

Description

This invention relates to pharmaceutical preparations for administration by percutaneous absorption that contain Nicorandil and to a method for their manufacture. More particularly, it relates to pharmaceutical preparations for administration by percutaneous absorption such as tapes and/or sheets (hereinafter refer to as tapes) and ointments, etc., that have excellent absorbability through the skin and that moreover are very stable in terms of the ingredients of the pharmaceutical agents contained therein.

Nicorandil, or N-(2-hydroxyethyl)nicotinamide nitrate, is an effective drug for the treatment of angina pectoris caused by many kinds of disorders, as it acts to dilate the coronary vessels and to inhibit contractions of the coronary veins, without much effect on the blood flow through the heart or on heart function (Japanese Patent Publication 58-17463). This Nicorandil is commercially available as a drug to be taken orally. However, in general, when a drug is taken orally, its rate of absorption varies according to the conditions in the stomach and the intestines, such as the pH, the present or absence of other contents, etc., and so it is difficult for the drug to be absorbed gradually at a steady rate over a long period of time. When the Nicorandil mentioned above is given orally, it sometimes causes side effects such as orthostatic hypotension and headache, caused when there is a rapid increase of the level of this agent in the blood.

It is known that some drugs for which it is difficult to achieve a uniform rate of absorption by the oral route can be given in the form of a pharmaceutical preparation with administration by percutaneous absorption. One typical drug for angina pectoris is a preparation of nitroglycerin in tape form (Japanese Patent Laid-Open 58-133381). A preparation of the Nicorandil mentioned above in tape form has also been proposed. For example, in Japanese Patent Laid-Open 59-10513, it has been proposed that a polymer with a glass transition point, T_g , of -70 to -10°C and with the property of adhesion with pressure at ordinary temperatures, be bound to Nicorandil, and that this pharmaceutical preparation be made into tape form by being layered onto a support.

In the pharmaceutical preparation in tape form disclosed in Japanese Patent Laid-Open 59-10513 mentioned above, the basic necessary conditions are given, such as that the structure of the polymer that makes up the base material must be suitably compatible with the Nicorandil, that the greater part of the Nicorandil must not become crystallized in the base material, that the Nicorandil is supplied from the base material at a rate suitable for absorption into the skin, etc. However, Nicorandil is relatively unstable at conditions of high temperature or high humidity, or in solution (Iyakuin Kenkyu, vol. 14 (issue 6), pp. 968 - 979, 1983), and among the agents absorbed percutaneously that satisfy the conditions mentioned above in the report, Nicorandil is extremely unstable, and the stability during storage for long periods of time needed for pharmaceutical preparations cannot be ensured.

The pharmaceutical preparation with administration by percutaneous absorption of this invention, which overcomes the above-discussed and numerous other disadvantages and deficiencies of the prior art, comprises Nicorandil and/or a pharmaceutically acceptable salt thereof and an absorbefacient for percutaneous absorption in a base material characterized in that said Nicorandil and/or a pharmaceutically acceptable salt thereof is evenly distributed throughout the base material as fine crystals that have a mean diameter of $2\text{ }\mu\text{m}$ to $50\text{ }\mu\text{m}$.

In a preferred embodiment, the mean diameter of granules of the Nicorandil and/or its salt mentioned above is $4 - 30\text{ }\mu\text{m}$.

In a preferred embodiment, the pharmaceutical preparation mentioned above is a tape or an ointment.

The method for the manufacture of the pharmaceutical preparation for administration by percutaneous absorption of this invention comprises dissolving the Nicorandil and/or its salt in a solvent that is a good solvent for said Nicorandil, and dissolving the base material in a solvent that is a poor solvent for said Nicorandil, mixing these two solutions to give a solution of a mixture that contains precipitated crystals of Nicorandil with a mean diameter of $2 - 30\text{ }\mu\text{m}$, and substantially removing said good solvent and said poor solvent from said solution of the mixture.

In a preferred embodiment, the solution of the mixture mentioned above has absorbefacient for percutaneous absorption.

In a preferred embodiment, the method mentioned above involves the application of the solution mixture mentioned above to a support, and the substantial removal of the solvents by drying, resulting in a tape with an adhesive layer that contains said Nicorandil on the flexible support.

In a preferred embodiment, the base material mentioned above is hydrophobic.

In a preferred embodiment, the base material mentioned above is an adhesive rubber base material.

In a preferred embodiment, the adhesive rubber base material mentioned above is 1,4-cis-polybutadiene.

In a preferred embodiment, the adhesive rubber base material is an adhesive of silicone rubber.

In a preferred embodiment, the salt of Nicorandil mentioned above is a salt of Nicorandil and an organic acid, and the organic acid is at least one selected from the group consisting of fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid and p-toluenesulfonic acid.

In a preferred embodiment, the absorbefacient for percutaneous absorption mentioned above is 1-dodecylazacycloheptane-2-one.

In a preferred embodiment, the absorbefacient for percutaneous absorption mentioned above is a combination of the fatty acid esters and compounds that have an amide bond, and the compounds that have an amide bond include at least one selected from the group consisting of N-acylsarcosine, monoethanolamides derived from fatty acids, diethanolamides derived from fatty acids, alkyleneoxide adducts of monoethanolamides derived from fatty acids, and alkyleneoxide adducts of diethanolamides derived from fatty acids.

In a preferred embodiment, the good solvent mentioned above is at least one selected from the group consisting of tetrahydrofuran, dichloromethane, and chloroform and the poor solvent mentioned above is at least one selected from the group consisting of n-hexane, cyclohexane, n-pentane, cyclopentane, n-heptane, cycloheptane, toluene, and freon.

Thus, the invention disclosed herein makes possible the objects of (1) providing a pharmaceutical preparation for administration by percutaneous absorption in which the stability of the Nicorandil and/or Nicorandil salt used therein as a drug is excellent, so that it is possible to store the preparation for long periods of time, and in which, moreover, the release and/or absorbability of said drug via the skin at the time of use are excellent; (2) providing a tape or an ointment that has the excellent properties described above in (1); and (3) providing a method for the ready manufacture of the preparation that has the excellent properties mentioned above in (1).

As the base material to be used in the pharmaceutical preparation of this invention, any of those base materials that are commonly used in tapes and ointments can be used, with the kind selected in accordance with the purposes of this pharmaceutical preparation. In general, hydrophobic base materials are selected in consideration of the adhesion to the skin, the rate of supply of the drug from the pharmaceutical preparation, and the stability of the drugs contained therein.

As the base material for an ointment, plastibase, white vaseline, liquid paraffin, or fatty triglycerides with three alkyl chains of medium length, and preferably plastibase, white vaseline, and liquid paraffin, are used.

As the base material for a tape, in general, base materials that have pressure-adhesive properties at ordinary temperatures can be used. These include polyvinylalkylether, poly(meth)acrylate, polyurethane, polyamide, ethylenevinylacetate copolymer, alkylacrylate-acrylic acid copolymer, polyisoprene rubber, SIS (styrene-isoprene-styrene block copolymer), styrene-butadiene rubber, polyisobutylene rubber, isobutylene-isoprene rubber, natural rubber, 1,4-cis-polybutadiene and silicone rubber. Polyisoprene rubber, polyisobutylene rubber, isobutylene-isoprene rubber, 1,4-cis-polybutadiene, silicone rubber, which have almost no compatibility with Nicorandil, are particularly preferred. Moreover, of the base materials mentioned above, rubber-type base materials, and in particular, base materials that contain 1,4-cis-polybutadiene, or silicone rubber are preferable. The 1,4-cis-polybutadiene mentioned above is preferably used in a proportion of 20 - 80% by weight in the base material. The inclusion of 1,4-cis-polybutadiene increases the stability and the release of the Nicorandil. If the proportion of 1,4-cis-polybutadiene is more than 80% by weight, the adhesion of the preparation is somewhat decreased.

The base materials listed above can be used in mixtures of two kinds or more, and stabilizers, preservatives, dispersing agents, tackifiers, softening agents, fillers, antioxidants, etc., can be added as needed.

The Nicorandil that is contained in the pharmaceutical preparation can also be in the form of the Nicorandil salt. As the Nicorandil salt, there are organic acids and/or inorganic acids of Nicorandil that are pharmaceutically acceptable. As acids from which Nicorandil salt can be formed, there are hydrochloric acid, oxalic acid, p-toluenesulfonic acid, fumaric acid, maleic acid, salicylic acid, tartaric acid, glutaric acid. By the formation of the salt of Nicorandil, the stability is increased. For the Nicorandil salt, either a salt made beforehand by the addition of an acid from the list given above to Nicorandil can be used, or a salt made during the preparation of the pharmaceutical (described below) can be used, at which time the salt is formed by the addition of an acid from the list given above to the mixture of base material. When acid is added in the latter case, said acid can be added in a proportion of 0.1% by weight or more of the entire mixture, and preferably, 0.1 - 20% by weight can be added. In these calculations of proportions, the entire content of the pharmaceutical preparation is meant in the case of an ointment, and the content with the support excluded is meant in the case of a tape. The meaning of content as used below in the discussions of absorbefacient content, etc., is the same as here.

The proportions of the Nicorandil and/or its salt (herein referred to as the Nicorandil (salt)) can be 0.1 -

30% by weight in the pharmaceutical preparation, and preferably, 2 - 15% by weight. Because the base materials that can be used in this invention have poor compatibility with Nicorandil (salt), most of the Nicorandil (salt) that is contained in the pharmaceutical preparation at the proportions mentioned above is dispersed throughout the base. The granule size of said drug at this time can be 2 μm or more. If the mean diameter is less than 2 μm , the stability decreases. There is no particular upper limit for the diameter of the granules, but a diameter of 50 μm or less is desirable for satisfactory release of the drug. A diameter of said drug of from 4 to 30 μm is more preferable. This diameter of the granules as defined in this text is obtained by Feret diameters under a microscope (Powders Engineering, by Shigeo Miwa; Asakura Books).

