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UV STABLE TRANSDERMAL PLASTER

The invention relates to a novel UV-stable transdermal therapeutic system (TTS) which consists of a backing layer, of at least one active ingredient-containing matrix and optionally of a detachable sheet, and comprises a UV absorber, with at least one UV absorber-containing adhesive layer being provided between the backing layer and the active ingredient-containing matrix which is furthest away from the surface of the skin, and at least one separating layer which is impermeable to active ingredient and impermeable to the UV absorber being present between the adhesive layer containing the UV absorber and the active ingredient-containing matrix which is furthest away from the surface of the skin.

Attempts are known to employ photosensitive active ingredients which absorb UV-A and UV-B rays and normally in suncreams as described by Briscart & Plaizier-Vercammen (Proc. 2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, APGI/APV, 1998, 1231-1232).

It is additionally known to protect transdermal therapeutic systems provided with photosensitive active ingredients by means of visually noticeable aluminized or lacquered cover sheets as backing layer of the TTS. DE-A1-19912623 describes a method for protecting therapeutic preparations, systems or ingredients thereof, the intention being to achieve protection, specific in each case, against breakdown by harmful factors such as atmospheric oxygen, water and/or light. Photoprotective substances which absorb or reflect electromagnetic waves are used, employing absorbing or reflecting agents whose absorption or reflection spectrum covers the wavelength range responsible for the instability of the photosensitive material or its ingredients. Coloured plastic sheets are used

inter alia as cover sheet in this case, shown by the example of the 1,4-dihydropyridine derivative lacidipine.

The colouring of highly flexible plastic sheets proves to be difficult and does not provide reliable protection from light owing to fissures which frequently occur in the coloured layer of the plastic sheet.

Furthermore, DE-C1-10053375 discloses transdermal therapeutic systems (TTS) which consist of an active ingredient-containing polymer matrix and a backing layer, with polymer matrix and backing layer being firmly connected and forming a laminate, and both the polymer matrix and the backing layer containing a colourless substance which absorbs in the UV region and which has no intrinsic pharmacological effect. This solution is disadvantageous

- in that interaction of the colourless substance which absorbs in the UV region with the active ingredient in the polymer matrix in some cases results in an unwanted influence on the stability of the TTS,
- in that the firm connection between polymer matrix and backing layer which is permeable to active ingredient may result in extensive unacceptable diffusion of active ingredient from the polymer matrix into the backing layer, principally in the case of backing layers composed of polypropylene, polyethylene or polyurethane, and may finally emerge or crystallize out on the upper side of the backing layer/cover sheet,
- in that skin irritation may be caused through direct contact of the skin with the substances which absorb in the UV region and which are present in the backing layer/cover sheet.

It is therefore an object of the invention to provide a pharmaceutical preparation which is provided with a

photosensitive active ingredient and is to be administered transdermally, and which achieves high stability without the aforementioned disadvantages.

The object is achieved according to the invention by a transdermal therapeutic system (TTS) consisting of a backing layer, of at least one active ingredient-containing matrix and optionally of a detachable sheet, and comprising a UV absorber, with at least one UV absorber-containing adhesive layer being provided between the backing layer and the active ingredient-containing matrix which is furthest away from the surface of the skin, and at least one separating layer which is impermeable to active ingredient and impermeable to the UV absorber being present between the adhesive layer containing the UV absorber and the active ingredient-containing matrix which is furthest away from the surface of the skin.

The sequence of layers of the transdermal therapeutic system starting from the side facing away from the skin can according to the invention be backing layer, UV absorber-containing adhesive layer, separating layer and finally a mono- or bilayer active ingredient-containing matrix whose pressure-sensitive adhesive surface is covered by a detachable protective sheet. The separating layer in the transdermal therapeutic system may moreover have according to the invention a layer thickness of from 4 to 23 μm, preferably from 4 to 10 μm, and consist of a barrier polymer. Suitable barrier polymers are polyethylene terephthalate, polyacrylonitrile, polyvinyl chloride, polyvinylidene chloride or its copolymers or colaminates. The matrix in the transdermal therapeutic system of the invention may be designed to be self-adhesive and have no membrane controlling the release of active ingredient, and consist essentially of polymers selected from the group of polyisobutylene, polybutene, polyacrylate, polydimethylsiloxane, styrene/isoprene block copolymer

or polyisoprene. The weight per unit area of the matrix can be according to the invention from 30 to 150 g/m^2, preferably 50 to 120 g/m^2, particularly preferably about 100 g/m^2.

