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(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: SCHERING AKTIENGESELLSCHAFT [DE/DE]; D-13342 Berlin (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: LIPP, Ralph [DE/DE]; Jenaer Strasse 8, D-10717 Berlin (DE). GÜNTHER, Clemens [DE/DE]; Gotschedstrasse 26, D-13357 Berlin (DE). RIEDL, Jutta [DE/DE]; Flensburger Strasse 14, D-10557 Berlin (DE). TÄUBER, Ulrich [DE/DE]; Soldiner Strasse 13, D-13359 Berlin (DE).

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(54) Title: SEXUAL STEROID-CONTAINING TRANSDERMAL THERAPEUTIC SYSTEMS

(54) Bezeichnung: TRANSDERMALE THERAPEUTISCHE SYSTEME ENTHALTEND SEXUALSTEROIDE

(57) Abstract

Transdermal therapeutic systems are disclosed that contain sexual steroids and, if required, penetration reinforcing agents and crystallisation inhibitors, with the exception of systems that contain non-fluid, active substance-containing gel phases or 3-keto-desorgestrel. These transdermal therapeutic systems are characterised in that they contain dimethylisosorbide.

(57) Zusammenfassung

Transdermale therapeutische Systeme enthaltend Sexualsteroide und gegebenenfalls Penetrationsverstärker und Kristallisationsinhibitoren werden beschrieben, welche dadurch gekennzeichnet sind, daß sie Dimethylisosorbid enthalten, mit Ausnahme von Systemen, die wirkstoffhaltige nicht fließfähige Gelphasen oder 3-Keto-desorgestrel enthalten.

Transdermal Therapeutic Systems That Contain Sex Steroids

The invention relates to transdermal therapeutic systems that contain sex steroids and optionally penetration-enhancers and crystallization inhibitors, which are characterized in that they contain dimethyl isosorbide, with the exception of systems that contain active ingredient-containing, non-free-flowing gel phases or 3-keto-desogestrel.

According to the invention, sex steroids are to be defined preferably as gestagens and/or estrogens although, in principle, other sex steroids, such as androgens, antiestrogens or antigestagens, are suitable for the production of the agent according to the invention.

Suitable gestagens for the agent according to the invention are, for example, gestodene, levonorgestrel, desogestrel, norethisterone and norethisterone acetate. For the production of the agent according to the invention, 3-keto-desogestrel is also suitable, as indicated by PCT/EP93/02224, which had not yet been prepublished as of the time of priority of this application.

Estrogens that are suitable for the agent according to the invention are, for example, estradiol, estriol, ethinylestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-triene-3,17ß-diol (WO 88/01275), 14α,17α-ethanoestra-1,3,5(10)-triene-3ß,16α,17α-ethanoestra-1,3,5(10)-triene-3ß,16α,17α-triol (WO91/08219) and their esters (EP-A 163596), such as estradiol-dipropionate, estradiol-dihexanoate and estradiol-didecanoate. In addition to at least one gestagen, the combination preparations according to

the invention preferably contain 1 to 3 -- especially 1 to 2 -- estrogen(s).

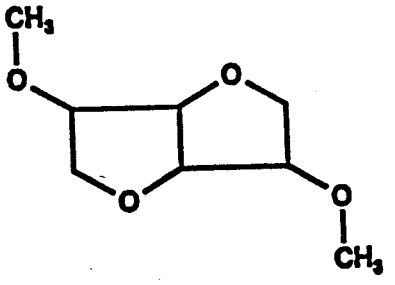
EP-B 0 137 278, which relates to transdermal therapeutic systems in which the active ingredient is embedded in a non-free-flowing gel phase, contains a general reference stating that dimethyl isosorbide can also be used in them as a solvent, but the patent specification does not indicate that the use of this agent could be of special benefit in the case of transdermal therapeutic systems.

As is generally known, therapeutic systems that are to be administered transdermally have the advantage that they make possible a more uniform release of the active ingredient over a longer period than is generally possible with other agents that are to be administered in other ways -- such as, for example, perorally. These properties can be used advantageously in the case of a number of endocrine diseases. For sparingly water-soluble steroid hormones, such as, for example, gestagens, however, it is generally quite problematical to provide transdermal systems that ensure a level of penetration of the active ingredient through the skin that is sufficient for treatment.

