Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2578534 C 2013/03/19

(11)(21) 2 578 534

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2005/09/06
(87) Date publication PCT/PCT Publication Date: 2006/03/23
(45) Date de délivrance/Issue Date: 2013/03/19
(85) Entrée phase nationale/National Entry: 2007/02/28
(86) N° demande PCT/PCT Application No.: EP 2005/009547
(87) N° publication PCT/PCT Publication No.: 2006/029740
(30) Priorité/Priority: 2004/09/13 (DE10 2004 044 578.8)

(51) Cl.Int./Int.Cl. *A61K 9/70* (2006.01), *A61F 13/00* (2006.01), *C08K 3/34* (2006.01)

(72) Inventeurs/Inventors:
MUELLER, WALTER, DE;
LEONHARD, JOHANNES, DE

(73) Propriétaire/Owner:
LTS LOHMANN THERAPIE-SYSTEME AG, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : SYSTEME THERAPEUTIQUE TRANSDERMIQUE A COUCHE ADHESIVE, METHODE DE SILICONAGE DE LA COUCHE ARRIERE DUDIT SYSTEME ET UTILISATION DE LADITE COUCHE ARRIERE

(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM COMPRISING AN ADHESIVE LAYER, METHOD OF SILICONIZING THE BACK LAYER OF THE SYSTEM AND USE OF SAID BACK LAYER

(57) Abrégé/Abstract:
The invention relates to a transdermal therapeutic system (5) which comprises a backing (1), an adhesive layer (4), a polymer layer (2) and a removable protective layer (3). The adhesive layer (4) is an organosiloxane layer and is anchored in the backing (1) by siliconization.

Abstract

The invention relates to a transdermal therapeutic system (5) which comprises a backing (1), an adhesive layer (4), a polymer layer (2) and a removable protective layer (3). The adhesive layer (4) is an organosiloxane layer and is anchored in the backing (1) by siliconization.

Transdermal therapeutic system comprising an adhesive layer, method of siliconizing the back layer of the system and use of said back layer

The invention relates to a transdermal therapeutic system comprising a backing layer, a polymer layer in contact with the backing layer and comprising silicone adhesives, and a detachable protective layer in contact with the polymer layer, to a method of producing a siliconized backing layer of the system, and to the use of the backing layer.

Transdermal therapeutic systems (TTS) or active ingredient patches have now become an established drug form. In spite of this, certain problems associated with this drug form have to date not been solved to satisfaction. One of these problems relates specifically to the so-called matrix systems or systems which have a construction related to the matrix systems. A matrix system of this kind, or matrix TTS, is composed at its most simple of a backing layer, an active ingredient matrix layer, preferably self-adhesive, and a protective layer, which is intended for removal prior to use. Oftentimes, during wearing of the TTS, after a certain time the formation of a more or less weak dark margin around the patch on the skin is observed, and/or residues of adhesive remain on the skin when the TTS is removed. This phenomenon is observed to a particularly marked extent in the case of TTS suitable for application for a number of days. The cause of both phenomena is inadequate adhesion of the patch matrix to the backing layer of the system. This inadequate adhesion, and movements of the body at the site of application, cause the adhesive to emerge at the edges of the system, and the adhesive which has emerged may come into contact with the clothing. As a result of contact with the clothing, fabric fibers remain suspended from the emerged adhesive and impart to it in the majority of cases a dark appearance. Following the removal of the TTS, the adhesive which has emerged remains on the skin in the form of dark marks. If adhesion to the backing layer is particularly poor, the matrix may also part over a substantial area from the backing layer, and may remain on the skin. Particularly susceptible to such phenomena are adhesives based on silicones. The reason for this is that silicone adhesives are very apolar and therefore adhere relatively poorly to the more or less polar surfaces of the backing layer,

which in the majority of cases is composed of polyethylene terephthalate (PET). A further factor is that the cohesion possessed by silicone adhesives is low and therefore they have a particularly strongly pronounced tendency to emerge from the system. Silicone adhesives therefore behave like a viscous liquid, and the spreading over a relatively large area is hence also referred to as “cold flow”.

It is an object of the present invention, accordingly, to improve the adhesion of the backing layer in a transdermal therapeutic system to the active ingredient polymer layer which comprises at least one silicone adhesive, and largely to prevent the emergence of silicone adhesive from the system.

This object is achieved in accordance with the invention by a transdermal therapeutic system as described at the outset by providing the contact face of the backing layer with an adhesive layer obtained by siliconization.

In embodiment of the invention the adhesive layer is an organopolysiloxane layer. In particular the adhesive layer comprises organopolysiloxanes containing vinyl groups and organopolysiloxanes containing Si-H groups.

