as the sole solvent, high amounts of TPGS (50% to 99.9%) are required.

U.S. Patent 5,583,105 describes pre-concentrated emulsion containing the active ingredient cyclosporine in a lipophilic and/or amphiphilic solvent. In this composition TPGS is mentioned as an emulsifier, adjuvant and antioxidant for fat oils. The antioxidant effect on a pharmaceutical active ingredient, and especially on a NK2 receptor antagonist, is not claimed.

WO2006036614 describes materials like surfactants suitable for solid formulations. The TPGS row material of waxy consistency is converted into properly shaped solid that can be incorporated for example into tablets. The use of the solid form for the preparation of solutions and/or emulsions is not described.

EP1216025 describes the use of a wide range of TPGS as a surfactant (from 0.1% to 90%) in solid formulations comprising a dispersant soluble in water and a soluble compound in lipid medium as a lipase inhibitor. The solidified mixture is loaded into HPMC capsules that reveal an increase in the efficiency and power.

Formulations for topical use containing TPGS and layers of alpha-tocopherol to solubilize or emulsify water insoluble drugs are mentioned in WO9531217.

TPGS is described as a stabilizer applied for the formation and stabilization of double-layer liposomes in acid environment (US5, 364.631).

In WO9808490 the preparation of solid co-precipitated for oral delivery of lipophilic substances with poor biodisponibility is described. Delivery tests are conducted on dry powders.

SUMMARY OF DISCLOSURE

In the first aspect, there is provided a liquid aqueous oral pharmaceutical composition comprising nepadutant as active ingredient and an additive and optionally a chelating agent and optionally other pharmaceutical acceptable excipients, characterized in that the selected additive is TPGS.

In another aspect, there is provided a liquid aqueous oral pharmaceutical composition comprising nepadutant as active ingredient and an additive and a chelating agent, characterized in that the selected additive is TPGS.

In ~~the first~~another aspect, there is provided a process for the preparation of the compositions as disclosed herein, comprising a step wherein nepadutant is mixed with TPGS, and optionally with a chelating agent.

In another aspect, there is provided the use of the liquid aqueous oral pharmaceutical composition as disclosed herein for the manufacture of a medicament for paediatric treatment.

DESCRIPTION OF THE INVENTION

The present invention relates to stable oral, liquid, pharmaceutical compositions containing Nepadutant and TPGS, even for paediatric use for the treatment of newborns and infants (nurslings) in the period from birth to one year, and preferably, from birth to six months of age.

The TPGS is a substance with solubilizer and antioxidant activity therefore acts as a stabilizer of substances which are highly unstable to oxidation. In addition, the TPSG is essentially tasteless and therefore suitable and acceptable for use in neonates and nurslings. Surprisingly the use of TPGS results in a solubilizing and antioxidant action allowing to obtain limpid, stable solutions of Nepadutant and acceptable from an organoleptic point of view. Additional excipients commonly used with TPGS, such as lipophilic or hydrophilic non-aqueous solvents or co-solvents, lipophilic antioxidant

CLAIMS

1.A liquid aqueous oral pharmaceutical composition comprising nepadutant as active ingredient and an additive and optionally a chelating agent and optionally other pharmaceutical acceptable excipients, characterized in that the selected additive is TPGS.

2. The pharmaceutical composition according to claim 1, wherein nepadutant is present in an amount from 0.01% to 1% weight/volume of the total composition.

3. The aqueous pharmaceutical composition according to claim 2, wherein nepadutant is present in an amount from 0.025% to 0.5% weight/volume on the total composition.

4. The aqueous pharmaceutical composition according to any one of claims 1-3, wherein TPGS is present in an amount of at least 0.1% weight/volume of the total composition.

5. The aqueous pharmaceutical composition according to claim 4, wherein TPGS is present in an amount from 0.1% to 20% weight/volume on the total composition.

6. The aqueous pharmaceutical composition according to claim 5, wherein TPGS is present in an amount from 0.5% to 5% weight/volume of the total composition.

7. The aqueous pharmaceutical composition according to any one of claims from 1 to 6, wherein the ratio between nepadutant and TPGS is from 1:1 to 1:50.

8. The aqueous pharmaceutical composition according to any one of claims from 1 to 7, wherein the ratio between nepadutant and TPGS is from 1:2 to 1:40.

9. The aqueous pharmaceutical composition according to any one of claims from 1 to 8, wherein the ratio between nepadutant and TPGS is from 1:4 to 1:30.

10. The aqueous pharmaceutical composition according to any one of claims from 1 to 9, further comprising a chelating agent selected from the group: EDTA, edetate disodium, and edetate calcium disodium.

11. The aqueous pharmaceutical composition according to claim 10, wherein the chelating agent is present in an amount comprised from 0.001% to 0.1% w/v of the total composition.

12. The aqueous pharmaceutical composition according to claim 11, wherein the chelating agent is present in an amount comprised from 0.005 % to 0.05 % w/v of the total composition.

13. The aqueous pharmaceutical composition according to claim 11, wherein the cheating agent is present in an amount comprised from 0.005% to 0.02% w/v of the total composition.