With the aid of the agent according to the invention, which in addition to sex steroid(s) also contains dimethyl isosorbide, it has now been found that it is possible, surprisingly enough, to achieve a therapeutically adequate, very uniform rate of penetration of the steroid hormones through the skin, while this is only conditionally possible with the known steroid hormones

that contain agents that are to be administered transdermally (EP-A 137278 and EP-A 275716), which makes it necessary to use comparatively large systems.

Dimethyl isosorbide is a substance of formula



As is generally known, it is a substance with good dissolving power for organic compounds (H. P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Dictionary of Adjuvants for Pharmaceutics, Cosmetics and Related Fields], Editio Cantor Aulendorf, 1989). This is used in, for example, USP 4082881 to keep high concentrations of organic pharmaceutical substances dissolved in various topical preparations, but not in transdermal systems. In USP 4814173, dimethyl isosorbide is used as a solvent for various pharmaceutical substances, but not for sex steroids, in solutions, emulsions as well as in complex synthesized transdermal therapeutic systems based on silicone skin contact adhesives.

It has now been found that dimethyl isosorbide is able to dissolve a number of sex steroids to a considerable extent. A selection of these steroids is presented in Tab. 1. Especially levonorgestrel, which is only slightly soluble in most standard

vehicles for transdermal use, can be dissolved in dimethyl isosorbide at significantly higher concentrations.

Tab. 1 Solubility of Sex Steroids in Vehicles for Transdermal Use

Sex Steroid	Vehicle				
	Dimethyl isosorbide	Paraffin	Isopropyl myristate	Tween 80	1,2-Propanediol
Levonorgestrel	9.0	0.006	0.42	3.2	1.0
Gestodene	74	0.022	2.2	18.7	13.4
Estradiol	55	0.008	1.5	34	84.4

Data in mg per ml

Moreover, dimethyl isosorbide evens out the solubilities of gestagens and estrogens. This is a significant added advantage, especially for the development of combination transdermal systems, since consequently, for the first time, highly concentrated binary mixtures of gestagens and estrogens can be dispersed together in a matrix in a molecularly disperse manner at advantageous concentration ratios of about 5:1 to 1:5. This

ensures that both active ingredients are present simultaneously in high thermodynamic activity in the system.

As described in DD-A- 217989, dimethyl isosorbide can be mixed to a suitable extent with skin contact adhesives that are commonly used for the production of transdermal systems.

It has now been found that certain mixed systems that consist of skin contact adhesives and dimethyl isosorbide exhibit significantly elevated dissolving power for sex steroids compared to systems without dimethyl isosorbide. These new systems, whose structure is depicted in Fig. 1, are single-phase, in contrast to the sex steroid-containing siloprene systems mentioned in EP-A 0 137 278, and are distinguished in that they adhere independently to the skin. Also, they differ from the topical preparations mentioned in WO 89/04179, especially the active ingredient-containing plasters mentioned there, because of their simple structure. They can be produced more simply than the above-named transdermal systems and are distinguished by more advantageous wearing properties owing to their thin, flexible design.

In addition to its good properties for dissolving organic molecules, dimethyl isosorbide also has penetration-enhancing properties. Thus, surprisingly enough, in-vitro penetration studies have revealed that the vehicle dimethyl isosorbide has strong penetration-promoting properties for sex steroids (see Tab. 2).

In the agents according to the invention, normally 1 to 40% by weight and preferably 5 to 25% by weight of dimethyl

isosorbide, relative to the entire active ingredient phase, is used.

Tab. 2: Percutaneous Resorption (in $\mu g/cm^2/h$) of Sex Steroids in Formulations Without Penetration Enhancers through the Skin of Hairless Mice

Steroid	Formulation	Average Flow Day 1	Average Flow Day 2	Maximum Flow
0.2 mg of LN	PG	0.18±0.06	0.53±0.07	0.74±0.14
0.2 mg of LN	PGML	0.25±0.06	0.42±0.03	0.64±0.06
0.2 mg of LN	DMI	0.31±0.14	0.66±0.10	1.23±0.32
1 mg of LN	DMI	0.62±0.20	1.02±0.40	1.62±0.61
0.2 mg of LN	IPM	0.13	0.11	0.16
0.2 mg of E_2	DMI	0.51±0.17	0.79±0.48	0.97±0.57
1 mg of E_2	DMI	2.63±1.21	3.10±1.99	4.17±1.57
0.2 mg of E_2	PG	0.92±0.26	0.25±0.01	1.34±0.24
0.2 mg of E_2	IPM	0.47	0.29	0.69

DMI: Dimethyl isosorbide

IPM: isopropyl myristate

PG: propylene glycol

PGML: propylene glycol monolaurate

LN: levonorgestrel

E2: estradiol

The transdermal flows of sex steroids that are achieved in vitro can be even further increased by properly combining dimethyl isosorbide with other known penetration enhancers (see Tab. 3).

