Solid transdermal therapeutic system comprising UV absorber

(Description)

Technical Field

The invention relates to a solid transdermal therapeutic system with UV absorber. The UV-stable transdermal therapeutic system (TTS) is particularly designed for photosensitive active pharmaceutical ingredients.

The transdermal therapeutic system according to the invention, if appropriate comprising a progestrogen and/or an estrogen, is also suitable for fertility control.

Prior Art

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

The patent literature further discloses the protection of transdermal therapeutic systems (TTS) provided with photosensitive active ingredients by means of visually conspicuous aluminized or lacquered covering films as backing layer of the TTS.

WO-A1-00/56289 describes a method for protecting therapeutic preparations, systems or their constituents, the intention being to achieve in each case specific protection from degradation by harmful factors such as atmospheric oxygen, water and/or light. Photoprotective substances which absorb or reflect electromagnetic waves are used, employing respectively

absorbents or reflectants whose absorption or reflection spectrum covers the wavelength range responsible for the instability of the photosensitive substance or its constituents. Coloured plastic films are used inter alia in this case as covering film, indicated by example of the 1,4-dihydopyridine derivative lacidipine.

The colouring of highly flexible plastic films proves to be difficult and does not provide reliable photoprotection owing to the frequently occurring fissures in the coloured layer of the plastic film.

WO-A2-02/34200 further discloses transdermal therapeutic systems (TTS) which consist of an active ingredient-containing polymer matrix and of a backing layer, where polymer matrix and backing layer are firmly connected or form a laminate, and both the polymer matrix and the backing layer comprise a colourless system which absorbs in the UV range but has no intrinsic pharmacological effect.

EP-A1-1452173 indicates transdermal therapeutic systems which consist of a backing layer, of at least one active ingredient-containing matrix and optionally of a detachable film and comprises a UV absorber, where 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, and 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. It is possible in this case to select as UV absorbers the UV absorbers 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')-methylbenzylidene-bornan-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, benzo-triazoles, preferably 2-(5-chloro-2H-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methylphenol, 2,4,6'-tri-aniline-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 benzo-phenone derivatives, preferably benzophenone-3 and/or benzophenone-4.

The known solutions have the disadvantage

- that the protective effect produced by the added UV absorber for the active ingredient is incomplete,
- that owing to the incomplete protective effect in some cases higher concentrations of UV absorbers must be employed, which may have adverse effects on the compatibility of the TTS with skin.

Summary of the invention

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 ensures an increased protective effect for the active ingredient on use of a minimal UV absorber concentration which

avoids the aforementioned disadvantages.

The object is achieved according to the invention by a solid transdermal therapeutic system with UV absorber. The UV-stable TTS consists in its sequence of layers in this case of a backing layer 1, of at least one active ingredient-containing matrix 2 and of a detachable protective film 3, it optionally being for an adhesive layer 4 and a separating layer 5 to be introduced between the backing layer 1 and the active ingredient-containing matrix 2. UV absorbers from the group of hydroxyphenyltriazines can be embedded in the backing layer 1 or in the active ingredient-containing matrix 2 or in the adhesive layer 4.

It is possible according to the invention for the UV absorber to be 2,4-bis-i[4-(2-ethylhexyloxy)-2-hydrody]phenyly-6-(4-methoxyphenyl)-(1,3,5)-triazine.

It is furthermore possible according to the invention for the weight per unit area of the matrix 2 to be from 30 to 150 g/m^2. In this connection, a weight per unit area of from 50 to 120 g/m^2 is preferred, and of 100 g/m^2 is particularly preferred.

It is also possible in the solid transdermal therapeutic system according to the invention for the weight per unit area of the adhesive layer 4 to be from 5 to 50 g/m^2. In this connection, a weight per unit area of from 20 to 30 g/m^2 is preferred.

The UV absorber can be present according to the invention in the adhesive layer 4 in the concentration of from 0.5 to 5% (m/m) in dissolved form. In this connection, a concentration of from 1.0 to 4.0% is preferred, and of from 1.5 to 3.0% is particularly preferred.

The matrix 2 and/or the adhesive layer 4 in the solid

transdermal therapeutic system can furthermore be designed according to the invention to be self-adhesive and to consist substantially of polymers which are selected from the groups of polyisobutylene, polybutene, polyacrylate, polydimethylsiloxane, styrene-isoprene block polymer or polyisoprene.

