COMMONWEALTH OF AUSTRALIA 614209

Patents Act 1952 46845/89

Form 1 Regulation 9

Case: Kl/sz 26189

APPLICATION FOR A STANDARD PATENT OR

A STANDARD PATENT OF ADDITION

We, LTS LOHMANN Therapie-Systeme GmbH & Co. KG, of Irlicher Str. 55,5450 Neuwied 12, Federal Republic of Germany, hereby apply for the grant of a Standard Patent for an invention entitled:

"TRANSDERMAL THERAPEUTICAL SYSTEM"

which is described in the accompanying complete specification.

This application is a Convention application and is based on an application numbered P 38 43 239.0 for a patent or similar protection made in the Federal Republic of Germany on 22nd December 1988.

Our address for service is care of E.F. WELLINGTON & CO., Patent and Trade Mark Attorneys, 457 St. Kilda Road, Melbourne, in the State of Victoria , Commonwealth of Australia.

DATED this 18th day of December, A.D. 1989

M 014611 181289

For and on behalf of
LTS LOHMANN Therapie-Systeme
GmbH & Co. KG.,

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BRUCE S. WELLINGTON
Patent Attorney for Applicant

To: The Commissioner of Patents,
Commonwealth of Australia.

Case: Kl/sz 26189

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Form 8 Regulation 12(2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In support of the Convention application made for patent by LTS LOHMANN Therapie-Systeme GmbH & Co. KG, for an invention entitled: "TRANSDERMAL THERAPEUTICAL SYSTEM COMPRISING PHYSOSTIGMINE AS ACTIVE COMPONENT AND PROCESS FOR THE PRODUCTION THEREOF"

I/We, Frank Becher and Juergen Maass of Irlicher Str. 55, 5450 Neuwied 12, Federal Republic of Germany, do solemnly and sincerely declare as follows:

1. We are authorized by LTS LOHMANN Therapie-Systeme GmbH & Co. the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made at the Patent Office, Munchen, Federal Republic of Germany on the 22nd day of December 1988 by KLINGE PHARMA GmbH and LTS LOHMANN Therapie-Systeme GmbH & Co. KG.

3. THOMAS HILLE, Reckstr. 17, 5450 Neuwied 1, Western Germany; HANS-RAINER HOFFMANN, Burghofstr. 123, 5450 Neuwied 22, Western Germany; HANS-JOACHIM HUBER, Ramoltstr. 28, 8000 Munchen 83, Western Germany; AXEL KNOCH, Neumarkter Str. 86D, 8000 Munchen 80, Western Germany; GERHARD SCHNEIDER, Finkenstr. 27, 8011 Baldham, Western Germany; and FRITZ STANISLAUS, Halserspitzstr. 12, 8000 Munchen 80, Western Germany, are the actual inventors of the invention and the facts upon which LTS LOHMANN Therapie-Systeme GmbH & Co. KG is entitled to make the application are as follows:
KLINGE PHARMA GmbH and LTS LOHMANN Therapie-Systeme GmbH & Co. KG were joint assignees of the actual inventors with respect to the right to lodge the basic application, and LTS LOHMANN Therapie-Systeme GmbH & Co. KG is the assignee of KLINGE PHARMA GmbH with respect to the right to lodge the present application.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Neuwied this 23rd day of April, AD 1990

LTS LOHMANN Therapie-Systeme GmbH & Co. KG

ppa. ppa.

Becher — Director of legal affairs department

Maass — Head of production

TO: The Commissioner of Patents
Commonwealth of Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-46845/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 614209

(54) Title
TRANSDERMAL THERAPEUTICAL SYSTEM COMPRISING PHYSOSTIGMINE AS ACTIVE COMPONENT AND PROCESS FOR THE PRODUCTION THEREOF

International Patent Classification(s)
(51)[5] A61K 009/70 A61K 031/40 A61K 047/32

(21) Application No. : 46845/89 (22) Application Date : 18.12.89

(30) Priority Data

(31) Number (32) Date (33) Country
3843239 22.12.88 DE FEDERAL REPUBLIC OF GERMANY

(43) Publication Date : 28.06.90

(44) Publication Date of Accepted Application : 22.03.91

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(57) Claim

1. A transdermal therapeutical system for the administration of physostigmine to the skin via a cover layer which is impermeable to active substances, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, characterized in that the reservoir layer comprises 10-90%-wt polymeric material selected from the groups consisting of block copolymers on the basis of styrene and 1,3-dienes, polyisobutylenes, polymers on the basis of acrylate and/or methacrylate and esters of hydrogenated colophonium, 0-30%-wt softeners on the basis of hydrocarbons and/or esters, and 0.1-20%-wt physostigmine.