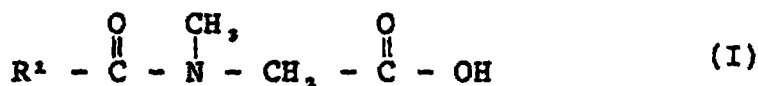
Methods that can be used to bring the Nicorandil (salt) mentioned above to the granule size mentioned above include a method of powdering said drug in a ball mill, powdering it in a jet mill, and then sieving it to obtain the preferred size; and a method in which Nicorandil (salt) is precipitated in the form of fine particles by the use of a poor solvent from a solution containing the Nicorandil (salt), etc.

The pharmaceutical preparation of this invention may contain absorbefacient for percutaneous absorption, so as to increase the absorbability of the drug mentioned above. There are no particular limits on which absorbefacients for percutaneous absorption can be used, but 1-dodecylazacycloheptane-2-one and/or a mixture of compounds that have an amide bond with fatty acid esters are particularly suitable. The compounds that have an amide bond, include at least one selected from the groups consisting of N-acylsarcosine, monoethanolamides derived from fatty acids, diethanolamides derived from fatty acids, alkyleneoxide adducts of monoethanolamides derived from fatty acids, and alkyleneoxide adducts of diethanolamides derived from fatty acids. Of course, absorbefacients other than those listed above can be used.

The absorbefacient mentioned above, 1-dodecylazacycloheptane-2-one, is available commercially from Nelson Research and Development Co., U.S.A., under the trade name of AZONE®. This compound is known for being added as an absorbefacient for percutaneous absorption to drugs such as anti-inflammatory agents, antifungal agents, etc. (Japanese Patent Laid-Open 52-1035, ditto 57-142918, ditto 58-210026, ditto 58-208216, ditto 61-27966). In addition, this compound is known for being used as an absorbefacient for absorption through the mucosa of the said drugs (Japanese Patent Laid-Open 61-109738). However, it has not yet been known as an absorbefacient for the absorption of Nicorandil. This absorbefacient can be added to the pharmaceutical preparation in a proportion of 10% by weight or less of the total weight, and preferably in a proportion of 2 - 6% by weight.

The fatty acid esters of the absorbefacients mentioned above can be used in combination with a compound that has an amide bond. These esters of fatty acids are formed by the reaction of fatty acids with an alcohol. It is preferable that the carbon number of the fatty acids be from 10 to 18, and that the number of carbons in the alcohol be from 1 to 20. As examples of such fatty acids, there are capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, sebacic acid, adipic acid; as such alcohols, there are methanol, ethanol, propanol, isopropanol, glycerin. As the fatty acid esters formed from the fatty acids and alcohols listed above, there are, for example, isopropyl caprate, propyl laurate, octyldodecyl myristate, myristyl myristate, isopropyl myristate, isopropyl palmitate, ethyl stearate, and methyl sebacate. Of these, isopropyl myristate and isopropyl palmitate are especially suitable. The fatty acid esters can be present in the proportion of 80% by weight or less, preferably 1 - 80 parts by weight, and more preferably 10 - 60 parts by weight to 100 parts by weight of the base material. That this fatty acid ester can be mixed with propylene glycol so as to be used as an absorbefacient for the absorption of Nicorandil is known (107th annual meeting of the Pharmaceutical Society of Japan, Proceedings, p. 841, March 10, 1987).

Of the compounds that have an amide bond, N-acylsarcosine is sarcosine (N-methylglycine) with the acyl group having 6 - 18 carbons replaced with the nitrogen of amino groups. Its structure is as shown in the formula (I) below.

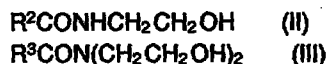


where R¹ is an aliphatic hydrocarbyl group with 5 - 17 carbons.

The above compound (I), N-acylsarcosine, is a sarcosine derivative of fatty acids with 6 - 18 carbons. As fatty acids for the formation of N-acylsarcosine, there include, among other compounds: caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, lauric acid, myristic acid, palmitic acid, margaric acid, stearic acid, hexadecenoic acid, oleic acid, and linoleic acid. The salt of N-acylsarcosine can also be used. Of the different forms of N-acylsarcosine, the lauric acid derivative, lauroylsarcosine, and its salt give

particularly good results. The proportion of N-acylsarcosine that can be used is 30 parts by weight or less, and preferably, 0.01 - 30 parts by weight; more preferably, 0.5 - 10 parts by weight to 100 parts by weight of the base material should be used.

Of the compounds that have an amide bond mentioned above, the structures of monoethanolamides derived from fatty acids (II) and diethanolamides derived from fatty acids (III) are as shown in the formulae below.



where R^2 and R^3 are aliphatic hydrocarbonyl groups with 5 - 17 carbons.

Monoethanolamides derived from fatty acids (II) are formed by a reaction of fatty acids with monoethanolamine, and diethanolamides derived from fatty acids (III) are formed by the reaction of fatty acids with diethanolamine. The fatty acids from which compounds (II) and (III) can be formed have 6 - 18 carbons (corresponding to an R^2 or R^3 of 5 - 17). Of such fatty acids, octanoic acid, capric acid, lauric acid, myristic acid, etc., can be mentioned. It is also suitable to use fatty acids derived from coconut oil, which is a mixture of the compounds above. Of the compounds that have the structural formula of (II) or (III), lauroylmonoethanolamide and lauroyldiethanolamide are particularly preferred.

As the compound that has an amide bond, compounds with the structures of (II) or (III) above to which alkyleneoxide is added (that is, polyoxyalkylene monoethanolamides derived from fatty acids, and polyoxyalkylene diethanolamides derived from fatty acids) can also be used. The number of moles of alkyleneoxide that can be added are 1 - 40, and preferably 2 - 20. Here, by "one mole is added" we mean, for the case of monoethanolamides derived from fatty acids, that one molecule of alkyleneoxide is added to the hydroxyl group in said molecule, and, for the case of diethanolamides derived from fatty acids, that for each of the two hydroxyl groups in said molecules, one molecule of alkyleneoxide is added to each. For the alkyleneoxide, ethylene oxide is suitable.

The above-mentioned N-acylsarcosine, monoethanolamides derived from fatty acids, diethanolamides derived from fatty acids, alkyleneoxide adducts of monoethanolamides derived from fatty acids, and alkyleneoxide adducts of diethanolamides derived from fatty acids can be mixed together with two or more of the compounds in the mixture, and can be used in a mixture with the further addition of the fatty acid esters mentioned above. These compounds that have an amide bond can be contained in a proportion of 30 parts by weight or less, preferably 0.5 - 10 parts by weight, and more preferably 0.5 - 10 parts by weight to 100 parts by weight of the base material, with only one or with a mixture of the compounds having an amide bond being used.

By the inclusion of an absorbefacient as mentioned above, Nicorandil (salt) is absorbed more quickly through the skin. Of the total weight of the formulation, the absorbefacient can be contained in a proportion of 100 parts by weight or less, and preferably 1 - 100 parts by weight to 100 parts by weight of the base material. If there is an excess, for example, the compatibility with the base material may be worsened, and the adhesive properties of the pharmaceutical preparation in the form of a tape may be decreased.

The support to be used when the pharmaceutical preparation of this invention is in the form of a tape can be formed at the surface of the base layer; moreover, there are no particular limits on suitable substances that are flexible provided that the flexibility is sufficient to ensure that there is no feeling of physical discomfort on the skin surface when the tape is being used. For example, films, sheets, non-woven cloth, cloth, made from polyolefin, polyurethane, polyvinylalcohol, polyvinylidenechloride, polyamide, ethylene-vinylacetate copolymer, rubber, can be used.

The pharmaceutical preparation of this invention can be obtained by, for example, the following method. First, powdered or solid Nicorandil (salt) is powdered in a ball mill, jet mill, etc., to give Nicorandil (salt) of the desired granule size prepared in advance. Next, the base material is dissolved in a solvent that is a poor solvent for the Nicorandil (salt) and a good solvent for the base material, and then the prepared Nicorandil (salt) of the desired granule size mentioned above is dispersed uniformly in the solution. The kind of base material is chosen so as to be appropriate for the intended use (whether a tape or an ointment). When a tape is to be obtained, this suspension can be painted onto the top of a support and dried so as to form an adhesive layer. It is also possible to obtain a tape by applying the above-mentioned suspension onto a suitable separating paper, and after drying it there, pasting the adhesive layer formed onto the top of the support mentioned above. An ointment can be obtained by a mixing method in which the granules of desired size of Nicorandil (salt) mentioned above are mixed directly with the base material together with other ingredients such as an absorbefacient if needed, or by other methods such as a method in which almost all of the solvent from the suspension is removed as mentioned above.

A pharmaceutical preparation that contains crystals of Nicorandil (salt) dispersed in a base material can be obtained, for example, as a tape by the application of a solution in which the Nicorandil (salt), base material, etc., are completely dissolved onto a support, and then by the removal of the solvent. However, in this method, there are several defects, such as that Nicorandil (salt) can be widely deposited from adhesive matrix onto the surface of adhesive layer, resulting in a lowered adhesion of the adhesive layer, that the absorption of the Nicorandil (salt) can decrease because large crystals of Nicorandil (salt) will gradually precipitate out.

In all of the methods mentioned above that use a fine powder of Nicorandil (salt), depending on the conditions of its manufacture, the powder particles of Nicorandil (salt) can adhere to each other during storage, and the particles can also adhere to each other in the dispersed solution, both of which are inconvenient. To avoid this, the following method of preparation can be recommended. First of all, Nicorandil (salt) is dissolved in an appropriate good solvent. As the good solvent, tetrahydrofuran, dichloromethane, chloroform, can be used. The concentration of Nicorandil (salt) is about 1 - 40% by weight. Next, the base material mentioned above is dissolved in a solvent that is a poor solvent for Nicorandil (salt) and a good solvent for said base material. As such a solvent, n-hexane, cyclohexane, n-pentane, cyclopentane, n-heptane, cycloheptane, toluene, freon, can be used. The concentration of the base material is about 5 - 50% by weight. One hundred parts by weight of this solution of base material is mixed with 0.5 - 150 parts by weight of the solution of Nicorandil (salt) mentioned above and agitated, which allows fine crystals of Nicorandil (salt) to precipitate out of solution. The mean particle size of the precipitated Nicorandil (salt) depends on the concentration of the Nicorandil (salt), the kind of solvent, the temperature, and so on, but is usually 2 - 30 μm . When a tape is to be prepared, it is possible to apply this suspension of Nicorandil (salt) to the support mentioned above, to dry it, and to remove thereby almost all of the solvents (the good solvent and the poor solvent mentioned above). In this way, it is possible to obtain a tape in which there are fine crystals of Nicorandil (salt) in a layer of base material. If the suspension mentioned above is applied to an appropriate separation paper, and dried, after which the layer of base material formed can be pasted to the support mentioned above, a tape can also be obtained. An ointment can be obtained by the removal of the solvents so as to concentrate the suspension of Nicorandil (salt) mentioned above. The diameter of the particles of the Nicorandil (salt) obtained is 2 μm or more, is usually 2 - 50 μm , and preferably is 4 - 30 μm .

