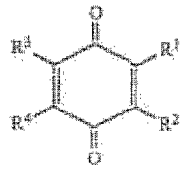
and as marketed product. In the course of our investigations on the pharmacological profile of idebenone, we discovered that the compound, after being absorbed in the gut, is metabolized very quickly during its first passage through the liver ("first-pass-effect"). Experiments showed that more than 98% of the idebenone is metabolized during its first passage through the liver. Hepatic metabolism of idebenone results in side chain oxidation, reduction of the quinone ring, sulphate and glucuronide conjugation and subsequent renal excretion. The high liver metabolism greatly reduces the potentially high plasma levels of the pharmacologically active idebenone. Because of this strong first pass metabolism, oral administration of idebenone requires high doses of the compound to achieve pharmacologically efficacious plasma levels in the body. Said high doses can result in unwanted side effects such as diarrhea.

In addition, the requirement for oral formulations of idebenone to be swallowed inflicts difficulties in the practical administration to patients with swallowing problems, e.g. a patient with a serious neuromuscular disease such as Duchenne Muscular Dystrophy or Friedreich's Ataxia, elderly or young patients.

Summary

In one aspect, there is provided a transmuccosal administration system for a pharmaceutical active ingredient wherein the system contains a suspension comprising 30-60% by weight, of an active ingredient which is a 1,4-benzoquinone of the structural formula (I)



(I)

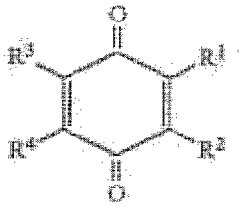
wherein R^1 is a C1-4 lower alkyl group; R^2 is a hydrogen atom or an optional substituted alkyl or an optional substituted alkenyl group; R^3 and R^4 each represents an optional substituted C1-6 lower alkyl or C1-3 lower alkoxy group or, R^3 and R^4 taken together a butadienylene group and 40-70% by weight of a polyalcohol and/or a cellulose derivative as carrier material and wherein the system is a mucoadhesive film which dissolves in the mouth.

Another solution to the above problem is presented in this disclosure which is based on data obtained with a specific type of transmucosal administration system consisting of especially a thin polymer-based film that when attached to the oral mucosa releases the active ingredient directly to the mucosa or partly into the saliva in the oral cavity, espphagus and stomach. The active ingredient is absorbed through the mucosa primarily in the oral cavity, espphagus and stomach, thus avoiding the first-pass metabolism observed after conventional oral administration and gastrointestinal absorption. This dosage form is also described as oral wafer.

The principle of this system is also applicable to analogues of idebenone, such as other benzoquinones or quinones, having a reversibly reducible quinone ring, with a lipophilic side chain. The term "ubiquinone analogues", as used herein, encompasses natural ubiquinones (coenzyme Q-n) as well as their structural analogs having a

THAT WHICH IS CLAIMED:

1. A transmuccosal administration system for a pharmaceutical active ingredient wherein the system contains a suspension comprising 30-60% by weight, of an active ingredient which is a 1,4-benzoquinone of the structural formula (I)



(I)

wherein R^1 is a C1-4 lower alkyl group; R^2 is a hydrogen atom or an optional substituted alkyl or an optional substituted alkenyl group; R^3 and R^4 each represents an optional substituted C1-6 lower alkyl or C1-3 lower alkoxy group or, R^3 and R^4 taken together a butadienylene group and 40-70% by weight of a polyalcohol and/or a cellulose derivative as carrier material and wherein the system is a mucoadhesive film which dissolves in the mouth.

2. The administration system as claimed in claim 1, wherein R^1 is a C1-4 lower alkyl group, R^2 is linear or branched, saturated or unsaturated, aliphatic hydrocarbon or hydroxyalkyl chain from 5 to 50 carbon atoms and R^3 and R^4 is a C1-4 alkyl group or a C1-3 alkoxy group.