13. A process for the production of a transdermal therapeutical system according to any one of claim 1 to 12, characterized in that the components of the reservoir layer are dissolved in a low-boiling solvent which makes possible a drying up to a maximum residual moisture of smaller than 0.4%-wt.

COMMONWEALTH OF AUSTRALIA 614209

PATENTS ACT 1952

FORM 10

Case: Kl/sz 26189

Application Number:
Lodged:

Class: Int. Class

Complete specification: Lodged:
Accepted:
Published:

Priority:

Related Art:

Name of Applicant: LTS LOHMANN Therapie-Systeme GmbH & Co. KG

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FRITZ STANISLAUS.

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457 St. Kilda Road,
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Complete Specification for the invention entitled:

"TRANSDERMAL THERAPEUTICAL SYSTEM COMPRISING PHYSOSTIGMINE AS ACTIVE COMPONENT AND PROCESS FOR THE PRODUCTION THEREOF"

The following statement is a full description of this invention including the best method of performing it known tc us.

The present invention relates to a transdermal therapeutical system comprising physostigmine as active component, and to a process for its production.

The application of physostigmine for the treatment of the Alzheimer disease is described in literature, whereby the efficiency of the substance has been judged differently by different authors. Since the alkaloid exhibits a high first pass effect - the bioavailability of physostigmine after oral administration is in the range of 5% - the differing results must be attributed to different forms of application.

DE-OS 35 28 979 describes a composition which in addition to physostigmine comprises a carboxylic acid of medium chain length; this composition may be applied on a bandage, an insert, or a compress, which are applied by means of a dressing. This kind of application is no therapeutical system per se; thus it is intended to provide the bandage, compress, or insert with an inner reservoir layer, an impermeable protective blocking foil, or an impermeable protective film and to apply a diffusion controlling membrane between the reservoir and the skin, which is not described in detail. Neither the diffusion controlling membrane nor the protective foils are described more precisely. The carboxylic acids are explicitly mentioned to be effective carriers for the administration of the pharmaceutical through the skin which otherwise could not penetrate through the barrier of the skin. However, this statement is not tenable from the scientific point of view.

DE-PS 36 06 892 describes a retarded application of physo-

stigmine and other active substances, which application may be carried out transdermally. A special formulation is not disclosed. What is more, it is hinted at a pre-described formulation (US-PS 3,921,363).

Besides the only vague statements concerning the transdermal therapeutical systems, none of both publications deal with the instability of physostigmine which was realized very early (Eber, W., Pharmaz. Ztg. 37, 483 (1888); Herzig, J., Mayer, H., Mh. Chem 18, 379 (1897); Herzig, J., Lieb, H., ibidem 39, 285 (1918); Solvay, A.A., J. chem. Soc. (London) 101, 978 (1912); instability due to a rapid decomposition extremely limits the use of physostigmine in pharmacy).

Thus it is the object of the present invention to provide physostigmine or one of its pharmaceutically acceptable salts in the form of a transdermal therapeutical system which provides the controlled release of physostigmine or its pharmaceutically acceptable salt over a period of 24 hours and guarantees that the physostigmine does not notably decompose during the storage of the pre-fabricated transdermal therapeutical system.

According to the present invention, this object is achieved in that the physostigmine or one its pharmaceutically acceptable salts are comprised in a reservoir layer of a transdermal therapeutical system, said reservoir layer consisting of particularly selected material; whereby the components of said reservoir layer, namely polymers, resins and softeners, do neither contain free hydroxyl groups nor polyethoxy groups. Thus those components of the compound group of the esters or hydrocarbons have been selected as resin and softener components of the polymeric layer.

The stability of the active substance may further be improved by the selection of a suitable solvent or solvent mixture in the production of the transdermal therapeutical system. In this connection, solvents or solvent mixtures are used which, at a low boiling point and thus mild drying, make possible the achievement of a very low residual moisture of smaller than 0.5, preferably smaller than 0.4%.