By the methods of manufacture mentioned above, the precipitated Nicorandil (salt) obtained during the manufacturing process ordinarily exists in the solvent, dispersed uniformly throughout the base material. For that reason, it is possible to obtain a pharmaceutical preparation with Nicorandil (salt) that is uniform in diameter and that moreover is uniformly distributed in the base material. With the use of this kind of pharmaceutical preparation, there are the advantages that said Nicorandil (salt) will remain stable, without being decomposed, and that the Nicorandil (salt) will be absorbed effectively through the skin at a fixed rate because the greater part of the Nicorandil (salt) is uniformly dispersed in the pharmaceutical preparation in the form of fine particles. By these methods, there is no need for a step in which the powdered Nicorandil (salt) is sieved.

40 Example 1.1

Silicone rubber	100 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 12 μm)	

To 200 parts by weight of a solution of 50% by weight of silicone rubber (trade name, Silascon 355 Medical Adhesive; Dow Corning Corp.) in freon, 3 parts by weight of Nicorandil suspended in cyclohexane was added. The mixture was agitated in a dissolver to give a suspension in which the Nicorandil was dispersed almost completely uniformly. The suspension was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried, which gave an adhesive layer. This adhesive layer was applied to a polyethylene film support, which resulted in a tape. This tape had an adhesive layer in which the Nicorandil was uniformly distributed, and in which the Nicorandil had the mean diameter of 12 μm . The amount of Nicorandil that was included was 0.29 mg/cm^2 .

This tape was placed in aluminium packaging, into which a desiccant was placed, after which the package was sealed and stored at 50°C for one week. The amount of Nicorandil in the tape was measured, and the percentage of Nicorandil remaining was calculated. Separately, a fresh preparation of tape

measuring 3 cm x 3 cm was made to adhere on the back of a rat from which the hair had been removed with a shaver, and left for 48 hours; then the area under the blood concentration vs. time curve, or AUC_{48} - (ng.hr/ml) was found. The results are shown in Table 1. Example 1.1 - 1.8 and Comparative Examples 1.1 - 1.3 were all done with the same measurements being made, and those results are also shown in Table 1.

Example 1.2

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 5.6 μ m)	

Instead of the silicone rubber, a base material composed of 25 parts by weight of SIS, 25 parts by weight of polyisoprene rubber, and 50 parts by weight of terpene resin was used. This base material was dissolved in cyclohexane at a concentration of 20% by weight. Except for the use of this solution instead of the freon solution, the procedures were carried out in the same way as in Example 1.1. The tape obtained had Nicorandil with a mean diameter of 5.6 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.3

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 25 μ m)	

Except that the mean diameter of the Nicorandil was 25 μ m, other conditions and procedures were the same as in Example 1.2. The tape obtained had Nicorandil with a mean diameter of 25 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.4

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 35 μ m)	

Except that the mean diameter of the Nicorandil was 35 μ m, other conditions and procedures were the same as in Example 1.2. The tape obtained had Nicorandil with a mean diameter of 35 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.5

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 12 μ m)	

Instead of the silicone rubber, a base material composed of 55 parts by weight of 1,4-cis-polybutadiene, 15 parts by weight of natural rubber, and 30 parts by weight of terpene resin was used. This base material was dissolved in cyclohexane at a concentration of 20% by weight. Except for the use of this solution instead of the freon solution, the procedures were carried out in the same way as in Example 1.1. The tape obtained had Nicorandil with a mean diameter of 12 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.6

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 4.3 μ m)	

Except that the mean diameter of the Nicorandil was 4.3 μ m, other conditions and procedures were the same as in Example 1.5. The tape obtained had Nicorandil with a mean diameter of 4.3 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.7

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 27 μ m)	

Except that the mean diameter of the Nicorandil was 27 μ m, other conditions and procedures were the same as in Example 1.5. The tape obtained had Nicorandil with a mean diameter of 27 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Comparative Example 1.1

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 1.5 μ m)	

Except that the mean diameter of the Nicorandil was 1.5 μ m, other conditions and procedures were the same as in Example 1.2. The tape obtained had Nicorandil with a mean diameter of 1.5 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Comparative Example 1.2

Polybutyl acrylate	100 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 12 μ m)	

Procedures were the same as in Example 1.1 except that polybutyl acrylate was used instead of the silicone rubber, and that this was put into a 20% solution by weight of ethyl acetate. The tape obtained had Nicorandil dissolved throughout the adhesive layer, and the amount of Nicorandil was 0.29 mg/cm².

Example 1.8

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandilfumarate	7.75 parts by weight
(Mean diameter: 13 μ m)	

Procedures were the same as in Example 1.5 except that 7.75 parts by weight of Nicorandilfumarate (mean diameter: 13 μ m) was used instead of Nicorandil. The tape obtained had Nicorandilfumarate with a mean diameter of 13 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.464 mg/cm².

Comparative Example 1.3

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandilfumarate	7.75 parts by weight
(Mean diameter: 1.5 μ m)	

Except that the mean diameter of the Nicorandilfumarate was 1.5 μ m, other conditions and procedures were the same as in Example 1.8. The tape obtained had Nicorandilfumarate with a mean diameter of 1.5 μ m dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.464 mg/cm².

Table 1

	Remaining Nicorandil (salt) (%) (50°C x 1 week)	AUC ₄₈ (ng.hr/ml)
Example 1.1	85.3	795
Example 1.2	66.2	891
Example 1.3	86.2	632
Example 1.4	90.5	387
Example 1.5	87.1	867
Example 1.6	83.2	926
Example 1.7	60.1	922
Comparative Example 1.1	1.2	924
Comparative Example 1.2	0.8	851
Example 1.8	99.7	1022
Comparative Example 1.3	7.1	1124

Example 1.9

Silicone rubber	100 parts by weight
Nicorandil	3 parts by weight
Salicylic acid	3 parts by weight

To 200 parts by weight of a solution of 50% by weight of silicone rubber (trade name, Silascon 355, Medical Adhesive; Dow Corning Corp.) in freon, three parts by weight of Nicorandil dissolved in 75 parts by weight of tetrahydrofuran and also 3 parts by weight of salicylic acid dispersed in cyclohexane were added. The mixture was agitated in a dissolver to give a suspension in which the drugs (Nicorandil, Nicorandil-salicylate, and salicylic acid) were dispersed almost completely uniformly. This was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried, which gave an adhesive layer. This adhesive layer was applied to a polyethylene film support, which resulted in a tape. This tape had an adhesive layer in which the drugs were uniformly distributed and in which the drugs had a mean diameter of 13 μm . The amount of Nicorandil that was included was 0.283 mg/cm². This tape was used to make measurements the same as those in Example 1.1. However, the storage period for the tape was 3 weeks. These results are shown in Table 2. Examples 1.10 to 1.14 and Comparative Examples 1.4 and 1.5 were conducted with the same measurements being made, and those results are also shown in Table 2.

Example 1.10

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
Oxalic acid	3 parts by weight

A base material is composed of 25 parts by weight of SIS, 25 parts by weight of polyisoprene rubber, and 50 parts by weight of terpene resin. In a solution of 20 percent by weight of the base material in cyclohexane, Nicorandil dissolved in 75 parts by weight of tetrahydrofuran (THF), and oxalic acid suspended in cyclohexane were added, and the mixture was agitated in a dissolver. A suspension in which the particles of the drugs (Nicorandil, Nicorandiloxalate, and oxalic acid) were almost completely uniformly dispersed was obtained. With the use of this suspension, a tape was made following the procedures of Example 1.9. This tape had an adhesive layer in which the drugs were uniformly distributed and in which the drugs had a mean diameter of 4.1 μm . The amount of Nicorandil that was included was 0.283 mg/cm².

Example 1.11

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 38 μm)	
Oxalic acid	3 parts by weight

Except for the use of a suspension of Nicorandil in cyclohexane instead of the solution of Nicorandil in THF, and for the use of a solution of oxalic acid in THF (75 parts by weight) instead of the suspension of oxalic acid in cyclohexane, the procedures were the same as in Example 1.9. The tape that was obtained had drugs dispersed therein (Nicorandil, Nicorandiloxalate and oxalic acid) the mean particle size of which was 36 μm , which particles were uniformly dispersed, and the amount of Nicorandil in the tape was 0.283 mg/cm².

Example 1.12

SIS	25 parts by weight
Polyisoprene rubber	25 parts by weight
Terpene resin	50 parts by weight
Nicorandil	3 parts by weight
(Mean diameter: 24 μm)	
Oxalic acid	3 parts by weight

Except that the mean diameter of the Nicorandil was 24 μm , other conditions and procedures were the same as in Example 1.11. The tape obtained had the drugs (Nicorandil, Nicorandil oxalate and oxalic acid) with a mean diameter of 22 μm dispersed uniformly throughout the adhesive layer, and the amount of Nicorandil was 0.283 mg/cm².

Example 1.13

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
Fumaric acid	3 parts by weight

A base material was utilized that was composed of 55 parts by weight of 1,4-cis-polybutadiene, 15 parts by weight of natural rubber, and 30 parts of terpene resin. In a solution of 20% by weight of the base material in cyclohexane, a solution of Nicorandil in THF (75 parts by weight) and a suspension of fumaric acid in cyclohexane were added, and the mixture was agitated in a dissolver. A suspension was obtained in which the particles of the drugs (Nicorandil, Nicorandilfumarate and fumaric acid) were almost completely uniformly dispersed. With the use of this suspension, a tape was made following the procedures of Example 1.9. This tape had an adhesive layer in which the drugs were uniformly distributed and in which the drugs had a mean diameter of 12 μm . The amount of Nicorandil that was included in the tape was 0.283 mg/cm².