The backing layer in the transdermal therapeutic system of the invention may be a transparent sheet from the group of polypropylene, polyethylene, polyurethane, polyester, ethylene/vinyl acetate copolymer or polyethylene terephthalate or mixtures thereof and may be permeable to active ingredient.

The UV absorber in the adhesive layer in the transdermal therapeutic system of the invention may moreover be present in dissolved form in a concentration of 0.5 to 10% (m/m), preferably 1.0 to 5.0% (m/m), particularly preferably 2.0 to 4.0% (m/m), and the adhesive layer may be designed to be self-adhesive and consist essentially of polymers selected from the group of polyisobutylene, polybutene, polyacrylate, polydimethylsiloxane, styrene/isoprene block copolymer or polyisoprene. The adhesive layer may moreover have a weight per unit area of from 5 to 50 g/m^2, preferably 20 to 30 g/m^2.

The adhesive layer in the transdermal therapeutic system of the invention may also have exclusively the UV absorber(s), it being possible for the latter to be colourless or yellowish.

The adhesive layer in the transdermal therapeutic system of the invention may moreover have a UV absorber content composed of a mixture of two or more substances which absorb in the UV region, it being possible to select the UV absorber(s) from the group of p-aminobenzoic acid, aminobenzoic acid derivative, preferably 2-ethylhexyl 4-dimethylaminobenzoate and/or polyethoxyethyl 4-bis(polyethoxyl)aminobenzoate, cinnamic acid, cinnamic acid derivatives, preferably isoamyl

4-methoxycinnamate and/or 2-ethylhexyl 4-methoxycinnamate, 3-benzylidenebornan-2-one, benzylidenebornan-2-one derivatives, preferably 3-(4')-methylbenzylindenebornan-2-one, 3-(4-sulphone)-benzylidenebornan-2-one and/or 3-(4'-trimethylammonium)benzylidenebornan-2-one methylsulphate, salicylic acid derivative, preferably 4-isopropylbenzyl salicylate, 2-ethylhexyl salicylate, and/or 3,3,5-trimethylcyclohexyl salicylate, benzotriazoles, preferably 2-(5-chloro-2H-benzotriazole-2-yl)-6-(1,1-dimethylethyl)-4-methylphenol, 2,4,6'-trianiline-p-(carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine, 3-imidazol-4-ylacrylic acid, 3-imidazol-4-yl-3-imidazol-4-ylacrylic ester, 2-phenylenebenzimidazole-5-sulphonic acid and/or its K, Na and triethanolamine (=TEA) salts, 2-cyano-3,3-diphenylacrylic acid, terephthaloylidenedicamphorsulphonic acid, butyl-methoxydibenzoylmethane, benzophenone and/or benzophenone derivatives, preferably benzophenone-3 and/or benzophenone-4. The UV absorber(s) may moreover be colourless or yellowish.

A further possibility is for the transdermal therapeutic system of the invention to be transparent or slightly opaque.

The active pharmaceutical ingredient acting in the transdermal therapeutic system of the invention may be at least one hormone and be progestogen(s), preferably gestodene or levonorgestrel.

The transdermal therapeutic system of the invention has the following advantages over conventional systems with photosensitive active ingredient content:

- It is possible by varying the thickness of the layer containing the UV absorber or the concentration of the UV absorber therein to adjust accurately the desired UV protection. This is a considerable advantage over the use of conventional TTS with incorporated UV protection.

