Description

The present invention relates to a method for producing a stable preparation of nicorandil [N-(2-hydroxyethyl)-nicotinamide nitrate ester]. More particularly, the present invention relates to a method for producing a stable preparation containing nicorandil, a saturated higher aliphatic acid or a saturated higher alcohol both of which are solid at ordinary temperatures, and optionally fumaric acid, oxalic acid, salicylic acid, tartaric acid and/or glutaric acid.

Nicorandil has coronary vasodilative and coronary vasoconstriction suppressing actions and is useful as a curative for various types of angina pectoris while causing minimum effects on the dynamics of cardiovascular circulation and on cardiac functions (see Japanese Patent Publication No. 17463/1983 and Unexamined Published Japanese Patent Application No. 9323/1978).

Nicorandil preparations are relatively stable in the dry state but are unstable in humid conditions and must be produced and stored with special care being taken to avoid direct contact with moisture by, for example, wrapping in a completely moisture-proof package which, however, is quite expensive.

Nicorandil is also relatively stable in its crystalline form but it has been shown that if nicorandil is compressed into a tablet by routine procedures it becomes unstable and its content in the tablet is likely to experience a time-dependent decrease. In order to avoid this problem it is conventional practice to coat the nicorandil crystals with one or more fatty or waxy substances which are solid at ordinary temperatures before compressing the same into a tablet (Unexamined published Japanese Patent Application No. 145659/1982). This is indeed an effective method for stabilizing nicorandil but, on the other hand, it is very expensive since not only does it require apparatus or equipment for coating the nicorandil crystals with normally solid fatty or waxy materials but also the coating step is time-consuming.

Thus, it is the object of the present invention to develop a method for providing a nicorandil preparation which is stable not only in humid conditions but also under the compressive pressure exerted by punching operations in tablet making. Since the stability of nicorandil preparations was found to decrease as more pressure was exerted in compressing them into tablets, the present inventors noted the need to avoid the deformation of the nicorandil crystals and distortion of its crystal lattices that would take place under compressive force. Magnesium stearate and calcium stearate are conventionally used for the purpose of reducing the friction that will occur between powder particles when they are compressed into compacts. Therefore, the inventors mixed nicorandil with progressively increasing amounts (i.e., several to ten-odd times the normally used amount) of these lubricants and compressed the mixture into tablets, which however proved to be still unsatisfactory in terms of the stability of nicorandil.

Surprisingly enough the solution of this object has been achieved, when nicorandil was mixed with a saturated higher aliphatic acid or a saturated higher alcohol both of which are solid at ordinary temperatures, and optionally with fumaric acid, oxalic acid, salicylic acid, tartaric acid and/or glutaric acid, leading to a nicorandil preparation having remarkably improved stability by compressing the mixture into tablets.

The present invention has been accomplished on the basis of this finding and the method it proposes is entirely different from the conventional method of coating the nicorandil crystals with a normally solid fatty or waxy material. In one aspect, the present invention relates to a method for producing a stable nicorandil preparation by mixing nicorandil with at least 0.5% (on the basis of the weight of the preparation) of a saturated higher aliphatic acid or a saturated higher alcohol both of which are solid at ordinary temperatures, and optionally with at least 0.1% (on the basis of the weight of the preparation) of fumaric acid, oxalic acid, salicylic acid tartaric acid and/or glutaric acid.

In addition to its ability to produce a stable nicorandil preparation, the method of the present invention has the advantage that it obviates the need to apply a coating on the nicorandil crystals and therefore that it does not require any coating apparatus or equipment.

Fig. 1 is a graph showing the dissolution profiles of the slow release tablet of nicorandil prepared in Example 8 (-•-) and of the tablet prepared in the comparative example (-o-).

