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Transdermal therapeutic system for administration of 17α-estradiol

DESCRIPTION

The invention relates to an active substance-containing plaster for the controlled release of 17α-estradiol or one of its pharmaceutically acceptable derivatives via the skin of the human body.

β-estradiol (estra-1,3,5(10)-triene-3,17-diol) is a natural female sex hormone. It serves to develop the primary and secondary sex characteristics and has an influence on the growth and structure of the body. Furthermore, it contributes to shaping the course of the menstrual cycle in women.

The natural sex hormones, their derivatives as well as their structural analogues are utilized for hormonal contraception, for substitution therapy or for the treatment of various diseases.

Estradiol exists in two conformations which differ from each other merely in the configuration of the hydroxyl group at the 17 position of the steroid skeletal structure. In the conformation designated as "α" (17α-estradiol), the hydroxyl group lies beneath the plane defined by the steroid skeletal structure, in the other conformation (17β-estradiol) the hydroxyl group projects beyond this plane. The known hormonal effects of natural estradiol are largely attributable to the 17β-isomer. In studies involving animal experiments and in biochemical studies, the 17α-isomer accounts for less than 1 percent of the hormonal action of the 17β-form.

17α-estradiol is however not biologically inactive as had originally been presumed. On the contrary, as findings in steroid biology of the recent past show, 17α-estradiol influences a number of physiological processes which are completely independent from the hormonal action of the 17β-isomer, which action attacks at the nucleus of the cell.

17β-estradiol inhibits, for example, the release of catecholamines from the suprarenal glands and causes direct relaxation of arteries, which relaxation is independent of the nitrogen oxide-mediated endothelial mechanisms. Thus, 17α-estradiol has shown an anti-atherogenic action comparable to that of the 17β-form in rabbits that received extremely cholesterol-rich food for prolonged periods of time, i.e. a reduction of the formation of atherosclerotic plaques on the cell walls.

Moreover, it was shown that 17α-estradiol has neuroprotective potential. In these studies, a protective action of 17α-estradiol against the neurotoxic effects of beta-amyloid, which serves as histopathologic symptom of Alzheimer's disease, was proved on cultivated neuroblastoma cells. The protective action is just as strong as that of the 17β-isomer. Comparable results were also obtained in respect of the protective action of both isomers against withdrawal of nutrients. In rats whose cognitive ability is significantly impaired by selective destruction of central cholinergic pathways, the 17α-isomer and the 17β-form also show the same action. Further experiments showed that both isomers of estradiol as well as their direct derivatives not only protect against cytotoxic action of beta amyloid

but also against peroxides, glutamate and buthionine sulfoximine.

Based on the fact that 17α-estradiol has some of the potentially therapeutically valuable properties of the 17β form without, however, sharing the - in this connection often unwanted - hormonal effects, such as promoting the formation and growth of estrogen-dependent tumours or feminisation in men, it has been proposed in US patent specification US 5,554,601 to use estradiols without hormonal effects as a therapeutic agent for Alzheimer's disease.

In WO 98/22113, 17α-estradiol is administered by means of subcutaneously implanted silicone tubes within the framework of animal experiment studies and is stated to be suitable for the therapy and prophylaxis of ischemic events such as apoplexy and cardiac infarction.

WO 99/42108 describes the use of selected steroids which, by contrast to systemically active natural and synthetic estrogens, including 17α-estradiol, are characterised by having a selective neurotropic estrogen-like transcription effect in the central nervous system. The selected steroids are claimed for the production of pharmaceutical preparations for selectively supplementing estrogen deficiency in the central nervous system without influencing other organs or systems.

The laid-open specification DE-195 24 937 and the EP-0 753 300, which is based thereon, refer especially to the anti-oxidative action of 17α-estradiol as well as to its suitability for the treatment of over-weight men. For example, 12 highly overweight men (body mass index >35) were orally administered a daily dose of 2 mg 17α-estradiol for a pe-

riod of 6 months. Hormonal side effects such as subjective complaints and an increase in the sex hormone-binding globuline were not observed, at the end of the study, however, a significant decrease of the total cholesterol, LDL cholesterol and triglycerides resulted.

