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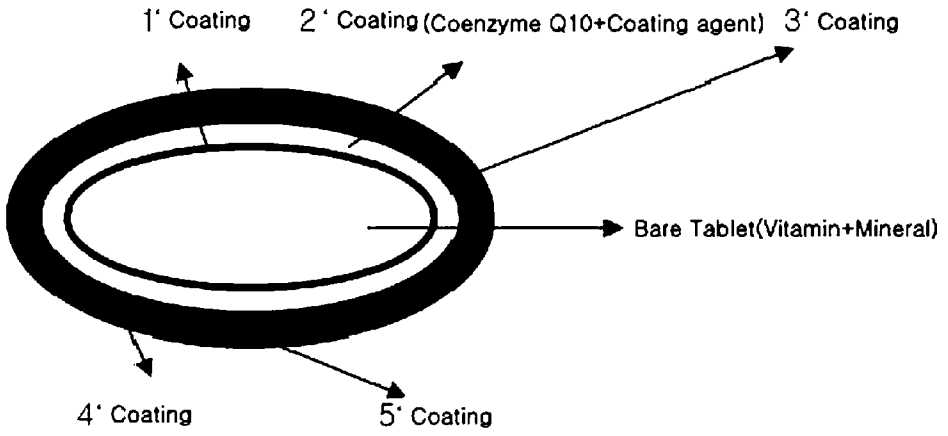
[Continued on next page]

(54) Title: STABILIZED PREPARATION CONTAINING COENZYME Q10 AND PROCESS FOR PREPARATION THEREOF

[Fig. 1]



(57) Abstract: A pharmaceutical agent of stabilized Coenzyme QlO and a method for the preparation thereof are provided. The agent may be a coated tablet composed of a bare tablet containing at least one vitamin and/or mineral ingredient in combination with a carrier and at least one coating layer containing Coenzyme QlO. In the agent, Coenzyme QlO is present in a film coating layer separated from the bare tablet comprising vitamins and/or minerals and thus is prevented from being unstabilized by the vitamins and/or minerals. In addition, the film coating layer of Coenzyme QlO is protected from conditions of the external environment such as water, temperature and light, by a protective layer.

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Description

STABILIZED PREPARATION CONTAINING COENZYME Q10 AND PROCESS FOR PREPARATION THEREOF

Technical Field

[1] The present invention relates to a pharmaceutical preparation with Coenzyme Q10 stabilized therein and a method for the preparation thereof. More particularly, the present invention relates to a pharmaceutical preparation, comprising Coenzyme Q10 and a pharmaceutically active ingredient having negative influence on stability of Coenzyme Q10, in which the pharmaceutically active ingredient is contained in a bare tablet and the Coenzyme Q10 is present in a coating layer separated from the bare tablet, whereby Coenzyme Q10 is prevented from being unstabilized by the vitamins and/or minerals and protected from conditions of the external environment such as water, temperature and light, by a protective layer. Also, the present invention is concerned with a method for the preparation thereof.

Background Art

[2] Coenzyme Q10, also known as ubidecarenone, is an oil-soluble quinone which is synthesized within cells and plays an important role in mitochondrial electron transport and ATP synthesis. In addition, this coenzyme is used for the treatment of congestive heart failure. Recent reports on the antioxidant activity thereof have increased the availability of Coenzyme Q10 for myocardial protection, cancer prevention, prevention of senescence, suppression of blood LDL oxidation, and hypertension resistance.

[3] Coenzyme Q10 is a crystalline powder with a low melting point and which is highly soluble in ether but insoluble in water due to its lipophilicity. Due to its poor water-solubility, Coenzyme Q10 shows low bioavailability when administered orally. Further, Coenzyme Q10 is likely to decompose in the presence of alkali, water, heat or light to produce hydroquinone, ubichromenol and the like. For example, Coenzyme Q10 becomes highly unstable when in contact with basic amino acids or water-soluble vitamins or minerals. This unstabilization is reported to act as a significant barrier to the development of products with Coenzyme Q10.

[4]

[5] Japanese Unexamined Patent Application Publication No. 2005-53923 discloses a stable unidecarenone composition formulated with organic acids and a method of stabilizing a ubidecarenone composition, in which a capsule composition comprising ubidecarenone and water-soluble vitamins is formulated with citric acid, succinic acid, tartaric acid, asparagic acid, lactic acid, malic acid, malonic acid, fumaric acid and maleic acid. Preferably, citric acid, tartaric acid, fumaric acid, maleic acid and

asparagic acid are used in an amount of from 20 % by weight to 400 % by weight.