Example 1.14

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
Fumaric acid	3 parts by weight

Except for the use of a mixture of cyclohexane:THF (1:1) in which the base material was dissolved, the procedures were the same as those of Example 1.13. A tape was obtained in which the drug particles with a mean diameter of 4.2 μm were evenly dispersed throughout the adhesive layer, and in which the amount of Nicorandil was 0.283 mg/cm².

Comparative Example 1.4

Polybutyl acrylate	100 parts by weight
Nicorandil	3 parts by weight
Salicylic acid	3 parts by weight

Except for the use of a 20% (by weight) solution of polybutyl acrylate in ethyl acetate instead of the solution of silicone rubber in freon, the procedures were the same as those of Example 1.9. A tape was obtained in which the drug was dissolved throughout the adhesive layer, and in which the amount of Nicorandil was 0.283 mg/cm².

Comparative Example 1.5

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight
Fumaric acid	3 parts by weight

Except for the use of THF in which the base material was dissolved, the procedures were the same as those of Example 1.13. A tape was obtained in which drug particles with a mean diameter of 1.7 μm were evenly dispersed throughout the adhesive layer, and in which the amount of Nicorandil was 0.283 mg/cm².

Table 2

	Remaining amount (%) (50 °C x 1 week)	AUC ₄₈ (ng.hr/ml)
Example 1.9	99.4	731
Example 1.10	91.5	851
Example 1.11	99.3	381
Example 1.12	99.1	607
Example 1.13	99.7	893
Example 1.14	96.8	1002
Comparative Example 1.4	2.1	893
Comparative Example 1.5	3.2	1080

Example 2.1 (Ointment)

Nicorandil	2 parts by weight
1-dodecylazacycloheptane-2-one (AZONE®)	5 parts by weight
Plastibase	93 parts by weight

Two parts of Nicorandil by weight and 5 parts of AZONE® by weight were put together in a mixing and grinding machine and mixed together in vacuo with the gradual addition of plastibase until a homogeneous ointment was obtained. The mean diameter of the Nicorandil in the ointment was 25 µm.

The ointment obtained was put into an airtight plastic container and stored at 50 °C for 2 weeks. After storage, the amount of Nicorandil in the ointment was assayed, and the amount remaining was calculated. Separately, 0.5 g of freshly prepared ointment was applied uniformly to a 4 × 4 cm area of the back of a rat that had had its hair removed with a shaver, and 48 hours later, the area under the blood concentration vs. time curve, or AUC₄₈, expressed as ng.hr/ml, was calculated. The calculation of AUC₄₈ × (% remaining/100) was made, and this was called the "stability parameter". These results are shown in Table 3. The same kinds of measurements were made in Examples 2.2 and 2.3, and Comparative Examples 2.1 to 2.3, and those results also are shown in Table 3.

Comparative Example 2.1

Except for the use of the same amounts of poly(oxyethylene) (9) laurylether instead of AZONE®, the procedures were the same as in Example 2.1.

Example 2.2 (Ointment)

Nicorandilfumarate	3.1 parts by weight
AZONE®	8 parts by weight
Plastibase	88.9 parts by weight

Eight parts by weight of AZONE and 3.1 parts by weight of Nicorandilfumarate were put into a mixing and grinding machine, and mixed together in vacuo with the gradual addition of plastibase, which resulted in a homogeneous ointment. The mean diameter of the Nicorandil in the ointment was 30 µm.

Comparative Example 2.2

Except for the use of poly(oxyethylene) (6) sorbitan monooleate instead of the AZONE®, the procedures were the same as in Example 2.2.

Example 2.3 (Ointment)

Nicorandil	2 parts by weight
AZONE	5 parts by weight
Fumaric acid	2 parts by weight
Plastibase	91 parts by weight

Two parts by weight of Nicorandil, 5 parts by weight of AZONE®, and 2 parts by weight of fumaric acid were put into a mixing and grinding machine, and mixed together in vacuo with the gradual addition of plastibase, which resulted in a homogeneous ointment. The mean diameter of the drugs (Nicorandil, Nicorandilfumarate and fumaric acid) in the ointment was 15 μ m.

Comparative Example 2.3

Except for the use of lauroyldiethanolamide instead of the AZONE®, the procedures were the same as in Example 2.3.

Table 3

	Remaining amount (%) (50°C x 2 weeks)	AUC ₀₋₁ (ng.hr/ml)	Stability parameter
Example 2.1	63.0	23400	14742
Comparative Example 2.1	13.3	17200	2288
Example 2.2	92.2	26842	24748
Comparative Example 2.2	26.3	13310	3500
Example 2.3	90.6	24760	22433
Comparative Example 2.3	3.9	27918	1089

Example 2.4

Polyvinylisobutylether	70 parts by weight
Polyvinylethylether	30 parts by weight
Nicorandil	5 parts by weight
(Mean diameter: 13 μ m)	
AZONE®	5.53 parts by weight

To a cyclohexane solution containing a mixture of 70 parts by weight of polyvinylisobutylether (trade name, Lutonal IC 125; BASF Co.) and 30 parts by weight of polyvinylethylether (trade name, Lutonal A50; BASF Co.) in a concentration of 15%, a suspension of 5 parts by weight of Nicorandil in cyclohexane and 5.53 parts by weight of AZONE were added. This mixture was agitated in a dissolver, and a suspension in which the Nicorandil was almost completely uniformly dispersed was obtained. This was applied to a release paper liner of polyethyleneterephthalate so that its thickness would be 100 μ m after being dried. The surface of the adhesive layer that was formed was applied to a polyethylene support, to give a tape.

The mean diameter of the Nicorandil was 13 μm , and the Nicorandil was uniformly dispersed in the adhesive layer of the tape that was obtained; the amount of the Nicorandil was 0.45 mg/cm² of tape.

The same test procedure as in Example 1.1 was repeated using this tape. The results are shown in Table 4. Example 2.5 and Comparative Examples 2.4 and 2.5 were conducted using the same procedure. Those results are also shown in Table 4.

Comparative Example 2.4

Except for the use of oleoylsarcosine instead of AZONE® in the same amounts, the procedures were the same as in Example 2.4

Example 2.5

Polyvinylisobutylether	70 parts by weight
Polyvinylethylether	30 parts by weight
Nicorandilfumarate	7.75 parts by weight
AZONE®	5.53 parts by weight

Except for the use of 7.75 parts by weight of Nicorandilfumarate (mean diameter: 12 μm) instead of 5 parts by weight of Nicorandil, the procedures were the same as in Example 2.4. A tape containing 0.44 mg of Nicorandil per cm² was obtained.

Comparative Example 2.5

Except for the use of lauroyldiethanolamide instead of AZONE® in the same amounts, the procedures were the same as in Example 2.5

Table 4

	Remaining amount (%) (50°C x 1 week)	AUC ₄₈ (ng.hr/ml)	Stability parameter
Example 2.4	58.3	8870	5171
Comparative Example 2.4	1.2	9182	110
Example 2.5	90.7	7920	7183
Comparative Example 2.5	4.0	8497	340

It can be seen from Tables 3 and 4 that the values of the stability parameters of the pharmaceutical preparation of this invention, namely, the product of 1/100 of the residual ratio (the index of drug stability) and AUC₄₈. (the index of drug absorption), are large. These results show that the absorbability of the drugs (Nicorandil (salt)) of the formulation of this invention is good, and that the stability of said drugs is excellent.

Example 3.1

1,4-cis-polybutadiene	80 parts by weight
Natural rubber	20 parts by weight
Terpene resin	20 parts by weight
Nicorandil	10 parts by weight
Fumaric acid	10 parts by weight
Isopropyl myristate	53.7 parts by weight
N-lauroylsarcosine	5.37 parts by weight

10 A base material is composed of 80 parts by weight of 1,4-cis-polybutadiene, 20 parts by weight of natural rubber, and 20 parts by weight of terpene resin. This base material was dissolved in cyclohexane at a concentration of 15% (by weight). To 100 parts by weight of polymer ingredients in the solution, a THF solution containing 10 parts by weight of Nicorandil, 10 parts by weight of fumaric acid, 5.37 parts by weight of N-lauroylsarcosine (an absorbefacient), and 53.7 parts by weight of isopropyl myristate (an absorbefacient and stabilizer) was added. This mixture was agitated in a dissolver, and a suspension that contained the drugs (Nicorandil, Nicorandilfumarate and fumaric acid) in a uniform suspension was obtained. This suspension was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried. The surface of the adhesive layer that was formed was applied to a polyethylene film support, to give a pharmaceutical preparation in the form of tape. This pharmaceutical tape had an adhesive layer in which the mean diameter of the drugs contained in it was 7 μm , and the amount of Nicorandil was 0.56 mg/cm² of tape.

20 The same test procedure as in Example 1.1 for the amount of drug remaining and the AUC₄₈, was repeated using the tape, and the stability parameter was calculated. The results are shown in Table 5. In Comparative Examples 3.1 and 3.2, the same measurements were also made. These results are also shown in Table 5.

Comparative Example 3.1

30 The procedures were the same as in Example 3.1, except that N-lauroylsarcosine (an absorbefacient) was not added.

Comparative Example 3.2

35 The procedures were the same as in Example 3.1, except that isopropyl myristate and N-lauroylsarcosine were not added.

Table 5

	Absorbefacient	AUC ₄₈	Remaining amount (%)	Stability parameter
40 Example 3.1	Isopropyl myristate + N-lauroylsarcosine	9125	95.2	8687
45 Comparative Example 3.1	Isopropyl myristate	1850	99.2	1835
50 Comparative Example 3.2	-	1205	97.2	1171

55 Example 3.2 (Ointment)

Nicorandil	5 parts by weight
Isopropyl palmitate	25 parts by weight
Lauroyldiethanolamide	2.5 parts by weight
Plastibase	67.5 parts by weight

Five parts by weight of Nicorandil, 25 parts by weight of isopropyl palmitate, and 2.5 parts by weight of lauroyldiethanolamide were placed in a mixing and grinding machine and mixed together in vacuo with the gradual addition of 67.5 parts by weight of plastibase to give an ointment. The mean diameter of the Nicorandil in the ointment was 17 μ m, and the particles of Nicorandil were dispersed uniformly.