It is also possible in the solid transdermal therapeutic system according to the invention for the separating layer 5 to have a layer thickness of from 4 to 23 μm. In this connection, the layer thickness of from 4 to 10 μm is preferred.

It is possible according to the invention in the solid transdermal therapeutic system for separating layer 5 to be impermeable to active ingredient and impermeable to the UV absorber.

It is furthermore possible according to the invention for the separating layer 5 in the solid transdermal therapeutic system to consist of a barrier polymer. Preference is given in this connection to polyethylene terephthalate or polyacrylonitrile or polyvinyl chloride or polyvinylidene chloride or its copolymers or colaminates.

It is also possible in the solid transdermal therapeutic system according to the invention for the backing layer 1 to be permeable to active ingredient and to consist of polypropylene, polyethylene, polyurethane, ethylene-vinyl acetate copolymer or of a multilayer composite of these materials with one another or with other materials.

The UV absorber(s) in the solid transdermal therapeutic system may according to the invention be colourless or yellowish.

It is furthermore possible for the solid transdermal

therapeutic system according to the invention to be transparent or slightly opaque.

It is also possible for at least one hormone to be active as active ingredient in the solid transdermal therapeutic system according to the invention.

It is possible according to the invention for the active pharmaceutical ingredients to be a progestogen. Preference is given in this case to gestodene or levonorgestrol.

It is furthermore possible to add an estrogen to the progestogen in the solid transdermal therapeutic system according to the invention. Preference is given in this case to ethinylestradiol.

It is also possible according to the invention for the solid transdermal therapeutic system to be used in fertility control.

It is further possible according to the invention to use one or more UV absorbers from the group of the hydroxyphenyltriazines for producing a solid trandermal system, whose sequence of layers consists of at least three layers, this sequence of layers starting furthest away from the skin with a backing layer 1, an at least monolayer active ingredient-containing matrix 2, a detachable protective film 3 and optionally, introduced between backing layer 1 and active ingredient-containing matrix 2, an adhesive layer 4 and separating layer 5 following the active ingredient-containing matrix 2 for fertility control, and where the UV absorber(s) from the group of hydroxyphenyltriazines is/are embedded in the backing layer 1 or in the active ingredient-containing matrix 2 or in the adhesive layer 4.

It is also possible according to the invention for the

solid transdermal therapeutic system to be equipped without a membrane controlling active ingredient release.

The transdermal therapeutic system according to the invention has the following advantages compared with conventional systems with photosensitive active ingredient content:

- The protective effect provided by the UV absorber from the group of hydroxyphenyltriazines is enhanced and
- the concentration of the UV absorber from the group of hydroxyphenyltriazines which is necessary to achieve a protective effect is reduced.
- It is thus possible in particular to avoid or reduce the risk of possible skin irritation.

Exemplary embodiments

The invention is explained further by the following examples.

Example 1

Two formulations of a photosensitive active ingredient from the group of progestogens were prepared. Formulation 2 comprises an adhesive layer and a separating layer, and the adhesive layer comprises 2.5% by weight of a UV-absorbing substance from the class of the hydroxyphenyltriazines.
Formulation 1 comprises no adhesive layer and separating layer and serves as comparative formulation. Both formulations comprise an active ingredient-containing matrix with a photosensitive progestogen and are equipped with a backing layer of polyethylene, resulting in a TTS in each case.
Formulation 2 has the following composition:

1. Active ingredient-containing matrix:
   - 1.9% progestogen

- 98.1% polyisobutylene-based adhesive

2. Adhesive layer:
   - 2.5% Tinosorb®S
   - 97.2% polyisobutylene-based adhesive

Tinosorb®S (from Ciba, Lampertheim) is a UV absorber of the hydroxyphenyltriazine class.

To investigate the photoprotective effect, both formulations were irradiated with light having a UV spectrum of 300-800 nm for a period of up to 34 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 irradiation under realistic conditions of use of the TTS. The active ingredient content in the TTS was then determined. It revealed that the TTS of formulation 2 which comprised an adhesive layer with UV-absorbing substance and a separating layer still comprised more than 95% of the originally employed amount of the photosensitive active ingredient after irradiation for 34 h, whereas the TTS of formulation 1 comprised only about 3% of the originally employed amount of the photosensitive active ingredient after irradiation (Fig. 1). This demonstrates that the system according to the invention displays an improved protection from the sun under realistic conditions of use because the UV-protective effect of the system according to the invention (formulation 2) was considerably greater than that of the comparative system (formulation 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 layer 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:
   - 2.5% Tinosorb®S
   - 97.5% polyacrylate-based adhesive

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:

1. Active ingredient-containing matrix:
   - 1.9% progestogen
   - 98.1% polyisobutylene-based adhesive
2. Adhesive layer 1 and 2:
   - 3% Tinuvin®400
   - 97% polyacrylate-based adhesive

Tinuvin®400 (from Ciba, Lampertheim) is a UV absorber of the hydroxyphenyltriazine class.