Thus the subject matter of the present invention is a transdermal therapeutical system for the administration of physostigmine to the skin via a cover layer being impermeable to active substances, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer of which comprises 10-90%-wt polymeric material selected from the groups consisting of block copolymers on the basis of styrene and 1,3-dienes, polyisobutylenes, polymers on the basis of acrylate and/or methacrylate, and esters of hydrogenated colophonium, 0-30%-wt softeners on the basis of hydrocarbons and/or esters, and 0.1-20%-wt physostigmine.

In this connection, the cover layer which is impermeable to active substances may consist of flexible or inflexible material. Substances suitable for its production are polymeric foils or metal foils, such as aluminium foils which can be used alone or coated with a polymeric substrate. Textile fabrics may be used as well, if the components of the reservoir, due to their physical properties, cannot penetrate through the fabrics. According to a preferred embodiment the cover layer is a nonwoven fabric from a foil vapourized with aluminium.

The reservoir layer consists of a polymeric matrix and the active substance, whereby the polymeric matrix guarantees

the coherence of the system. The matrix consists of a basic polymer and optionally of common additives. The selection of the basic polymer depends on the chemical and physical properties of the physostigmine. Examples of polymers are rubber, rubber-like synthetic homopolymers, copolymers or block polymers, polyacrylic acid esters and their copolymers. In principle all polymers are suitable which are used in the production of pressure-sensitive adhesives, which are physiologically acceptable and do not decompose physostigmine. It is particularly preferred to use those polymers consisting of block copolymers on the basis of styrene and 1,3-dienes, polyisobutylenes, or polymers of acrylate and/or methacrylate. In particular, linear styrene-isoprene block copolymers are used from the group of block copolymers on the basis of styrene and 1,3-dienes.

Acrylate-copolymers of 2-ethylhexyl acrylate, vinyl acetate, and acrylic acid with or without titane chelate ester are preferred as polymers on acrylate basis. Copolymers on the basis of dimethylaminoethyl methacrylates and neutral methacrylic acid esters are preferred as methacrylates. As esters of hydrogenated colophonium its methyl and glyceryl esters are particularly preferred.

The kind of possible additive depends on the polymer used and the active substance: According to their function they can be divided into softeners, tackifiers, stabilizers, carriers, diffusion and penetration regulating additives or fillers. Suitable physiologically acceptable substances are known to the man skilled in the art. The reservoir layer exhibits such a self-adhesiveness that a constant contact to the skin is guaranteed.

Examples for suitable softeners are diesters of dicarboxylic

acids, such as di-n-butyl adipate and triglycerides, particularly medium chain triglycerides of the caprylic/capric acid of coconut oil. Further examples for suitable softeners are isopropylmyristate, dioctyl cyclohexane, etc.

The removable protective layer, which is in contact with the reservoir layer and is removed prior to application, for example, consists of the same materials as are used for the production of the covering layer, provided that they are rendered removable, for example by way of a silicone treatment. Further detachable protective layers, e.g., are polytetrafluoroethylene, treated paper, cellophane, polyvinyl chloride, etc. If the laminate according to the present invention is cut into suitable sizes (plasters) prior to applying the protective layer, the dimensions of the protective layer to be applied may have an overlapping end, so that they may be removed from the plaster more easily.

The transdermal therapeutical system according to the present invention is produced in that the active substance together with the components of the pressure-sensitive adhesive reservoir layer, optionally in solution are homogeneously admixed and coated onto the cover layer which is impermeable to the active substance, then the solvent or solvents is/are removed, if necessary. Subsequently, the adhesive layer is provided with a suitable protective layer.

The invention is illustrated but not limited by the following examples:

Example 1:

20 g n-heptane and 80 g methylethyl ketone are mixed. 7.2 g physostigmine, free base, are dissolved in 90 g of said

mixture. After complete dissolution of the active substance, there is added by portions 40 g of a glyceryl ester of completely hydrogenated colophonium, and 40 g of a linear styrene-isoprene-styrene block copolymer and 5.6 g triglycerides of the caprylic/capric acids of coconut oil ("medium chain triglycerides" DAB 8 (= The German Pharmacopeia, 1978). Under elimination of light it is stirred at room temperature for 8 hours up to complete dissolution, and the solution obtained is coated onto an aluminized and siliconized polyethylene foil with a 250 µm coating knife.

