UV-stable, liquid or semisolid transdermal administration form comprising a photosensitive active ingredient

(Description)



Technical field

The invention relates to semisolid and liquid pharmaceutical administration forms for transdermal application containing a pharmaceutical active ingredient which is photosensitive in the UV range and at least one UV light-absorbing excipient (UV absorber).

Among the semisolid and liquid transdermal administration forms, the invention relates in particular to transdermal gels whose gel base is composed of water, alcohol, at least one gel-forming polymer and optionally further ingredients. Such gels are also designated as hydroalcoholic gels.

The UV absorber is present dissolved or dispersed in the gel.

Prior art



It is known from the patent and technical literature that a transdermal application of pharmaceutically active substances has various advantages compared to an oral administration of the pharmaceutical, such as, for example,

- no first-pass metabolization of the active ingredient by circumvention of the gastrointestinal tract,
- simultaneous release of the active ingredient over a number of hours, caused by the depot function of the skin
- as a result the maintenance of a constant plasma level.

In the case of the known transdermal therapeutic

systems, up to now essentially two different pharmaceutical forms have been able to gain acceptance. A large number of therapeutic patches exist which contain the active ingredient dissolved or suspended in a matrix.

In recent years, moreover, semisolid transdermal administration forms, and here especially gels, have established themselves. A significant advantage of this form compared to the transdermal patches consists in the better skin tolerability of the nonocclusive pharmaceutical form. Further advantages are seen in an individual doseability and in that the user is not visibly stigmatized as a person who is sick or otherwise worthy of treatment.

Various pharmaceutical active ingredients which are suitable for transdermal application (e.g. nifedipine, nicotine, arylpropionic acid and benzophenone derivatives, gestodene, levonorgestrel, estradiol and other hormones suitable for transdermal application) are photosensitive. Photosensitive substances absorb radiation within the wavelength spectrum of sunlight, especially within the ultraviolet range (UV, 280-400 nm). By exposure of pharmaceutical preparations containing photosensitive active ingredients to light, photochemical breakdown of the active ingredients and thus, in the extreme case, a loss of action of the preparation can occur. Moreover, the breakdown products can be a cause of phototoxic or photoallergic reactions of the skin. For example, it is known that under the influence of sunlight ketoprofen gels and other arylpropionic acid and benzophenone derivatives result in an increased occurrence of phototoxic and in some cases photoallergic skin reactions, which are to be attributed to photosensitizing properties of this class of substance. In order to prevent such decomposition processes, suitable protective measures must be taken

for transdermal preparations containing photosensitive active ingredients.

In the field of transdermal patches, because of the layered construction typically having at least one active ingredient-containing adhesive layer and a plastic film at the back (backing layer), there is the possibility of accommodating the UV absorber spatially separate from the active ingredient. Inventive solutions for this situation are proposed, for example, in EP 1449526. In the case of patches constructed in layers, there is in particular the possibility of providing the UV absorber in a layer which is spatially in front of the active ingredient-containing layer, in the sense that the harmful light rays must first pass through the UV absorber layer before they reach the active ingredient-containing layer. The active ingredient can thus be protected particularly well from UV light.

This principle, however, is not transferable to other transdermal pharmaceutical forms such as solutions and semisolid preparations, since such unequivocal possibilities of spatial separation of active ingredient and UV absorber within the administration form are not afforded there.

In the case of the transdermal gels known up to now, protection against light only gets attention inasmuch as the preparations are manufactured in light-impermeable packs, usually aluminized sealed-edge pouches/sachets. This method of protection of semisolid TTS from light during storage can, however, be inadequate on its own. It presupposes that the photosensitive active ingredient is no longer exposed to sunlight after application of the preparation to the skin. Protection from sunlight can take place, for example, by the wearing of clothing over the

application site. However, this represents for the user, in combination with less clothing, an undesired restriction of the application sites on the body, in particular in climatically warm areas or during climatically warm periods of the year.

It is known that the UV portion of sunlight penetrates into the skin. Thus, UVB light (280-320) penetrates the entire epidermis down to the basal layer. The longer-wave UVA light (320-400 nm) penetrates down to the connective tissue. Transdermal gels, as a rule, are applied to a very large area (100-200 cm^2 and more), and the complete active ingredient transport from the outermost layer of the skin (stratum corneum) down to the systemic circulation takes up to 24 hours. The stratum corneum especially as a main penetration barrier functions as an active ingredient reservoir, which stores large parts of the pharmaceutical for a number of hours. The complete spectrum of UV light can penetrate into this area and thus cause photochemical decomposition reactions.