[6]

[7] Japanese Unexamined Patent Application Publication No. 2006-320311 discloses a food containing Coenzyme Q10 and magnesium and/or calcium in a stable manner in which Coenzyme Q10, and magnesium and/or calcium are formulated after Coenzyme Q10 is made to separate from magnesium and calcium, that is, one of the components Coenzyme Q10, and magnesium and/or calcium is separately assembled or sealed in microcapsules.

[8]

[9] Japanese unexamined patent Application Publication No. 2006-182770 discloses a solid agent comprising a group consisting of ubidecarenone and an acid and B vitamins, characterized in that the two groups are formulated after at least one of the groups is separately assembled. Particularly, the acid is selected from among citric acid, succinic acid, malic acid, tartaric acid, fumaric acid, maleic acid, phosphoric acid, acetic acid and a combination thereof.

Disclosure of Invention

Technical Problem

[10] Leading to the present invention, intensive and thorough research into the stabilization of Coenzyme Q10 in the presence of vitamins and minerals, resulted in the finding that Coenzyme Q10 is labile to vitamins and minerals and can be stably maintained when it is not in contact with them. Also, a coated tablet composed of a bare tablet containing vitamins and minerals therein and a coating containing Coenzyme Q10 therein does not require a special device for the preparation thereof.

Technical Solution

[11] It is therefore an object of the present invention to provide a pharmaceutical preparation of stabilized Coenzyme Q10 comprising vitamins and/or minerals, and a method for the preparation thereof.

Brief Description of Drawings

[12] FIG. 1 is a schematic view showing the structure of the pharmaceutical preparation of stabilized Coenzyme Q10 in accordance with the present invention

Best Mode for Carrying out the Invention

[13] In accordance with an aspect thereof, the present invention provides a coated tablet composed of a bare tablet containing at least one vitamin and/or mineral ingredient in combination with a carrier and at least one coating layer containing Coenzyme Q10.

[14]

[15] In the present invention, vitamins and/or minerals, which may have a negative influence on the stability of Coenzyme Q10, are contained in a bare tablet while

Coenzyme Q10 is present in a coating layer.

[16] As long as it may be used in vitamin compounds, any vitamin may be used in the present invention, examples of which include vitamin A (retinyl palmitate), vitamin C (ascorbic acid), vitamin D (ergocalcipherol), vitamin E (tocopherol acetate), B vitamins (thiamine nitrate, riboflavin, pyridoxine hydrochloride, cyanocobalamine, calcium pantothenate, nicotinamide, folic acid and combinations thereof), but are not limited thereto. The bare tablet according to the present invention may contain vitamin A (retinyl palmitate) in an amount of from 100 to 10,000 I.U., vitamin C (ascorbic acid) in an amount of from 10 to 1,500 milligrams, vitamin D (ergocalcipherol) in an amount of from 10 to 1,000 I.U., vitamin E (tocopherol acetate) in an amount of from 2 to 1,000 I.U., thiamine nitrate in an amount of from 0.2 to 100 milligrams, riboflavin in an amount of from 0.2 to 100 milligrams, pyridoxine hydrochloride in an amount of from 0.2 to 250 milligrams, cyanocobalamine in an amount of from 0.2 to 1,000 micrograms, calcium pantothenate in an amount of from 5 to 500 milligrams, nicotinamide in an amount of from 2 to 500 milligrams and folic acid in an amount of from 2 to 500 micrograms per tablet.

[17]

[18] As long as it is found in general mineral supplements, any mineral may be used in the present invention. Examples of the minerals useful in the present invention include anhydrous dibasic calcium phosphate, zinc oxide, potassium sulfate, potassium iodide, ferrous fumarate, magnesium oxide, manganese sulfate, selenium-enriched yeast, and combinations thereof, but are not limited thereto. The bare tablet according to the present invention may contain calcium in an amount of from 1 to 1,500 milligrams, iodide in an amount of from 0.01 to 0.5 milligrams, iron in an amount of from 1 to 35 milligrams, magnesium in an amount of from 1 to 500 milligrams, manganese in amount of from 0.1 to 30 milligrams, potassium in an amount of from 1 to 780 milligrams, selenium in an amount of from 1 to 200 micrograms, and/or zinc in an amount of from 0.1 to 50 milligrams.