- Contact between the UV absorber and the active ingredient or active ingredients in the active ingredient-containing matrix is precluded, so that neither the UV absorber nor its breakdown products which may arise under the influence of light can react with the active ingredient(s).
- If a cover sheet which is permeable to active ingredient is used, diffusion of active ingredient on storage of the system may reach unacceptably high levels, so that active ingredient may emerge or crystallize out on the surface of the cover sheet. This effect can be observed for example with cover sheets composed of polypropylene, polyethylene or polyurethane. The separating layer provided according to the invention between the layer with UV absorber and the active ingredient-containing layer now represents a barrier against loss of active ingredient by diffusion through the cover sheet.

In addition, contact of the skin with UV absorbers, and thus possible skin irritation, can be avoided.

The invention and its advantageous properties are explained in detail by the following examples.

Example 1

Two formulations of a photosensitive active ingredient from the group of progestogens were produced. Formulation I contains an adhesive layer and a separating layer, with the adhesive layer containing 3% by weight of a UV-absorbing substance.
Formulation II contains no adhesive layer and separating layer and serves as comparative formulation. Both formulations contain an active ingredient-containing matrix with a photosensitive progestogen and were provided with a polyethylene backing layer, resulting in a TTS in each case.

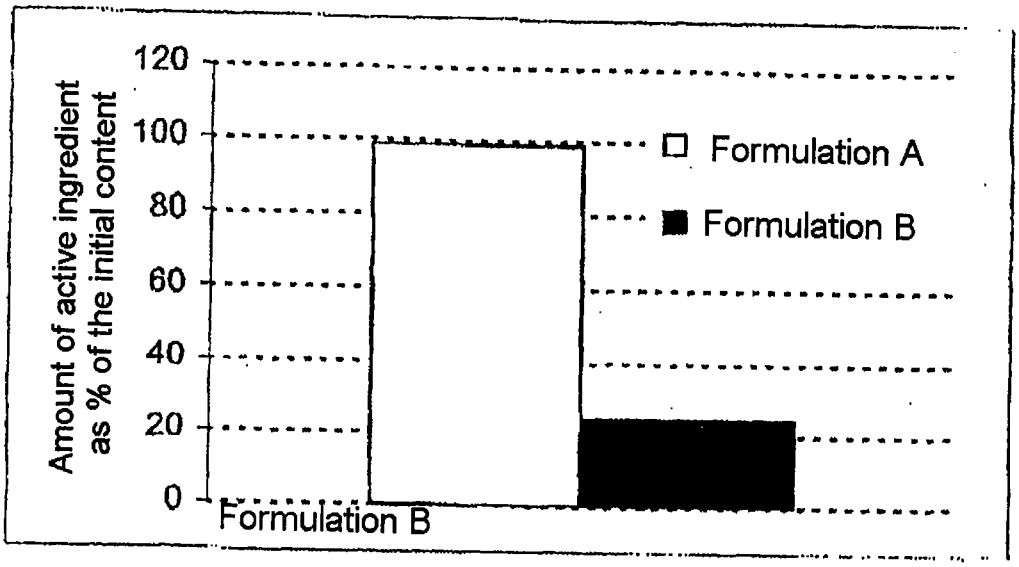
Formulation I has the following composition:

1. Active ingredient-containing matrix:
   - 1.9% progestogen
   - 98.1% polyisobutylene-based adhesive
2. Adhesive layer:
   - 3% Tinuvin® 326
   - 97% polyisobutylene-based adhesive

Tinuvin®326 (from CIBA, Lampertheim) is a UV absorber of the hydroxyphenylbenzotriazole class.

To investigate the light protection effect, both formulations were irradiated with light having a UV spectrum of 300-800 nm over a period of up to 14 h. The radiation source used was a xenon lamp. A filter system (type: Suprax® filter) was placed between the radiation source and the samples to be irradiated in order to simulate the irradiation under realistic conditions of TTS use. The active ingredient content in the TTS was then determined. It emerged that the TTS of formulation A containing an adhesive layer with UV-absorbing substance and a separating layer still contained about 99% of the originally employed amount of the photosensitive active ingredient after irradiation for 14 h, whereas the TTS of formulation B contained only about 24% of the originally employed amount of the photosensitive active ingredient after irradiation for only 7 h (Fig. 1). This shows that the system of the invention displays improved protection from the sun under realistic conditions of use, because the UV-protective effect of the system of the invention (formulation A) was considerably greater than that of the comparative system (formulation B).

