Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT SPECIFICATION (11) 1 510 999

1 510 999

(21) Application No. 28252/75 (22) Filed 4 July 1975
(31) Convention Application No. 2 432 925
(32) Filed 5 July 1974
(31) Convention Application No. 2 449 865
(32) Filed 17 Oct. 1974 in
(33) Fed. Rep. of Germany (DE)
(44) Complete Specification published 17 May 1978
(51) INT CL² A61K 9/70, 31/565
(52) Index at acceptance A5B 240 24Y 38Y 396 753 757 75Y 764

(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:—

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.

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.

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.

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

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.

As foil formers there come into consideration, for example, poly-N-vinyl-pyrrolidone, 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 methylhydroxy-propyl-cellulose.

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

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.

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.

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.

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.

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).

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.

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.

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.

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.

The pharmaceutical preparations of the invention may be in the form of a 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 contain no active ingredient. Thus, foils can be made with a sheet in which 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 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 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 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.

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 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 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.

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.

Example 1.

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
95.00 grams of ethyl alcohol while stirring, and into this is introduced a 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 sheet having a thickness of 500 μm, and is then dried.

The composition of one unit:

0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.93 mg of hydroxypropyl-cellulose
16.93 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
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
0.25 gram of micronised *d*-norgestrel and
0.05 gram of micronised ethinyl-oestradiol and if necessary homogenised.
Into the suspension are introduced
22.10 grams of hydroxypropyl-cellulose and
16.50 grams of cellulose.

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.
The composition for one unit:
0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
1.10 mg of Cremophor EL
22.10 mg of hydroxypropyl-cellulose
16.50 mg of cellulose

40.00 mg

One unit corresponds to an area of about 3 cm².
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 3.

A preparation for 1000 units:
0.03 gram of *d*-norgestrel and
0.84 gram of polyoxyl-40-stearate are dissolved, while stirring, in
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.

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.
The composition of one unit:
0.03 mg of *d*-norgestrel
0.84 mg of polyoxyl-40-stearate
16.93 mg of hydroxypropyl-cellulose
17.20 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm².
Appearance of the foil: white, paper-like.
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
0.03 gram of micronised *d*-norgestrel, and if necessary homogenised. Into the suspension are introduced
22.10 grams of hydroxypropyl-cellulose and
16.77 grams of cellulose.

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.
The composition for one unit:
0.03 mg of *d*-norgestrel
1.10 mg of polyoxyethylene-polyoxypropylene polymer
22.10 mg of hydroxypropyl-cellulose
16.77 mg of cellulose

40.00 mg

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.