[19]

[20] The bare tablet according to the present invention may comprise a pharmaceutically acceptable carrier in addition to vitamins and/or minerals. For use in oral dosage forms, the pharmaceutically acceptable carrier is well known in the art and includes a binder, a lubricant, a disintegrant, a diluent, a solubilizer, a dispersant, a stabilizer, a suspending agent, a colorant, a flavor, etc. For example, a typical excipient for oral administration may be used as a diluent, examples of which include low-substituted hydroxypropylcellulose, corn starch, potato starch, di-mannitol, Ludipress, lactic acid, and microcrystalline cellulose, but are not limited thereto. Preferable is lactic acid or microcellulose. All general disintegrants for oral administration may be used in the

present invention with the exception that sodium starch glycolate is excluded when vitamin C is contained in the bare tablet. Examples of the disintegrant include carboxymethylcellulose sodium, hydroxypropylcellulose, croscamellose sodium, corn starch, pregelatinized starch and crospovidone with preference for corn starch, pregelatinized starch and crospovidone. Likewise, any binder may be used in the present invention as long as it is suitable for use in oral administration. Examples of the binder include polyvinylpyrrolidone or its derivatives, hydroxypropylmethylcellulose, and hydroxypropylcellulose, but are not limited thereto. Preferable are hydroxypropylcellulose and hydroxypropylmethylcellulose characteristic of granulation. Examples of the lubricant useful in the present invention include light anhydrous silicic acid, talc, magnesium stearate, and sodium stearylfumarate, but are not limited thereto.

[21]

[22] The vitamins and/or minerals may be formulated in combination with a pharmaceutically acceptable carrier using a typical method to produce a bare tablet.

[23] For example, the tablet is formed by wet granulation, dry granulation or direct compression.

[24]

[25] As described above, the present invention pertains to an oral dosage form comprising Coenzyme Q10 in combination with a vitamin and/or mineral ingredient which may have negative influence on Coenzyme Q10, in which the vitamin and/or mineral ingredient is formulated into a bare tablet with Coenzyme Q10 present in a film coating layer. Thus, the oral dosage form of the present invention comprises at least one coating applied to the bare tablet.

[26] The coating is designed to prevent Coenzyme Q10 from being unstabilized by the vitamin and/or mineral ingredient and from being decomposed by external factors such as moisture, temperature, light, etc. In a preferred embodiment of the present invention, the coating may have a monolayer structure or a multilayer structure with Coenzyme Q10 present in at least one layer. Preferably, the coating has a bi- to pentalayered structure.

[27] The coating may comprise a coating base typically used in the film coatings of tablets. Preferably, water-insoluble, water-soluble and/or enteric coating polymers, for example, hydroxypropylmethyl cellulose, ethyl cellulose, polyvinyl alcohol, polymethacrylate copolymers, carboxymethylcellulose sodium, etc. may be used. This coating base may be used in an amount of from 1 to 20 weight % based on the total weight of the tablet, and preferably in an amount of from 2 to 10 weight %. More preferably, hydroxypropylmethyl cellulose, polyvinyl alcohol, or a polymethacrylate copolymer is used as a coating base. Alternatively, a polymethacrylate copolymer is used in combination with hydroxypropylmethyl cellulose or polyvinyl alcohol at a

weight ratio of from 50:50 to 30:70, and preferably at a weight ratio of 40:60.