Tab. 3 Percutaneous Resorption (in $\mu g/cm^2/h$) of Sex Steroids in Formulations with Penetration Enhancers through the Skin of Hairless Mice

Steroid	Formulation	Average Flow		Maximum Flow
		Day 1	Day 2	
0.2 mg of LN	DMI+10%LA	1.70±0.18	0.91±0.16	3.62±0.76
0.2 mg of LN	DMI+10%LS	1.95±0.81	1.27±0.62	3.28±1.40
0.2 mg of LN	PG+10%LA	0.67±0.04	0.64±0.11	1.32±0.05
0.2 mg of LN	PG+5%azone	0.71±0.22	0.75±0.16	1.13±0.43
0.2 mg of E2	DMI+10%LA	7.35±1.15	4.86±1.97	11.57±1.72
0.2 mg of E2	DMI+10%LS	9.06±0.50	7.55±0.33	15.29±0.61
0.2 mg of E2	PG+5%azone	1.92±0.18	0.90±0.10	5.15±0.84

With the aid of the agent according to the invention, transdermal therapeutic systems can be produced with high concentrations of sex steroids that are dissolved in a molecular disperse way. When using these new systems, an especially high effective concentration gradient between pharmaceutical agent and skin is achieved. The high concentration gradient and the strong penetration-promoting action of the dimethyl isosorbide or the

dimethyl isosorbide-enhancer combinations, respectively, together produce the high transdermal flows of the processed steroid hormones.

In individual cases, an addition of crystallization inhibitors to the matrix of the previously mentioned systems, as described in WO 93/08795, can improve the shelf life of the transdermal systems according to the invention.

Very uniform administration with a set dosage of the active ingredient or active ingredient mixture can be achieved if the active ingredient or the mixture is embedded in a transdermal therapeutic system (TTS) and here especially in a matrix system. Suitable matrix systems are those that are usually used for percutaneous administration of active ingredients (Yie W. Chien: "Transdermal Controlled Systemic Medications," Marcel Dekker, Inc., New York and Basel, 1987, Dr. Richard Baker: "Analysis of Transdermal Drug Delivery Patents 1934 to 1984" and "Analysis of Recent Transdermal Delivery Patents, 1984-1986 and Enhancers" Membrane Technology & Research 1030 Hamilton Court Menlo Park CA 94025 (415) 328-2228).

Thus, for example, a transdermal therapeutic system can be used, which consists of

a) an impermeable cover layer,

one to three matrix layer(s) that adhere to the cover layer and that contain gestagen and/or estrogen, and dimethyl isosorbide and optionally penetration-enhancing agents and one or more crystallization inhibitors that are permeable and self-adhesive to these components or are covered or surrounded by a

skin contact adhesive that optionally contains penetration-enhancing agents; a removable protective layer, or

b) a cover that is provided with a contact adhesive that optionally contains penetration-enhancing agents,

one to three matrix layer(s) that leave uncovered a contact adhesive border and that are attached by means of a cover to the contact adhesive, gestagen and/or estrogen and dimethyl isosorbide and that optionally contain penetration-enhancing agents and crystallization inhibitors; and a removable protective layer.

A transdermal therapeutic system according to variant a) represents a simple matrix system. It can be, for example, of round, oval or rectangular shape and can be produced as follows.

A solution of up to 25% by weight of active ingredient or active ingredient mixture, 1-40% by weight of dimethyl isosorbide or a mixture of dimethyl isosorbide and other penetration-enhancing agents, 30-70% by weight of a medicinally usual adhesive filled up with a suitable volatile solvent to 100% by weight is coated with a plane, impermeable cover layer. After drying, a second and optionally later even a third layer, that optionally contains active ingredients, penetration-enhancing agents and adhesives, can be applied on this layer and dried. Then, the matrix system is provided with a removable protective layer.

If a medicinally usual matrix former is used, which does not adhere or insufficiently adheres to the skin after the system is dried, the system can be covered or surrounded in addition with a

skin contact adhesive before the removable protective layer is applied.