The same test procedure as in Example 2.1 for the amount of drug remaining and the AUC₄₈ was repeated using the ointment, and the stability parameter was calculated. The storage time for the ointment was 1 week. The results are shown in Table 6. Measurements were made in the same way as in Comparative Examples 3.3 to 3.5. Those results are also shown in Table 6.

Comparative Example 3.3 (Ointment)

The procedures were the same as in Example 3.2, except that isopropyl palmitate (an absorbefacient and stabilizer) was not added.

Comparative Example 3.4

The procedures were the same as in Example 3.2, except that lauroyldiethanolamide (an absorbefacient) was not added.

Comparative Example 3.5

The procedures were the same as in Example 3.2, except that isopropyl palmitate and lauroyldiethanolamide were not added.

Table 6

	Absorbefacient	AUC ₄₈	Remaining amount (%)	Stability parameter
Example 3.2	Isopropyl palmitate + lauroyldiethanolamide	22180	79.0	17522
Comparative Example 3.3	lauroyldiethanolamide	20300	8.2	1665
Comparative Example 3.4	Isopropyl palmitate	2300	87.2	2006
Comparative Example 3.5	-	2020	85.2	1721

Example 3.3

Polyvinylisobutylether	70 parts by weight
Polyvinylethylether	30 parts by weight
Nicorandiloxalate	15 parts by weight
Isopropyl myristate	30 parts by weight
Lauroyldiethanolamide	3 parts by weight

A cyclohexane solution containing a mixture of 70 parts by weight of polyvinylisobutylether (trade name, Lutonal IC 125; BASF Co.) and 30 parts by weight of polyvinylethylether (trade name, Lutonal A50; BASF Co.) at a concentration of 15% by weight was prepared. For each 100 parts by weight of polymer ingredients in the solution, a solution of THF containing 15 parts by weight of Nicorandiloxalate, 3 parts by weight of lauroyldiethanolamide (an absorbefacient) and 30 parts by weight of isopropyl myristate (an absorbefacient and stabilizer) was added. This mixture was agitated in a dissolver, and a suspension in which the drugs were uniformly dispersed was obtained. This suspension was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried. The surface of the adhesive layer that was formed was applied to a polyethylene film support, so as to give a pharmaceutical preparation in the form of tape. This pharmaceutical tape had an adhesive layer in which the mean diameter of the Nicorandil oxalate was 11 μm and in which the Nicorandiloxalate was uniformly dispersed. The same test procedure as in Example 1.1 for the amount of drug remaining and the AUC_{48} was repeated using the tape, and the stability parameter was calculated. The results are shown in Table 7. In Comparative Examples 3.6 to 3.8, the same measurements were also made. These results are also shown in Table 7.

Comparative Example 3.6

The procedures were the same as in Example 3.3, except that isopropyl myristate (an absorbefacient and stabilizer) was not added.

Comparative Example 3.7

The procedures were the same as in Example 3.3, except that lauroyldiethanolamide (an absorbefacient) was not added.

Comparative Example 3.8

The procedures were the same as in Example 3.3, except that isopropyl myristate and lauroyldiethanolamide were not added.

Table 7

	Absorbefacient	AUC_{48}	Remaining amount (%)	Stability parameter
Example 3.3	Isopropyl myristate + lauroyldiethanolamide	9540	92.1	8786
Comparative Example 3.6	Lauroyldiethanolamide	8870	18.3	1623
Comparative Example 3.7	Isopropyl myristate	1750	99.4	1739
Comparative Example 3.8	-	1150	96.8	1113

Example 4

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight

5

10 A base material was composed of 55 parts by weight of 1,4-cis-polybutadiene, 15 parts by weight by weight of natural rubber, and 30 parts by terpene resin. This base material was dissolved in cyclohexane at the concentration of 20% by weight. To this solution, a 75 parts (by weight) THF solution containing Nicorandil at a concentration of 3 parts by weight was added, and the resulting mixture was agitated in a dissolver so that particles of Nicorandil precipitated out. In this way, a suspension was obtained in which

15 fine crystals of Nicorandil were almost uniformly dispersed. This suspension was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried, and the whole was dried, so as to form an adhesive layer. The surface of the adhesive layer was applied to a polyethylene film support, so as to give a pharmaceutical preparation in the form of a tape. This pharmaceutical preparation in the form of a tape had an adhesive layer in which the mean diameter of the Nicorandil was 14 μm and in

20 which the Nicorandil was uniformly dispersed; the amount of Nicorandil was 0.29 mg/cm² of tape.

The same test procedure as in Example 1.1 for the amount of drug remaining and the AUC₄₈ was repeated using the tape, and the stability parameter was calculated. The amount of drug remaining was 90.2%, and the AUC₄₈ was about 873 ng.hr/ml.

25 Claims

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

1. A pharmaceutical preparation for percutaneous absorption comprising Nicorandil and/or a pharmaceutically acceptable salt thereof and an absorbefacient for percutaneous absorption in a base material characterized in that said Nicorandil and/or a pharmaceutically acceptable salt thereof is evenly distributed throughout the base material as fine crystals that have a mean diameter of 2 μm to 50 μm .
2. A pharmaceutical preparation according to Claim 1, wherein said base material is hydrophobic.
3. A pharmaceutical preparation according to Claim 2, wherein said base material is an adhesive rubber base.
4. A pharmaceutical preparation according to Claim 3, wherein said adhesive rubber base material is 1,4-cis-polybutadiene.
5. A pharmaceutical preparation according to Claim 4, wherein said 1,4-cis-polybutadiene is used in a proportion of 20 - 80 % by weight in the base material.
6. A pharmaceutical preparation according to Claim 3, wherein said adhesive rubber base material is an adhesive silicone rubber.
7. A pharmaceutical preparation according to Claim 1, wherein said mean diameter of granules of Nicorandil and/or its salts is 4 - 30 μm .
8. A pharmaceutical preparation according to Claim 1, wherein said Nicorandil salts are organic salts of Nicorandil, organic acids constituting said salts being at least one selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
9. A pharmaceutical preparation according to Claim 1, wherein said preparation has at least one organic acid selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
10. A pharmaceutical preparation according to Claim 1, wherein the absorbefacient for percutaneous

Example 4

5

1,4-cis-polybutadiene	55 parts by weight
Natural rubber	15 parts by weight
Terpene resin	30 parts by weight
Nicorandil	3 parts by weight

10 A base material was composed of 55 parts by weight of 1,4-cis-polybutadiene, 15 parts by weight by weight of natural rubber, and 30 parts by terpene resin. This base material was dissolved in cyclohexane at the concentration of 20% by weight. To this solution, a 75 parts (by weight) THF solution containing Nicorandil at a concentration of 3 parts by weight was added, and the resulting mixture was agitated in a dissolver so that particles of Nicorandil precipitated out. In this way, a suspension was obtained in which
 15 fine crystals of Nicorandil were almost uniformly dispersed. This suspension was applied to a release liner of polyethyleneterephthalate so that its thickness would be 100 μm after being dried, and the whole was dried, so as to form an adhesive layer. The surface of the adhesive layer was applied to a polyethylene film support, so as to give a pharmaceutical preparation in the form of a tape. This pharmaceutical preparation in the form of a tape had an adhesive layer in which the mean diameter of the Nicorandil was 14 μm and in
 20 which the Nicorandil was uniformly dispersed; the amount of Nicorandil was 0.29 mg/cm² of tape.

The same test procedure as in Example 1.1 for the amount of drug remaining and the AUC₄₈ was repeated using the tape, and the stability parameter was calculated. The amount of drug remaining was 90.2%, and the AUC₄₈ was about 873 ng.hr/ml.

25 **Claims**

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

1. A pharmaceutical preparation for percutaneous absorption comprising Nicorandil and/or a pharmaceutically acceptable salt thereof and an absorbefacient for percutaneous absorption in a base material
 30 characterized in that said Nicorandil and/or a pharmaceutically acceptable salt thereof is evenly distributed throughout the base material as fine crystals that have a mean diameter of 2 μm to 50 μm .
2. A pharmaceutical preparation according to Claim 1, wherein said base material is hydrophobic.
- 35 3. A pharmaceutical preparation according to Claim 2, wherein said base material is an adhesive rubber base.
4. A pharmaceutical preparation according to Claim 3, wherein said adhesive rubber base material is 1,4-cis-polybutadiene.
- 40 5. A pharmaceutical preparation according to Claim 4, wherein said 1,4-cis-polybutadiene is used in a proportion of 20 - 80 % by weight in the base material.
6. A pharmaceutical preparation according to Claim 3, wherein said adhesive rubber base material is an
 45 adhesive silicone rubber.
7. A pharmaceutical preparation according to Claim 1, wherein said mean diameter of granules of Nicorandil and/or its salts is 4 - 30 μm .
- 50 8. A pharmaceutical preparation according to Claim 1, wherein said Nicorandil salts are organic salts of Nicorandil, organic acids constituting said salts being at least one selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
9. A pharmaceutical preparation according to Claim 1, wherein said preparation has at least one organic
 55 acid selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
10. A pharmaceutical preparation according to Claim 1, wherein the absorbefacient for percutaneous



absorption is 1-dodecylazacycloheptane-2-one.