[28] These polymers may be prepared using well-known techniques or may be commercially available. In an embodiment of the present invention, Opadry OY-C-7000A (containing 54.85 weight % of hydroxypropylmethyl cellulose, 13.72 weight % of ethylcellulose, 22.86 weight % of titania, and 8.57 weight % of diethylphthalate, Colorcon, hereinafter referred to as "Opadry (HPMC;EC)"), Opadry 80W65174 (containing 45.52 weight % of polyvinyl alcohol, 20.0 weight % of talc, 13.55 weight % of iron oxide red, 11.39 weight % of titania, 4.33 weight % of sunset yellow aluminum lake, 2.72 weight % of tartrazine aluminum lake, 2.0 weight % of lecithin, 0.480 weight % of xanthan gum, 0.010 weight % of indigo carmine aluminum lake, Colorcon, hereinafter referred to as "Opadry AMB PVA"), Opagross 97W19196 (containing 54.16 weight % of carboxymethylcellulose sodium, 20.79 weight % of maltodextrin, 16.95 weight % of glucose, 6.1 weight % of lecithin, and 2.0 weight % of sodium citrate, Colorcon, hereinafter referred to as "Opagross CMC-Na"), Opadry 03F62589 (62.5 weight % of hydroxypropylmethyl cellulose, 31.1 weight % of titania, 6.25 weight % of polyethylene glycol 3350, 0.13 weight % of iron oxide yellow, 0.02 weight % of quinoline yellow aluminum lake, Colorcon, hereinaftered referred to as "Opadry HPMC"), Opadry 85F18422 (containing 40.0 weight % of polyvinyl alcohol, 25.0 weight % of titania, 20.2 weight % of polyethylene glycol 3350, and 14.8 weight % of talc, Colorcon, hereinafter referred to as "Opadry PVA"), and Acrylease 93O18509 (containing 40.0 weight % of methacrylic acid copolymer type C, 37.25 weight % of talc, 15.0 weight % of titania, 4.8 weight % of triethyl citrate, 1.25 weight % of light anhydrous silicic acid, 1.2 weight % of sodium hydrogen carbonate, and 0.5 weight % of sodium lauryl sulfate, Colorcon, hereinafter referred to as "Acrylease (methacrylic acid copolymer Type C)" were used as coating bases.

[29]

[30] As described above, the oral dosage form of the present invention comprises Coenzyme Q10 in at least one layer of the coating. The Coenzyme Q10 useful in the present invention may be synthesized using a well-known method or the commercially available product may be used. In an embodiment of the present invention, the ubidecarenone produced from Daewoong Bio. Co. Ltd. was used. Coenzyme Q10 is preferably used in an amount of from 5 to 200 milligrams.

[31]

[32] In the oral dosage form of the present invention, Coenzyme Q10 is preferably present in a coating layer which is not in contact with the bare tablet. Thus, Coenzyme Q10 is not substantially contained in a first coating layer (numbered in the order of being near to the surface of the bare tablet) in accordance with a preferred embodiment of the

present invention. More preferably, Coenzyme Q10 is contained in a second coating layer.

[33]

[34] In another preferred embodiment of the present invention, the coating layer containing Coenzyme Q10 therein may further comprise a stabilizer for stabilizing Coenzyme Q10. Any well-known stabilizer may be used without limitation. Preferable is anhydrous citric acid. Anhydrous citric acid is used in an amount of from 50 to 150 weight % based on the weight of Coenzyme Q10, and preferably in an amount of from 50 to 100 weight %.

[35]

[36] Composed of a bare tablet containing at least one vitamin and/or mineral ingredient and a coating containing Coenzyme Q10 therein, the oral dosage form according to the present invention can remove the instability of Coenzyme Q10 attributable to interaction with the vitamin and/or mineral ingredient and can effectively prevent the Coenzyme Q10 from being decomposed by external environments including moisture, temperature and light thanks to the protective layer which covers the layer of Coenzyme Q10.

[37]

[38] In accordance with another aspect thereof, the present invention provides a method for preparing an oral dosage form of stabilized Coenzyme Q10.

[39]

[40] In greater detail, the method comprises:

[41] (a) forming a bare tablet containing at least one ingredient selected from among vitamins and minerals;

[42] (b) dissolving a polymer coating base in a solvent to afford a polymer coating solution;

[43] (c) dispersing Coenzyme Q10 in a polymer coating solution to afford a Coenzyme Q10 dispersion; and

[44] (d) coating the bare tablet of step (a) with the Coenzyme Q10 dispersion alone or in combination with at least one coating solution in a predetermined order.

[45]

[46] In step (a), the bare tablet containing at least one vitamin and/or mineral ingredient, as mentioned above, may be formed using a dry granulation method, a wet granulation method or a direct compression method. Wet or dry granulation techniques are classified by the use of liquid in the tablet-pressing process. Dry granulation can be conducted on a press using a slugging machine or on a roller compactor. The resulting material in a slug or sheet phase is crushed and mixed with lubricants before compression. Wet granulation is a process of adding a liquid binder or adhesive to the

powder mixture. The damp granulates prepared using an extrusion or crash granulation method are compressed into a tablet. The damp granulates are dried, passed through a sieve and compressed, in admixture with lubricants and optionally disintegrants, into tablets. As for direct compression, it is a method in which a powder of active ingredients is mixed with excipients, binders, and disintegrants and the resulting homogenous mixture is directly compressed into tablets. These wet granulation, dry granulation and direct compression techniques are well known in the art. Preferably, the bare tablet is formed using dry granulation.

