Disclosed is a dermal or transdermal therapeutic system comprising a reservoir that contains at least one active substance, an active substance-permeable membrane which delimits the active substance reservoir, and a closing layer. The closing layer is impermeable to the at least one active substance at a temperature lying below the skin temperature while being permeable thereto at the skin temperature or above.
Abstract

Reservoir System

Comprising a Closed Membrane

Dermal or transdermal therapeutic system (100) comprising a reservoir (5) that contains at least one active substance (4), an active substance-permeable membrane (3) which delimits the active-substance reservoir, and a closing layer (2), the closing layer (2) being impermeable to the at least one active substance at a temperature lying below the skin temperature while being permeable at skin temperature or above.

Fig. 1
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Reservoir System
Comprising a Closed Membrane

The subject-matter of the invention is a dermal or transdermal therapeutic system comprising a reservoir that contains at least one active substance, an active substance-permeable membrane which delimits the active substance reservoir, and a closing layer, the closing layer being impermeable to the at least one active substance at a temperature lying below the skin temperature while being permeable at skin temperature or above.

Therapeutic systems for administering active substances by way of absorption through the skin (dermal or transdermal administration) have become highly important during the recent decades. In the course of time an ever-growing number of dermally or transdermally applicable medicaments have become known. The advantage of this form of administration consists in the migration of active substances into the blood vessels by evading the gastrointestinal tract. Thus, a passage through the hepatic system is avoided before the active substance has reached its destination.

The mentioned systems such as plasters can be categorized into two main groups as regards their mode of operation: the so-called matrix systems and the reservoir systems. Those of the first group contain the active substance or the active-substance formulation in the adhesive layer, among the second category there are such systems which contain the active substance or active-substance formulation in a reservoir, in the filling material of which the active substance is usually present in dispersed form. The filling
material of the reservoir system can consist of a polymer and/or a liquid. For avoiding a leakage of the active substance-containing liquid, dermal or transdermal therapeutic systems of the reservoir type are usually delimited by an active substance-permeable membrane which is provided with an adhesive layer facing the skin. Such systems are described, e.g., in the patents US 4 379 454, WO 03/011 291, EP 0 366 240 as well as DE 689 29 533.

In spite of advantageous possibilities of application the known reservoir systems also have disadvantages. Because of the - in most cases - only low stability of the skin-facing adhesive layer in the presence of liquids the storage stability often causes problems. An instability of the adhesive layer due to the contact with liquids can lead to a leakage from the reservoir and, thus, to an unusable system. Furthermore, the skin-facing adhesive layer represents an additional barrier for active substances regarding the permeation of the active substance from the reservoir, what can be a restricting factor particularly for active substances that are needed in high dosages. In the case of very potent active agents of a narrow therapeutic index, the accumulation of the active substance in the adhesive layer can lead to an undesirable too high initial release of the active agent after the application of the system. Furthermore, numerous active agents able of permeating are often instable in the presence of oxygen, or the terminal adhesive layer allows the access of oxygen, so that the systems only have a short durability.

EP 0 273 004 describes a transdermal or topical system in which activating agents start the release of the active substance. In one embodiment, the barrier between the skin and the active-substance layer can be modified. In this embodiment the permeable membrane represents a xerogel or an ionic
gel which is permeable for the active substance or constituents of the active substance formulation only in its/their hydrated form. The functional system comprises an additional compartment comprising water or a buffer solution which, after the activation, causes a hydration of the xerogel or an increase of the water content and, thus, makes the pores of the membrane permeable for the active agent. As a membrane material crosslinked poly-acrylates and as an activating agent a base are mentioned. The described embodiment is extremely elaborate to manufacture and the functional mechanism mostly leads to not very well reproducible release kinetics.

It is the object of the present invention to provide improved dermal or transdermal therapeutic systems not including the described disadvantages.