3. The administration system as claimed in claim 1, wherein R^1 is a C1-4 alkyl; R2 is (a) hydrogen, (b) a C1-22 alkyl which may be substituted by 1 to 10 substituents selected from the group consisting of (i) C1-4 alkyl, (ii) hydroxy, (iii) oxo, (iv) amino, (v) mono-C1-6 alkylamino, (vi) di-C1-6 alkylamino, (vii) carboxy, (viii) C1-4 alkoxy-carbonyl, (ix) C6-14 aryl which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4, alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, (x) 5 or 6-membered heterocyclic group which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, and (xi) halogen, or (c) a C2-15 alkenyl which may be substituted by 1 to 10 substituents selected from the group consisting of (i) C1-4 alkyl, (ii) hydroxy, (iii) oxo, (iv) amino, (v) mono-C1-6 alkylamino, (vi) di-C1-6 alkylamino, (vii) carboxy, (viii) C1-4 alkoxy-carbonyl, (ix) C6-14 aryl which may be substituted by 1 or 2 substituents selected

from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, (x) 5- or 6 membered heterocyclic group which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, and (xi) halogen; R^3 and R^4 each is a C1-6 alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, C1-3 alkyl which may be halogenated, carboxy, C1-6 alkoxy-carbonyl, 3-pyridyl, 1-imidazolyl and 5-thiazolyl or a C1-3 alkoxy; or R^3 and R^4 form, taken together with the respective adjacent carbon atoms, a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of C1-3 alkyl, C1-3 alkoxy, hydroxy, nitro and halogen.

4. The administration system as claimed in claim 1, 2 or 3, wherein R^1 is a C1-3 alkyl, R2 is a C6-14 alkyl optionally substituted by hydroxy and R3 and R4 each is C1-3 alkoxy.

5. The administration system as claimed in one of claims 1 to 4, wherein said active ingredient is selected from the group consisting of idebenone, decylubiquinone, and ubiquinone.

6. The administration system as claimed in one of claims 1 to 5, wherein the carrier material is selected from the group consisting of cellulose derivatives, polyvinyl-alcohol, and combinations thereof, wherein preferably the cellulose derivative is methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose or combinations thereof.

7. The administration system as claimed in one of claims 1 to 6, wherein said system comprises 50% by weight of a 1,4-benzoquinone as active ingredient selected from the group consisting of idebenone, or ubiquinone and 40% by weight polyvinyl alcohol and 10% by weight of sodium carboxymethyl-cellulose as carrier material.

8. The administration system as claimed in one of claims 1 to 7, wherein the film dissolves completely in a period of less than 30, more preferably less than 15 minutes in the mouth.

9. The administration system as claimed in one of claims 1 to 8, wherein a maximum concentration of the active ingredient in the blood is reached in a period of less than 240 minutes preferably of less than 60 minutes more preferably between 5 and 30 min after application.

10. The administration system as claimed in one of claims 1 to 9, wherein the system additionally comprises at least one excipient from the group of flavorings, colorants, sweeteners, fillers, plasticizers, surface-active substances, solubilizers, liquid excipient, pH stabilizers, disintegrants, solubility enhancers and absorption enhancers.

11. The administration system as claimed in one of claims 1 to 10, wherein the active ingredient present is dissolved in the carrier material and/or a liquid excipient wherein preferably the liquid excipient is a liquid lipophilic excipient.

12. The administration system as claimed in one of claims 1 to 6 and 8 to 11, wherein the system contains a suspension comprising 40-50% by weight of the active ingredient and 50-60% by weight of a polyalcohol and/or a cellulose derivative as carrier material.

13. The administration system as claimed in one of claims 1 to 12, wherein the active ingredient is micronized.

14. The administration system as claimed in one of claims 1 to 13, wherein the system has a monolayer or double-layer construction.

