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PATENT SPECIFICATION

(11) 1 510 999

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(54) A PHARMACEUTICAL PREPARATION IN THE FORM OF A FOIL HAVING AN ACTIVE SUBSTANCE INCORPORATED THEREIN

- (71) We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- 5 This invention is concerned with a pharmaceutical preparation in the form of a foil having an active substance incorporated therein, for internal and external use.
- 10 Belgian Specification No. 637,363 describes paper foils coated with active substances suitable for oral use. The foils consist of cellulose fibres insoluble in water and a water-soluble binding agent. As water-soluble binding agent there is preferably used sodium carboxymethyl-cellulose. The active substance may be applied to the paper foil by dropping onto it a solution of the active substance, by spreading the solid active substance on the foil or by drawing the foil through a solution of the active substance. The discontinuous process of separately making the foil and applying the active substance has the disadvantage that the accuracy of the dosage is not very good, accuracy being of great importance as active substances are generally administered in small doses at the present time. Inaccuracies arise not only in applying the active substance, but also in the manufacture and pretreatment of the foil and owing to variations during storage of the foil material. Thus, for example, it has been found that in using foil drawing machines as prescribed in Belgian Specification No. 637,363 non-uniform layers of foil are formed, and that the foil shrinks during drying. However, it is easy to understand that with non-uniform material the take-up of active substance is also not uniform. Moreover, an active substance bound only on the surface can be partially removed during the handling of the foils, for example, during packing. The sodium carboxymethyl-cellulose used as binding agent becomes detached in the stomach and there is liberated carboxymethyl-cellulose, which includes some of the active substance and liberates it only slowly or not at all.
- 20 The present invention is based on the observation that foils having a constant thickness and a uniform distribution of active substance can be obtained by making foils having the active substance incorporated therein and using foil formers that are soluble in water or certain organic solvents.
- 25 The present invention provides a pharmaceutical preparation in the form of a foil (as hereinafter defined), wherein the foil incorporates from a foil forming material or materials that is or are soluble in at least one of the following solvents:— water, aliphatic alcohols containing up to 6 carbon atoms, chlorinated aliphatic hydrocarbons containing up to 8 carbon atoms, aliphatic ketones containing from 3 to 7 carbon atoms and mixtures of any two or more of these solvents. There are preferably used foil forming materials that are soluble in water, ethyl alcohol, isopropanol, acetone or methylene chloride, or in a mixture of any two or more of such solvents. Especially suitable are foil forming materials that are soluble both in water and in at least one of the organic solvent selected from aliphatic alcohols containing up to 6 carbon atoms, chlorinated aliphatic hydrocarbons containing up to 6 carbon atoms and aliphatic ketones containing
- 30
- 35
- 40
- 45

from 3 to 7 carbon atoms, more particularly those that are soluble in mixtures of ethyl alcohol and water.

The term "foil" as used herein includes a lamina strip and a film.

5 As foil formers there come into consideration, for example, poly-N-vinylpyrrolidone, vinylpyrrolidone-vinyl acetate, methyl- and ethyl-cellulose, but preferably non-ionic water-soluble hydroxyalkyl ethers of cellulose such, for example, as hydroxypropyl-cellulose, hydroxyethyl-cellulose and methylhydroxypropyl-cellulose. 5

10 In addition to the active substance or substances the foil may contain fillers and advantageously a small amount of a release agent. 10

15 Suitable release agents are, *inter alia*, polyoxyethylene-polyoxypropylene polymer (PLURONIC F 68), polyoxyl stearates, alkyl- or acyl-substituted polyaddition products of ethylene oxide, for example, CREMOPHOR EL, silicones and silicone parting emulsions, glycerine, propylene glycol and metal soaps. The terms PLURONIC F 68 and CREMOPHOR EL are Registered Trade Marks. 15

20 As fillers there may be mentioned, for example, cellulose, sugars, for example, lactose, dextrose and cane sugar, starches, polyhydric alcohols, for example, mannitol, calcium carbonate, calcium phosphate, talcum and dyestuffs in water-soluble form or as pigments. The fillers used in the preparations of the invention are generally insoluble or only sparingly soluble in water and organic solvents. When fillers and active substances are used which are soluble in water or organic solvents a transparent smooth foil is formed, and when insoluble fillers, especially cellulose, or insoluble active substances are used a white or coloured paper-like foil is formed. 20 25