Figure 1



Example 2

Formulation with a photosensitive active ingredient from the group of progestogens with, in each case, an adhesive layer and separating layer, in which the separating layers consists of polyethylene terephthalate (Hostaphan® from Mitsubishi Polyester, Wiesbaden).

The formulation has the following composition:

1. Active ingredient-containing matrix:
   - 1.9% progestogen
   - 98.1% polyisobutylene-based adhesive
2. Adhesive layer 1 and 2:
   - 3% Uvinul®MC80
   - 97% polyacrylate-based adhesive

Uvinul®MC 80 (from BASF, Ludwigshafen) is a methoxy-cinnamic acid derivative.

Example 3

Formulation with a photosensitive active ingredient from the group of progestogens with, in each case, two adhesive layers and separating layers, in which the separating layers consist of polyethylene terephthalate (Hostaphan® from Mitsubishi Polyester, Wiesbaden).

Formulation I has the following composition:

3. Active ingredient-containing matrix:
   - 1.9% progestogen
   - 98.1% polyisobutylene-based adhesive
4. Adhesive layer 1 and 2:
   - 3% Uvinul®M40
   - 97% polyacrylate-based adhesive

Uvinul®M40 (from BASF, Ludwigshafen) is a benzophenone derivative.

Example 4 to 12

Formulation with a photosensitive active ingredient from the group of progestogens with, in each case, at least one adhesive layer and separating layer, in which the active ingredient-containing matrix is configured in analogy to Examples 1 to 3, and the adhesive layer comprises a polyisobutylene-based adhesive and has the following compositions.

Composition of the adhesive layer	Example 4	Example 5	Example 6	Example 7	Example 8	Example 9	Example 10	Example 11	Example 12
Tinuvin® 326 [%]	2	2	2	3	3	3	4	4	4
Polyisobutylene-based adhesive [%]	98	98	98	97	97	97	96	96	96
Weight per unit area [g/m^2]	20	30	50	20	30	50	20	30	50

Example 13 to 21

Formulation with a photosensitive active ingredient from the group of progestogens with, in each case, at least one adhesive layer and separating layer, in which the active ingredient-containing matrix is configured

in analogy to Examples 1 to 3, and the adhesive layer comprises a polyacrylate-based adhesive and has the following compositions.

Composition of the adhesive layer	Example 13	Example 14	Example 15	Example 16	Example 17	Example 18	Example 19	Example 20	Example 21
Tinuvin® 326 [%]	2	2	2	3	3	3	4	4	4
Polyacrylate-based adhesive [%]	98	98	98	97	97	97	96	96	96
Weight per unit area [g/m^2]	20	30	50	20	30	50	20	30	50

Example 22 to 30

Formulation with a photosensitive active ingredient from the group of progestogens with, in each case, at least one adhesive layer and separating layer, in which the active ingredient-containing matrix is configured in analogy to Examples 1 to 3, and the adhesive layer has the following compositions.

Composition of the adhesive layer	Example 22	Example 23	Example 24	Example 25	Example 26	Example 27	Example 28	Example 29	Example 30
Uvinul®MC80	2	5	8	-	-	-	-	-	-
Uvinul®M40	-	-	-	2	5	8	2	5	8
Polyisobutylene-based adhesive [%]	98	95	92	98	95	92	-	-	-
Polyacrylate-based adhesive [%]	-	-	-	-	-	-	98	95	92
Weight per unit area [g/m^2]	20	30	50	20	30	50	20	30	50

Claims

1. Transdermal therapeutic system (TTS) consisting of a backing layer, of at least one active ingredient-containing matrix and optionally of a detachable sheet, and comprising a UV absorber, characterized in that
   - at least one UV absorber-containing adhesive layer is provided between the backing layer and the active ingredient-containing matrix which is furthest away from the surface of the skin,
   - at least one separating layer which is impermeable to active ingredient and impermeable to the UV absorber is present between the adhesive layer containing the UV absorber and the active ingredient-containing matrix which is furthest away from the surface of the skin.