Suitable volatile solvents are, for example, lower alcohols, ketones or lower carboxylic acid esters, such as ethanol, isopropanol, acetone or ethyl acetate, polar ethers, such as tetrahydrofuran, lower hydrocarbons, such as cyclohexane or benzine, or else halogenated hydrocarbons, such as dichloromethane, trichloromethane, trichlorotrifluoroethane and trichlorofluoromethane. There is no need for an explanation that mixtures of these solvents are also suitable.

Suitable penetration-enhancing agents are, for example, monovalent or multivalent alcohols, such as ethanol, 1,2-propanediol or benzyl alcohol, saturated and unsaturated fatty alcohols with 8 to 18 carbon atoms, such as lauryl alcohol or cetyl alcohol, hydrocarbons, such as mineral oil, saturated and unsaturated fatty acids with 8 to 18 carbon atoms, such as stearic acid or oleic acid, fatty acid esters with up to 24 carbon atoms or dicarboxylic acid diesters with up to 24 carbon atoms.

As medicinally usual adhesives, for example, polyacrylates, silicones, polyurethanes, block polymers, styrene-butadiene copolymers as well as natural or synthetic rubbers, such as, e.g., polyisobutylenes and especially polyacrylates, are suitable. As additional matrix formers, cellulose ether, polyvinyl compounds or silicates are to be considered. To increase the stickiness, the usual additives, such as, for

example, tackifying resins and oils, can be added to the matrix obtained.

Fatty acid esters, which are suitable for the agent according to the invention, are, for example, those of acetic acid, caproic acid, lauric acid, myristic acid, stearic acid and palmitic acid, such as, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, tert-butyl ester or monoglyceric acid esters of these acids. Especially preferred esters are those of myristic acid or oleic acid, such as their methyl esters and especially their isopropyl esters. Suitable dicarboxylic acid diesters are, for example, diisopropyl adipate, diisobutyl adipate and diisopropyl sebacate.

Other penetration-enhancing agents are phosphatide derivatives, such as lecithin, terpenes, amides, ketones, urea and its derivatives or ethers, such as, for example, dimethyl isosorbide and diethylene glycol monoethyl ether. There is no need for a more detailed explanation that also mixtures of these penetration-enhancing agents are suitable for the production of the agent according to the invention.

As crystallization inhibitors, which in individual cases can improve the storage stability of the systems according to the invention, for example, additives of highly dispersed silicon dioxide or macromolecular substances, such as polyvinylpyrrolidone (for example, Kollidon 12 PF, Kollidon 17 PF, Kollidon 25 and Kollidon 30 of BASF), vinylpyrrolidone-vinyl acetate copolymer (for example, Kollidon VA 64 of BASF),

crosslinked polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, ethyl cellulose, gelatin, starch (derivatives) and dextran are suitable.

As protective layers, all films that are usually used in transdermal therapeutic systems are suitable. Such films are, for example, siliconized or fluoropolymer-coated.

As a cover layer, for example, 10 to 100 μm-thick films made of polyethylene or polyester can be used selectively pigmented or metallized in this system. The pharmaceutical agent layer applied on it preferably has a thickness of 20 to 500 μm. The release of the active ingredients usually takes place over a surface area of 1-100 cm^2 and preferably less than 5 to 100 cm^2.

In the case of multilayer matrix systems, gestagen, dimethyl isosorbide and optionally penetration-enhancers can be introduced, for example, in the matrix applied on the impermeable cover layer, while the layer or layers below contain the estrogens in addition to dimethyl isosorbide and optionally also penetration-enhancers. In contrast, however, it is also possible in such a transdermal system to arrange several active ingredient-containing matrix systems side by side.

A transdermal therapeutic matrix system according to variant b can be, for example, also round, oval or rectangular and can be produced as follows:

A cover is coated with a skin contact adhesive. Then, one or two punched-out areas of a matrix layer that is provided with an impermeable cover and that contains gestagen, dimethyl isosorbide, optionally estrogen(s) and optionally penetration-

enhancing agents, is bonded to the cover pro TTS, so that the cover has a sufficient edge for attaching to the skin and also sufficient interspaces in several areas and provides it with a removable protective layer. The materials that are used in this matrix system can be the same as in those of variant a.

In addition to dimethyl isosorbide, the above-mentioned penetration-enhancing agents can be used in this system. As a permeable polymer layer, for example, a 20 to 200 μm-thick film made of cellulose esters, cellulose ethers, silicones or polyolefin compounds is used. By variation of this polymer layer, the rate of diffusion of the active ingredient or active ingredient mixture can vary within wide limits.

