Therefore, a need exists to provide for Lysyl-Prolyl-Threonine having an increased storage stability. In particular, a need exists to provide for Lysyl-Prolyl-Threonine in a form suitable to be administered as a medicament that remains safe and efficacious over an extended time period.

## Summary

In one aspect, the present invention refers to a stable lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, wherein the Lysyl-Prolyl-Threonine is present in an amount of 1-25 mg free base, based on 100 mg total weight of the lyophilized formulation; further comprising one or more bulking agents, wherein the bulking agent is trehalose; and one or more buffering agents, and wherein the buffering agent is citric acid; further comprising one or more pH adjusting agents. In one example, there is described a lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, further comprising one or more bulking agents and one or more buffering agents, wherein the bulking agent is selected from the group consisting of mannitol, sucrose and trehalose and wherein the buffering agent is selected from the group consisting of citric acid, sodium dihydrogenphosphate, acetic acid, succinic acid, glutamate, Tris and histidine; further comprising one or more pH adjusting agents. In one example, there is disclosed a lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, further comprising one or more bulking agents and one or more buffering agents, wherein the bulking agent is selected from the group consisting of mannitol, sucrose and trehalose and wherein the buffering agent is selected from the group consisting of citric acid, sodium dihydrogenphosphate, acetic acid, succinic acid, glutamate, Tris and histidine. In another aspect, the present invention refers to a process for preparing the lyophilized formulation as defined herein comprising the steps of: (a) mixing in any order the following components: (i) Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, (ii) an aqueous carrier, (iii) one or more bulking agents, wherein the bulking agent is trehalose, (iv) one or more buffering agents wherein the buffering agent is citric acid, and (v) if present, one or more pH adjusting agents; to provide for an aqueous preparation having a pH in the range of 3.0-5.0, wherein the free base of Lysyl-Prolyl-Threonine has a concentration of 0.1-175 mg/g, based on the aqueous preparation; (b) lyophilizing the aqueous preparation to provide for the lyophilized formulation in solid form. In one example, there is described a process for preparing the lyophilized formulation as defined herein comprising the steps of: (a) mixing in any order the following components: (i) Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, (ii) an aqueous carrier, (iii) one or more bulking agents, selected from mannitol, sucrose and trehalose, (iv) one or more buffering agents selected from the group consisting of citric acid, sodium dihydrogenphosphate, acetic acid, succinic acid, glutamate, Tris and histidine, and (v) if present, one or more pH adjusting agents; to provide for an aqueous preparation having a pH in the range of 3.0-5.0, wherein the free base of Lysyl-Prolyl-Threonine has a concentration of 0.1-175 mg/g, based on the aqueous preparation; (b) lyophilizing the aqueous preparation to provide for the lyophilized formulation in solid form. In yet another aspect, the present invention refers to non-therapeutic use of the lyophilized formulation disclosed herein as a cosmetic. In a further aspect, the present invention refers to non-therapeutic use of the lyophilized formulation disclosed herein for the cosmetic treatment of the skin and/or mucosa of a mammal. In one example, disclosed herein is a lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof. In another example, there is disclosed a process for preparing the lyophilized formulation as defined herein comprising the steps of: (a) mixing in any order the following components: (i) Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, (ii) an aqueous carrier, (iii) optionally one or more bulking agents, (iv) optionally one or more buffering agents, and (v) optionally one or more pH adjusting agents; to provide for an aqueous preparation having a pH in the range of 3.0-5.0, wherein the free base of Lysyl-Prolyl-Threonine has a concentration of 0.1-175 mg/g, based on the

aqueous preparation; (b) lyophilizing the aqueous preparation to provide for the lyophilized formulation in solid form. In yet another example, disclosed herein is a lyophilized formulation obtainable by the process as disclosed herein. In a further example, the present invention refers to a pharmaceutical composition comprising the lyophilized formulation as defined herein and one or more pharmaceutical excipients. In one aspect, the present invention refers to a cosmetic composition comprising the lyophilized formulation as defined herein and one or more cosmetic excipients. In yet another example, non-therapeutic use of the lyophilized formulation according to the present disclosure as a cosmetic is disclosed, preferably for the cosmetic treatment of the skin and/or mucosa of a mammal.

Detailed description

The object underlying the invention therefore is the provision of storage stable Lysyl-Prolyl-Threonine and medicaments containing it that remain safe and efficacious over an extended time period.

This object has surprisingly been solved in accordance with the present invention as indicated in the claims attached.