This object is achieved by the present invention which relates to a dermal or transdermal system comprising a reservoir that contains at least one active substance, an active substance-permeable membrane which delimits the active substance reservoir, and a closing layer, the closing layer being impermeable to the at least one active substance at a temperature lying below the skin temperature while being permeable at skin temperature or above. In this connection "below skin temperature" means the temperature of the human skin which can vary in dependence on the individual and the environmental conditions and which lies in the range from 30 to 35°C. In particular, the skin temperature lies in the range from 31 to 33°C, and particularly preferably at about 32°C.

The invention makes it possible to produce dermal and transdermal therapeutic systems to have a higher storage stability and, thus, a higher
product safety, and in the course thereof, to be able to enlarge the range of active substances that are suitable for the systems.

Since in the system according to the invention an additional adhesive layer provided at the skin-facing side of the membrane can be avoided, it is possible to administer active substances also in higher dosages.

A further advantage of the system according to the invention resides in the manufacture of dermal or transdermal systems in which the active substance cannot accumulate in the adhesive layer during storage, so that a too high initial release of the active substance is avoided.

The dermal or transdermal therapeutic system according to the invention comprises the following components of the same or of different size: closed cover layer impermeable for the constituents of the active-substance formulation; liquid or solid reservoir layer comprising one or a plurality of active substances, the active substance-containing reservoir being limited by an active substance-permeable membrane provided with a closing layer at the side of the skin. In principle it is possible that the reservoir matrix is present as a liquid, in the form of a gel, or as a self-supporting solid material. Of course, in the case of a liquid or fluent matrix, the skilled person will make appropriate provisions for avoiding a "leaking" of the matrix or of the contained active substance(s). Examples for this are, e.g., the provision of a solid, liquid-impermeable coating being delimited by an active substance-permeable membrane on the skin-facing side, or the thickening of the matrix by means of suitable gelling agents. Preferably, the matrix is a polymer-based matrix.
For the production of the reservoir matrix basically all polymers are suitable that are employed in the manufacture of transdermal systems and which are physiologically harmless. The polymers can be selected among the group comprising cellulose derivatives such as ethyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, polyethylene, chlorinated polyethylene, polypropylene, polyurethanes, polycarbonates, polyacrylic acid esters, polyacrylates, polymethacrylates, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chlorides, polyvinyl pyrrolidones, polyethylene terephthalates, polytetrafluoro ethylenes, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, ethylene/vinyl alcohol copolymers, vinyl chloride/vinyl acetate copolymers, vinyl pyrrolidone/ethylene/vinyl acetate copolymers, rubber, rubber-like, synthetic homo-, co- or block-polymers, silicones, silicone derivatives and the mixtures thereof. Exemplarily, also polymers on the basis of styrene-butadiene-styrene block-copolymers, polyisobutylene, etc., can be used.

The active substance-containing reservoir of the plaster can also comprise skin penetration enhancers, fillers (such as zinc oxide or silica), solubilizers, cross-linking agents, stabilizing agents, emulsifiers, preserving agents, antioxidants and/or solvents. Of course, the skilled person will provide for the stability of the closing layer not being affected by the mentioned additives.

Where necessary, the system has a peelable protective film on the (skin-facing) application surface.

By action of the user, the closing layer is converted from an impermeable into a permeable state, what takes place when the system is applied to the
skin. The temperature increase caused by the skin brings about an increase of the permeability of the closing layer and, thus, a release of the active substance through the active substance-permeable membrane into the skin layer. In the further course, the closing layer can take on the function of a permeation enhancer and, thus, accelerate the release of the active substance. The closing layer being impermeable at a temperature below the skin temperature is preferably impermeable to oxygen.

Moreover, the closing layer can be self-adhesive for fixing the system to the skin with its total surface area.

For improving the stability of active agents which are subject to oxidative decomposition, the closing layer can be provided with one or several antioxidants.