As an adhesive and protective layer, the same materials that are described in the transdermal therapeutic system according to variant a are suitable.

In the production of transdermal therapeutic systems with two active ingredient-containing matrix layers or pharmaceutical agent reservoirs that are arranged side by side, it is often suitable to introduce gestagen in one and estrogen in the other. In such cases, the active ingredient-containing matrix systems or pharmaceutical agent reservoirs can contain not only different active ingredients, but in addition different penetration-enhancing agents.

In the case of the matrix systems according to variant a or b, care must be taken for a sufficient spacing of the areas to prevent a diffusion of the active ingredients in the respective other area.

Other features of the transdermal systems according to the invention can be explained based on the attached drawings that are not true-to-scale.

Fig. 1 shows a cross section through a simple round matrix system according to variant a without the removable protective layer. It consists of impermeable cover layer 1 and pharmaceutical agent-containing matrix layer 2.

Fig. 2 shows a cross section through a matrix system according to variant b without the removable protective layer.

Fig. 3 shows a longitudinal section through this system. The system consists of cover 3, which is provided with a contact adhesive layer 4. Two pharmaceutical agent-containing matrix layers 6 and 8 are attached to this contact adhesive layer by impermeable covers 5 and 7.

The gestagen agents for transdermal administration according to the invention can be used for treating the same diseases as the previously known agents, for example, agents to be administered orally, that contain highly effective gestagens. Moreover, the optionally estrogen-containing preparations according to the invention also can be used for contraception and for substitution therapy in post-menopause. The agents according to the invention have special advantages in the treatment of diseases that require a long-term treatment at relatively high dosage of the active ingredients. Here, the frequency of administration can be significantly reduced and an essentially uniform blood plasma level can be achieved. Further, it is advantageous that no gastrointestinal side effects are to be

expected, and in estrogen-containing combination preparations, the first liver passage is avoided, and that the dose of estrogen can be reduced.

These advantages make the gestagen-containing monotherapeutic agents of this invention appear to be especially suitable to treat, for example, endometriosis, gestagen-dependent tumors, benign breast diseases or the premenstrual syndrome.

The transdermal use of estrogens optionally in sequential or continuous combination with gestagen offers special advantages, for example, for treating menopausal symptoms, for the prevention of osteoporosis, for regulation of the menstrual cycle and for stabilization of the menstrual cycle.

The following embodiments are used for a more detailed explanation of the invention. The following commercial products were used in the embodiments:

Polyester film of 0.074 mm thickness (Skotchpak(R) 1009) of the 3M manufacturer; polypropylene film (Celgard(R) 2500) of the Celanese manufacturer, Linerfolie Skotchpak [liner film Scotchpak](R) 1022 and 1360 of the 3M manufacturer; Transferkleber [transfer adhesive] 9871 of the 3M manufacturer, polyacrylester adhesive of Sichello(R) J 6610-21 type of the Henkel KG manufacturer, silicone adhesive of X-7-2960 type of the Dow Corning manufacturer and hydroxypropyl cellulose of the Klucel(R) HXF type of the Hercules manufacturer, polyisobutylene of Oppanol(R) B 15 SF type of the BASF AG company, dimethyl isosorbide of Arlasolve(R) DMI type of the ICI Surfactionts company, polyvinylpyrrolidone of Kollidon 12 PF type as well as

the vinyl acetate-vinylpyrrolidone copolymers of Kollidon VA 64 type of the BASF AG company.

Example 1

0.8 g of desogestrel

8.0 g of dimethyl isosorbide

are introduced in succession in 62.4 g of a 50% solution of silicone adhesive in benzine while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 40 g/m^2 of solid coating results. Then, it is laminated with a fluoropolymer-coated polyester liner. The thus obtained laminate is divided by a punching device into round individual plasters of 10 cm^2 area and packaged in aluminum foil. Fig. 1 shows a cross section through this plaster without a polyester liner. After the liner film is removed, the plaster adheres to the skin.

The determination of content yields a uniform active ingredient distribution of 0.08 mg/cm^2 on average.

Example 2

5.0 g of gestodene

10.0 g of dimethyl isosorbide

are dissolved in succession in 170 g of a 50% solution of polyacrylester adhesive in acetone/benzine while being stirred. After the batch is degassed, the solution is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching

device into individual plasters of 10 cm^2 area and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

The content of gestodene is 0.5 mg/cm^2 on average.