[47]

[48] In step (b), the polymer for each coating layer is dissolved in a suitable solvent to give a polymer coating solution. The solvent is preferably ethanol or water. The solvent is preferably used in an amount five to twenty times greater than the weight of the polymer.

[49]

[50] In step (c), Coenzyme Q10 is dissolved or dispersed in at least one of the coating solutions for the coating layers. In accordance with a preferred embodiment of the present invention, Coenzyme Q10 is dissolved or dispersed in the presence of anhydrous citric acid so as to stabilize Coenzyme Q10. The step (c) may be conducted simultaneously with or subsequently to step (b).

[51]

[52] In step (d), the coating solutions are applied to the surface of the bare tablet in a predetermined order. For this, a typical coating technique may be used. Examples include a pan-coating method in which a coating solution is sprayed over a bare tablet or granulate rotating in a coating pan and the solvent is evaporated by hot dry air to form a coating, and a fluid bed coating method in which a tablet or granulate is placed in a cylindrical device and a coating solution is sprayed with air blown from the device, but the methods are not limited thereto. In an embodiment of the present invention, the bare tablet was coated using Hicoater (HC-LABO, Freund Corporation).

Mode for the Invention

[53] A better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as the limit of the present invention.

[54]

[55] **EXAMPLES**

[56] In the following Examples and Comparative Examples, the ubidecarenone produced by Daewoong Bio Co. Ltd. was used as Coenzyme Q10.

[57]

[58] **EXAMPLE 1**

[59]

[60] **(1) Preparation of Dry Vitamin and Mineral Granulate Mixture**

[61] As indicated in Table 1, below, materials for vitamin layers and minerals were separately weighed, mixed and granulated using a roller compactor. Thereafter, the resulting separate dry granulates were mixed with crospovidone, sodium stearylfumarate to give a dry vitamin and mineral granule mixture.

[62] Table 1

[Table 1]

[Table]

Ex. 1		Per Tablet (mg)	Per 10,000 Tablets(g)
Dry Vitamin Granulate layer	Retinyl palmitate Granulate	5.0	50.0
	ascorbic acid 97% Granulate	77.32	773.2
	Ergocalcipherol Granulate	0.236	2.36
	Tocopherol acetate 50%	50.0	500.0
	Thiamine nitrate	12.5	125.0
	Riboflavin	15.337	153.37
	Pyridoxine hydrochloride	3.067	30.67
	0.1%cyanocobalamine	2.5	25.0
	Calcium pantothenate	14.643	146.43
	Nicotinamide	10.0	100.0
	Folic acid	0.20	2.0
	Microcrystalline cellulose	6.018	60.18
	Light anhydrous silicic acid	2	20
	Talc	3	30
Dry Mineral Granulate layer	Anhydrous dibasic calcium Phosphate	181.45	1,814.5
	Zinc oxide	9.35	93.5
	Potassium sulfate	5.57	55.7
	Potassium iodide	0.196	1.96
	Ferrous fumarate	22.82	228.2
	Magnesium oxide	4.975	49.75

	Manganese sulfate	3.08	30.8
	Selenium-enriched yeast	35.0	350
	Microcrystalline cellulose	97.738	977.38
	Hydroxypropyl cellulose	10	100
	Light anhydrous silicic acid	2	20
	Talc	3	30
Post-Mixing	Crospovidone	14.0	140.0
	Sodium stearyl fumarate	9.0	90.0
Total Wt(mg)		600	6,000

[63]

[64] **(2) Formulation of Coating Solution**

[65] 1) Opadry (HPMC;EC, Colorcon) Film Coating Formulation

[66] 70 Grams of Opadry HPMC;EC (Colorcon) was slowly added to 5 weights of ethanol and completely dissolved by stirring.

[67] 2) Drug-Containing Film Coating Formulation

[68] 50 Grams of Opadry HPMC;EC (Colorcon) was slowly added to about 10 weights of ethanol and warmed to 45~50℃ to give a solution to which 50 g of Coenzyme Q10 was then slowed added before cooling to room temperature. Anhydrous citric acid as a stabilizer might or might not be added in an amount of 25g or 50g.