The carrier layer or cover layer of the plaster is preferably impermeable and inert for the substances contained in the active substance-containing layer and in the adhesive layer, in particular for the active substance, and can be based on polymers such as polyester, e.g. polyethylene terephthalate, polyolefins such as polyethylenes, polypropylenes or polybutylenes, polycarbonates, polyethylene oxides, polyurethanes, polystyrenes, polyamides, polyimides, polyvinyl acetates, polyvinyl chlorides, polyvinylidene chlorides and/or copolymers such as acrylonitrile/butadiene/styrene copolymers, possibly comprising paper fibers, textile fibers and/or mixtures thereof, which - if needed - can be metallized or pigmented. The carrier layer or cover layer of the plaster can also consist of a combination of a metal foil and a polymer layer. The thickness of the carrier layer is preferably 3 to 100 μm.
In a further embodiment, the system can be fixed to the skin by means of a cover plaster (overtape).

Further features of the invention can be inferred from the present description of exemplary embodiments in connection with the claims and the Figure. The single features can be realized in an embodiment of the invention individually or in combination with each other. In the following explanation of some exemplary embodiments of the invention reference is made to the attached Figure which shows a schematic representation of the system according to the invention.

Figure 1 shows a view of a preferred exemplary embodiment of the invention in the form of a liquid-filled reservoir system 100 with limiting active substance-permeable membrane and closing layer. The lowermost layer 1 is a peelable protective layer which is removed by the user or another person before the system is applied to the skin. The applicable plaster is fixed to the skin as a whole. The closing layer 2 on the side of the skin is connected with the active substance-permeable membrane 3 and faces the skin of the patient. The reservoir 5 containing the active substance 4 is limited on the skin-verted side by the impermeable cover layer 6. The cover layer 6 is connected with the membrane 3 or, preferably, welded thereto. In the following, the free surface facing the cover layer is called skin-facing surface of the transdermal application system 100.

The described structure of the transdermal application system 100 serves for transporting one or more of the active substances 4 contained in the reservoir 5, through the active substance-permeable membrane 3 and the subsequent skin-facing closing layer 2 in a sufficient concentration and in a
controlled manner over a long period of time, to the skin surface on which the system is fixed.

Examples for suitable active agents are analgetics, \( \mu \)-opioid-receptor-agonists, anaesthetics, parasympathomimetics, parasympatholytics, antiemetics, emetics, sympathomimetics, hormons, anti-migraine agents, antiallergics, anticonvulsants, anti-dementia agents, antidepressants, beta blockers, alpha blockers and analeptics.

The analgetics can be opioids, among which the full agonists, the mixed agonists/antagonists, the partial agonists and the full antagonists can be mentioned. Full agonists are, e.g., fentanyl, remifentanil, oxycodone and methadone. Among the full antagonists naloxone and naltrexone can be mentioned. An agonist/antagonist is, e.g., nalbuphine, a partial antagonist is, e.g., buprenorphine. Salicylic acid derivatives such as acetylsalicylic acid, etofenamate or diclofenac are examples for acidic analgetics.

Of the \( \mu \)-opioid-receptor-antagonists there can be mentioned, e.g., almi-
vopan and methylnaltrexone.

Among the anaesthetics, e.g., the local anaesthetics come into considera-
tion, such as lidocaine, tetracaine or etidocaine.

Examples for parasympathomimetics are the cholinesterase inhibitors, among them particularly physostigmine, rivastigmine, neostigmine, donepezil and galantamine are to be mentioned.

Among the parasympatholytics, e.g, scopolamine can be indicated.
The antiemetics can be selected among the parasympatholytics, 5-HT3-receptor-antagonists such as ondansetron and granisetron, and dopamine-D2-receptor-antagonists such as domperidone.

Of the emetics dopamine-D2-receptor-agonists such as apomorphine are to be considered.

Among the sympathomimetics, the catecholamines come into consideration, such as dobutamine. Furthermore, also the β-2-sympathomimetics are to be mentioned, such as salbutamol, fenoterol and clenbuterol.

The hormones can be selected, e.g., among estradiol, norelgestromin, goserelin or buserelin.

Examples for anti-migraine agents are 5-HT1-receptor-agonists such as triptanes and, among those, in particular zolmitriptan, sumatriptan or naratriptan.

As antagonist for alpha-1-adrenoreceptors tamsulosin can be mentioned.

An example for anticonvulsants is gabapentin.

