Description

The present invention relates to an N-(2-hydroxyethyl)-nicotinamide nitrate ester (generally known as nicorandil)-containing preparation for injection. More particularly, the present invention pertains to a nicorandil-containing non-liquid type preparation for injection that has improved stability.

Nicorandil has coronary vasodilative, peripheral circulation improving and antispasmodic actions and is widely used in tablet form for ischemic heart disease treatment, particularly for remission or prevention of anginose attack. Nicorandil also has antiarrhythmia and cerebral circulation improving actions and it is therefore expected that it may be effectively used as a nicorandil-containing preparation for injection which may be used to improve the systemic circulation state of a patient undergoing a surgical operation and for treating patients suffering from cerebral disease in an acute condition.

However, nicorandil involves the following disadvantages. Since nicorandil has a nitric ester group, nicorandil preparations are not stable in aqueous solutions in the same manner as other drugs that have nitric ester groups, and consequently a nicorandil preparation in an aqueous solution undergoes a decomposition reaction which starts with hydrolysis of the nitric ester. Nicorandil preparations also undergo a polymerization reaction on heating. For these reasons, it has heretofore been impossible to form a stable nicorandil-containing preparation for injection.

Thus, the technical problem underlying the present invention is to provide nicorandil-containing preparations for injection that have improved stability. As a result, it was found that nicorandil-containing preparations for injection that have excellent stability can be obtained by using an alkali metal salt of an organic acid as a stabilizer and forming the preparation to be of the non-liquid type.

Thus, the present invention relates to a non-liquid type preparation for injection which comprises nicorandil and an alkali metal salt of an organic acid.

Examples of alkali metal salts of organic acids are those of acetic acid, propionic acid, butyric acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, maleic acid, fumaric acid, tartaric acid, citric acid, alginic acid, glutamic acid, preferably the Na and K salts.

Particularly preferred alkali metal salts of organic acids are the Na and K salts of citric acid, malonic acid, succinic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid and salicylic acid. These alkali metal salts may be employed alone or in the form of a mixture consisting of two or more selected from the above-described substances.

The proportion of the alkali metal salt of the organic acid to be blended with the ester component is generally from 10% to 1,000%, preferably from 50% to 500%, relative to the amount of nicorandil. If the proportion of the stabilizer is less than 10%, the stability of the resultant nicorandil preparation will not be improved satisfactorily. Any proportion exceeding 1,000% fails to provide any greater improvement in the stability of the nicorandil preparation.

In the preparation for injection according to the present invention, an excipient, a solubilizer, an osmotic pressure adjuster, a pH adjuster and the like, provided that they are pharmaceutically permissible, may be employed if necessary. Examples of excipients that may be used in the present invention include mannitol, inositol, glucose, lactose, dextran, etc. As the solubilizer, it is possible to use cyclodextrin, lecithin, polyethyleneglycol, polyoxyethylene sorbitan monolaurylate, polyoxyethylene stearic acid, triglyceride and HC0-60 a commodity code denoting polyoxyethylene hydrogenated castor oil 60.

Examples of suitable osmotic pressure adjusters are sodium chloride, potassium chloride, sodium bromide, sorbitol and glucose.

Examples of suitable pH adjusters are citric acid, tartaric acid and sodium hydroxide.

The preparation for injection according to the present invention may be produced by any known method. Above all, the freeze-drying method and the powder packing method are preferred. According to the freeze-drying method, nicorandil, the alkali metal salt of the organic acid as a stabilizer, and additives including an excipient, are dissolved in an appropriate solvent and sterilized by filtration. Thereafter, the solution is frozen to remove water or the solvent by means of sublimation. The nicorandil may be crystallized during the freeze-drying operation, or may be left in an amorphous state.