A further embodiment relates to a transdermal therapeutic system comprising a backing layer, a polymer layer in contact with the backing layer and comprising silicone adhesives, and a detachable protective layer in contact with the polymer layer, wherein the contact face of the backing layer has been provided with an adhesive layer which is obtained by siliconization, is firmly anchored to the backing layer and comprises organopolysiloxanes containing vinyl groups and organopolysiloxanes containing Si-H groups.

In a preferred way the backing layer is a polymeric film material selected from the group consisting of polyesters, especially polyethylene terephthalate, polypropylene, polyethylene, polyurethane, EVA layers in combination with polyester, polyvinylidene chloride, polyaramid, and ethylene-(meth)acrylate copolymers.

A further embodiment relates to the transdermal therapeutic system as described herein, wherein the silicone adhesives are selected from the group consisting of polysiloxanes and polysiloxane mixtures.

A still further embodiment relates to the transdermal therapeutic system as described herein, wherein the polymer layer comprises microreservoirs for active pharmaceutical ingredients which are in solution in an ambiphilic solvent.

A still further embodiment relates to the transdermal therapeutic system as described herein, wherein the ambiphilic solvent is selected from the group consisting of 1,3-butanediol, diethylene glycol monoethyl ether, diethylene glycol dimethyl ether, dipropylene glycol, propylene glycol, tetrahydrofurfuryl alcohol, diethylene glycol monobutyl ether, carboxylic esters of tri- and diethylene glycol, polyoxyethylated fatty alcohols of 6-18 carbon atoms, and mixtures thereof.

A still further embodiment relates to a method of producing a backing layer used in a transdermal therapeutic system as described herein, which comprises siliconizing the surface of the backing layer that is to be contacted with a polymer layer which has been provided with microreservoirs by mixing organopolysiloxanes containing vinyl groups and organopolysiloxanes containing functional Si-H groups and coating the surface of the backing layer with the mixture in the presence of a catalyst.

A still further embodiment relates to the method as described herein, wherein the coated surface of the backing layer is heat-treated until an organopolysiloxane layer forms that is firmly anchored on the backing layer.

The method of the invention, namely a method of producing a backing layer used in a transdermal therapeutic system, is distinguished by the fact that it comprises siliconizing the surface of the backing layer that is to be contacted with a polymer layer which has been provided with microreservoirs. This is accomplished preferably by mixing organopolysiloxanes containing vinyl

groups and organopolysiloxanes containing functional Si-H groups and coating the surface of the backing layer with the mixture in the presence of a catalyst. Thereafter the coated surface of the backing layer is heat-treated until an organopolysiloxane layer forms that is firmly anchored on the backing layer. The catalyst used is, for example, a platinum catalyst. The heat treatment takes place in a thermal oven or in a thermal tunnel. The temperature is about 80 to 100 °C, but can also be below 80 °C.

Any self-adhesive system, whether it be a transdermal therapeutic system, a non-active ingredient patch (plaster), a label or an adhesive tape, must be protected prior to use by a protective layer which can be redetached. The protective layer may be composed of various materials such as PET, polyethylene or polypropylene, for example, and on the adhesive contact side has been treated specifically in order to make it detachable from the adhesive layer as easily as possible. For use in combination with adhesives not based on silicones, this surface treatment usually consists of a siliconization. This siliconization involves coating, for example, organopolysiloxanes containing vinyl groups and organopolysiloxanes containing SiH-functional groups in a mixture onto the film that is to be treated, in a coating operation in the presence of a platinum catalyst, with a heat treatment resulting in formation of an organopolysiloxane layer that adheres firmly to the substrate. Whereas non-silicone-based adhesives, such as polyacrylate adhesives, for example, attach extremely poorly to surfaces thus treated, silicone adhesives attach extremely well to such surfaces. In plaster-wearing tests it has been found that non-active ingredient patches based on silicone adhesives and a backing layer treated in this manner leave considerably lesser/fewer adhesive residues on the skin following removal, and that the tendency toward formation of "black" margins around the patch is considerably reduced.

In the case of TTS based on silicone adhesives, the permeation rate of the active ingredient through the skin is increased by the external application of heat to the applied TTS. Systems of this kind are described in detail in, for example, US 6,488,599 A1 and US 6,261,595 A1. As a result of the temperature, which in this context can easily climb up to about 45 °C, the

tendency of the silicone adhesive to spread by cold flow is massively increased. Under such conditions it is more likely that dark edges will form around the patch and that adhesive residues will be left on the skin following the removal of the patch. In such systems great advantage attaches to siliconizing the backing layer, since despite the application of heat the spreading of the adhesive is largely prevented.