From these points of view, the problem of light sensitivity during application in the case of transdermal gels is even greater than in the case of transdermal patches. In the case of the latter, the exposed application surface is as a rule much smaller and furthermore at least one backing layer of a plastic film lying outside is provided, which as a rule always offers a minimal UV protection.

Semisolid TTS (gels) containing pharmaceutical, also photosensitive, active ingredients are known from the patent literature.
WO-A1-03/082960 describes the preparation of a gel which can contain pharmaceutical active ingredients. In WO-A1-01/60399, a diclofenac-containing gel is demonstrated and the patent specification WO-A2-

02/051421 describes a gel composition having at least one androgenic steroid for the treatment and/or prophylaxis of hypogonadism. All the patent specifications make no reference to the sensitive problem of the photosensitivity and of the protection from light in the case of semisolid transdermal administration forms.

Description of the invention

It is therefore the object of the invention to make available a semisolid transdermal administration form containing a photosensitive pharmaceutical active ingredient, where the application system realizes a high stability without the disadvantages known when using the conventional semisolid transdermal application forms.

At the same time, the harmful concomitant effects, such as, for example, absorption of lightscreen substances into the body possibly resulting from the intentional light protection for the user, should be kept as low as possible.

According to the invention, the object is achieved by a semisolid or liquid administration form containing a UV photosensitive pharmaceutical active ingredient and at least one UV absorber without pharmacological activity in the concentrations employed, this being present dissolved or dispersed in the administration form.

According to the invention, the semisolid administration form can be a hydroalcoholic gel. Application forms such as creams, solutions and suspensions also prove to be advantageous.

Surprisingly, with a suitable selection of the UV absorber, a spatial separation between pharmaceutical

active ingredient and UV absorber can be achieved under the application conditions:

While the transdermal active ingredient necessarily belongs to the group of readily skin-permeating pharmaceutical active ingredients, the UV absorber is selected according to the invention from the group of substances penetrating or permeating the skin as little as possible. Since in the pharmaceutical forms according to the invention transdermal gel or transdermal solution are initially present mixed with one another in the starting state of the active ingredient and the absorber, on diffusion into and through the skin a spatial separation of both components occurs. The poorly penetrating UV absorber remains in the outer skin layers and thus lies spatially between the deeper-penetrating active ingredient and the UV radiation acting from outside the body.

For the selection of a suitable UV absorber, according to the invention the logarithm of the partition coefficient between 1-octanol and water (log $P_{oct/H20}$, designated log P below) and the molecular weight are used.

The partition coefficient(s) [log P] of the UV absorber(s) is/are preferably greater than 3.0 or less than 1.0, particularly preferably greater than 5.0 or less than 0.0. Thus, UV absorbers are preferred which can penetrate or permeate the skin only to a small extent, since they are either too lipophilic or too hydrophilic.

The molar mass of the UV absorber(s) is preferably greater than 250 $gmol^{-1}$ be.

(A) UV absorber(s) having a molar mass of greater than 500 g/mol is/are particularly preferred. UV absorbers

having a molecular weight above 500 g/mol only have a low penetration and permeation power for the skin.

In the transdermal administration form according to the invention, the UV absorber(s) can be present in a proportion of 1-10%, preferably 2-5%.

If the semisolid administration form according to the invention contains readily volatile constituents such as, for example, ethanol, methanol, isopropanol or DMSO, the quantitative proportion relates to the sum of the non-readily volatile vehicle constituents or, expressed otherwise, to the formulation remaining on the skin after the escape of all volatile constituents.

It was possible to establish (a) UV-absorbing substance(s) whose absorption maximum lies within the waveband which is responsible for the photochemical decomposition of the active ingredient to be protected. If protection over a broader UV spectral range or absorption maxima of the active ingredient lying therein is necessary, it proves advantageous to combine two UV-absorbing substances having different absorption maxima.