With the exception of the mention of hard gelatine capsules, which were used in the study cited in DE-195 24 937/EP-0 753 300 but not described in greater detail in these publications, the prior art does not reveal any suitable concrete means for administering 17α-estradiol, so that hitherto no clinically practicable form of a possible application of 17α-estradiol has been available.

Estrogen-containing active substance patches are known as such.

From DE-OS 32 05 258 and EP 0 285 563 it is known to administer estradiol and ethanol simultaneously in a patch formulation. However, the production of this patch is very costly, and the wear comfort after application is poor because of a lack of flexibility.

EP 0 285 563 describes a transdermal therapeutic system for the combined application of estrogens and gestagens. The reservoir contains the active substance formulation and optionally a membrane, as well as ethanol as a percutaneous absorption-enhancing agent. Since the release of the active substance is mainly controlled by the membrane, this transdermal therapeutic system is fundamentally different from the active substance patch according to the present invention. In the patch described in that document, the adhesive merely has the function of fixing the patch on the skin. The fact that it is able to contribute to the control of the active substance release does not constitute its main

task but is merely a side effect - possibly even an unwanted one. The patch in question is a so-called "pouch patch" because the active substance preparation is present within a pouch, consisting of an impermeable backing layer and a membrane with an adhesive layer. As a result of its complicated structure, the manufacture of the patch is costly since the individual components have to be produced separately and then combined in a further operation to form a patch.

EP 0 275 716 describes a two-layer transdermal system for simultaneous administration of one or more estrogens, which are dissolved or micro-dispersed in the polymer layer. Apart from the active substances, the pressure-sensitive adhesive layer here contains substances improving transdermal absorption. Polymer layers and pressure-sensitive layers may consist of polyacrylates, silicones or polyisobutylenes.

EP 0 328 806 describes a membrane-free transdermal therapeutic system whose matrix consists of a polyacrylate adhesive, a solvent, a penetration enhancer, and estrogens, derivatives of estrogen, and combinations thereof.

In WO 87/07138 there is described an estradiol patch comprising a backing layer, a matrix containing the active substance, and a pressure-sensitive adhesive, the latter being covered by a detachable protective layer. The production of the matrix and the pressure-sensitive adhesive takes place in technologically very costly operations by homogenisation, degassing, coating, drying and separating. In one embodiment, the backing layer even has to be coated with a pressure-sensitive adhesive, which entails another operation. Combining the individual components takes place in a separate operational step. The overall production of this patch is therefore very costly and complicated.

From US 4 624 665 there are known systems containing the active agent in microencapsulated form in the reservoir. The reservoir is embedded between the backing layer and a membrane. The outer margin of the system is equipped with a pressure-sensitive adhesive. The structure and the production of this system is very complicated since the active substance is microencapsulated and is homogeneously distributed in a liquid phase which is then embedded in further operations between the backing layer and the membrane. In addition, the systems must thereafter be provided with an adhesive margin, and covered with a protective layer.

Furthermore, from EP 0 186 019 active substance patches are known wherein water-swellable polymers are added to a caoutchouc/adhesive resin compound, and which are able to release estradiol. It has, however, been shown that the release of estradiol from these active substance patches is by far too low and does not meet the therapeutic requirements.

DE-OS 195 00 662 describes a transdermal therapeutic system comprising an estradiol-containing active substance reservoir based on ethyl cellulose with a high content of colophony esters as tackifying resin, along with up to 20%-wt. of lauric acid which is to counteract the recrystallisation of the active substance and thereby the decrease in its release rate.
In the literature, several further substances have been described which act as crystallisation inhibitors and are to prevent the crystallisation of estradiol in particular; these are, for example, silicon dioxide (US patent 5,676,968) or water-free glycerine (WO 96/05814). The addition of substances of this kind frequently involves drawbacks; for instance, the mechanical properties (cohesion)

of the patch may be impaired, or problems may occur in the production of these patches.

In DE-OS 20 06 969 there is described a patch or an adhesive bandage having systemic action wherein contraceptive substances are incorporated in the adhesive component or the adhesive film. The adhesive film may be an acrylate.

The object of the present invention therefore was to develop a transdermal therapeutic system (TTS) which is suitable for the administration of 17α-estradiol or one of its pharmaceutically acceptable derivatives to a person in need of such treatment.