As anti-dementia drugs memantine can be mentioned.

Among the antihistamines the antiallergics such as mizolastine, triprolidine and desloratadine come into consideration.

Among the antidepressants nortriptyline can be indicated.
A suitable beta blocker is, e.g., nebivolol.

An example for an analeptic is, e.g., methylphenidate.

The matrix can also contain more than one active substance, e.g., a combination of 2 active substances, such as a parasympathomimetic in combination with a parasympatholytic, in particular physostigmine/scopolamine, an analgetic in combination with an antiemetic, such as fentanyl in combination with granisetron, or two analgetics such as a μ-receptor-agonist and a μ-receptor-antagonist, e.g., fentanyl/naloxone.

The system according to the invention is particularly preferably used for active substances which show a temperature instability and for which a storage temperature below 26°C, in particular a temperature in the range of 2 to 8°C, is recommendable.

According to the present application, under a closing layer a layer is to be understood which is impermeable at a temperature below the skin temperature, and which is permeable at skin temperature or above. Under skin temperature the temperature of the skin is to be understood which can vary in dependence on the individual and the environmental conditions and which lies in the range of 30 to 35°C. In particular, the skin temperature lies in the range of 31 to 33°C, particularly preferably at about 32°C. In the system according to the invention the closing material has a melting temperature in the range of the skin temperature, preferably in the range of 30 to 35°C, and in particular of 31 to 33°C.
Mixtures of substances can also be used, and by suitably selecting the components and the proportions thereof the desired melting temperature can be set.

The substance for the closing layer can be selected from the group of vegetable fats, animal fats, fatty acids, alkanols, mono-, di- and triglycerides of long-chain saturated fatty acids (C_{12}H_{24}O_{2} to C_{18}H_{36}O_{2}) as well as medium-chain triglycerides (C_{6}H_{12}O_{2} to C_{10}H_{20}O_{2}), esters of long-chain alcohols and acids, natural resins, high-molecular paraffines, polyethylene glycol derivatives of hydrated castor oil, polyethylene glycol derivatives of tocopherol, polysaccharides and the polymers of acrylic acid. Particularly suitable are homogeneous mixtures from the mentioned groups of substances.

Among the group of vegetable fats there can be mentioned: cocoa butter, carnauba wax, cupuacu butter, candelilla wax and shea butter. Homogeneous mixtures of the mentioned vegetable fats can be advantageous.

Among the animal fats there are to be mentioned: beeswax, lanolin. Spermaceti substitute can serve as a synthetic substitute for spermaceti.

As an example for a compound of the mono-, di- and triglycerides of long-chain saturated fatty acids (C_{10}H_{20}O_{2} to C_{18}H_{36}O_{2}) hard fat (adeps solidus) can be mentioned; from the group of the medium-chain triglycerides (C_{6}H_{12}O_{2} to C_{10}H_{20}O_{2}) exemplarily neutral oil is to be mentioned comprising, in particular, the fatty acids octanoic acid and/or decanoic acid.
From the group of the alkanols dodecanol, tridecyl alcohol and cetyl alcohol can be mentioned.

Undecenoic acid and stearic acid serve as examples for free fatty acids.

As esters of long-chain alcohols and acids palmitic acid myricyl ester can be mentioned.

Colophony serves as an example from the group of the natural resins.

Examples of polysaccharides are xanthane, guar flour and hyaluronic acid.

An example for polyacrylic acid is Carbopol.

Tocophersolan represents an example for a material of the polyethylene glycol derivative of tocopherol.

In the system according to the invention the closing material can be provided having a layer thickness of 50 μm to 600 μm and, in particular, from 100 μm to 500 μm. Particularly preferred is a layer thickness of 200 μm to 400 μm.

The system according to the invention can be characterized by a closing material on the basis of vegetable fat and animal fat. It is advantageous to add a natural resin for improving the adhesiveness of the system.