In the powder packing method, nicorandil which has been recrystallized in advance under an aseptic condition is blended, in an aseptic environment, with additives including an excipient, and an alkali metal salt of the organic acid as a stabilizer which have been sterilized by heating, filtration or a sterilizing gas separately from the nicorandil, and the blend is packed in a suitable vessel to obtain a nicorandil-containing preparation.

The preparation for injection according to the present invention shows substantially no degradation of the pharmacological action due to decomposition of nicorandil even when it is stored for a long period of time. Thus, it is possible, according to the present invention, to obtain a nicorandil-containing preparation for

injection that has greatly improved stability.

The following examples are provided for the purpose of further illustrating the present invention but are not to be construed as limiting.

Example 1

Nicorandil (0.2 g), sodium citrate (0.5 g) and mannitol (3 g) were dissolved in 100 ml of distilled water for injection. After filtration for sterilization, the solution was pipetted into vials, 1 ml for each, and the freeze-dried by a conventional method to obtain a freeze-dried preparation.

Example 2

Nicorandil (0.2 g), sodium citrate (0.5 g) and mannitol (3 g) were dissolved in a solvent under an aseptic condition and recrystallized, and 37.0 mg of the crystals thus formed was packed into each of the vials to obtain an injectable powder.

Example 3

A freeze-dried preparation was obtained in the same way as in Example 1 except that the sodium citrate (0.5 g) employed in Example 1 was replaced by sodium maleate (0.5 g).

Example 4

A freeze-dried preparation was obtained in the same way as in Example 1 except that the sodium citrate (0.5 g) employed in Example 1 was replaced by sodium malonate (0.5 g).

Comparative Example 1

A freeze-dried preparation having no stabilizer added thereto was obtained in the same way as in Example 1 except that the system did not use sodium citrate (0.5 g) as in Example 1.

Comparative Example 2

A injectable powder having no stabilizer added thereto was obtained in the sane way as in Example 2 except that the system did not use sodium citrate (0.5 g) as in Example 2.

Experimental Example

The preparations for injection which were obtained in Examples 1 to 4 and Comparative Examples 1 and 2 were stored in a constant temperature bath at 40° C, and the time-dependent change of the residual amounts of nicorandil was measured by HPLC. The results are shown in Table 1 wherein the numerals indicate the residual amounts of nicorandil in each preparation as a percentage of the initial weight. As will be clear from Table 1, it is confirmed that the preparations according to the present invention exhibit excellent stability.

Table 1

Samples	Residual nicorandil (%)	
	15 days at 40°C	30 days at 40°C
Example 1	96.5	89.0
2	99.7	92.1
3	98.0	90.2
4	98.5	92.0
Comparative Example 1	28.9	0
2	92.3	75.0

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A non-liquid type preparation for injection which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester and an alkali metal salt of an organic acid.

2. A freeze-dried preparation which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, these ingredients having been dissolved in a solvent, sterilized by filtration and freeze-dried.

3. A powdery preparation for injection which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, these ingredients having been dissolved in a solvent under an aseptic condition and recrystallized.

4. A preparation according to any one of claims 1 to 3, wherein the proportion of the alkali metal salt of the organic acid to the nitrate ester is 10 to 1000 %, preferably 50 to 500 %, relative to the amount of the nitrate ester.

5. A method for producing a freeze-dried preparation which comprises the steps of:
dissolving in a solvent N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable; sterilizing the solution by filtration; and freeze-drying the sterilized solution.

6. A method for producing an injectable powder which comprises the steps of:
dissolving N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, in a solvent under an aseptic condition; and recrystallizing the solution.

Claims for the following Contracting States : AT, ES, GR

1. A method for producing a non-liquid type preparation for injection which comprises combining N-(2-hydroxyethyl)-nicotinamide nitrate ester and an alkali metal salt of an organic acid.

2. A method for producing a freeze-dried preparation which comprises the steps of:
dissolving in a solvent N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable; sterilizing the solution by filtration; and

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1. A non-liquid type preparation for injection which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester and an alkali metal salt of an organic acid.