[69] 3) Opadry AMB PVA (Colorcon) Film Coating Formulation

[70] 200 Grams of Opadry AMB PVA (Colorcon) was slowly added to 5 weights of purified water and completely dissolved by stirring.

[71] 4) Opadry HPMC (Colorcon) Film Coating Formulation

[72] 200 Grams of Opadry HPMC (Colorcon) was slowly added to 10 weights of pure water and completely dissolved by stirring.

[73] 5) Opadry PVA (Colorcon) Film Coating Formulation

[74] 200 Grams of Opadry PVA (Colorcon) was slowly added to 5 weights of pure water and completely dissolved by stirring.

[75] 6) 6:4 Opadry AMB PVA (Colorcon) : Acrylease (methacrylic acid copolymer Type C, Colorcon) Mixture Film Coating Formulation

[76] A mixture of 120 grams of Opadry AMB PVA (Colorcon) and 80 grams of Acrylease (methacrylic acid copolymer Type C, Colorcon) was slowly added to 5 weights of pure water and completely dissolved by stirring.

[77] 7) 6:4 Opadry PVA (Colorcon) : Acrylease (methacrylic acid copolymer Type C (Colorcon) Mixture Film Coating Formulation

[78] A mixture of 120 grams of Opadry PVA (Colorcon) and 80 grams of Acrylease (methacrylic acid copolymer Type C, Colorcon) was slowly dissolved in 5 weights of pure water and completely dissolved by stirring.

[79] 8) 6:4 Opadry HPMC (Colorcon) : Acrylease (methacrylic acid copolymer Type C, Colorcon) Mixture Film Coating Formulation

[80] A mixture of 120 grams of Opadry HPMC (Colorcon) and 80 grams of Acrylease (methacrylic acid copolymer Type C, Colorcon) was slowly added to 5 weights of pure water and completely dissolved by stirring.

[81] 9) Opagross CMC-Na (Colorcon) Film Coating Formulation

[82] 30 Grams of Opagross (CMC-Na, Colorcon) was slowly dissolved in 15 weights of pure water and completely dissolved by stirring.

[83]

[84] **COMPARATIVE EXAMPLE 1: Preparation of Tablet Containing Coenzyme Q10 in Contact with Vitamin and Mineral Layer**

[85]

[86] Tablets similar to currently commercially available products in which Coenzyme Q10 was simply mixed with vitamins and minerals were prepared as comparisons. For these tablets, anhydrous citric acid was used as a stabilizer for Coenzyme Q10 in the same amount as the Coenzyme Q10.

[87] A mixture of 50 g of Coenzyme Q10, 50g of lactose, 50g of anhydrous citric acid and 20 g of hydroxypropylcellulose was granulated with ethanol. The resulting granulates were dried at 40°C using a hot-air blower and then passed through a sieve. These Coenzyme Q10 granulates were mixed with the dry vitamin and mineral granulate mixture, followed by compressing the resulting mixtures into tablets each weighing 617 mg. Each coating solution was formulated according to the coating composition of Table 2 and the method of Example 1. Using Hicoater (HC-LABO, Freund Corporation), the bare tablets (360g, 600 tablets) were primarily coated with Opadry HPMC;EC (Colorcon) in an amount of 7 mg per tablet. Afterwards, a mixture of Opadry AMB PVA (Colorcon) or Acrylease (methacrylic acid copolymer Type C, Colorcon) was sprayed in an amount of 20 mg per tablet over the primarily coated tablets, followed by applying Opagross CMC-Na (Colorcon) in an amount of 3 mg per tablet to produce coated tablets, each weighing 647 mg.

[88] Table 2

[Table 2]

[Table]

Preparation of Tablets with Coenzyme Q10 in Contact with Vitamin and Mineral

	Ingredients	C. Ex. 1
Bare Tablet	Dry Vitamin and mineral grnulate mixture	600
	CoenzymeQ10	5
	Lactose	5
	Anhydrous citric acid	5
	Hydroxypropyl cellulose	2
1' Coating	Opadry HPMC;EC, (Colorcon)	7
2' Coating	OpadryAMB PVA, (Colorcon)	12
	Acrylease (methacrylic acid copolymer Type C, (Colorcon)	8
3' Coating	Opagross CMC-Na, (Colorcon)	3
Coated Tablet Wt.(mg)		647

[89]