According to the invention, the closing material can have antioxidant properties, what is of relevance, in particular, in the case of active substances which are oxidized in the presence of oxygen. Preferable in this
connection are vegetable fats containing a proportion of antioxidants or is the addition of antioxidants. Among the group of the vegetable fats cupuacu butter is to be distinguished as particularly preferable, in particular palmitic acid myricyl ester; tocophersolan can also be used as an antioxidant.

Furthermore, the system according to the invention can be characterized by a closing material on the basis of hard fat (adeps solidus) and neutral oil. The mixture of hard fat and neutral oil preferably comprises 60 to 90 % by weight of hard fat and 10 to 40 % by weight of neutral oil, even more preferably 75 to 90 % by weight of hard fat and 10 to 25 % by weight of neutral oil.

In the system according to the invention the consistency of the closing material can be adjusted by the addition of a fatty acid. In this connection it is advantageous to use the fatty acid undecenoic acid or stearic acid in a proportion of 1 - 20 % by weight. A proportion of 5 - 10 % by weight is particularly preferable. Furthermore, alkanols such as cetyl alcohol, tridecyl alcohol or dodecanol can be added in a proportion of 1 - 20 % by weight. In particular, a proportion of 5 - 10 % by weight is advantageous.

Furthermore, the closing material of the system according to the invention can consist of a polymer with an added additive. Particularly preferable is polyacrylic acid with the added polyethylene glycol derivative of hydrated castor oil.

The active substance-permeable membrane of the reservoir system according to the invention preferably consists of an inert polymer which is selected, e.g., among polyethylenes, polypropylenes, polyvinyl acetates,
polyamides, ethylene/vinyl acetate copolymers and/or silicones. The thickness of the membrane is 5 to 100 μm, preferably between 10 to 50 μm, and particularly preferably 15 to 40 μm.

The active substance-permeable membrane preferably has pores, the size of which can lie in the range of 0.1 μm to 50 μm. The pores preferably have a size in the range of 0.2 μm to 10 μm, and particularly preferably in the range of 0.5 μm to 5 μm.

The system according to the invention can be provided with a foil serving as a cover plaster. The foil extends beyond the system at all sides and can be provided with a pressure-sensitive adhesive at least in a circumferential zone.

The releasable protective layer of the reservoir system according to the invention can consist of polyethylene, polyester, polyethylene terephthalate, polypropylene, polysiloxane, polyvinylchloride or polyurethane and, if applicable, of treated paper fibers, such as cellophane, and, as the case may be, preferably have a coating of silicone, fluorosilicone or fluorocarbon.

The dermal and transdermal therapeutic systems according to the invention can generally be produced in a way as it is described for the special exemplary embodiments in the following Examples 1 and 2.

In the following, exemplary embodiments of the invention are explained in more detail.
Example 1

For the production of the closing layer a mixture of hard fat (80 % by weight) and neutral oil (20 % by weight) are melted at 75 °C and maintained in liquid phase at 40 °C. Palmitic acid myrcyl ester is homogeneously worked therein in an amount of 2 % by weight. The coating of the active substance-permeable membrane (in the present case the microporous polyethylene membrane DSM Solupor) is performed on a continuous coating machine by means of a knife coater in a thickness of 250 μm.

After being coated the membrane is cooled until the closing layer hardens at 4 °C. For producing the reservoir system the coated membrane is welded, at 175 °C and under pressure by maintaining a small filling opening, to a cover layer (backing foil) by means of a conventional seal machine. Tamulosin Base (2 % by weight) is dissolved in ethanol (75 % by weight) and stirred to a homogeneous solution by adding 23 % by weight of isopropyl myristate. The reservoir is filled with the active substance-containing solution through the filling opening, welded and punched out. The system is stored at 2 to 8 °C. After the removal of the protective foil, the system is fixed to the skin by means of an adhesive-coated overtape.

Example 2

For producing the closing layer a mixture of bees wax (70 % by weight), carnauba wax (20 % by weight) and colophony (10 % by weight) are melted at 110 °C and maintained in liquid phase at 45 °C. Tocophersolan is added in an amount of 5 - 10 % by weight. The liquid mixture is stirred until it reaches homogeneity. The coating of the active substance-permeable membrane (in the present case the polypropylene Celgard 2400) is per-
formed on a continuous coating machine by means of a knife coater at a thickness of 300 μm.