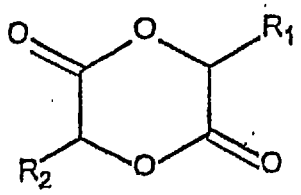
This object is achieved by an active substance-containing patch in accordance with the main claim. The subclaims relate to especially preferred embodiments of the subject-matter of the invention.

The invention thus relates to an active substance-containing patch for the controlled release of 17α-estradiol or its pharmaceutically acceptable derivatives, consisting of a backing layer, an active substance-containing reservoir attached thereto and prepared using pressure-sensitive adhesives, and a detachable protective layer.

As pharmaceutically acceptable derivatives of 17α-estradiol also having the potentially therapeutically valuable properties of 17α-estradiol without causing the unwanted hormonal effects of 17β-estradiol, one may also use the 8-dehydro-17-α-estradiol and the 14α-,15α-methylene-estra-1,3,5(10),8-3-17α-diol as active substance.

Furthermore, the active substance-containing reservoir may contain at least one enhancer; "enhancer" here meaning a substances improving the skin permeation of the active substance to be administered. The enhancer or enhancers is/are added in a concentration of 0.5 to 50%-wt., relative to the active substance-containing reservoir.

The enhancer or enhancers may be selected from a group containing the following substances: lauric acid diethanol amide (e.g. Comperlan LD), oleic acid diethanol amide (e.g. Comperlan OD), coconut fatty acid diethanol amide (e.g. Comperlan COD), D-α-tocopherol (e.g. Copherol), lauric acid, lauric acid hexyl ester (e.g. Cetiol A), 2-octyldodecanol (e.g. Eutanol), and dexpanthenol, ethanol, glycerol, and additives based on the 1,4-dioxane-2,5-dione basic structure and having the general formula



where R_1 and R_2 are hydrocarbon groups or substituted hydrocarbon groups or functional groups.

The transdermal system according to the present invention may be manufactured as a so-called "pouch patch", wherein the active substance preparation is present in a pouch consisting of an impermeable backing layer and an active substance permeable membrane with an adhesive layer.

An especially preferred structure of the transdermal 17α-estradiol-containing patch is a matrix system, i.e. containing at least one polymer matrix layer which on the

one hand serves as a reservoir for the active substance or active substances and on the other hand has an adhesive function, in order to attach the TTS to the skin and enable close contact thereto. As is known, the matrix controls the active substance release, and follows the $\sqrt{t}$ law according to Higuchi. This does, however, not mean that in special cases a membrane system may not be of advantage too. In that case, a membrane controlling the active substance release is positioned between the reservoir and a separate pressure-sensitive adhesive layer.

As essential polymer for the active substance-containing matrix, a substance is preferably used which is selected from the group comprising derivatives of cellulose, polymethyl methacrylates and polyacrylates.

Acrylic acid copolymers in this connection are copolymers originating from radical polymerisation of esters of acrylic acid and methacrylic acid with C_1 to C_{18} alcohols, dimethyl aminoethanol or other suitable alcoholic reaction partners, vinyl acetate, vinylpyrrolidone, styrene, butadiene, acrylonitrile, or other suitable monomers containing a vinyl group.

Among the cellulose derivatives, ethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methyl cellulose are especially preferred. Ethyl cellulose is a cellulose ether which is prepared by reaction of ethyl chloride with alkali cellulose. Concerning the structure it is generally assumed that a cellulose molecule is a chain of anhydroglucose or cellobiose units which are linked via oxygen bridges. These long chains of anhydroglucose with oxygen bridges have good strength while also possessing good flexibility. These characteristics are made use of in the 17α-estradiol-containing patch in order to impart suffi-

cient cohesion on the pressure-sensitive adhesive, which is a prerequisite for the residue-free removal of the patch from the skin when the application has terminated. The pressure-sensitive adhesive may contain ethyl cellulose in an amount of 5-25%-wt, preferably 8-14%-wt.

Combinations of different matrix polymers may also be used. The portion of the matrix polymer(s) preferably amounts to 10 to 50%-wt, relative to the active substance-containing reservoir.