2. A freeze-dried preparation which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, these ingredients having been dissolved in a solvent, sterilized by filtration and freeze-dried.

3. A powdery preparation for injection which comprises N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, these ingredients having been dissolved in a solvent under an aseptic condition and recrystallized.

4. A preparation according to any one of claims 1 to 3, wherein the proportion of the alkali metal salt of the organic acid to the nitrate ester is 10 to 1000 %, preferably 50 to 500 %, relative to the amount of the nitrate ester.

5. A method for producing a freeze-dried preparation which comprises the steps of:
dissolving in a solvent N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable; sterilizing the solution by filtration; and freeze-drying the sterilized solution.

6. A method for producing an injectable powder which comprises the steps of:
dissolving N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, in a solvent under an aseptic condition; and recrystallizing the solution.

Claims for the following Contracting States : AT, ES, GR

1. A method for producing a non-liquid type preparation for injection which comprises combining N-(2-hydroxyethyl)-nicotinamide nitrate ester and an alkali metal salt of an organic acid.

2. A method for producing a freeze-dried preparation which comprises the steps of:
dissolving in a solvent N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable; sterilizing the solution by filtration; and

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freeze-drying the sterilized solution.

3. A method for producing an injectable powder which comprises the steps of:
dissolving N-(2-hydroxyethyl)-nicotinamide nitrate ester, an alkali metal salt of an organic acid, and an excipient that is pharmaceutically acceptable, in a solvent under an aseptic condition; and recrystallizing the solution.

4. A method according to any one of claims 1 to 3, wherein the proportion of the alkali metal salt of the organic acid to the nitrate ester is 10 to 1000 %, preferably 50 to 500 %, relative to the amount of the nitrate ester.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Préparation de type non liquide à injecter qui comprend de l'ester nitrique de N-(2-hydroxyéthyl)-nicotinamide et un sel de métal alcalin d'un acide organique.

2. Préparation lyophilisée qui comprend de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, un sel de métal alcalin d'un acide organique et un excipient qui est pharmaceutiquement acceptable, ces constituants ayant été dissous dans un solvant, stérilisés par filtration et lyophilisés.

3. Préparation en poudre à injecter qui comprend de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, un sel de métal alcalin d'un acide organique et un excipient qui est pharmaceutiquement acceptable, ces constituants ayant été dissous dans un solvant dans des conditions aseptiques et recristallisés.

4. Préparation suivant l'une quelconque des revendications 1 à 3, dans laquelle la proportion du sel de métal alcalin de l'acide organique à l'ester nitrique est de 10 à 1000%, de préférence de 50 à 500%, par rapport à la quantité de l'ester nitrique.

5. Procédé de production d'une préparation lyophilisée, qui comprend les stades :
de dissolution de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, d'un sel de métal alcalin d'un acide organique et d'un excipient qui est pharmaceutiquement acceptable dans un solvant;
de stérilisation de la solution par filtration, et
de lyophilisation de la solution stérilisée.

6. Procédé de production d'une poudre à injecter, qui comprend les stades :
de dissolution de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, d'un sel de métal alcalin d'un acide organique et d'un excipient qui est pharmaceutiquement acceptable dans un solvant dans des conditions aseptiques, et
de recristallisation de la solution.

Revendications pour les Etats contractants suivants : AT, GR, ES

1. Procédé de production d'une préparation de type non liquide à injecter, qui comprend la combinaison de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide et d'un sel de métal alcalin d'un acide organique.

2. Procédé de production d'une préparation lyophilisée, qui comprend les stades :
de dissolution de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, d'un sel de métal alcalin d'un acide organique et d'un excipient qui est pharmaceutiquement acceptable dans un solvant;
de stérilisation de la solution par filtration, et
de lyophilisation de la solution stérilisée.