30 All active substances used in human and veterinary medicine can be used in accordance with the invention. For internal use there comes into consideration especially oral administration. As external use there is to be understood, more especially, topical administration on the skin and in body cavities such, for example, as the nose, ears and vagina. As active substances there may be mentioned, for example: Gestagens, oestrogens, mixtures of gestagens and oestrogens, tranquillizers, anti-diabetics, sulphonamides, antibiotics, trichomonal agents and inflammation inhibitors, for example corticoids. 30

35 The medicaments may be present in the carrier materials in a dissolved or uniformly suspended state. The proportion of active substance in the foil may be up to 60 per cent by weight of the foil. The surfaces may be cut or perforated to form unit dosage portions which can be readily separated and which contain quantities of active substance such as are usually present also in tablets, dragées, salves and suppositories. Thus, the quantity of active substance per single dose may be as high as desired depending on the mode of use and from 1 µ gram to 0.5 gram, and the lower and upper dose may easily be smaller or greater. 35 40

45 For the production of the medicinal preparations in foil form of the invention the active substance and/or parting compound is dissolved or suspended, the foil former and optionally the filler is introduced, optionally homogenised, and the solution or suspension is drawn out on a foil drawing machine to a sheet. The foil obtained by drying the sheet is divided into sections (units). 45

50 Into the solution or suspension are introduced the foil former in a proportion by weight of from 6 to 20 per cent, the filler in a proportion by weight of up to 30 per cent and the release agent preferably in a proportion by weight of 0.01 to 2 per cent, the percentages being calculated on the total weight of the solution or suspension. 50

55 The content of solvent or suspension medium is from 48 to 84 per cent by weight and consists of water and/or one or more organic solvents. As organic solvents there come into consideration physiologically tolerable solvents or solvents that are removed except for a physiologically unobjectionable residue. Such solvents are, for example, aliphatic alcohols containing up to 6 carbon atoms, chlorinated hydrocarbons, especially chlorinated aliphatic hydrocarbons containing up to 6 carbon atoms, aliphatic ketones containing from 3 to 7 carbon atoms and mixtures of any two or more of such solvents. There may be mentioned, more especially, ethyl alcohol, isopropanol, acetone and methylene chloride, and mixtures thereof. There are preferably used water and ethyl alcohol or mixtures of water and ethyl alcohol. 55 60

65 The layer thickness of the wet sheet is generally 0.1 to 2 mm and that of the dry foil is from 0.05 to 1 mm, and preferably 0.07 to 0.3 mm. 65

The process of making the medicinal preparation in foil form in one operation

(a continuous process) has the advantage that the active substance is homogeneously and uniformly distributed in the medicament carrier. By varying the concentration of the active substance in the carrier, the thickness of the foil and the area of the foil the unit dose can be varied in a very simple manner.

5 The pharmaceutical preparations of the invention may be in the form of a 5
two-phase or multi-phase preparation wherein the foil contains different active
ingredients and/or different concentrations of active ingredient in different
sections or zones of the foil, and/or in which one or more sections or zones may
10 contain no active ingredient. Thus, foils can be made with a sheet in which 10
different active substances and/or varying concentrations of active substance are
incorporated side by side over the width of the web of foil. By means of a special
doctor, which consists of two or more compartments, different solutions or
15 suspensions can be drawn out without mixing to form a coherent sheet. The width
and thickness of the sheet is separately adjustable for each compartment. If
desired, zones (strips) having different active substances or different
20 concentrations are made visible by different dyestuffs. By drying the wet sheet
there is obtained a foil, which by being divided in an appropriate way, for example,
by perforation, yields units containing different active substances and/or
concentrations of active substance or units containing no active substance. Foils
25 containing different active substances and/or different concentrations of active
substance are required for making multi-phase preparations, for example, for
making contraceptive preparations. The possibility of the spatial separation of
active substances that are incompatible with one another in one foil unit improves
the stability of the individual active substances. Foils for intravaginal application
may, for example, also be rolled round an ordinary commercial tampon. 25