In accordance with the present invention, a composition consisting of crystalline nicorandil and a pharmaceutical vehicle such as an excipient, disintegrator, lubricant, colorant or binder is blended with at least 0.5% by weight of a saturated higher aliphatic acid or a saturated higher alcohol both of which are solid at ordinary temperatures, and optionally with at least 0.1% by weight of fumaric acid, oxalic acid, salicylic acid, tartaric acid and/or glutaric acid, and the resulting blend is processed into a desired dosage form, such as tablet, capsule, granule or suppository, by a conventional method.

Particularly preferred examples of the saturated higher aliphatic acid which is solid at ordinary temperatures are palmitic acid and stearic acid. Particularly preferred examples of the saturated higher alcohol which is solid at ordinary temperatures are cetyl alcohol and stearyl alcohol. Suitable pharmaceutical vehicles include: lactose, cornstarch, mannitol, kaolin, crystalline cellulose, carboxymethyl cellulose,

croscarmellose sodium (a cross-linked polymer of carboxymethylcellulose sodium), talc, anhydrous calcium hydrogenphosphate, calcium carbonate, calcium citrate, calcium stearate and magnesium stearate.

Among the organic acids which exhibit the activity of stabilizing nicorandil, fumaric acid displays the additional advantage of enabling the production of a slow-release nicorandil preparation wherein nicorandil is slowly released over time.

The sustained release preparation of nicorandil may be produced by weighing predetermined amounts of nicorandil and an excipient, then mixing them, by a routine method, with at least about 10% by weight of the preparation of fumaric acid and with at least one of the saturated higher aliphatic acids or saturated higher alcohols which are solid at ordinary temperatures. To the so prepared mixed powder, a lubricant such as magnesium stearate, calcium stearate or talc is added and the mixture is subsequently compressed into tablets.

If desired, nicorandil may be formulated in troches by mixing it with the necessary ingredients and with sucrose, flavor or colorant, then compressing the mixture into a desired shape.

In order to obtain the increase in the amount of released nicorandil after the elapse of a predetermined time after administration, nicorandil may be formulated in a multi-layered tablet by laminating a nicorandil-containing layer A on a layer B which is free from nicorandil, then compressing the two layers into a tablet.

Alternatively, nicorandil may be formulated in granules, capsules, or enteric granules having a coating of hydroxypropylmethyl cellulose phthalate or carboxymethylethyl cellulose.

The nicorandil preparation produced by the method of the present invention has the advantage of exhibiting high stability not only in humid conditions but also when it is compressed into tablets.

The following examples are provided for the purpose of further illustrating the present invention but are in no way to be taken as limiting.

Example 1

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Stearic acid	8
Mannitol	65.7
Cornstarch	15
Methyl cellulose	0.3
Magnesium stearate	1
Total	100.0 (mg)

Mannitol (65.7 g), cornstarch (15 g) and methyl cellulose SM-400 (0.3 g, product of Shinetsu Chemical Industry Co., Ltd.) were mixed well in a mortar and kneaded with water. The blend was passed through a 0.55mm (30-mesh) screen and dried at 45° C for 3 hours. The dried particles were classified by passage through a 0.55mm (30-mesh) sieve to prepare a granulation.

Nicorandil (10 g), stearic acid that had been sieved through a 0.42mm (35-mesh) screen (8 g), the granulation (81 g) and magnesium stearate (1 g) were mixed in a polyethylene bag, and the mixture was compressed at 196 MPa (2,000 kg/cm^2) in die (7 mm$^{\phi}$) to make tablet each weighing 100 mg.

Comparative tablets were made under the same conditions except that stearic acid was replaced by the same amount of mannitol.

Each of the two groups of tablets was divided into two subgroups. The tablets in one subgroup were vacuumdried (with P_2O_5 as a desiccant) to make them substantially water-free, and the tablets in the other subgroup remained undehydrated. All of the tablets were then put into glass bottles, screw-capped, and stored at 40° C for 3 months. The stability of the tablets was evaluated in terms of the residual amount of nicorandil as a percentage of the initial weight before acceleration. The results are shown in Table 1 below.