The TTS according to the invention may, as a further main component of the active substance-containing reservoir, contain at least one polymer preventing the crystallisation of the active substance(s); the portion of this polymer or these polymers amounts to 10 to 50%-wt, relative to the active substance-containing reservoir. As crystallisation-inhibiting polymer an ethylene-vinylacetate-vinyl-pyrrolidone copolymer is especially preferred.

It may prove particularly advantageous for the active substance-containing matrix to be composed of two or more layers. In this case, the individual layers may contain different active substances or active substance concentrations, or have a different polymer composition, or they may differ in their composition in another way. Furthermore, there may be inserted a flat-shaped body between the individual layers of the active substance-containing reservoir which may be, for instance, a membrane, a film, a textile fabric or a textile material. A further embodiment consists in that the TTS according to the invention is provided with an additional pressure-sensitive layer and/or a pressure-sensitive margin or edge; this is useful especially if the tackiness of the active substance-containing matrix is not sufficient.

In further embodiments it is provided that tackifying or tackiness-improving resins and/or fillers are added to the active substance-containing reservoir. Substances suitable for this purpose are in principle known to those skilled in the art. For example, esters of unhydrogenated and/or hydrogenated colophony are to be considered in this connection.

Among the esters of colophony are, for instance, the methyl ester, the glycerol ester, the pentaerythrite ester, the maleic acid-modified pentaerythrite ester, the maleic acid-modified glycerol ester, and the triethylene glycol ester. The amount of esters of colophony contained in the estrogen-containing pressure-sensitive adhesive is 50-90%-wt, preferably 60-80%-wt.

The pressure-sensitive adhesive may contain esters of hydrogenated colophony, singly or together with esters of the non-hydrogenated colophony.

Especially preferred esters of colophony are the triethylene glycol ester, the glycerol ester and the pentaerythrite ester of the hydrogenated colophony.

The estradiol-containing reservoir may contain at least one component of the group comprising anti-aging agents, plasticizers, antioxidants and absorption enhancers. These components may be present in a concentration of up to 10%-wt. in the reservoir. Suitable plasticizers are known to those skilled in the art and are described, for example, in DE 37 43 946. The estradiol-containing matrix usually contains softeners in a portion of up to 5%-wt.

In cases where the reservoir does not have sufficient self-tackiness on the skin, it may be provided with an additional active substance-free pressure-sensitive layer or

with a surrounding pressure-sensitive margin. In this way, it is ensured that the transdermal patch adheres to the skin for the entire application period.

The TTSs according to the invention are characterized by a small layer thickness; the layer thickness of the active substance-containing reservoir is preferably 0.02 mm to 0.5 mm, especially preferred 0.03 to 0.2 mm.

The estradiol-containing reservoir may be produced both from solution and from the melt.

The structure of the TTSs according to the invention comprises, apart from an active substance reservoir, an active substance-impermeable backing layer, as well as a likewise active substance-impermeable, detachable backing layer. The materials for the impermeable backing layer and the detachable protective layer are likewise known to the skilled artisan (e.g. DE 38 43 239). Suitable as a backing layer are above all polyesters which are characterized by a particularly high strength, but also almost any other skin-tolerated plastics such as polyvinyl chloride, ethyl vinyl acetate, vinyl acetate, polyethylene, polypropylene, cellulose derivatives, or combinations of different films, and many more. In a given case, the backing layer may be provided with an additional coat, e.g. by vapour deposition with metals or other diffusion-blocking additives such as silicon dioxide, aluminium oxide, or similar substances known to those skilled in the art. For the detachable protective layer, the same materials can be used as for the backing layer, provided that the protective layer has been made detachable by appropriate surface treatment such as, for example, siliconisation. But other detachable protective layers, such as polytetrafluoroethylene-treated paper, cellophane, polyvinyl chloride or the like may be used as well.

To take into account the therapeutical requirements, a 17α-estradiol-containing patch must be provided which has sufficient active substance release. The amount released per day by the transdermal therapeutic system according to the invention is between 0.05 and 20 mg 17α-estradiol, preferably between 0.05 and 10 mg, and especially preferred between 1 and 5 mg.