Furthermore, in the semisolid administration forms according to the invention the substance(s) absorbing in the UV range can be selected from the group which comprises p-aminobenzoic acid and aminobenzoic acid derivatives, preferably 2-ethylhexyl 4-dimethylamino-benzoate, and also cinnamic acid and its derivatives, preferably isoamyl 4-methoxycinnamate, and 3-benzylidenebornan-2-one and benzylidenebornan-2-one derivatives, preferably 3-(4')methylbenzylidenebornan-2-one, 3-(4-sulfo)benzylidenebornan-2-one, and also salicylic acid derivatives, preferably 4-isopropyl-benzyl salicylate, 2-ethylhexyl salicylate, 3,3,5-trimethylcyclohexyl salicylate, and also 3-imidazol-4-

yl-acrylic acid and its esters, 2-phenylenebenzimidazole-5-sulfonic acid, methylenebisbenzotriazolyltetramethyl-butylphenol, 2-cyano-3,3-diphenylacrylic acid, butyl-methoxydibenzoylmethane, and also benzophenones or benzophenone derivatives, preferably benzophenone-3, benzophenone-4.

Within the meaning of the present invention, the following substances absorbing in the UV range, in this case chiefly in the UVA range, have proven to be particularly suitable:
polyethoxyethyl 4-bis(polyethoxyl)aminobenzoate, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone 5,5'-disodium sulfonate, 2-ethylhexyl 4-methoxycinnamate, 3-(4'-trimethylammonium)benzylidenebornan-2-one methyl-sulfate,
2,4,6-trianiline-p-(carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine, dioctyl butamido triazine, bisethylhexyloxy-phenol methoxyphenyltriazine, terephthaloylidenedi-camphorsulfonic acid, polymer of N-[2 (and 4)-(2-oxo-born-3-ylidenemethyl)benzyl] acrylamide, drometriazole trisiloxane and 2,2'-(1,4-phenylene)bis(1H-benzimid-azole-4,6-disulfonic acid, monosodium salt). The trade names of particularly preferred UV absorbers for the UVA range are Tinuvin® 326 and Tinosorb® S and also Mexoryl® XL.

In the case of substances which have an acidic chemical reaction such as carboxylic acids or sulfonic acids, their pharmaceutically acceptable salts such as, preferably and without claim to completeness, K, Na and triethanolamine (= TEA) salts can also be used.

Further, the administration form according to the invention can contain at least one hormone as a pharmaceutical active ingredient.

Furthermore, in the semisolid TTS according to the invention, the pharmaceutical active ingredient(s) can be gestagen(s), preferably gestodene or levonorgestrel or estrogen(s), preferably ethinylestradiol or a combination of estrogen and gestagen, preferably gestodene and ethinylestradiol, and furthermore androgens, preferably testosterone, methyltestosterone or methylnortestosterone (MENT) and also 7α-methyl-11β-fluoro-19-nortestosterone (eF-MENT).

The gel-forming agents of the semisolid administration form are preferably selected from the group which comprises celluloses, preferably hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, Na carboxymethylcellulose, chitosan-EDTA, highly disperse silica, precipitated silica, bentonite, starches, preferably cornstarch, rice starch, potato starch, wheat starch, carboxymethylamylopectin Na, tragacanth, alginates, polyacrylates, polymethacrylates, polyacrylate-polyalkylacrylate crosspolymer, acryloyldimethyl taurate/vinylpyrrolidone copolymer, poly-vinyl alcohol, polyvinylpyrrolidone.

The invention is explained in more detail by the following examples.

Example 1

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID), which is used in the form of gels for the treatment of swellings and inflammation of the soft parts near joints (e.g. tendons, tendon sheaths, ligaments and joint capsules), in particular in the shoulder and elbow regions, sports and accidental injuries such as contusions, sprains and strains. Under the influence of sunlight, the occurrence of phototoxic and photoallergic skin reactions is described for such

gels. The active ingredient ketoprofen is protected from the light-induced decomposition by the addition of the UV absorber Uvinul DS 49.

Ketoprofen	2.5%
Carbopol 940	1%
Uvinul DS 49 (2,2'-dihydroxy-4,4'-dimethoxybenzophenone-5,5'-disodium sulfonate)	2%
Triethanolamine (TEA)	1%
Isopropanol	20%
Propylene glycol	20%
EDTA	0.1%
Water to	100%

Uvinul DS 49 has a molecular weight of about 478.4 g/mol and an arithmetical log P value of -1.9.

The gel base is prepared from Carbopol, TEA and water according to the generally known pharmaceutical procedures. Uvinul DS 49 and EDTA is then incorporated into this base. Isopropanol, propylene glycol and ketoprofen are blended and subsequently incorporated into the gel base.