After removal of the solvent by drying at 50°C for 25 minutes, the adhesive film is covered with a polyester foil of 15µm. A size of 16cm² is punched with an adequate cutting tool and the edges are separated off. The release diagrams of the preparation example 1 are shown in figures 1-2. The diagrams show the controlled release of the active substance both into physiological saline and through excised rodent skin.

The curve of figure 1, the line of which is continuous, represents the in-vitro releases by samples which were examined immediately after their production. The discontinuous curve shows releases of samples after a three-months storage at room temperature. Since both curves are nearly congruent, the above mentioned stability can be demonstrated in an impressive manner. Figure 2 shows that the penetration rate of samples examined immediately after their production and after a three-months storage, respectively, is nearly congruent as well.

The stability of the active substance in the system was also shown by way of content determinations immediately after the production and after a three-months storage, respectively.

In this connection, neither eseroline and rubreserine, the decomposition products known in the literature, nor other unknown products could be detected. The following method was applied:

Preparation of the sample: 1 plaster with cover foil is divided into four parts by means of a scissors; the cover foil is removed and shaken which 50.0 ml tetrahydrofurane (of reagent purity) for at least 2 hours in a glass vessel which is capable of being closed and protected from light together with the plaster parts, then subjected to ultrasonic treatment and subsequently centrifugated. Dilution for HPLC with methanol; and further centrifugation.

Subsequently the physostigmine content in the centrifugate per HPLC is determined.

Example 2:

The method is carried out according to example 1, except for the fact that instead of 5.6 g triglycerides of the caprylic/capric acids 3.2 g di-n-butyl adipate are used. The release diagrams of preparation example 2 are shown in figures 3-4. The diagrams show the controlled release of the active substance both into a physiological saline and through excised rodent skin.

As in example 1, the continuous line curve, represents the release of samples immediately after production. The discontinuous curve shows releases of samples which were stored for three months at room temperature. Again, the curves are nearly congruent in this case, and thus stable plasters are obtained in this example, too.

As in example 1 the physostigmine content was determined; no decomposition product could be detected after a three-months storage.

Example 3:

2.0 g physostigmine, free base, are weighed into a flask. 25 g of a 60% solution of glycerol colophonium ester in butanone and 25 g of a 40% solution of a styrene-butadiene block copolymer in a mixture of n-heptane and butanone at a ratio of 1:2 are added under stirring. After intense mixing, 2.5 g methylester of hydrogenated colophonium and 1.95 g triglycerides of caprylic/capric acids were added under stirring. Further performance as described in example 1. The release diagrams are shown in figures 5-6. The diagrams show the controlled release of the active substance both into physiological saline and through excised rodent skin.

As in the case of examples 1 and 2, the continuous line curve shows the release of samples immediately after production. However, in contrast to the foregoing samples, the release was determined not only after a three-months storage but also after a six-months storage. Again, the three curves are nearly congruent, so that after a six-months storage the same release as immediately after production is achieved.

No decomposition product per HPLC could be detected after a

six-months storage, as was the case in examples 1 and 2.

Example 4:

8.5 g physostigmine, free base, are dissolved in 21.4 g ethyl acetate together with 21.3 g of a cationic copolymer on the basis of dimethylaminoethyl methacrylate and neutral methacrylic acid esters. 8.5 g triglycerides of caprylic/capric acids and 68.3 g of a non-self-crosslinking acrylate copolymer of 2-ethylhexyl acrylate, vinyl acetate and acrylic acid (50% in ethyl acetate) were added under stirring. After a maximum stirring of 30 minutes at room temperature, the adhesive mass is homogeneous. Further execution as described in example 1. The release data are given in figures 7-8. The digrams show the controlled release of the active substance into physiological saline as well as through excised rodent skin.

As was the case in the preceeding examples, the continuous line curve shows the release of the samples immediately after production. However, in contrast to the foregoing samples, the release was determined after a six-months storage in addition to the determination after a three-months storage. Again, the three curves are nearly congruent, so that even after a six-months storage the same release as immediately after production is achieved.

As was the case in the preceeding examples, no decomposition product could be detected by the HPLC method described under example 1 after the six-months storage.

Example 5:

The same procedure as described in example 4 is used, with

the exception that the acrylate copolymer is not dissolved 50% in ethyl acetate, but 40% in a solvent mixture (ethyl acetate : ethanol : heptane : methanol 64:25:9:2). The release diagrams are shown in figures 9-10.