15. Use of the administration system of any of the foregoing claims 1-14 in the manufacture of a medicament for treating a mitochondrial disease, preferably selected from the group consisting of Leber's hereditary optic neuropathy (LHON), autosomal dominant optic atrophy (DOA), macular degeneration, glaucoma, retinopathy, cataract, optic disc drusen (ODD), mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), myoneurogenic gastrointestinal encephalomyopathy (MNGIE), Kearns-Sayre syndrome, CoQ10 deficiency, and mitochondrial complex deficiencies (1-5, CPEO);

a neurodegenerative disease, preferably selected from the group consisting of Friedreich's ataxia (FRDA), amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke/reperfusion injury, and dementia;

a neuromuscular disease, preferably selected from the group consisting of Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), Limb-Girdle muscular dystrophy (LGMD), X-linked dilated cardiomyopathy (XLDCM), Pantothenate kinase-associated neurodegeneration (PKAN), spinal muscular atrophy (SMA), multiple sclerosis, relapsing remitting multiple sclerosis (RR-MS), primary progressive multiple sclerosis (PP-MS), secondary progressive multiple sclerosis (SP-MS), Kugelberg-Welander disease, and Werdnig-Hoffmann disease;

a psychiatric disorder, preferably selected from the group consisting of schizophrenia, major depressive disorder, bipolar disorder, and epilepsy;

a metabolic disorder, preferably selected from the group consisting of ageing-related physical decline, obesity, overweight, type II diabetes, and metabolic syndrome;

cancer; multiple sclerosis; or

immune dysfunction, preferably selected from the group consisting of arthritis, psoriasis and rheumatoid arthritis.

16. The use according to claim 15 comprising a dose of the system as claimed in one of claims 1 to 14 in an amount of equal to or less than 60 mg/kg/day.

17. The use according to claim 15 or 16 , wherein the pharmaceutical active ingredient is idebenone and the idebenone is administered in a dosage from 0.01 mg/kg/day to 10 mg/kg/day.

18. The use according to one of claims 15 to 17, wherein the pharmaceutical active ingredient is idebenone and the system further comprises a polymer matrix wherein the idebenone is incorporated within the matrix as a suspension, or a suspension after micronization.

19. The use according to one of claims 15 to 18, wherein the drug is administered via the oral mucosa on or under the tongue in the buccal cavity or any other location in the oral cavity.

20. The use according to one of claims 15 to 19, further comprising a second therapeutic agent.

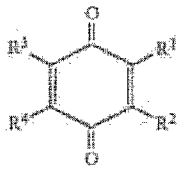
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Summary

In one aspect, there is provided a transmuccosal administration system for a pharmaceutical active ingredient wherein the system contains a suspension comprising 30-60% by weight, of an active ingredient of the structural formula (I)



(I)

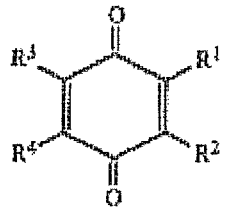
wherein R^1 is a C1-4 lower alkyl group; R^2 is a hydrogen atom or an optional substituted alkyl or an optional substituted alkenyl group; R^3 and R^4 each represents an optional substituted C1-6 lower alkyl or C1-3 lower alkoxy group or, R^3 and R^4 taken together a butadienylene group and 40-70% by weight of a polyalcohol and/or a cellulose derivative as carrier material and wherein the system is a mucoadhesive film which dissolves in the mouth.

Another solution to the above problem is presented in this disclosure which is based on data obtained with a specific type of transmucosal administration system consisting of especially a thin polymer-based film that when attached to the oral mucosa releases the active ingredient directly to the mucosa or partly into the saliva in the oral cavity, espphagus and stomach. The active ingredient is absorbed through the mucosa primarily in the oral cavity, espphagus and stomach, thus avoiding the first-pass metabolism observed after conventional oral administration and gastrointestinal absorption. This dosage form is also described as oral wafer.