The siliconization of the backing layer likewise proves particularly important for the active ingredient in conjunction with systems of the kind known as microreservoir systems based on silicone adhesives and ambiphilic solvents. Microreservoir systems of this kind are described in detail in EP 1 191 927 B1. In the production of such systems the active ingredient is dissolved in an ambiphilic solvent such as dipropylene glycol or 1,3-butanediol, for example, and the solution is dispersed in the solution of the adhesive. Thereafter the dispersion is coated onto the protective layer of the subsequent TTS, the solvent of the adhesive is removed, and the dried film is laminated to the backing layer. It has now emerged that an unsiliconized backing layer exhibits virtually no adhesion to such a film. The reason for this is the formation of a very thin film of the ambiphilic solvent on the surface of the dried active ingredient film. Altering the production method, e.g., coating directly onto the backing layer, does not improve the adhesion of the dried film. A siliconized backing layer, however, irrespective of the chemical nature of the film material itself, produces very good adhesion immediately after contact with a microreservoir layer. Although improved adhesion can also be achieved through the use of materials which are less inert, such as copolymers of ethylene and vinyl acetate, for example, for the backing layer of such systems, materials of this kind have the drawback that they absorb active ingredient as well as the solvent. Microreservoir systems as described above are therefore best realizable using siliconized backing layers of polyester or similarly inert materials.

The single figure shows a transdermal therapeutic system 5 which comprises a backing layer 1, an adhesive layer 4 firmly anchored on the backing layer, a polymer layer 2, and a detachable protective layer 3. The adhesive layer 4 is

an organopolysiloxane layer which comprises organopolysiloxanes containing vinyl groups and organopolysiloxanes containing functional Si-H groups. The backing layer 1 is composed of a polymeric film material. Suitable polymers are polyesters, especially polyethylene terephthalate, polypropylene, polyethylene, polyurethane, EVA layers in combination with polyester, PVDC, polyaramids, and ethylene-(meth)acrylate copolymers. Further suitable materials are ethylcellulose, cellulose acetate, cellophane, paper, metal-polymer composite, and ethylene-vinyl acetate copolymers.

The silicone adhesives in the polymer layer 2 are selected for example from the group consisting of polysiloxanes and polysiloxane mixtures.

Present in the polymer layer 2 are microreservoirs which contain at least one active ingredient which is in solution in an ambiphilic solvent. Suitable ambiphilic solvents are 1,3-butanediol, diethylene glycol monomethyl ether, diethylene glycol dimethyl ether, dipropylene glycol, propylene glycol, tetrahydrofurfuryl alcohol, diethylene glycol monobutyl ether, carboxylic esters of tri- and diethylene glycol, and polyoxyethylated fatty alcohols of 6-18 carbon atoms.

The protective layer 3 overhangs both sides of the polymer layer 2, so that it can be grasped and detached without problems.

The use of a siliconized backing layer has no influence whatsoever on the production of microreservoir systems. Even in the case of TTS already on the market, it is possible from a purely technical standpoint to replace the non-siliconized backing layer without problems by a siliconized backing layer. The properties of the TTS in respect of active ingredient delivery remain unaffected in the case of such replacement, since with a thickness of less than 10 micrometers the applied silicone layer absorbs virtually no active ingredient.

In summary, therefore, it can be stated that the use of siliconized backing layers decisively improves the wear properties of TTS based on silicone

adhesives, and now makes specific systems, such as microreservoir systems based on silicone adhesives and ambiphilic solvents, for example, technically feasible.

30307-5

CLAIMS:

1. A transdermal therapeutic system comprising a backing layer, a polymer layer in contact with the backing layer and comprising silicone adhesives, and a detachable protective layer in contact with the polymer layer, wherein the contact face of the backing layer has been provided with an adhesive layer which is obtained by siliconization, is firmly anchored to the backing layer and comprises organopolysiloxanes containing vinyl groups and organopolysiloxanes containing Si-H groups.

2. The transdermal therapeutic system as claimed in claim 1, wherein the backing layer is a polymeric film material selected from the group consisting of polyesters, polypropylene, polyethylene, polyurethane, EVA layers in combination with polyester, polyvinylidene chloride, polyaramids, and ethylene-(meth)acrylate copolymer.

3. The transdermal therapeutic system as claimed in claim 2, wherein the polyester is polyethylene terephthalate.

4. The transdermal therapeutic system as claimed in claim 1, wherein the backing layer is composed of a material selected from the group consisting of ethylcellulose, cellulose acetate, cellophane, paper, metal-polymer composite, and ethylene-vinyl acetate copolymers.