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 embodied in analogy to Examples 1 to 3, and the adhesive layer comprises a polyisobutylene-based adhesive and has the compositions mentioned below.

Composition of the adhesive layer	Example								
	4	5	6	7	8	9	10	11	12
Tinosorb®S [%]	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 embodied in analogy to Examples 1 to 3, and the adhesive layer comprises a polyacrylate-based adhesive and has the compositions mentioned below.

Composition of the adhesive layer	Example								
	13	14	15	16	17	18	19	20	21
Tinosorb®S [%]	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

Claims

1. Solid transdermal therapeutic system with UV absorber, whose sequence of layers consists of at least three layers, this sequence of layers starting furthest away from the skin with a backing layer (1), an at least monolayer active ingredient-containing matrix (2), a detachable protective film (3) and optionally, introduced between backing layer (1) and active ingredient-containing matrix (2), an adhesive layer (4) and separating layer (5) following the active ingredient-containing matrix (2), characterized in that the UV absorber(s) from the group of hydroxyphenyltriazines is/are embedded in the backing layer (1) or in the active ingredient-containing matrix (2) or in the adhesive layer (4).

2. Solid transdermal therapeutic system according to Claim 1, characterized in that the UV absorber from the group of hydroxyphenyltriazines is 2,4-bis-i[4-(2-ethylhexyloxy)-2-hydrody]phenyly-6-(4-methoxyphenyl)-(1,3,5)-triazine.

3. Solid transdermal therapeutic system according to at least one of Claims 1 and 2, characterized in that the weight per unit area of the matrix (2) is from 30 to 150 g/m^2, preferably 50 to 120 g/m^2.

4. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the weight per unit area of the adhesive layer (4) is from 5 to 50 g/m^2, preferably 20 to 30 g/m^2.

5. Solid transdermal therapeutic system according to Claim 4, characterized in that at least one UV absorber is present in a concentration of from 0.5

to 5% (m/m), preferably 1.0 to 4.0% (m/m), in dissolved form in the adhesive layer (4).

6. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the matrix (2) and/or the adhesive layer (4) is/are designed to be self-adhesive and substantially consists of polymers which are selected from the groups of polyisobutylene, polybutene, polyacrylate, polydimethylsiloxane, styrene-isoprene block polymer or polyisoprene.

7. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the separating layer (5) has a layer thickness of from 4 to 23 μm, preferably from 4 to 10 μm.

8. Solid transdermal therapeutic system according to Claim 7, characterized in that the separating layer (5) is impermeable to active ingredient and impermeable to the UV absorber.

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

10. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the backing layer (1) 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.

11. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the UV absorber is colourless or yellowish.

12. Solid transdermal therapeutic system according to at least one of the preceding Claims 1 to 10, characterized in that the transdermal therapeutic system is transparent or slightly opaque.

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

14. Solid transdermal therapeutic system according to Claim 14, characterized in that the active pharmaceutical ingredient is progestogen, preferably gestodene or levonorgestrel.

15. Solid transdermal therapeutic system according to Claims 13 and 14, characterized in that an estrogen, preferably ethinylestradiol, is added to the progestogen, preferably gestodene.

16. Use of UV absorbers from the group of hydroxyphenyltriazines according to Claim 1 for producing a solid transdermal system, whose sequence of layers consists of at least three layers, this sequence of layers starting furthest away from the skin with a backing layer (1), an at least monolayer active ingredient-containing matrix (2), a detachable protective film (3) and optionally, introduced between backing layer (1) and active ingredient-containing matrix (2), an adhesive layer (4) and separating layer (5) following the active ingredient-containing matrix

(2) for fertility control, and where the UV absorber(s) from the group of hydroxyphenyltriazines is/are embedded in the backing layer (1) or in the active ingredient-containing matrix (2) or in the adhesive layer (4).

17. Solid transdermal therapeutic system according to at least one of the preceding claims, characterized in that the transdermal therapeutic system is equipped without a membrane controlling active ingredient release.