Example 3

3.5 g of estradiol

3.5 g of levonorgestrel and

7.0 g of dimethyl isosorbide with 10% lauric acid are dissolved or suspended in succession in 112 g of a 50% solution of polyacrylester adhesive in acetone/benzine while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 70 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 10 cm^2 area and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

In a like manner, the content of estradiol and levonorgestrel is about 0.35 mg/cm^2 each.

Example 4

Analogously to Example 1, two different segment-type matrix systems are produced, which have the design represented in Figs. 2 and 3. Matrix system I consists of matrix layer 8 -- provided

with a polyester film 7 -- of the following composition:

1.0 mg of norethisterone acetate

5.0 mg of dimethyl isosorbide and

44 mg of acrylate adhesive solid

and has an area of 5 cm^2.

Matrix system II consists of matrix layer 6 -- provided with a polyester film 5 -- of the following composition:

2.0 mg of ethinylestradiol

10.0 mg of dimethyl isosorbide and

88 mg of acrylate adhesive solids

and has an area of 10 cm^2.

Both matrix systems are bonded to a linen cloth that is coated with a skin contact adhesive, as Fig. 3 shows. After lamination and punching out, plasters of the type shown in Figs. 2 and 3 result.

Example 5

3.5 g of ethinylestradiol

3.5 g of desogestrel and

7.0 g of isopropyl myristate

are added in succession to 112 mg of a 50% solution of polyisobutylene-plastic (Oppanol(R) B 15 SF of the BASF AG company) in acetone-benzine while being stirred, and prepared as described in Example 3.

Example 6

1.0 g of gestodene

8.0 g of dimethyl isosorbide and

9.0 g of Kollidon 12 PF

are dissolved in succession in 100 g of a 50% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 80 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 15 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 7

1.0 g of gestodene

2.0 g of estradiol

8.0 g of dimethyl isosorbide and

9.0 g of Kollidon 12 PF

are dissolved in succession in 100 g of a 50% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 80 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is

divided by a punching device into individual plasters of 15 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 8

1.0 g of levonorgestrel

8.0 g of dimethyl isosorbide and

9.0 g of Kollidon 12 PF

are dissolved in succession in 100 g of a 50% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 80 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 9

1.0 g of levonorgestrel

1.0 g of estradiol

8.0 g of dimethyl isosorbide and

9.0 g of Kollidon 12 PF

are dissolved in succession in 100 g of a 50% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by

a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 80 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 10

2.0 g of estradiol

8.0 g of dimethyl isosorbide and

9.0 g of Kollidon VA 64

are dissolved in succession in 100 g of a 50% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 80 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 15 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 11

0.9 g of levonorgestrel

1.8 g of estradiol

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon VA 64

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 12

0.9 g of levonorgestrel

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon VA 64

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating

results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 13

0.9 g of gestodene

1.8 g of estradiol

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon VA 64

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 14

0.9 g of gestodene

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon VA 64

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 15

0.9 g of levonorgestrel

1.8 g of estradiol

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon 12 PF

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating

results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 16

0.9 g of levonorgestrel

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon 12 PF

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 17

0.9 g of gestodene

1.8 g of estradiol

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon 12 PF

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Example 18

0.9 g of gestodene

19.0 g of dimethyl isosorbide

4.5 g of lauric acid and

13.5 g of Kollidon 12 PF

are dissolved in succession in 170 g of a 38% solution of polyacrylester adhesive in ethyl acetate/isopropanol while being stirred. After the batch is degassed, the mixture is applied by a coating device to polyester film, so that after the volatile solvent is removed, a uniform film of 100 g/m^2 of solid coating

results. Then, it is laminated with a siliconized, active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 20 cm^2 and packaged in aluminum foil. After the liner film is removed, the plaster adheres to the skin.

Claims

1. Transdermal therapeutic systems that contain sex steroids and optionally penetration-enhancers and crystallization inhibitors, characterized in that they contain dimethyl isosorbide, with the exception of systems that contain active ingredient-containing, non-free-flowing gel phases or 3-keto-desogestrel.

2. Transdermal therapeutic systems according to claim 1, wherein they contain a gestagen and/or an estrogen as a sex steroid.

3. Transdermal therapeutic systems according to claim 2, wherein they contain gestodene, levonorgestrel, desogestrel, norethisterone or norethisterone acetate as a gestagen.