- 5 11. A pharmaceutical preparation according to Claim 1 wherein said absorbefacient for percutaneous absorption is a combination of fatty esters and compounds that have an amide bond, said compounds that have an amide bond being at least one selected from the group consisting of N-acylsarcosine, monoethanolamides derived from fatty acids, diethanolamides derived from fatty acids, alkyleneoxide adducts of monoethanolamides derived from fatty acids, and alkyleneoxide adducts of diethanolamides derived from fatty acids.
- 10 12. A pharmaceutical preparation according to Claim 11, wherein said fatty esters are formed by fatty acids with a carbon number of 10 to 18 and alcohols with a carbon number of 1 to 20.
13. A pharmaceutical preparation according to Claim 12, wherein said fatty esters are isopropyl myristate and/or isopropyl palmitate.
- 15 14. A pharmaceutical preparation according to Claim 11, wherein the carbon number of acyl group of said N-acylsarcosine is from 6 - 18.
- 20 15. A pharmaceutical preparation according to Claim 14, wherein said N-acylsarcosine is N-lauroylsarcosine.
- 25 16. A pharmaceutical preparation according to Claim 14, wherein said monoethanolamides derived from fatty acids are lauroylmonoethanolamide and/or monoethanolamides of fatty acids derived from coconut oil, and the alkyleneoxide adducts of the monoethanolamides derived from fatty acids are polyoxyethylene adducts of the monoethanolamides of the fatty acids derived from coconut oil.
17. A pharmaceutical preparation according to Claim 14, wherein said diethanolamides derived from fatty acids are lauroyldiethanolamide and/or diethanolamides of the fatty acids derived from coconut oil.
- 30 18. A pharmaceutical preparation according to Claim 10 or 11, wherein said absorbefacient for percutaneous absorption is present in a proportion of 1 - 100 parts by weight to 100 parts by weight of the base material.
- 35 19. A pharmaceutical preparation according to Claim 11, wherein said fatty esters are present in a proportion of 1 - 80 parts by weight to 100 parts by weight of the base material, and the compounds that have an amide bond are present in a proportion of 0.01 - 30 parts by weight to 100 parts by weight of the base material.
- 40 20. A pharmaceutical preparation according to Claim 1, wherein said preparation is a tape or an ointment.
- 45 21. A method for the manufacture of a pharmaceutical preparation in accordance with claim 1, said method including:
 - dissolving the Nicorandil and/or its salts in a solvent that is a good solvent for said Nicorandil; and
 - dissolving the base material in a solvent that is a poor solvent for said Nicorandil;
 - 45 mixing these two solutions to give a solution of a mixture that contains precipitated crystals of Nicorandil and/or its salts with a mean diameter of 2 - 50 μm ; and
 - substantially removing said good solvent and said poor solvent from said solution of the mixture.
- 50 22. A method according to claim 21, wherein said good solvent is at least one selected from the solvents consisting of tetrahydrofuran, dichloromethane and chloroform, and the poor solvent is at least one selected from n-heptane, cyclohexane, n-pentane, cycloheptane, toluene and a freon.

Claims for the following Contracting State : ES

- 55 1. A method for the manufacture of a pharmaceutical preparation for percutaneous absorption comprising Nicorandil and/or a pharmaceutically acceptable salt thereof and an absorbefacient for percutaneous absorption in a base material whereby said Nicorandil and/or a pharmaceutically acceptable salt thereof is evenly distributed throughout the base material as fine crystals that have a mean diameter of 2 μm



to 50 μm , said method including:

dissolving the Nicorandil and/or its salts in a solvent that is a good solvent for said Nicorandil; and
dissolving the base material in a solvent that is a poor solvent for said Nicorandil;

mixing these two solutions to give a solution of a mixture that contains precipitated crystals of
Nicorandil and/or its salts with a mean diameter of 2 - 50 μm ; and
substantially removing said good solvent and said poor solvent from said solution of the mixture.

2. A method according to claim 1, wherein said good solvent is at least one selected from tetrahydrofuran, dichloromethane and chloroform, and the poor solvent is at least one selected from n-heptane, cyclohexane, n-pentane, cycloheptane, toluene and a freon.
3. The method according to Claim 1, wherein said base material is hydrophobic.
4. The method according to Claim 3, wherein said base material is an adhesive rubber base.
5. The method according to Claim 4, wherein said adhesive rubber base material is 1,4-cis-polybutadiene.
6. The method according to Claim 5, wherein said 1,4-cis-polybutadiene is used in a proportion of 20 - 80 % by weight in the base material.
7. The method according to Claim 4, wherein said adhesive rubber base material is an adhesive silicone rubber.
8. The method according to Claim 1, wherein said mean diameter of granules of Nicorandil and/or its salts is 4 - 30 μm .
9. The method according to Claim 1, wherein said Nicorandil salts are organic salts of Nicorandil, organic acids constituting said salts being at least one selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
10. The method according to Claim 1, wherein said preparation has at least one organic acid selected from fumaric acid, oxalic acid, salicylic acid, tartaric acid, glutaric acid, maleic acid, and p-toluenesulfonic acid.
11. The method according to Claim 1, wherein the absorbefacient for percutaneous absorption is 1-dodecylazacycloheptane-2-one.
12. The method according to Claim 1, wherein said absorbefacient for percutaneous absorption is a combination of fatty esters and compounds that have an amide bond, said compounds that have an amide bond being at least one selected from N-acylsarcosine, monoethanolamides derived from fatty acids, diethanolamides derived from fatty acids, alkyleneoxide adducts of monoethanolamides derived from fatty acids, and alkyleneoxide adducts of diethanolamides derived from fatty acids.
13. The method according to Claim 12, wherein said fatty esters are formed by fatty acids with a carbon number of 10 to 18 and alcohols with a carbon number of 1 to 20.
14. The method according to Claim 13, wherein said fatty esters are isopropyl myristate and/or isopropyl palmitate.
15. The method according to Claim 12, wherein the carbon number of acyl group of said N-acylsarcosine is from 6 - 18.
16. The method according to Claim 15, wherein said N-acylsarcosine is N-lauroylsarcosine.
17. The method according to Claim 15 wherein said monoethanolamides derived from fatty acids are lauroylmonoethanolamide and/or monoethanolamides of fatty acids derived from coconut oil, and the alkyleneoxide adducts of the monoethanolamides derived from fatty acids are polyoxyethylene adducts of the monoethanolamides of the fatty acid derived from coconut oil.



18. The method according to Claim 15, wherein said diethanolamides derived from fatty acids are lauroyldiethanolamide and/or diethanolamides of the fatty acids derived from coconut oil.
19. The method according to Claim 11 or 12, wherein said absorbefacient for percutaneous absorption is present in a proportion of 1 - 100 parts by weight to 100 parts by weight of the base material.
20. The method according to Claim 12, wherein said fatty esters are present in a proportion of 1 - 80 parts by weight to 100 parts by weight of the base material, and the compounds that have an amide bond are present in a proportion of 0.01 - 30 parts by weight to 100 parts by weight of the base material.
21. The method according to Claim 1, wherein said preparation is a tape or an ointment.

Patentansprüche

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

1. Pharmazeutisches Präparat für die perkutane Absorption, enthaltend Nicorandil und/oder ein pharmazeutisch verträgliches Salz davon und ein Absorptionsmittel für die perkutane Absorption in einem Grundmaterial, dadurch gekennzeichnet, daß das Nicorandil und/oder ein pharmazeutisch verträgliches Salz davon gleichmäßig im Grundmaterial in Form von feinen Kristallen mit einem durchschnittlichen Durchmesser von 2 µm bis 50 µm verteilt ist.
2. Pharmazeutisches Präparat nach Anspruch 1, wobei das Grundmaterial hydrophob ist.
3. Pharmazeutisches Präparat nach Anspruch 2, wobei es sich beim Grundmaterial um ein adhäsives Kautschukgrundmaterial handelt.
4. Pharmazeutisches Präparat nach Anspruch 3, wobei es sich beim adhäsiven Kautschukgrundmaterial um 1,4-cis-Polybutadien handelt.
5. Pharmazeutisches Präparat nach Anspruch 4, wobei das 1,4-cis-Polybutadien in einer Menge von 20 bis 80 Gew.-% im Grundmaterial eingesetzt ist.
6. Pharmazeutisches Präparat nach Anspruch 3, wobei es sich bei dem adhäsiven Kautschukgrundmaterial um einen adhäsiven Siliconkautschuk handelt.
7. Pharmazeutisches Präparat nach Anspruch 1, wobei der durchschnittliche Durchmesser des Granulats von Nicorandil und/oder von dessen Salzen 4 bis 30 µm beträgt.
8. Pharmazeutisches Präparat nach Anspruch 1, wobei es sich bei den Nicorandilsalzen um organische Salze von Nicorandil handelt, wobei die organischen Säuren zur Bildung dieser Salze unter mindestens einem der Bestandteile Fumarsäure, Oxalsäure, Salicylsäure, Weinsäure, Glutarsäure, Maleinsäure und p-Toluolsulfonsäure ausgewählt sind.
9. Pharmazeutisches Präparat nach Anspruch 1, wobei das Präparat mindestens eine organische Säure aufweist, die unter Fumarsäure, Oxalsäure, Salicylsäure, Weinsäure, Glutarsäure, Maleinsäure und p-Toluolsulfonsäure ausgewählt ist.
10. Pharmazeutisches Präparat nach Anspruch 1, wobei das Absorptionsmittel für die perkutane Absorption 1-Dodecylazacycloheptan-2-on ist.
11. Pharmazeutisches Präparat nach Anspruch 1, wobei es sich bei dem Absorptionsmittel für die perkutane Absorption um eine Kombination von Fettsäureestern und Verbindungen mit einer Amidbindung handelt, wobei es sich bei den Verbindungen mit einer Amidbindung um mindestens einen aus der Gruppe N-Acylsarcosin, von Fettsäuren abgeleitete Monoethanolamide, von Fettsäuren abgeleitete Diethanolamide, Alkylenoxidaddukte von von Fettsäuren abgeleiteten Monoethanolamiden und Alkylenoxidaddukte von von Fettsäuren abgeleiteten Diethanolamiden ausgewählten Bestandteil handelt.
12. Pharmazeutisches Präparat nach Anspruch 11, wobei die Fettsäureester aus Fettsäuren mit 10 bis 18



Kohlenstoffatomen und aus Alkoholen mit 1 bis 20 Kohlenstoffatomen gebildet sind.