Table 1

Tablet	Residual nicorandil (%)	
	Dried	Undried
sample of the present invention	99.1	97.8
comparative sample	71.5	35.9

Example 2

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Stearyl alcohol	10
Mannitol	72.4
Carboxymethyl cellulose calcium	5
Hydroxypropyl cellulose	1.6
Calcium stearate	1
Total	100.0 (mg)

Stearyl alcohol (10 g) that had been passed through a 0.42mm (35-mesh) screen, mannitol (72.4 g), carboxymethyl cellulose calcium (5 g) and hydroxypropyl cellulose HPC-L (1.6 g, product of Nippon Soda Co., Ltd.) were mixed well in a mortar and kneaded with water. The blend was passed through a 30-mesh screen and dried at 40° C for 5 hours. The dried particles were classified by passage through a 0.55mm (30-mesh) sieve to prepare a granulation.

Nicorandil (10 g), the granulation (89 g) and calcium stearate (1 g) were mixed in a polyethylene bag and the mixture was compressed at 196 MPa (2,000 kg/cm^2) in die (7 mm$^\Phi$) to make tablets each weighing 100 mg.

Comparative samples were made under the same conditions except that stearyl alcohol was replaced by the same amount of mannitol.

The two types of tablets thus prepared were subjected to a stability test as in Example 1. The results are shown in Table 2.

Table 2

Tablet	Residual nicorandil (%)	
	Dried	Undried
sample of the present invention	99.4	96.1
comparative sample	72.3	41.1

Example 3

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Palmitic acid	3
Lactose	82
Croscarmellose sodium	5
Total	100.0 (mg)

Nicorandil (10 g), palmitic acid (3 g) that had been comminicated to an average particle size 1 - 3 µm with a micro jet mill (Model FS-4 of Seishin Kigyo K.K.), lactose (82 g) and croscarmellose sodium (5 g, Ac-Di-Sol® of FMC Corporation) were mixed in a polyethylene bag. The mixed powder was compressed at 196 MPa (2,000 kg/cm^2) in die (7 mm$^\phi$) to make tablets each weighing 100 mg.

Comparative tablets were made under the same conditions except that palmitic acid was replaced by the same amount of magnesium stearate.

The two types of tablets thus prepared were subjected to a stability test as in Example 1. The results are shown in Table 3.

Table 3

Tablet	Residual nicorandil (%)	
	Dried	Undried
sample of the present invention	97.3	90.6
comparative sample	75.8	56.2

Example 4

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Stearic acid	16
Lactose	65
Croscarmellose sodium	8
Cornstarch	1.0
Total	100.0 (mg)

Stearic acid (16 g), lactose (65 g) and croscarmellose sodium (8 g, Ac-Di-Sol® of FMC Corporation) were mixed well in a mortar and then kneaded with 20 g of 5% cornstarch paste. The blend was sieved through a 0.55mm (30-mesh) screen and dried at 45°C for 4 hours. The dried particles were classified by passage through a 0.55mm (30-mesh) sieve to make a granulation.

The granulation (90 g) and nicorandil (10 g) were mixed in a polyethylene bag and the mixture was compressed at 196 MPa (2,000 kg/cm^2) in die (7 mm$^\phi$) to make tablets each weighing 100 mg.

Three types of comparative tablets were made under the same conditions as above except that stearic acid was replaced by equal amounts of calcium stearate, hardened castor oil (Lubri Wax 101® of Freund Sangyo K.K.), and carnauba wax.

Each of the four groups of tablets was divided into two subgroups. They were put into glass bottles and stored under accelerated conditions at 50°C. One set of subgroups was held for 14 days with the bottles screw-capped, whereas the other set of subgroups was held for 7 days at 50% R.H., with the bottles left open. The results of this stability test are shown in Table 4.