As was the case in the preceeding examples, the continuous line curve shows the release of the samples immediately after production. However, in contrast to the foregoing samples, the release was determined after a six-months storage in addition to the determination after a three-months storage. Again, the three curves are nearly congruent, so that after a six-months storage the same release as immediately after production is achieved.

With respect to example 5, it has to be hinted at the fact that physostigmine is subjected to a solvent - i.e. ethanol - which can hydrolytically decompose this active substance (Pfeiffer, S.; Behnsen, G. and Kühn, L., Pharmazie 27, 639 (1972), however, it is decisive that this happens only for a short period of time and under exclusion of light, since the solvent is completely removed after coating by means of gentle drying. For reasons already stated, neither the basic polymer nor the hard resin or softener attack the active substance.

It is decisive for the stability of the active substance, that the polymers, resins and softeners used do neither contain free hydroxyl groups nor polyethoxy groups, since the active substance portion, which is present in dissolved form, would be subjected to hydrolysis. For this reason, resins and softeners belonging to the compound class of the esters were chosen.

Furthermore, the selection of the solvent or solvent mix-

ture, respectively, is decisive for the stability of the active substance, if physostigmine is subjected to the solvent prior to the drying for several hours. The portion of high-boiling solvent, possibly necessary to suppress bubble formation has to be very small. According to the present invention this is achieved in examples 1-3 in that a mixture of butanone and n-heptane forming an azeotropic mixture is chosen (ratio butanone : n-heptane 70:30; boiling point: 77°C; boiling point of butanone: 79.6°C, boiling point of n-heptane: 98.5°C). In doing this a maximum residual moisture of smaller than 0.4% can be achieved despite mild drying.

Since polyacrylates do not tend to form bubbles, this method was not required in examples 4 and 5.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.

The claims defining the invention are as follows:

1. A transdermal therapeutical system for the administration of physostigmine to the skin via a cover layer which is impermeable to active substances, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, characterized in that the reservoir layer comprises 10-90%-wt polymeric material selected from the groups consisting of block copolymers on the basis of styrene and 1,3-dienes, polyisobutylenes, polymers on the basis of acrylate and/or methacrylate and esters of hydrogenated colophonium, 0-30%-wt softeners on the basis of hydrocarbons and/or esters, and 0.1-20%-wt physostigmine.

2. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises linear styrene-isoprene-styrene block copolymer.

3. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises linear styrene-butadiene-styrene block copolymer.

4. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises self-crosslinking acrylate copolymer of 2-ethylhexyl acrylate, vinyl acetate, acrylic acid and titane chelate ester.

5. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises non-self-crosslinking acrylate copolymers of 2-ethylhexyl acrylate, vinyl acetate, and acrylic acid.

6. The transdermal therapeutical system according to claim

1, characterized in that the polymeric material comprises as polymer on the basis of methacrylates a copolymer on the basis of dimethylaminoethyl methacrylate and neutral methacrylic acid esters.

7. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises as ester of the hydrogenated colophonium its methylester.

8. The transdermal therapeutical system according to claim 1, characterized in that the polymeric material comprises as ester of the hydrogenated colophonium its glycerol ester.

9. The transdermal therapeutical system according to claim 1, characterized in that the reservoir layer comprises as softener dioctyl cyclohexane.

10. The transdermal therapeutical system according to claim 1, characterized in that the reservoir layer comprises as softener di-n-butyl adipate.

11. The transdermal therapeutical system according to claim 1, characterized in that the reservoir layer comprises as softener triglycerides.

12. The transdermal therapeutical system according to claim 1, characterized in that the reservoir layer comprises as softener isopropylmyristate.

13. A process for the production of a transdermal therapeutical system according to any one of claim 1 to 12, characterized in that the components of the reservoir layer are dissolved in a low-boiling solvent which makes possible a drying up to a maximum residual moisture of smaller than 0.4%-wt.

14. The process for the production of a transdermal therapeutical system according to claim 13, characterized in that a solvent mixture of butanone and n-heptane is used.

15. The transdermal therapeutical system according to any one of claims 1 to 12 when obtained by the process according to claim 13 or 14.

DATED this 18th day of December, A.D. 1989

LTS LOHMANN Therapie-System
GmbH & Co. KG,
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

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