13. Pharmazeutisches Präparat nach Anspruch 12, wobei es sich bei den Fettsäureestern um Isopropylmyristat und/oder Isopropylpalmitat handelt.
14. Pharmazeutisches Präparat nach Anspruch 11, wobei die Anzahl der Kohlenstoffatome des Acylrestes des N-Acylsarcosins 6 bis 18 beträgt.
15. Pharmazeutisches Präparat nach Anspruch 14, wobei es sich bei dem N-Acylsarcosin um N-Lauroylsarcosin handelt.
16. Pharmazeutisches Präparat nach Anspruch 14, wobei es sich bei den von Fettsäuren abgeleiteten Monoethanolamiden um Lauroylmonoethanolamid und/oder von Fettsäuren aus Kokosöl abgeleitete Monoethanolamide handelt und es sich bei den Alkylenoxidaddukten von von Fettsäuren abgeleiteten Monoethanolamiden um Polyoxyethylenaddukte von Monoethanolamiden von aus Kokosöl abgeleiteten Fettsäuren handelt.
17. Pharmazeutisches Präparat nach Anspruch 14, wobei es sich bei den von Fettsäuren abgeleiteten Diethanolamiden um Lauroyldiethanolamid und/oder um von Fettsäuren aus Kokosöl abgeleitete Diethanolamide handelt.
18. Pharmazeutisches Präparat nach Anspruch 10 oder 11, wobei das Absorptionsmittel für die perkutane Absorption in einer Menge von 1 bis 100 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, vorhanden ist.
19. Pharmazeutisches Präparat nach Anspruch 11, wobei die Fettsäureester in einem Anteil von 1 bis 80 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, und die Verbindungen mit einer Amidbindung in einem Anteil von 0,01 bis 30 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, vorhanden sind.
20. Pharmazeutisches Präparat nach Anspruch 1, wobei das Präparat in Form eines Pflasters oder einer Salbe vorliegt.
21. Verfahren zur Herstellung eines pharmazeutischen Präparats nach Anspruch 1, umfassend folgende Stufen:
 - Auflösen von Nicorandil und/oder von dessen Salzen in einem Lösungsmittel, das ein gutes Lösungsmittel für das Nicorandil darstellt; und
 - Auflösen des Grundmaterials in einem Lösungsmittel, das ein schlechtes Lösungsmittel für das Nicorandil darstellt;
 - Vermischen der beiden Lösungen unter Bildung einer Lösung eines Gemisches, das ausgefällte Kristalle von Nicorandil und/oder von dessen Salzen mit einem durchschnittlichen Durchmesser von 2 bis 50 μm aufweist; und
 - im wesentlichen Entfernen des guten Lösungsmittels und des schlechten Lösungsmittels aus der Lösung des Gemisches.
22. Verfahren nach Anspruch 21, wobei es sich bei dem guten Lösungsmittel um mindestens ein unter Tetrahydrofuran, Dichlormethan und Chloroform ausgewähltes Lösungsmittel und bei dem schlechten Lösungsmittel um mindestens ein unter n-Heptan, Cyclohexan, n-Pentan, Cycloheptan, Toluol und Freon ausgewähltes Lösungsmittel handelt.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines pharmazeutischen Präparats für die perkutane Absorption, enthaltend Nicorandil und/oder ein pharmazeutisch verträgliches Salz davon und ein Absorptionsmittel für die perkutane Absorption in einem Grundmaterial, dadurch gekennzeichnet, daß das Nicorandil und/oder das pharmazeutisch verträgliche Salz davon gleichmäßig im Grundmaterial in Form von feinen Kristallen mit einem durchschnittlichen Durchmesser von 2 μm bis 50 μm verteilt sind, wobei das Verfahren folgende Stufen umfaßt:



Auflösen von Nicorandil und/oder von dessen Salzen in einem Lösungsmittel, das ein gutes Lösungsmittel für das Nicorandil darstellt; und

Auflösen des Grundmaterials in einem Lösungsmittel, das ein schlechtes Lösungsmittel für das Nicorandil darstellt;

Vermischen der beiden Lösungen unter Bildung einer Lösung eines Gemisches, das ausgefällte Kristalle von Nicorandil und/oder von dessen Salzen mit einem durchschnittlichen Durchmesser von 2 bis 50 µm aufweist; und

im wesentlichen Entfernen des guten Lösungsmittels und des schlechten Lösungsmittels aus der Lösung des Gemisches.

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2. Verfahren nach Anspruch 1, wobei es sich bei dem guten Lösungsmittel um mindestens ein unter Tetrahydrofuran, Dichlormethan und Chloroform ausgewähltes Lösungsmittel und bei dem schlechten Lösungsmittel um mindestens ein unter n-Heptan, Cyclohexan, n-Pentan, Cycloheptan, Toluol und Freon ausgewähltes Lösungsmittel handelt.

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3. Verfahren nach Anspruch 1, wobei das Grundmaterial hydrophob ist.

4. Verfahren nach Anspruch 3, wobei es sich beim Grundmaterial um ein adhäsives Kautschukgrundmaterial handelt.

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5. Verfahren nach Anspruch 4, wobei es sich beim adhäsiven Kautschukgrundmaterial um 1,4-cis-Polybutadien handelt.

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6. Verfahren nach Anspruch 5, wobei das 1,4-cis-Polybutadien in einer Menge von 20 bis 80 Gew.-% im Grundmaterial eingesetzt ist.

7. Verfahren nach Anspruch 4, wobei es sich bei dem adhäsiven Kautschukgrundmaterial um einen adhäsiven Silikonkautschuk handelt.

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8. Verfahren nach Anspruch 1, wobei der durchschnittliche Durchmesser des Granulats von Nicorandil und/oder von dessen Salzen 4 bis 30 µm beträgt.

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9. Verfahren nach Anspruch 1, wobei es sich bei den Nicorandilsalzen um organische Salze von Nicorandil handelt, wobei die organischen Säuren zur Bildung dieser Salze unter mindestens einem der Bestandteile Fumarsäure, Oxalsäure, Salicylsäure, Weinsäure, Glutarsäure, Maleinsäure und p-Toluolsulfonsäure ausgewählt sind.

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10. Verfahren nach Anspruch 1, wobei das Präparat mindestens eine organische Säure aufweist, die unter Fumarsäure, Oxalsäure, Salicylsäure, Weinsäure, Glutarsäure, Maleinsäure und p-Toluolsulfonsäure ausgewählt ist.

11. Verfahren nach Anspruch 1, wobei das Absorptionsmittel für die perkutane Absorption 1-Dodecylazacycloheptan-2-on ist.

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12. Verfahren nach Anspruch 1, wobei es sich bei dem Absorptionsmittel für die perkutane Absorption um eine Kombination von Fettsäureestern und Verbindungen mit einer Amidbindung handelt, wobei es sich bei den Verbindungen mit einer Amidbindung um mindestens einen aus der Gruppe N-Acylsarcosin, von Fettsäuren abgeleitete Monoethanolamide, von Fettsäuren abgeleitete Diethanolamide, Alkylenoxidaddukte von von Fettsäuren abgeleiteten Monoethanolamiden und Alkylenoxidaddukte von von Fettsäuren abgeleiteten Diethanolamiden ausgewählten Bestandteil handelt.

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13. Verfahren nach Anspruch 12, wobei die Fettsäureester aus Fettsäuren mit 10 bis 18 Kohlenstoffatomen und aus Alkoholen mit 1 bis 20 Kohlenstoffatomen gebildet sind.

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14. Verfahren nach Anspruch 13, wobei es sich bei den Fettsäureestern um Isopropylmyristat und/oder Isopropylpalmitat handelt.

15. Verfahren nach Anspruch 12, wobei die Anzahl der Kohlenstoffatome des Acylrestes des N-Acylsarcosins



sins 6 bis 18 beträgt.

16. Verfahren nach Anspruch 15, wobei es sich bei dem N-Acylsarcosin um N-Lauroylsarcosin handelt.
- 5 17. Verfahren nach Anspruch 15, wobei es sich bei den von Fettsäuren abgeleiteten Monoethanolamiden um Lauroylmonoethanolamid und/oder von Fettsäuren aus Kokosöl abgeleitete Monoethanolamide handelt und es sich bei den Alkylenoxidaddukten von von Fettsäuren abgeleiteten Monoethanolamiden um Polyoxyethylenaddukte von Monoethanolamiden von aus Kokosöl abgeleiteten Fettsäuren handelt.
- 10 18. Verfahren nach Anspruch 15, wobei es sich bei den von Fettsäuren abgeleiteten Diethanolamiden um Lauroyldiethanolamid und/oder um von Fettsäuren aus Kokosöl abgeleitete Diethanolamide handelt.
19. Verfahren nach Anspruch 11 oder 12, wobei das Absorptionsmittel für die perkutane Absorption in einer Menge von 1 bis 100 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, vorhanden ist.
- 15 20. Verfahren nach Anspruch 12, wobei die Fettsäureester in einem Anteil von 1 bis 80 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, und die Verbindungen mit einer Amidbindung in einem Anteil von 0,01 bis 30 Gewichtsteilen, bezogen auf 100 Gewichtsteile des Grundmaterials, vorhanden sind.
- 20 21. Verfahren nach Anspruch 1, wobei das Präparat in Form eines Pflasters oder einer Salbe vorliegt.

Revendications

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

- 25 1. Préparation pharmaceutique pour absorption percutanée comprenant du nicorandil *et/ou* un sel pharmaceutiquement acceptable de celui-ci et un résorbant pour absorption percutanée dans une matière de base, caractérisée en ce que ledit nicorandil *et/ou* un sel pharmaceutiquement acceptable de celui-ci est régulièrement réparti dans toute de la matière de base sous forme de fins cristaux ayant un
- 30 2. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite matière de base est hydrophobe.
- 35 3. Préparation pharmaceutique selon la revendication 2, dans laquelle ladite matière de base est une base en caoutchouc adhésif.
- 40 4. Préparation pharmaceutique selon la revendication 3, dans laquelle ladite matière de base en caoutchouc adhésif est du 1,4-*cis*-polybutadiène.
- 45 5. Préparation pharmaceutique selon la revendication 4, dans laquelle ledit 1,4-*cis*-polybutadiène est utilisé en une proportion de 20 à 80 % en poids dans la matière de base.
6. Préparation pharmaceutique selon la revendication 3, dans laquelle ladite matière de base en caoutchouc adhésif est un caoutchouc de silicone adhésif.
7. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit diamètre moyen des particules de nicorandil *et/ou* de ses sels est de 4 à 30 μm .
- 50 8. Préparation pharmaceutique selon la revendication 1, dans laquelle lesdits sels de nicorandil sont des sels organiques de nicorandil, les acides organiques constituant lesdits sels étant au moins l'un de l'acide fumarique, l'acide oxalique, l'acide salicylique, l'acide tartrique, l'acide glutarique, l'acide maléique et l'acide *p*-toluène-sulfonique.
- 55 9. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite préparation contient au moins un acide organique choisi parmi l'acide fumarique, l'acide oxalique, l'acide salicylique, l'acide tartrique, l'acide glutarique, l'acide maléique et l'acide *p*-toluènesulfonique.