Table 4

Tablet		Residual nicorandil (%)	
		7 days in open bottles at 50% R.H.	14 days in closed bottles
sample of the invention	stearic acid	89.9	83.6
comparative samples	calcium stearate	59.3	45.5
	hardened castor oil	18.2	58.3
	carnauba wax	42.5	57.1

Example 5

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Lactose	65.5
Stearic acid	8
Croscarmellose sodium	5
Fumaric acid	10
Cornstarch	1
Magnesium stearate	0.5
Total	100.0 (mg)

Lactose (65.5 g), stearic acid (8 g) and croscarmellose sodium (5 g, Ac-Di-Sol® of FMC Corporation) were mixed in a mortar, then kneaded with 20 g of 5% cornstarch paste. The blend was sieved through a 0.55mm (30-mesh) screen and dried at 45° C for 4 hours. The dried particles were classified by passage through a 0.55mm (30-mesh) screen to prepare a granulation.

Nicorandil (10 g), fumaric acid (10 g), the granulation (79.5 g) and magnesium stearate (0.5 g) were mixed in a polyethylene bag.

Using a single-punch tablet machine equipped with 7-mm$^{\phi}$ flat-faced punches, the mixed powder was compressed for a total pressure of about 98 MPa (1 ton) to make tablets each weighing 100 mg.

Comparative tablets were made under the same conditions except that stearic acid and fumaric acid were replaced by an equal amount of lactose.

Each of the two groups of tablets was divided into two subgroups. They were put into glass bottles and stored under accelerated conditions at 40° C. One set of subgroups was held for 3 months with the bottles screw-capped, whereas the other set of subgroups was held for 3 months at 61.5% R.H., with the bottles left open. The results of this stability test are shown in Table 5.

Table 5

Tablet	Residual nicorandil (%)	
	in closed bottles	in open bottles at 61.5% R.H.
sample of the present invention	98.5	97.8
comparative sample	63.2	25.6

Example 6

Capsule formulation (for one capsule)

Nicorandil	10 (mg)
Mannitol	40
Fumaric acid	10
Stearyl alcohol	30
Carboxymethyl cellulose calcium	10
Total	100.0 (mg)

Nicorandil (10 g), mannitol (40 g), fumaric acid (10 g), stearyl alcohol (30 g) and carboxymethyl cellulose calcium (10 g) were mixed in a mortar and then kneaded with 22 g of 20% ethanol. The blend was sieved through a 1.19mm (14-mesh) screen and dried at 40°C for 6 hours. The dried particles were classified by passage through a 1.68mm (10-mesh) screen to prepare a granulation.

The granules were filled into No. 3 capsules so that each of them would contain 100 mg of the granules.

Comparative capsules were prepared under the same conditions except that fumaric acid and stearyl alcohol were replaced by an equal amount of mannitol.

Each of the two groups of capsules was divided into two subgroups. They were put into glass bottles and stored under accelerated conditions at 40°C. One set of subgroups was held for 3 months with the bottles screw-capped in the presence of a desiccant (silica gel), whereas the other set was held for 3 months with the bottles screw-capped but in the absence of silica gel. The results of this stability test are shown in Table 6.

Table 6

Tablet	Residual nicorandil (%)	
	with a desiccant	without desiccant
sample of the invention	98.9	96.5
comparative sample	56.3	19.2

Example 7

Tablet formulation (for one tablet)

Nicorandil	10 (mg)
Mannitol	52
Salicylic acid	5
Palmitic acid	2
Cornstarch	10
Crystalline cellulose	20
Calcium stearate	1
Total	100.0 (mg)

Nicorandil (10 g), mannitol (52 g), salicylic acid (5 g), palmitic acid (2 g), cornstarch (10 g), crystalline cellulose (20 g) and calcium stearate (1 g) were mixed in a polyethylene bag.

Using a single-punch tablet machine equipped with 7-mm$^{\phi}$ flat-faced punches, the mixed powder was compressed at 98 MPa (1 ton) to make tablets each weighing 100 mg.