2. Transdermal therapeutic system according to Claim 1, characterized in that the sequence of layers in the system starting from the side facing away from the skin is backing layer, UV absorber-containing adhesive layer, separating layer and finally a mono- or bilayer active ingredient-containing matrix whose pressure-sensitive adhesive surface is covered by a detachable protective sheet.

3. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the weight per unit area of the adhesive layer is from 5 to 50 g/m^2, preferably 20 to 30 g/m^2.

4. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the separating layer has a layer thickness of

from 4 to 23 μm, preferably from 4 to 10 μm.

5. Transdermal therapeutic according to at least one of the preceding claims, characterized in that the separating layer consists of a barrier polymer, preferably of polyethylene terephthalate, polyacrylonitrile, polyvinyl chloride, polyvinylidene chloride or its copolymers or colaminates.

6. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the matrix and/or the adhesive layer is/are designed to be self-adhesive and consists/consist essentially of polymers selected from the groups of polyisobutylene, polybutene, polyacrylate, polydimethylsiloxane, styrene/isoprene block copolymer or polyisoprene.

7. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the weight per unit area of the matrix is from 30 to 150 g/m^2, preferably 50 to 120 g/m^2.

8. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the backing layer is permeable to active ingredient and preferably consists of polypropylene, polyethylene, polyurethane, ethylene/vinyl acetate copolymer or a multilayer composite of these materials with one another or with other materials.

9. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the UV absorber is present in dissolved form in the adhesive layer in a concentration of from 0.5 to 10% (m/m), preferably 1.0 to 5.0% (m/m).

10. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that exclusively the adhesive layer has/have the UV absorber(s).

11. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the UV absorber is/are selected about a substance or a mixture of substances from the group of p-aminobenzoic acid, aminobenzoic acid derivative, preferably 2-ethylhexyl 4-dimethylaminobenzoate and/or polyethoxyethyl 4-bis(polyethoxyl)aminobenzoate, cinnamic acid, cinnamic acid derivatives, preferably isoamyl 4-methoxycinnamate and/or 2-ethylhexyl 4-methoxycinnamate, 3-benzylidenebornan-2-one, benzylidenebornan-2-one derivatives, preferably 3-(4')-methylbenzylidenebornan-2-one, 3-(4-sulphone)benzylindenebornan-2-one and/or 3-(4'-trimethylammonium)benzylidenebornan-2-one methylsulphate, salicylic acid derivative, preferably 4-isopropylbenzyl salicylate, 2-ethylhexyl salicylate, and/or 3,3,5-trimethylcyclohexyl salicylate, benzotriazoles, preferably 2-(5-chloro-2H-benzotriazole-2-yl)-6-(1,1-dimethylethyl)-4-methylphenol, 2,4,6'-trianiline-p-(carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine, 3-imidazol-4-ylacrylic acid, 3-imidazol-4-yl-3-imidazol-4-ylacrylic ester, 2-phenylene-benzimidazole-5-sulphonic acid and/or its K, Na and triethanolamine (=TEA) salts, 2-cyano-3,3-diphenylacrylic acid, terephthaloylidenedicamphor-sulphonic acid, butylmethoxydibenzoylmethane, benzophenone and/or benzophenone derivatives, preferably benzophenone-3 and/or benzophenone-4.

12. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the UV absorber(s) is/are colourless or

yellowish.

13. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the system is transparent or slightly opaque.

14. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that at least one hormone acts as active ingredient.

15. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the active pharmaceutical ingredient(s) is/are progestogen(s), preferably gestodene or levonorgestrel.

16. Transdermal therapeutic system according to at least one of the preceding claims, characterized in that the transdermal therapeutic system has no membrane controlling the release of active ingredient.