The invention also provides a process for the manufacture of a
pharmaceutical preparation in the form of a foil, wherein two or more solutions or
suspensions are prepared each containing a different active ingredient and/or
30 different concentrations of active ingredient and in which one or more solutions or
suspensions may contain no active ingredient, the solutions or suspensions are
drawn on a suitable foil drawing apparatus having doctor means to give a sheet
containing in different sections or zones of the sheet different active ingredients
and/or different concentrations of active ingredient (including zero
35 concentration), and the foil is appropriately divided by cutting, perforation or
other means to give a two-phase or multi-phase preparation in which unit dosage
portions can be readily detached. 35

The following Examples 1 to 19 illustrate the invention; with the exception of
Examples 5 and 15 the preparations described in the Examples are primarily
suitable for oral administration.

40 Example 1. 40
Preparation for 1000 units:
0.25 gram of *d*-norgestrel,
0.05 gram of ethinyl-oestradiol and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in
45 95.00 grams of ethyl alcohol while stirring, and into this is introduced a 45
powdered mixture of
16.93 grams of hydroxypropyl-cellulose and
16.93 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a
50 sheet having a thickness of 500 μm , and is then dried. 50
The composition of one unit:
0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
0.84 mg of polyoxyethylene-polyoxypropylene polymer
55 16.93 mg of hydroxypropyl-cellulose 55
16.93 mg of cellulose
35.00 mg

One unit corresponds to an area of about 3 cm^2 .
60 Appearance of the foil: white, paper-like. 60
The dry foil has a thickness of about 170 μm .

Example 2.

A preparation for 1000 units:

1.10 grams of Cremophor EL are dissolved in
152.00 grams of water. In this solution are suspended
5 0.25 gram of micronised *d*-norgestrel and
0.05 gram of micronised ethinyl-oestradiol and if necessary homogenised. 5

Into the suspension are introduced

22.10 grams of hydroxypropyl-cellulose and
16.50 grams of cellulose.

10 The suspension so obtained is drawn on a suitable foil drawing apparatus to a
sheet having a thickness of 500 μm , and is then dried. 10

The composition for one unit:

0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
15 1.10 mg of Cremophor EL 15
22.10 mg of hydroxypropyl-cellulose
16.50 mg of cellulose

40.00 mg

20 One unit corresponds to an area of about 3 cm^2 .
Appearance of the foil: white, paper-like. 20
The dry foil has a thickness of about 170 μm .

Example 3.

A preparation for 1000 units:

0.03 gram of *d*-norgestrel and
25 0.84 gram of polyoxyl-40-stearate are dissolved, while stirring, in 25
95.00 grams of ethyl alcohol. Into this solution is introduced a powdered
mixture of

16.93 grams of hydroxypropyl-cellulose and
17.20 grams of cellulose.

30 The suspension so obtained is drawn on a suitable foil drawing apparatus to a
sheet having a thickness of 500 μm , and is then dried. 30

The composition of one unit:

0.03 mg of *d*-norgestrel
0.84 mg of polyoxyl-40-stearate
35 16.93 mg of hydroxypropyl-cellulose 35
17.20 mg of cellulose

35.00 mg

40 One unit corresponds to an area of about 3 cm^2 .
Appearance of the foil: white, paper-like. 40
The dry foil has a thickness of about 170 μm .

Example 4.

A preparation for 1000 units:

1.10 grams of polyoxyethylene-polyoxypropylene polymer are dissolved in
152.00 grams of demineralised water. In this solution is suspended
45 0.03 gram of micronised *d*-norgestrel, and if necessary homogenised. Into the 45
suspension are introduced

22.10 grams of hydroxypropyl-cellulose and
16.77 grams of cellulose.

50 The suspension so obtained is drawn on a suitable foil drawing apparatus to a
sheet having a thickness of 500 μm , and is then dried. 50

The composition for one unit:

0.03 mg of *d*-norgestrel
1.10 mg of polyoxyethylene-polyoxypropylene polymer
22.10 mg of hydroxypropyl-cellulose
55 16.77 mg of cellulose 55

40.00 mg

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