The principle of this system is also applicable to analogues of idebenone, such as other benzoquinones or quinones, having a reversibly reducible quinone ring, with a lipophilic side chain. The term "ubiquinone analogues", as used herein, encompasses natural ubiquinones (coenzyme Q-n) as well as their structural analogs having a

THAT WHICH IS CLAIMED:

1. A transmuccosal administration system for a pharmaceutical active ingredient comprising 0.01-80% by weight of an active ingredient of the structural formula (I)



(I)

wherein R^1 is a C1-4 lower alkyl group; R^2 is a hydrogen atom or an optional substituted alkyl or an optional substituted alkenyl group; R^3 and R^4 each represents an optional substituted C1-6 lower alkyl or C1-3 lower alkoxy group or, R^3 and R^4 taken together a butadienylene group and 20-99.99% by weight of a carrier material.

2. The administration system as claimed in claim 1, wherein R^1 is a C1-4 lower alkyl group, R^2 is linear or branched, saturated or unsaturated, aliphatic hydrocarbon or hydroxyalkyl chain from 5 to 50 carbon atoms and R^3 and R^4 is a C1-4 alkyl group or a C1-3 alkoxy group.

3. The administration system as claimed in claim 1, wherein R^1 is a C1-4 alkyl; R2 is (a) hydrogen, (b) a C1-22 alkyl which may be substituted by 1 to 10 substituents selected from the group consisting of (i) C1-4 alkyl, (ii) hydroxy, (iii) oxo, (iv) amino, (v) mono-C1-6 alkylamino, (vi) di-C1-6 alkylamino, (vii) carboxy, (viii) C1-4 alkoxy-carbonyl, (ix) C6-14 aryl which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4, alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, (x) 5 or 6-membered heterocyclic group which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, and (xi) halogen, or (c) a C2-15 alkenyl which may be substituted by 1 to 10 substituents selected from the group consisting of (i) C1-4 alkyl, (ii) hydroxy, (iii) oxo, (iv) amino, (v) mono-C1-6 alkylamino, (vi) di-C1-6 alkylamino, (vii) carboxy, (viii) C1-4 alkoxy-carbonyl, (ix) C6-14 aryl which may be substituted by 1

or 2 substituents selected from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, (x) 5- or 6 membered heterocyclic group which may be substituted by 1 or 2 substituents selected from the group consisting of C1-4 alkyl, hydroxy, carboxy and C1-6 alkoxy-carbonyl, and (xi) halogen; R^3 and R^4 each is a C1-6 alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, C1-3 alkyl which may be halogenated, carboxy, C1-6 alkoxy-carbonyl, 3-pyridyl, 1-imidazolyl and 5-thiazolyl or a C1-3 alkoxy; or R^3 and R^4 form, taken together with the respective adjacent carbon atoms, a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of C1-3 alkyl, C1-3 alkoxy, hydroxy, nitro and halogen.

4. The administration system as claimed in claim 1, 2 or 3, wherein R^1 is a C1-3 alkyl, R2 is a C6-14 alkyl optionally substituted by hydroxy and R3 and R4 each is C1-3 alkoxy.

5. The administration system as claimed in one of claims 1 to 4, wherein said active ingredient is selected from the group consisting of idebenone, idebenone analogues, decylubiquinone, ubiquinone and ubiquinone analogues.

6. The administration system as claimed in one of claims 1 to 5, wherein the carrier material is selected from the group consisting of cellulose, cellulose derivatives, polyvinyl-alcohol, poly-N-vinylpyrrolidones, vinylpyrrolidone-vinyl acetate copolymers, starch, starch derivatives, gelatine, gelatine derivatives, Soluplus, Kollicoat, and combinations thereof, wherein preferably the cellulose derivative is methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose or combinations thereof.

7. The administration system as claimed in one of claims 1 to 6, wherein said system comprises 50% by weight of a 1,4-benzoquinone as active ingredient selected from the group consisting of idebenone, ubiquinone or ubiquinone analogues and 40% by weight polyvinyl alcohol and 10% by weight of sodium carboxymethyl-cellulose as carrier material,
or wherein

said system comprises 10% by weight of a 1,4-benzoquinone as active ingredient selected from the group consisting of idebenone, or ubiquinone and 90% by weight of hydroxypropylmethylcellulose as carrier material.

8. The administration system as claimed in one of claims 1 to 7, wherein the film dissolves completely in a period of less than 30, more preferably less than 15 minutes in the mouth.