3. Procédé de production d'une poudre à injecter, qui comprend les stades :
de dissolution de l'ester nitrique de N-(2-hydroxyéthyl)nicotinamide, d'un sel de métal alcalin d'un acide organique et d'un excipient qui est pharmaceutiquement acceptable dans un solvant dans des conditions aseptiques, et
de recristallisation de la solution.

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4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel la proportion du sel de métal alcalin de l'acide organique à l'ester nitrique est de 10 à 1000%, de préférence de 50 à 500%, par rapport à la quantité de l'ester nitrique.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Injektionspräparat in nicht-flüssiger Form, das N-(2-Hydroxyethyl)-nicotinamidnitratester und ein Alkalimetallsalz einer organischen Säure umfaßt.

2. Gefriergetrocknetes Präparat, das N-(2-Hydroxyethyl)-nicotinamidnitratester, ein Alkalimetallsalz einer organischen Säure und einen pharmazeutisch verträglichen Exzipienten umfaßt, wobei diese Bestandteile in einem Lösungsmittel gelöst, durch Filtration sterilisiert und gefriergetrocknet worden sind.

3. Pulverförmiges Injektionspräparat, das N-(2-Hydroxyethyl)-nicotinamidnitratester, ein Alkalimetallsalz einer organischen Säure und einen pharmazeutisch verträglichen Exzipienten umfaßt, wobei diese Bestandteile in einem Lösungsmittel unter keimfreien Bedingungen gelöst und umkristallisiert worden sind.

4. Präparat nach einem der Ansprüche 1 bis 3, worin das Mengenverhältnis des Alkalimetallsalzes der organischen Säure zu dem Nitratester 10 bis 1000%, vorzugsweise 50 bis 500%, relativ zur Menge des Nitratesters, beträgt.

5. Verfahren zur Herstellung eines gefriergetrockneten Präparats, das die folgenden Schritte umfaßt: Lösen von N-(2-Hydroxyethyl)-nicotinamidnitratester, eines Alkalimetallsalzes einer organischen Säure und eines pharmazeutisch verträglichen Exzipienten in einem Lösungsmittel, Sterilisation der Lösung durch Filtration und Gefriertrocknung der sterilisierten Lösung.

6. Verfahren zur Herstellung eines injizierbaren Pulvers, das die folgenden Schritte umfaßt: Lösen von N-(2-Hydroxyethyl)-nicotinamidnitratester, eines Alkalimetallsalzes einer organischen Säure und eines pharmazeutisch verträglichen Exzipienten in einem Lösungsmittel unter keimfreien Bedingungen und Umkristallisation der Lösung.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung eines Injektionspräparats in nicht-flüssiger Form, umfassend das Vereinigen von N-(2-Hydroxyethyl)-nicotinamidnitratester und einem Alkalimetallsalz einer organischen Säure.

2. Verfahren zur Herstellung eines gefriergetrockneten Präparats, das die folgenden Schritte umfaßt: Lösen von N-(2-Hydroxyethyl)-nicotinamidnitratester, eines Alkalimetallsalzes einer organischen Säure und eines pharmazeutisch verträglichen Exzipienten in einem Lösungsmittel, Sterilisation der Lösung durch Filtration und Gefriertrocknung der sterilisierten Lösung.

3. Verfahren zur Herstellung eines injizierbaren Pulvers, das die folgenden Schritte umfaßt: Lösen von N-(2-Hydroxyethyl)-nicotinamidnitratester, eines Alkalimetallsalzes einer organischen Säure und eines pharmazeutisch verträglichen Exzipienten in einem Lösungsmittel unter keimfreien Bedingungen und mkristallisation der Lösung.

4. Verfahren nach einem der Ansprüche 1 bis 3, worin das Mengenverhältnis des Alkalimetallsalzes der organischen Säure zu dem Nitratester 10 bis 1000%, vorzugsweise 50 bis 500%, relativ zur Menge des Nitratesters, beträgt.