Comparative tablets were made under the same conditions except that salicylic acid and palmitic acid were replaced by an equal amount of mannitol.

Each of the two groups of tablets was divided into two subgroups. They were put into glass bottles and stored under accelerated conditions at 40°C. One set of subgroups was held for 3 months with the bottles screw-capped, whereas the other set of subgroups was held for 3 months at 61.5% R.H. with the bottles left open. The results of this stability test are shown in Table 7.

Table 7

Tablet	Residual nicorandil (%)	
	in closed bottles	in open bottles at 61.5% R.H.
sample of the invention	78.2	81.3
comparative sample	41.8	5.5

Example 8

Slow-release tablet formulation (for one tablet)

	Lower layer	Upper layer
Nicorandil	10 (mg)	-
Fumaric acid	85.5	39.8 (mg)
Stearic acid	4	-
Calcium stearate	0.5	0.2
Total	100.0 (mg)	40.0 (mg)

Nicorandil (10 g), fumaric acid (85.5 g), stearic acid (4 g) and calcium stearate (0.5 g) were mixed well in a polyethylene bag to prepare a mixture (mixed powder A).

In a separate step, fumaric acid (39.8 g) and calcium stearate (0.2 g) were mixed in a polyethylene bag to prepare a mixture (mixed powder B).

Using a single-punch tablet machine equipped with 8-mm$^{\phi}$ flat-faced punches, mixed powder A (100 mg) was filled into the die and lightly compressed. Then, mixed powder B (40 mg) was fed on the compressed mixed powder A and compressed at 128 MPa (1.3 tons) to make slow-release tablets.

Comparative Example

Slow-release tablet formulation (for one tablet)

	Lower layer	Upper layer
Nicorandil	10 (mg)	-
Hydroxypropyl cellulose	89.5	39.8 (mg)
Calcium stearate	0.5	0.2
Total	100.0 (mg)	40.0 (mg)

Nicorandil (10 g), hydroxypropyl cellulose (89.5 g, HPC-L of Nippon Soda Co., Ltd.) and calcium stearate (0.5 g) were mixed well in a polyethylene bag to make a mixture (mixed powder A).

In a separate step, hydroxypropyl cellulose (39.8 g, HPC-L) and calcium stearate (0.2 g) were mixed well in a polyethylene bag to make a mixture (mixed powder B).

Using a single-punch tablet machine equipped with 8-mm$^{\phi}$ flat-faced punches, mixed powder A (100 mg) was filled into the dies and lightly compressed. Then, mixed powder B (40 mg) was fed on the compressed mixed powder A and compressed at 128MPa (1.3 tons) to make comparative slow-release tablets.

The two types of slow-release tablets were subjected to a dissolution test and the results are shown as dissolution profiles in Fig. 1. The dissolution test was conducted in 500 ml of distilled water by the method defined in Japanese Pharmacopoeia, 10th Edition, Dissolution Test Method 1 (the rotary basket method) at a rotational speed of 100 rpm.

Each of the two groups of slow-release tablets was divided into two subgroups. They were put into glass bottles and stored under accelerated conditions at 50°C. One set of subgroups was held for 10 days in the presence of a desiccant (silica gel) with the bottles screw-capped. The other set of subgroups was held for 5 days at 50% R.H. with the bottles left open. The results of this stability test are shown in Table 8.

Table 8

Tablet	Residual nicorandil (%)	
	in closed bottles containing silica gel	in open bottles at 50% R.H.
sample of the invention	91.3	95.6
comparative sample	65.4	44.5

Claims

1. A process for producing a stable nicorandil-containing pharmaceutical preparation which comprises mixing nicorandil with a saturated higher aliphatic acid or a saturated higher alcohol both of which are solid at ordinary temperatures, and formulating the mixture in a suitable dosage form.

2. A process according to claim 1 wherein in addition fumaric acid, oxalic acid, salicylic acid, tartaric acid and/or glutaric acid are admixed.