In particular, it has surprisingly been found out by the inventors that Lysyl-Prolyl-Threonine in lyophilized formulations (i.e. as a lyophilisate) shows an increased storage stability ascompared to Lysyl-Prolyl-Threonine alone (i.e. non-lyophilized or lyophilized form). This finding is surprising since the lyophilisate, mainly containing the active ingredient Lysyl-Prolyl-Threonine in non-crystalline form due to lyophilsation, is more stable than Lysyl-Prolyl-Threonine alone that at least partly exists in crystalline form. This increased storage stability is even more surprising as Lysyl-Prolyl-Threonine in lyophilized formulations has a significantly higher surface area so that the skilled person actually would have expected a reduced storage stability. In other words, it was fully unexpected in the prior art that non-crystalline forms of Lysyl-Prolyl-Threonine also having a higher surface area are less susceptible to degradation into lysine-proline diketopiperazines and, consequently, are more storage stable than crystalline forms of Lysyl-Prolyl-Threonine.

Therefore, the subject-matter of the present invention is a lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof.

Further, according to the present invention the lyophilized formulation is for use as a medicament, preferably for use in the therapeutic and/or prophylactic treatment, diagnosis and/or therapy of pain-related diseases, pruritus-related diseases, inflammatory diseases, and/or other diseases.

## Claims

1. A stable lyophilized formulation comprising Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, wherein the Lysyl-Prolyl-Threonine is present in an amount of 1-25 mg free base, based on 100 mg total weight of the lyophilized formulation; further comprising one or more bulking agents, wherein the bulking agent is trehalose; and one or more buffering agents, and wherein the buffering agent is citric acid; further comprising one or more pH adjusting agents.

2. The lyophilized formulation according to claim 1, wherein the bulking agent is present in an amount of 40-90 mg, based on 100 mg total weight of the lyophilized formulation.

3. The lyophilized formulation according to claim 1, wherein the buffering agent is present in an amount of 5-15 mg, based on 100 mg total weight of the lyophilized formulation.

4. The lyophilized formulation according to claim 1 obtainable by lyophilizing an aqueous preparation having a pH of 3.0-5.0, wherein the aqueous preparation comprises:

(i) Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof, wherein the free base has a concentration of 0.1-175 mg/g, based on the aqueous preparation,

(ii) aqueous carrier,

(iii) one or more bulking agents, wherein the bulking agent is trehalose, and

(iv) one or more buffering agents, wherein the buffering agent is citric acid.

5. The lyophilized formulation according to any one of claims 1 to 4, wherein the Lysyl-Prolyl-Threonine is (L)Lys-(D)Pro-(L)Thr, (L)Lys-(L)Pro-(D)Thr, (L)Lys-(D)Pro-(D)Thr, (L)Lys-(L)Pro-(L)Thr, (D)Lys-(D)Pro-(L)Thr, (D)Lys-(D)Pro-(D)Thr, (D)Lys-(L)Pro-(L)Thr, (D)Lys-(L)Pro-(D)Thr, or mixtures thereof.

6. The lyophilized formulation according to any one of claims 1 to 5, wherein the pH adjusting agent is an acid or a base that maintains a pH value at 3.0-5.0 selected from sodium hydroxide and hydrochloric acid.

7. The lyophilized formulation according to any one of claims 1 to 6 for use as a medicament.

8. The lyophilized formulation according to any one of claims 1 to 7 for use in the therapeutic and/or prophylactic treatment of diseases chosen from the group comprising pain-related diseases, pruritus-related diseases, inflammatory diseases, and/or multiple sclerosis.

9. The lyophilized formulation for use according to any one of claims 7 to 8, wherein the lyophilized formulation is to be administered to a patient in solid form, or wherein the solid lyophilized formulation is reconstituted with an aqueous carrier to form an aqueous preparation, the aqueous preparation subsequently to be administered to a patient.

10. A process for preparing the lyophilized formulation as defined in any one of claims 1 to 9 comprising the steps of:

(a) mixing in any order the following components:

(i) Lysyl-Prolyl-Threonine or a pharmaceutically acceptable salt thereof,

(ii) an aqueous carrier,

(iii) one or more bulking agents, wherein the bulking agent is trehalose

(iv) one or more buffering agents wherein the buffering agent is citric acid, and

(v) if present, one or more pH adjusting agents;

to provide for an aqueous preparation having a pH in the range of 3.0-5.0, wherein the free base of Lysyl-Prolyl-Threonine has a concentration of 0.1-175 mg/g, based on the aqueous preparation;

(b) lyophilizing the aqueous preparation to provide for the lyophilized formulation in solid form.

11. A pharmaceutical composition comprising the lyophilized formulation as defined in any one of claims 1 to 9 and one or more pharmaceutical excipients.

12. A cosmetic composition comprising the lyophilized formulation as defined in any one of claims 1 to 6 and one or more cosmetic excipients.

13. Non-therapeutic use of the lyophilized formulation according to any one of claims 1 to 6 as a cosmetic.

14. Non-therapeutic use of the lyophilized formulation according to claim 13 for the cosmetic treatment of the skin and/or mucosa of a mammal.