[90] **EXAMPLES 2 TO 4: Stability of Coenzyme Q10 Depending on Amount of Anhydrous Citric Acid**

[91]

[92] On the basis of the disclosure of the prior art (Japanese Unexamined Patent Application Publication No. 2006-182770) that anhydrous citric acid functions to stabilize Coenzyme Q10, tablets were prepared. In this regard, the dry vitamin and mineral granulate mixture of Example 1 was compressed into tablets each weighing 600 mg, after which they were coated with the coating solutions prepared according to Table 4 and the method of Example 1. For all Examples 2 to 4, the same coating base and amount were used. Anhydrous citric acid was used in an amount of 0, 50 and 100 weight % based on the weight of Coenzyme Q10. The tablets obtained in Examples 2 to 4 weighed 645 mg, 647.5mg and 650mg, respectively.

[93] Table 3

[Table 3]

[Table]

		Ex.2(mg)	Ex. 3(mg)	Ex. 4(mg)
Bare Tablet	Weight	600	600	600
1' Coating	Opadry HPMC;EC, (Colorcon)	7	7	7
2' Coating	Opadry HPMC;EC, (Colorcon)	5	5	5
	CoenzymeQ10	5	5	5
	Anhydrous citric acid	-	2.5	5
3' Coating	Opadry HPMC;EC, (Colorcon)	5	5	5
4' Coating	Opadry AMB (PVA, (Colorcon)	12	12	12
	Acrylease (methacrylic acid copolymer Type C, (Colorcon)	8	8	8
5' Coating	Opagross CMC-Na, (Colorcon)	3	3	3
Coated Tablet Wt.		645	647.5	650

[94]

[95] **EXAMPLES 4 TO 9: Stability of Coenzyme Q10 Depending on Coating Base of Protective Coating Layer**

[96]

[97] Tablets were prepared in which Coenzyme Q10 was separated from the vitamins and minerals and protected from water and light by a protective layer. In this regard, first, coating solutions were formulated according to the coating compositions of Table 4 and the method of Example 1 and the dry vitamin and mineral granulate of Example 1 was compressed into tablets each weighing 600 mg. 1', 2', 3', and 5' coatings were conducted in the same manner as in Example 4 while Opadry HPMC (Colorcon), Opadry PVA (Colorcon) and Opadry AMB (PVA, Colorcon) were used as 4' coating bases and sprayed using a coating pan to give tablets of Examples 5 to 7, respectively. Separately, since Acrylease methacrylic acid copolymer type C (Colorcon) alone did not allow the coated tablets to readily disintegrate, it was used in combination with

Opadry HPMC (Colorcon), Opadry PVA (Colorcon), and Opadry AMB (PVA, Colorcon) and sprayed using a coating pan to produce the film-coated tablets of Examples 8, 9 and 4, respectively.

[98] Table 4

[Table 4]

[Table]

		Ex. 5(mg)	Ex. 6(mg)	Ex. 7(mg)	Ex. 8(mg)	Ex. 9(mg)	Ex. 4(mg)
Bare Tablet	Weight	600	600	600	600	600	600
1' Coating	Opadry HPMC;EC, (Colorcon)	7	7	7	7	7	7
2' Coating	Opadry HPMC;EC, (Colorcon)	5	5	5	5	5	5
	CoenzymeQ10	5	5	5	5	5	5
	Anhydrous citric acid	5	5	5	5	5	5
3' Coating	Opadry HPMC;EC, (Colorcon)	5	5	5	5	5	5
4' Coating	Opadry HPMC, (Colorcon)	20	-	-	12		-
	Opadry PVA, (Colorcon)	-	20	-	-	12	-
	OpadryAMB PVA, (Colorcon)			20			12
	Acrylease methacrylic acid copolymer type C, (Colorcon)	-	-		8	8	8
5' Coating	Opagross sodium carboxymethyl cellulose, (Colorcon)	3	3	3	3	3	3
Coated Tablet Wt.		650	650	650	650	650	650

[99]

[100] **TEST EXAMPLE 1: Accelerated Stability Test**

[101]

[102] While the film-coated tablets obtained in Comparative Example 1 and Examples 2 to 9 were stored at 40℃, 75% RH for 6 months within a sealed container, the content of Coenzyme Q10 was analyzed at week 0, 2, 4, and 6, and month 2, 4 and 6. The remaining contents of Coenzyme Q10 were expressed as percentages to the content of Coenzyme Q10 at Week 0.