3. A process according to Claim 1 or 2 wherein the saturated higher aliphatic acid is palmitic acid or stearic acid.

4. A process according to Claim 1 or 2 wherein the saturated higher alcohol is cetyl alcohol or stearyl alcohol.

5. A process according to Claim 2 wherein the organic acid is present in an amount of at least 0.1% of the total weight of the nicorandil-containing preparation.

6. A process according to Claim 1 or 2 wherein the saturated higher aliphatic acid and/or the saturated higher alcohol both of which are solid at ordinary temperatures is present in an amount of at least 0.5% of the total weight of the nicorandil-containing preparation.

Revendications

1. Procédé de production d'une préparation pharmaceutique stable contenant du nicorandil, qui comprend le mélange du nicorandil avec un acide aliphatique supérieur saturé ou un alcool supérieur saturé qui sont tous deux solides aux températures ordinaires, et le façonnage du mélange en une forme dosée appropriée.

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4. A process according to Claim 1 or 2 wherein the saturated higher alcohol is cetyl alcohol or stearyl alcohol.

5. A process according to Claim 2 wherein the organic acid is present in an amount of at least 0.1% of the total weight of the nicorandil-containing preparation.

6. A process according to Claim 1 or 2 wherein the saturated higher aliphatic acid and/or the saturated higher alcohol both of which are solid at ordinary temperatures is present in an amount of at least 0.5% of the total weight of the nicorandil-containing preparation.

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2. Procédé suivant la revendication 1, dans lequel de l'acide fumarique, de l'acide oxalique, de l'acide salicylique, de l'acide tartrique et/ou de l'acide glutarique sont incorporés de surcroît.

3. Procédé suivant la revendication 1 ou 2, dans lequel l'acide aliphatique supérieur saturé est l'acide palmitique ou l'acide stéarique.

4. Procédé suivant la revendication 1 ou 2, dans lequel l'alcool supérieur saturé est l'alcool cétylique ou l'alcool stéarylique.

5. Procédé suivant la revendication 2, dans lequel l'acide organique est présent en une quantité d'au moins 0,1% du poids total de la préparation contenant du nicorandil.

6. Procédé suivant la revendication 1 ou 2, dans lequel l'acide aliphatique supérieur saturé et/ou l'alcool supérieur saturé, qui sont tous deux solides aux températures ordinaires, sont présents en une quantité d'au moins 0,5% du poids total de la préparation contenant du nicorandil.

Ansprüche

1. Verfahren zur Herstellung von stabilen Nicorandil-haltigen Arzneimitteln, umfassend das Vermischen von Nicorandil mit gesättigten höheren aliphatischen Säuren oder gesättigten höheren Alkoholen, die beide bei Normaltemperatur fest sind, und das Aufbereiten des Gemisches zu einer geeigneten Verabreichungsform.

2. Verfahren nach Anspruch 1, wobei zusätzlich Fumarsäure, Oxalsäure, Salicylsäure, Weinsäure und/oder Glutarsäure mit vermischt wird.

3. Verfahren nach Anspruch 1 oder 2, wobei die gesättigte höhere aliphatische Säure Palmitinsäure oder Stearinsäure ist.

4. Verfahren nach Anspruch 1 oder 2, wobei der gesättigte höhere Alkohol Cetylalkohol oder Stearylalkohol ist.

5. Verfahren nach Anspruch 2, wobei die organische Säure in einer Menge von mindestens 0,1 % bezogen auf das Gesamtgewicht der Nicorandil-haltigen Zubereitung enthalten ist.

6. Verfahren nach Anspruch 1 oder 2, wobei die gesättigte höhere aliphatische Säure und/oder der gesättigte höhere Alkohol, die beide bei gewöhnlichen Temperaturen fest sind, in einer Menge von mindestens 0,5 % bezogen auf das Gesamtgewicht der Nicorandil-haltigen Zubereitung enthalten sind.