After being coated the membrane is cooled until the closing layer hardens (4 °C). For producing the reservoir system the coated membrane is welded, at 175 °C and under pressure by maintaining a small filling opening, to a cover layer (backing foil) by means of a conventional seal machine. Physostigmin base is dissolved in an ethanolic solution. Hydroxypropyl cellulose is added in a proportion of 2.5 % by weight; the mixture is allowed to rest until the hydroxypropyl cellulose has completely swollen. The reservoir is filled with the active-substance-containing hydrogel through the filling opening, welded and punched out. The system is stored at a temperature below 25 °C. After the removal of the protective foil the system is fixed to the skin.
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Claims

1. Dermal or transdermal therapeutic system comprising a reservoir that contains at least one active substance, an active substance-permeable membrane which delimits the active substance reservoir, and a closing layer, the closing layer being impermeable to the at least one active substance at a temperature lying below the skin temperature while being permeable at skin temperature or above.

2. Dermal or transdermal therapeutic system according to claim 1, wherein the closing material is selected from substances from the group of vegetable fats, animal fats, alkanols, fatty acids, mono-, di- and triglycerides of long-chain saturated fatty acids (C_{12}H_{24}O_{2} to C_{18}H_{36}O_{2}) as well as medium-chain triglycerides (C_{6}H_{12}O_{2} to C_{10}H_{20}O_{2}), esters of long-chain alkohols and acids, natural resins, high-molecular paraffines, polyethylene glycol derivatives of hydrated castor oil, polyethylene glycol derivatives of tocopherol, polysaccharides and polymers of acrylic acid and mixtures thereof.

3. Dermal or transdermal system according to claim 1 or 2, wherein the closing material is selected among cocoa butter and cupuacu butter, spermaceti substitutes, beeswax, hard fat, neutral oil, dodecanol, cetyl alcohol, undecenoic acid, palmitic acid myricyl ester, colophony, tocophersolan, guar flour and Carbopol and the mixtures thereof.
4. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the materials for the closing layer consist of a homogeneous mixture.

5. Dermal or transdermal system according to one of the preceding claims, wherein the closing layer is selected among mixtures of vegetable fats and animal fats, preferably vegetable fats and animal fats in combination with resins.

6. Dermal or transdermal system according to claim 4 or 5, wherein the mixture consists of bees wax and carnauba wax, with the proportion of bees wax being in the range of 40 to 95 % by weight and the proportion of carnauba wax being in the range of 5 to 60 % by weight.

7. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the substances for the closing layer are a homogeneous mixture of mono-, di- and triglycerides of long-chain saturated fatty acids (C_{12}H_{24}O_{2} to C_{18}H_{36}O_{2}) and medium-chain triglycerides (C_{6}H_{12}O_{2} to C_{10}H_{20}O_{2}).

8. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the mixture consists of hard fat and neutral oil, with the hard fat being contained in a proportion of 60 to 90 % by weight and the neutral oil being contained in a proportion of 10 to 40 % by weight.

9. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the closing layer comprises 0.1 to 10 % by weight of antioxidants.
10. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the antioxidant or the antioxidants are polyethylene glycol derivatives of tocopherol, in particular tocopher-solan.

11. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the closing layer has permeation-enhancing properties at skin temperature or above.

12. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the closing layer has pressure-sensitive adhesive properties.

13. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the layer thickness of the closing layer lies in the range of 50 \( \mu m \) to 600 \( \mu m \), in particular of 100 \( \mu m \) to 500 \( \mu m \), and preferably of 200 \( \mu m \) to 400 \( \mu m \).

14. Dermal or transdermal therapeutic system according to one of the preceding claims, wherein the layer comprising the at least one active substance is formed as a solid, semi-solid or liquid reservoir.

15. Use of a dermal or transdermal therapeutic system according to one of the claims 1 to 14 for the release of at least one active substance to the skin.