9. The administration system as claimed in one of claims 1 to 8, wherein a maximum concentration of the active ingredient in the blood is reached in a period of less than 240 minutes preferably of less than 60 minutes more preferably between 5 and 30 min after application.

10. The administration system as claimed in one of claims 1 to 9, wherein the system additionally comprises at least one excipient from the group of flavorings, colorants, sweeteners, fillers, plasticizers, surface-active substances, solubilizers, liquid excipient, pH stabilizers, disintegrants, solubility enhancers and absorption enhancers.

11. The administration system as claimed in one of claims 1 to 10, wherein the active ingredient present is dissolved in the carrier material and/or a liquid excipient wherein preferably the liquid excipient is a liquid lipophilic excipient.

12. The administration system as claimed in one of claims 1 to 11, wherein the system contains a suspension comprising 40-50% by weight of the active ingredient and 50-60% by weight of a polyalcohol and/or a cellulose derivative as carrier material.

13. The administration system as claimed in one of claims 1 to 12, wherein the active ingredient is micronized.

14. The administration system as claimed in one of claims 1 to 13, wherein the system contains an amorphous presentation comprising 3-20%, preferably 5-10% by weight of the active ingredient and 80-97%, preferably 90-95% by weight of a water

soluble polymer as carrier material, wherein preferably the carrier material is a substituted carbohydrate.

15. The administration system as claimed in one of claims 1 to 14, wherein the system has a monolayer or double-layer construction.

16. Use of the administration system of any of the foregoing claims 1-15 in the manufacture of a medicament for treating a mitochondrial disease, preferably selected from the group consisting of Leber's hereditary optic neuropathy (LHON), autosomal dominant optic atrophy (DOA), macular degeneration, glaucoma, retinopathy, cataract, optic disc drusen (ODD), mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), myoneurogenic gastrointestinal encephalomyopathy (MNGIE), Kearns-Sayre syndrome, CoQ10 deficiency, and mitochondrial complex deficiencies (1-5, CPEO);

a neurodegenerative disease, preferably selected from the group consisting of Friedreich's ataxia (FRDA), amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke/reperfusion injury, and dementia;

a neuromuscular disease, preferably selected from the group consisting of Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), Limb-Girdle muscular dystrophy (LGMD), X-linked dilated cardiomyopathy (XLDCM), Pantothenate kinase-associated neurodegeneration (PKAN), spinal muscular atrophy (SMA), multiple sclerosis, relapsing remitting multiple sclerosis (RR-MS), primary progressive multiple sclerosis (PP-MS), secondary progressive multiple sclerosis (SP-MS), Kugelberg-Welander disease, and Werdnig-Hoffmann disease;

a psychiatric disorder, preferably selected from the group consisting of schizophrenia, major depressive disorder, bipolar disorder, and epilepsy;

a metabolic disorder, preferably selected from the group consisting of ageing-related physical decline, obesity, overweight, type II diabetes, and metabolic syndrome;

cancer; multiple sclerosis; or

immune dysfunction, preferably selected from the group consisting of arthritis, psoriasis and rheumatoid arthritis.

17. The use according to claim 16 comprising a dose of the system as claimed in one of claims 1 to 15 in an amount of equal to or less than 60 mg/kg/day.

18. The use according to claim 16 or 17, wherein the pharmaceutical active ingredient is idebenone and the idebenone is to be administered in a dosage from 0.01 mg/kg/day to 10 mg/kg/day.

19. The use according to one of claims 16 to 18, wherein the pharmaceutical active ingredient is idebenone and the system further comprises a polymer matrix wherein the idebenone is incorporated within the matrix as a suspension, a suspension after micronization, an emulsion, a micro- or nano-emulsion, or in solubilised form.

20. The use according to one of claims 16 to 19, wherein the drug is to be administered via the oral mucosa on or under the tongue in the buccal cavity or any other location in the oral cavity.

21. The use according to one of claims 16 to 20, further comprising a second therapeutic agent.

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