10. Préparation pharmaceutique selon la revendication 1, dans laquelle le résorbant pour absorption percutanée est la 1-dodécylazacycloheptane-2-one.
- 5 11. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit résorbant pour absorption percutanée est une association d'esters gras et de composés ayant une liaison amide, lesdits composés ayant une liaison amide étant au moins membre du groupe formé par une N-acylsarcosine, les monoéthanolamides dérivés d'acides gras, les diéthanolamides dérivés d'acides gras, les produits d'addition d'oxyde d'alkylène sur des monoéthanolamides dérivés d'acides gras, et les produits d'addition d'oxyde d'alkylène sur des diéthanolamides dérivés d'acides gras.
- 10 12. Préparation pharmaceutique selon la revendication 11, dans laquelle lesdits esters gras sont formés par des acides gras ayant un nombre d'atomes de carbone de 10 à 18 et des alcools ayant un nombre d'atomes de carbone de 1 à 20.
- 15 13. Préparation pharmaceutique selon la revendication 12, dans laquelle lesdits esters gras sont le myristate d'isopropyle et/ou le palmitate d'isopropyle.
14. Préparation pharmaceutique selon la revendication 11, dans laquelle le nombre d'atomes de carbone du groupe acyle de ladite N-acylsarcosine est de 6 à 18.
- 20 15. Préparation pharmaceutique selon la revendication 14, dans laquelle ladite N-acylsarcosine est la N-lauroylsarcosine.
- 25 16. Préparation pharmaceutique selon la revendication 14, dans laquelle lesdits monoéthanolamides dérivés d'acides gras sont le lauroylmonoéthanolamide et/ou des monoéthanolamides d'acides gras dérivés d'huile de coprah, et les produits d'addition d'oxyde d'alkylène sur des monoéthanolamides dérivés d'acides gras sont des produits d'addition de polyoxyéthylène sur des monoéthanolamides d'acides gras dérivés d'huile de coprah.
- 30 17. Préparation pharmaceutique selon la revendication 14, dans laquelle lesdits diéthanolamides dérivés d'acides gras sont le lauroyldiéthanolamide et/ou des diéthanolamides d'acides gras dérivés d'huile de coprah.
- 35 18. Préparation pharmaceutique selon la revendication 10 ou 11, dans laquelle ledit résorbant pour absorption percutanée est présent en une proportion de 1 à 100 parties en poids pour 100 parties en poids de la matière de base.
- 40 19. Préparation pharmaceutique selon la revendication 11, dans laquelle lesdits esters gras sont présents en une proportion de 1 à 80 parties en poids pour 100 parties en poids de la matière de base, et les composés ayant une liaison amide sont présents en une proportion de 0,01 à 30 parties en poids pour 100 parties en poids de la matière de base.
- 45 20. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite préparation est un timbre ou une pommade.
- 50 21. Procédé pour la fabrication d'une préparation pharmaceutique selon la revendication 1, ledit procédé consistant à :
dissoudre le nicorandil et/ou ses sels dans un solvant qui est un bon solvant dudit nicorandil ; et
dissoudre la matière de base dans un solvant qui est un mauvais solvant dudit nicorandil ;
mélanger ces deux solutions pour obtenir une solution d'un mélange qui contient des cristaux précipités de nicorandil et/ou de ses sels ayant un diamètre moyen de 2 à 50 µm ; et
éliminer substantiellement le bon solvant et le mauvais solvant de ladite solution du mélange.
- 55 22. Procédé selon la revendication 21, dans lequel le bon solvant est au moins un solvant choisi parmi le tétrahydrofuranne, le dichlorométhane et le chloroforme, et le mauvais solvant est au moins un solvant choisi parmi le *n*-heptane, le cyclohexane, le *n*-pentane, le cycloheptane, le toluène et un Fréon.

Revendications pour l'Etat contractant suivant : ES



1. Procédé pour la fabrication d'une préparation pharmaceutique pour absorption percutanée comprenant du nicorandil et/ou un sel pharmaceutiquement acceptable de celui-ci et un résorbant pour absorption percutanée dans une matière de base, dans lequel le nicorandil et/ou un sel pharmaceutiquement acceptable de celui-ci est uniformément réparti dans toute la matière de base sous forme de fins cristaux ayant un diamètre moyen de 2 μ m à 50 μ m, ledit procédé consistant à :
- 5 dissoudre le nicorandil et/ou ses sels dans un solvant qui est un bon solvant dudit nicorandil ; et
 dissoudre la matière de base dans un solvant qui est un mauvais solvant dudit nicorandil ;
 mélanger ces deux solutions pour obtenir une solution d'un mélange qui contient des cristaux précipités de nicorandil et/ou de ses sels ayant un diamètre moyen de 2 à 50 μ m ; et
10 éliminer substantiellement le bon solvant et le mauvais solvant de ladite solution du mélange.
2. Procédé selon la revendication 1, dans lequel le bon solvant est au moins un solvant choisi parmi tétrahydrofuranne, le dichlorométhane et le chloroforme, et le mauvais solvant est au moins un solvant choisi parmi le *n*-heptane, le cyclohexane, le *n*-pentane, le cycloheptane, le toluène et un Fréon.
- 15 3. Procédé selon la revendication 1, dans lequel ladite matière de base est hydrophobe.
4. Procédé selon la revendication 3, dans lequel ladite matière de base est une base en caoutchouc adhésif.
- 20 5. Procédé selon la revendication 4, dans lequel ladite matière de base en caoutchouc adhésif est du 1,4-*cis*-polybutadiène.
6. Procédé selon la revendication 5, dans lequel ledit 1,4-*cis*-polybutadiène est utilisé en une proportion de 20 à 80 % en poids dans la matière de base.
- 25 7. Procédé selon la revendication 4, dans lequel ladite matière de base en caoutchouc adhésif est un caoutchouc de silicone adhésif.
- 30 8. Procédé selon la revendication 1, dans lequel ledit diamètre moyen des particules de nicorandil et/ou de ses sels est de 4 à 30 μ m.
9. Procédé selon la revendication 1, dans lequel lesdits sels de nicorandil sont des sels organiques de nicorandil, les acides organiques constituant lesdits sels étant au moins l'un de l'acide fumarique, l'acide oxalique, l'acide salicylique, l'acide tartrique, l'acide glutarique, l'acide maléique et l'acide *p*-toluène-sulfonique.
- 35 10. Procédé selon la revendication 1, dans lequel ladite préparation contient au moins un acide organique choisi parmi l'acide fumarique, l'acide oxalique, l'acide salicylique, l'acide tartrique, l'acide glutarique, l'acide maléique et l'acide *p*-toluène-sulfonique.
- 40 11. Procédé selon la revendication 1, dans lequel le résorbant pour absorption percutanée est la 1-dodécylazacycloheptane-2-one.
- 45 12. Procédé selon la revendication 1, dans lequel ledit résorbant pour absorption percutanée est une association d'esters gras et de composés ayant une liaison amide, lesdits composés ayant une liaison amide étant au moins un choisi membre du groupe formé par une N-acylsarcosine, les monoéthanolamides dérivés d'acides gras, les diéthanolamides dérivés d'acides gras, les produits d'addition d'oxyde d'alkylène sur des monoéthanolamides dérivés d'acides gras, et les produits d'addition d'oxyde d'alkylène sur des diéthanolamides dérivés d'acides gras.
- 50 13. Procédé selon la revendication 12, dans lequel lesdits esters gras sont formés par des acides gras ayant un nombre d'atomes de carbone de 10 à 18 et des alcools ayant un nombre d'atomes de carbone de 1 à 20.
- 55 14. Procédé selon la revendication 13, dans lequel lesdits esters gras sont le myristate d'isopropyle et/ou le palmitate d'isopropyle.



15. Procédé selon la revendication 12, dans lequel le nombre d'atomes de carbone du groupe acyle de ladite N-acylsarcosine est de 6 à 18.

16. Procédé selon la revendication 15, dans lequel ladite N-acylsarcosine est la N-lauroylsarcosine.

17. Procédé selon la revendication 15, dans lequel lesdits monoéthanolamides dérivés d'acides gras sont le lauroylmonoéthanolamide et/ou des monoéthanolamides d'acides gras dérivés d'huile de coprah, et les produits d'addition d'oxyde d'alkylène sur des monoéthanolamides dérivés d'acides gras sont des produits d'addition de polyoxyéthylène sur des monoéthanolamides d'acides gras dérivés d'huile de coprah.

18. Procédé selon la revendication 15, dans lequel lesdits diéthanolamides dérivés d'acides gras sont le lauroyldiéthanolamide et/ou des diéthanolamides d'acides gras dérivés d'huile de coprah.

19. Procédé selon la revendication 11 ou 12, dans lequel ledit résorbant pour absorption percutanée est présent en une proportion de 1 à 100 parties en poids pour 100 parties en poids de la matière de base.

20. Procédé selon la revendication 12, dans lequel lesdits esters gras sont présents en une proportion de 1 à 80 parties en poids pour 100 parties en poids de la matière de base, et les composés ayant une liaison amide sont présents en une proportion de 0,01 à 30 parties en poids pour 100 parties en poids de la matière de base.

21. Procédé selon la revendication 1, dans lequel ladite préparation est un timbre ou une pommade.