4. Transdermal therapeutic systems according to claim 2, wherein they contain estradiol, estriol, 17α-ethinylestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-triene-3,17ß-diol, 14α,17α-ethanoestra-1,3,5(10)-triene-3,16α,17ß-triol or esters of these compounds as estrogen(s).

5. Transdermal therapeutic systems according to claims 1-5, wherein they contain 1 to 40% by weight of dimethyl isosorbide relative to the entire active ingredient phase.

6. Transdermal therapeutic system according to claims 1-5, wherein it consists of

a) an impermeable cover layer,

one to three matrix layer(s) that adhere to the cover layer and that contain gestagen and/or estrogen, and dimethyl isosorbide and optionally penetration-enhancing agents and

crystallization inhibitors and are covered or surrounded by a skin contact adhesive that optionally contains penetration-enhancing agents; a removable protective layer, or

b) a cover that is provided with a contact adhesive that optionally contains penetration-enhancing agents,

one or two matrix layer(s) that leave uncovered a contact adhesive border and that are attached by means of a cover to the contact adhesive, gestagen and/or estrogen and dimethyl isosorbide and that optionally contain penetration-enhancing agents and crystallization inhibitors; and a removable protective layer.

7. Agent for transdermal administration according to claim 6, wherein it contains an active ingredient-containing matrix layer.

8. Agent for transdermal administration according to claim 6, wherein it contains two or three active ingredient-containing matrix layers.

9. Agent for transdermal administration according to claim 8, wherein active ingredient-containing matrix layers contain different active ingredients.

10. Use of estrogen-free agents for transdermal administration according to claims 1 to 9 for transdermal contraception, for treating endometriosis, for treating gestagen-dependent tumors and for treating the premenstrual syndrome.

11. Use of agents for transdermal administration according to claims 1 to 9 optionally in combination with estrogen-containing agents for treating menopausal symptoms, for

prevention of osteoporosis, for regulation of the menstrual cycle, for stabilization of the menstrual cycle and for transdermal contraception.

Abstract

Transdermal therapeutic systems that contain sex steroids and optionally penetration-enhancers and crystallization inhibitors are described, which are characterized in that they contain dimethyl isosorbide, with the exception of systems that contain active ingredient-containing, non-free-flowing gel phases or 3-keto-desogestrel.

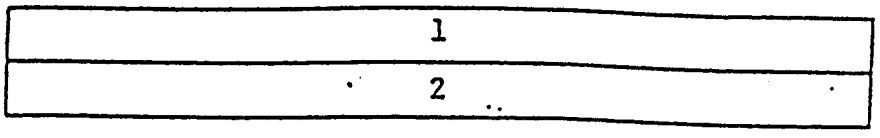


Fig. 1

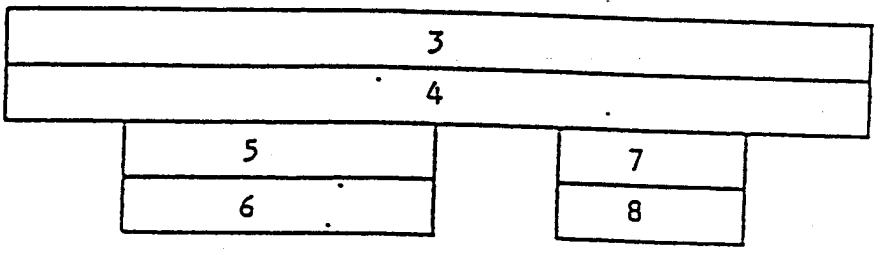


Fig. 2

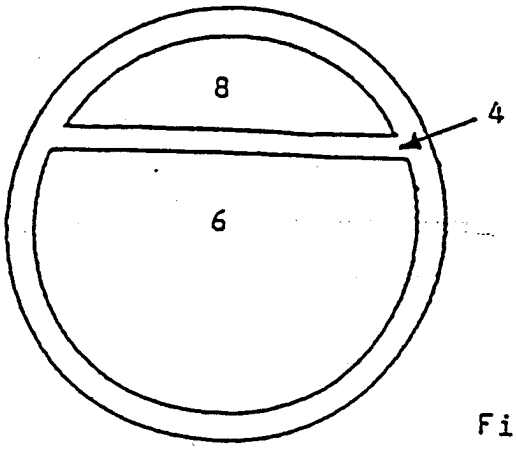


Fig. 3