5. The transdermal therapeutic system as claimed in claim 1, wherein the polymer layer comprises a silicone adhesive based on silicone polymers and resin.

6. The transdermal therapeutic system as claimed in claim 1, wherein the silicone adhesives are selected from the group consisting of polysiloxanes and polysiloxane mixtures.

30307-5

7. The transdermal therapeutic system as claimed in claim 1, wherein the polymer layer comprises microreservoirs for active pharmaceutical ingredients which are in solution in an ambiphilic solvent.

8. The transdermal therapeutic system as claimed in claim 7, wherein the ambiphilic solvent is selected from the group consisting of 1,3-butanediol, diethylene glycol monoethyl ether, diethylene glycol dimethyl ether, dipropylene glycol, propylene glycol, tetrahydrofurfuryl alcohol, diethylene glycol monobutyl ether, carboxylic esters of tri- and diethylene glycol, polyoxyethylated fatty alcohols of 6-18 carbon atoms, and mixtures thereof.

9. A method of producing a backing layer used in a transdermal therapeutic system as claimed in any one of claims 1 to 7, which comprises siliconizing the surface of the backing layer that is to be contacted with a polymer layer which has been provided with microreservoirs by mixing organopolysiloxanes containing vinyl groups and organopolysiloxanes containing functional Si-H groups and coating the surface of the backing layer with the mixture in the presence of a catalyst.

10. The method as claimed in claim 9, wherein the coated surface of the backing layer is heat-treated until an organopolysiloxane layer forms that is firmly anchored on the backing layer.

11. The use of a siliconized backing layer in a transdermal therapeutic system as claimed in claims 1 to 8.

12. The use of a backing layer, as claimed in claim 11, on which an organopolysiloxane layer is firmly anchored by siliconization.

13. The use of a backing layer, as claimed in claim 12, whereby a polymer layer of the system, comprising microreservoirs and at least one active ingredient dissolved therein and also at least one silicone adhesive, being self-adhesively connected to the organopolysiloxane layer.

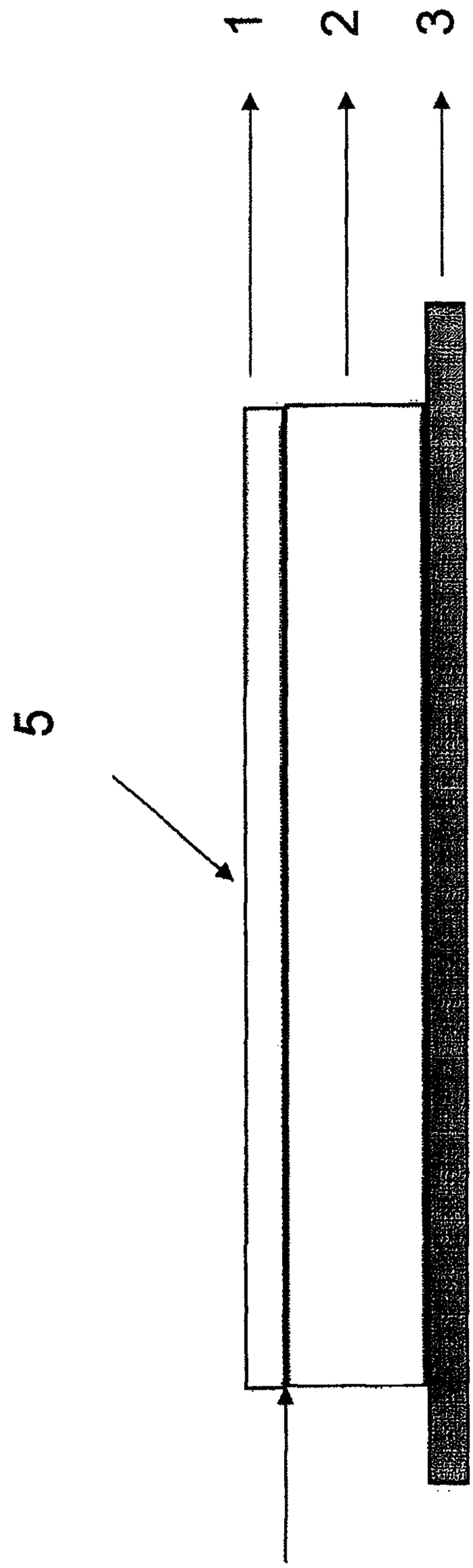

Figure 1