14. The aqueous pharmaceutical composition according to any one of claims from 1 to 13, further comprising pharmaceutical acceptable excipients such as sweeteners, preservatives, or solubilizers.

15. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 14, comprising:

a) from 0.01% to 1% w/v of nepadutant
b) from 0.1% to 20% w/v of TPGS
c) optionally from 0.001% to 0.1% w/v of chelating agent
d) one or more pharmaceutically acceptable excipients

16. The aqueous oral pharmaceutical composition according to claim 14, selected from the group:

a) nepadutant 0.40 mg/ml, TPGS 10.00 mg/ml, dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethyl cellulose 20.00 mg/ml, purified water qs 1.0 ml;

b) nepadutant 0.40 mg/ml, TPGS 10.00 mg/ml, edetate disodium 0.100 mg/ml, dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethylcellulose 20:00 mg / ml, purified water qs 1.0 ml;

c) nepadutant 2.00 mg/ml, TPGS 10.00 mg/ml, edetate disodium

0.100 mg/ml,

dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethylcellulose 20.00 mg/ml, purified water qs 1.0 ml.

17. The aqueous oral pharmaceutical composition according to any one of claims 1 to 16 for use in the paediatric treatment of newborns and nurslings.

18. The aqueous oral pharmaceutical composition according to claim 17 for use in the paediatric treatment of gastrointestinal diseases.

19. A process for the preparation of the compositions according to any one of claims from 1 to 18, comprising a step wherein nepadutant is mixed with TPGS, and optionally with a chelating agent.

CLAIMS

1. A liquid aqueous oral pharmaceutical composition comprising nepadutant as active ingredient and an additive and a chelating agent, characterized in that the selected additive is TPGS.

2. The liquid aqueous oral pharmaceutical composition according to claim 1, wherein nepadutant is present in an amount from 0.01% to 1% weight/volume of the total composition.

3. The liquid aqueous oral pharmaceutical composition according to claim 2, wherein nepadutant is present in an amount from 0.025% to 0.5% weight/volume on the total composition.

4. The liquid aqueous oral pharmaceutical composition according to any one of claims 1-3, wherein TPGS is present in an amount of at least 0.1% weight/volume of the total composition.

5. The liquid aqueous oral pharmaceutical composition according to claim 4, wherein TPGS is present in an amount from 0.1% to 20% weight/volume on the total composition.

6. The liquid aqueous oral pharmaceutical composition according to claim 5, wherein TPGS is present in an amount from 0.5% to 5% weight/volume of the total composition.

7. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 6, wherein the ratio between nepadutant and TPGS is from 1:1 to 1:50.

8. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 7, wherein the ratio between nepadutant and TPGS is from 1:2 to 1:40.

9. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 8, wherein the ratio between nepadutant and TPGS is from 1:4 to 1:30.

10. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 9, wherein the chelating agent is selected from the group: EDTA, edetate disodium, and edetate calcium disodium.

11. The liquid aqueous oral pharmaceutical composition according to claim 10, wherein the chelating agent is present in an amount comprised from 0.001% to 0.1% w/v of the total composition.

12. The liquid aqueous oral pharmaceutical composition according to claim 11, wherein the chelating agent is present in an amount comprised from 0.005 % to 0.05 % w/v of the total composition.

13. The liquid aqueous oral pharmaceutical composition according to claim 11, wherein the cheating agent is present in an amount comprised from 0.005% to 0.02% w/v of the total composition.

14. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 13, further comprising pharmaceutical acceptable excipients selected from sweeteners, preservatives, or solubilizers.

15. The liquid aqueous oral pharmaceutical composition according to any one of claims from 1 to 14, comprising:

a) from 0.01% to 1% w/v of nepadutant

b) from 0.1% to 20% w/v of TPGS

c) from 0.001% to 0.1% w/v of chelating agent

d) one or more pharmaceutically acceptable excipients selected from sweeteners, preservatives, or solubilizers.

16. The liquid aqueous oral pharmaceutical composition according to claim 14, selected from the group:

a) nepadutant 0.40 mg/ml, TPGS 10.00 mg/ml, dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethyl cellulose 20.00 mg/ml, purified water qs 1.0 ml;

b) nepadutant 0.40 mg/ml, TPGS 10.00 mg/ml, edetate disodium 0.100 mg/ml, dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethylcellulose 20:00 mg / ml, purified water qs 1.0 ml;

c) nepadutant 2.00 mg/ml, TPGS 10.00 mg/ml, edetate disodium 0.100 mg/ml,

dextrose 400.00 mg/ml, sorbic acid 1.00 mg/ml, sodium carboxymethylcellulose 20.00 mg/ml, purified water qs 1.0 ml.

17. Use of the liquid aqueous oral pharmaceutical composition according to any one of claims 1 to 16 for the manufacture of a medicament for paediatric treatment.

18. The use according to claim 17 for the manufacture of a medicament for the

paediatric treatment of gastrointestinal diseases.

19. A process for the preparation of the liquid aqueous oral pharmaceutical compositions according to any one of claims from 1 to 16, comprising a step wherein nepadutant is mixed with TPGS, and with a chelating agent.