion complex as disclosed herein.

The object is solved by the examples of the present disclosure.

According to the disclosure there is provided an inclusion complex comprising forskolin and ɣ-cyclodextrin in a weight ratio of 1:0.2 to 1:4 (w/w), wherein forskolin and ɣ-cyclodextrin are comprised as an aqueous soluble complex.

According to a specific example, the ɣ-cyclodextrin is hydroxypropyl-ɣ-cyclodextrin.

According to an example of the disclosure, the weight ratio of forskolin and hydroxypropyl-ɣ-cyclodextrin is in the range of about 1:0.5 to 1:3.3 (w/w).

In an alternative example, about 2.5 – 4.5 mg, specifically about 3 to 4 mg forskolin are present in 100 mg forskolin-cyclodextrin complex. Specifically about 2.5%, specifically about 3%, specifically about 3.5%, specifically about 3.7%, specifically about 4%, specifically about 4.5% (w/w), more specifically more than 5% (w/w) forskolin are present in the inclusion complex of the disclosure.

It was surprisingly shown that complexing of forskolin with cyclodextrin highly improves the solubility in water. Forskolin cyclodextrin complex has approximately about 100 times, specifically about 120 times the solubility of native forskolin. It was also surprisingly shown that the native structure of forskolin is preserved when complexed with cyclodextrin and that the activation potential of forskolin for adenylyl

cyclase is also preserved thus complexation with cyclodextrins does not reduce the activation.

In another example, the disclosure provides an administration formulation comprising an inclusion complex of the present disclosure together with suitable pharmaceutical auxiliaries.

In a further example, a pharmaceutical composition comprising the inventive forskolin cyclodextrin inclusion complex, optionally together with further excipients, is provided.

In examples, the disclosure additionally provides a method of treating or preventing a condition treatable or preventable with forskolin, comprising administering to a subject in need of such treatment or prevention a pharmaceutically acceptable effective amount of a stable inclusion complex comprising forskolin and a cyclodextrin, specifically hydroxypropyl-ɣ-cyclodextrin.

The present disclosure provides a method for preparing a forskolin cyclodextrin inclusion complex comprising the steps:

a) mixing forskolin and cyclodextrin in a weight ratio of 1:0.5 to 1:4,

b) adding water and solvent to form a pasty mixture,

c) heating said mixture up to a temperature ranging from 200 °C to 230 °C, specifically to about 220 °C,

d) adding water to said mixture followed by mixing and allowing the mixture to precipitate,

e) isolating the precipitate from the mixture and optionally drying the precipitate.

In a specific example, the cyclodextrin used in the method is selected from the group consisting of α-cyclodextrin, hydroxypropyl-α-cyclodextrin (HP- α -CD), ß-cyclodextrin, hydroxypropyl-ß-cyclodextrin (HP-ß-CD), ɣ-cyclodextrin, hydroxypropyl-ɣ-cyclodextrin (HP-ɣ-CD), delta (δ)-cyclodextrin, hydroxypropyl-δ-cyclodextrin (HP-δ-CD) and randomly methylated-ß-cyclodextrin (RAMEB-CD).

HP-ß-CD, RAMEB-CD, and HP-ɣ-CD provide significantly increased occupancy rates and are specifically used in the method described herein.

Specifically, the heating temperature used in the method is about 220 °C.

According to an example of the disclosure, the method is used for producing a powdered inclusion complex of forskolin and HP-ɣ-cyclodextrin.

In a specific example, the solvent used in the present disclosure is an alcohol, specifically it is 2-propanol.

According to an example, the precipitate is heat dried, specifically the drying step is carried out for about 1 to 30 minutes.

According to a further example, the precipitate is filtered, specifically by membrane filtration and optionally the precipitate is dried.

FIGURES

Figure 1: Structure of forskolin and binding sites to the C1 and C2 domain of adenylyl cyclase. The two OH-groups (marked with cycles) are essential for binding and must not be derivatized for these applications.

Figure 2: Calibration of forskolin: y = 9431x – 84 (approximate).

Figure 3: cAMP assay for forskolin dissolved in DMSO and forskolin-CD complex, according to Hussain et al., 2013.

Figure 4: cAMP assay for forskolin dissolved in DMSO and forskolin-CD complex. Comparison of ɣ-CD and ß-CD.

DETAILED DESCRIPTION

Specific terms as used throughout the specification have the following meaning.