The transdermal therapeutic system according to the invention is suited for the preventive treatment of atherosclerosis and the disorders resulting therefrom, such as ischemic infarction, cardiac infarction, and peripheral occlusive diseases. It is furthermore suited for the therapy of neurodegenerative diseases such as Alzheimer's or Parkinson's disease and of their prodromal symptoms, multiple sclerosis, amyotrophic lateral sclerosis (motor neuron disease) and chorea (Huntington's disease). It is also suitable for the treatment of states of stress which lead to the release of catecholamines, and for the treatment of rheumatoid arthritis.

CLAIMS

1. Transdermal therapeutic system consisting of an active substance-impermeable backing layer, an active substance-containing reservoir of at least one layer, and a detachable protective layer, characterized in that it contains 17α-estradiol or one of its pharmaceutically acceptable derivatives as active substance.

2. Transdermal therapeutic system according to claim 1, characterized in that the pharmaceutically acceptable derivative of 17α-estradiol is selected from the group consisting of 8-dehydro-17α-estradiol and 14α,15α-methylene-estra-1,3,5(10),8-3-17α-diol.

3. Transdermal therapeutic system according to claim 1 or 2, characterized in that the active substance-containing reservoir contains one or more substances improving the permeation of the active substance(s) through the skin, at a concentration of 0.5 to 50%-wt.

4. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir contains emulsifiers and/or plasticizers and/or antioxidants at a concentration of up to 10%-wt., preferably from 0.1 to 5%-wt.

5. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir contains resins improving tackiness.

6. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir contains fillers.

7. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir is made up of two or more layers.

8. Transdermal therapeutic system according to claim 7 characterized in that the individual reservoir layers have different active substance concentrations and/or differ from each other in terms of their polymer composition.

9. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir has a layer thickness of 0.02 mm to 0.5 mm, preferably 0.03 to 0.2 mm.

10. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the active substance-containing reservoir is provided with an additional pressure-sensitive adhesive layer and/or a pressure-sensitive adhesive margin or edge.

11. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that its daily release quantity is between 0.05 and 20 mg, preferably between 0.05 and 10 mg, and especially preferred between 1 and 5 mg.

12. Use of the transdermal therapeutic system according to one or more of claims 1 to 11 for the prophylactic treatment of atherosclerosis and diseases resulting therefrom, such as ischemic infarction, cardiac infarction and peripheral occlusive diseases.

13. Use of the transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of neurodegenerative diseases of the central nervous system such as Alzheimer's disease or Parkinson's disease, and their prodromal syndroms, multiple sclerosis, amyotrophic lateral sclerosis (motor neuron disease) or chorea (Huntington's disease).

14. Use of the transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of states of stress which lead to a release of catecholamines.

15. Use of the transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of rheumatoid arthritis.

16. Process for the manufacture of a transdermal therapeutic system according to one or more of claims 1 to 11 for the prophylactic treatment of atherosclerosis and diseases resulting therefrom such as ischemic infarction, cardiac infarction and peripheral occlusive diseases, characterized in that 17α-estradiol or one of its pharmaceutically acceptable derivatives is used as essential active substance.

17. Process for the production of a transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of neurodegenerative diseases of the central nervous systems such as Alzheimer's disease or Parkinson's disease, and their prodromal syndromes, multiple sclerosis, amyotrophic lateral sclerosis (motor neuron disease) or chorea (Huntington's disease), characterized in that 17α-estradiol or one of its pharmaceutically acceptable derivatives is used as essential active substance.

18. Process for the production of a transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of states of stress which lead to the release of catecholamines, characterized in that 17α-estradiol or one of its pharmaceutically acceptable derivatives is used as essential active substance.

19. Process for the production of a transdermal therapeutic system according to one or more of claims 1 to 11 for the therapy of rheumatoid arthritis, characterized in that 17α-estradiol or one of its pharmaceutically acceptable derivatives is used as essential active substance.

20. Process according to any one of claims 16 to 19, characterized in that the pharmaceutically acceptable derivative of 17α-estradiol is selected from the group consisting of 8-dehydro-17α-estradiol and 14α,15α-methylene-estra-1,3,5(10),8-3-17α-diol.