[103]

[104] Table 5

[Table 5]

[Table]

	C. Ex.1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
Week 0	100.0±1.1	100.0±2.1	100.0±1.6	100.0±4.6	100.0±3.1	100.0±0.6	100.0±0.3	100.0±1.2	100.0±0.9
Week 2	97.1±1.2	96.9±3.3	99.8±4.2	99.9±1.1	93.0±2.6	96.3±4.1	98.2±1.5	104.9±1.1	100.0±1.0
Week 4	95.8±2.9	97.2±1.9	100.4±2.8	98.8±0.4	96.4±3.3	99.7±4.1	101.2±3.0	103.6±1.4	98.5±3.0
Week 6	95.2±3.2	94.5±3.2	101.2±4.6	97.1±1.5	93.5±2.4	96.2±3.3	100.2±3.1	103.5±2.8	100.5±2.8
Month 2	93.5±2.5	95.8±3.3	98.3±3.6	97.1±7.8	98.0±2.8	97.7±1.6	99.1±2.8	101.0±2.6	102.2±2.0
Month 4	91.7±0.4	94.6±1.4	102.3±2.2	94.1±5.5	93.7±1.6	96.1±0.9	99.7±1.8	99.7±1.2	99.7±1.6
Month 6	80.9±1.3	90.6±2.8	95.4±4.93	97.2±1.2	96.0±6.7	96.8±2.2	100.8±4.9	99.9±1.5	98.6±1.5

[105]

[106] As apparent from data of Table 5, the oral dosage forms according to the present invention show far better Coenzyme Q10 stability than do those of the prior art. Although the remaining contents of Coenzyme Q10 were measured to be over the initial content, the differences were within the allowance attributable to the testers and machines.

[107]

Industrial Applicability

[108] As described hitherto, the present invention provides a film-coated oral dosage form in which Coenzyme Q10 is present in a film coating layer separated from the bare tablet comprising vitamins and/or minerals and thus is prevented from being un-stabilized by the vitamins and/or minerals. In addition, the film coating layer of Coenzyme Q10 is protected from conditions of the external environment such as water, temperature and light, by a protective layer.

[109] Requiring no special equipment for the preparation thereof, the tablets of the present invention can be prepared economically.

Claims

[1] A pharmaceutical preparation, comprising Coenzyme Q10 and a pharmaceutically active ingredient having negative influence on the stability of Coenzyme Q10, in which the pharmaceutically active ingredient is contained in a bare tablet comprising at least one ingredient selected from among vitamins, minerals and combinations thereof and the Coenzyme Q10 is present in a coating layer separated from the bare tablet.

[2] The pharmaceutical preparation according to claim 1, wherein the pharmaceutically active ingredient having negative influence of the stability of Coenzyme Q10 is selected from vitamins, minerals and combinations thereof.

[3] The pharmaceutical preparation according to claim 1, wherein the pharmaceutically active ingredient is selected from a group consisting of vitamin A (retinyl palmitate), vitamin C(ascorbic acid), vitamin D(ergocalcipherol), vitamin E (tocopherol acetate), B vitamins (thiamine nitrate, riboflavin, pyridoxine hydrochloride, cyanocobalamine, calcium pantothenate, nicotinamide, and folic acid) and combinations thereof.

[4] The pharmaceutical preparation according to claim 1, wherein the pharmaceutically active ingredient is selected from a group consisting of anhydrous dibasic calcium phosphate, zinc oxide, potassium sulfate, potassium iodide, ferrous fumarate, magnesium oxide, manganese sulfate, selenium-enriched yeast, and combinations thereof.

[5] The pharmaceutical preparation according to claim 1, wherein the coating layer has a penta-layered structure in which a first layer is in contact with a surface of the bare tablet and the Coenzyme Q10 is contained in one of a second to a fourth layer.

[6] A method for preparing a pharmaceutical preparation of stabilized Coenzyme Q10, comprising:

(a) forming a bare tablet containing at least one ingredient selected from among vitamins, minerals and combinations thereof;

(b) dissolving a polymer coating base in a solvent to afford a polymer coating solution;

(c) dispersing Coenzyme Q10 in a polymer coating solution to afford a Coenzyme Q10 dispersion; and

(d) coating the bare tablet of step (a) with the Coenzyme Q10 dispersion alone or in combination with at least one coating solution in a predetermined order.

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[Fig. 1]