Example 2

Gestodene-containing preparations can be used for hormone replacement therapy. Under UV light, decomposition of the active ingredient and a loss of action accompanying it can occur.

Gestodene	1%
Uvinul MC 80 (2-ethylhexyl 4-methoxycinnamate)	2%
Diethylene glycol monoethyl ether	10%
Isopropyl myristate	10%
Ethanol	70%
Hydroxypropylcellulose	1.5
Water to	100%

Uvinul MC 80 has a molecular weight of about 290 g/mol

and an arithmetical log P value of 5.37.

Gestodene and Uvinul MC 80 are dissolved in ethanol. Subsequently, diethylene glycol monoethyl ether, isopropyl myristate and water are added and well blended. The gel is then formed by incorporation of hydroxypropylcellulose in portions and allowed to swell adequately according to the pharmaceutical procedures.

Example 3

Ethinylestradiol-containing preparations can be used for hormone replacement therapy. Under the influence of UV light, decomposition of ethinylestradiol and a loss of action accompanying it can occur.

Ethinylestradiol	0.2%
Tinosorb S (bisethylhexyloxyphenyl methoxyphenyltriazine)	2%
Diethylene glycol monoethyl ether	10%
Isopropyl myristate	10%
Ethanol	70%
Hydroxypropylcellulose	1.5%
Water to	100%

Tinosorb S has a molecular weight of 627.80 g/mol and a partition coefficient log P of 9.

Ethinylestradiol and Tinosorb S are dissolved in ethanol. Subsequently, diethylene glycol monoethyl ether, isopropyl myristate and water are added and well blended. The gel is then formed by incorporation of hydroxypropylcellulose in portions and allowed to swell adequately according to the pharmaceutical procedures.

Example 4

A combination of the hormones ethinylestradiol and gestodene can be used for contraception. Under the influence of UV light, breakdown of the active ingredients and thus a loss of action can occur.

Ethinylestradiol	0.4%
Gestodene	1%
Tinosorb S (bisethylhexyloxyphenyl methoxyphenyltriazine)	2%
Diethylene glycol monoethyl ether	10%
Propylene glycol	5%
Carbopol 940	1%
Ethanol	50%
Triethanolamine (TEA)	1%

Ethinylestradiol, gestodene and Tinosorb S are dissolved in the ethanolic phase. The gel base is prepared from Carbopol, TEA and water according to the generally known pharmaceutical procedures. Propylene glycol and diethylene glycol monoethyl ether are blended and subsequently the ethanolic phase is incorporated into the gel.

Example 5

The active ingredient 7α-methyl-11β-fluoro-19-nor-testosterone (eF-MENT) can be employed for hormone replacement therapy in hypogonadal men.

Propylene carbonate	10.0%
Ethanol	54.0%
Purified water	~29.0%
eF-MENT	0.8%
Tinosorb S	1.0%
Acrylate/C10-30 alkylacrylate Crosspolymer (Permulen TR-1)	0.8%
Methylcellulose (Tylopur MH 1000)	0.5%
Glycerol 86%	1.0%
Cyclomethicone	1.5%
Isopropyl myristate	0.5%
Tris(hydroxymethyl)aminomethane to pH	5.8

eF-MENT and Tinosorb S were initially dissolved in ethanol 96%. Pemulen TR-1 and HPC (Klucel HF) were

swollen in this ethanolic solution. Propylene carbonate was added and mixed with stirring. Subsequently, isopropyl myristate was added, and mixing was carried out again. The entire mixture was via a funnel into a mixer/homogenizer system and with stirred briefly. It was then homogenized (e.g. using a rotor-stator homogenizer) at 2000-3500 rpm for 1 minute. Glycerol 86%, and the entire amount of the purified water was added (sucked in) as a schlieren-free mixture in a number of substeps, and the gel distinctly swelled again. It was stirred (about 5 minutes) until a distinct clarification of the gel was visible. Subsequently, cyclomethicone was incorporated into the mixture with stirring. Subsequently, a 10% strength aqueous tromethamine solution was added with stirring in 3 substeps for neutralization. At the end of the incorporation, the mixture was homogenized again for 2 minutes at 2700 rpm.

Claims

1. A semisolid or liquid transdermal administration form containing a UV photosensitive pharmaceutical active ingredient,
characterized in that at least one UV absorber without pharmacological activity is contained in the concentrations employed and this is present dissolved or dispersed in the administration form.

2. The semisolid or liquid transdermal administration form as claimed in claim 1,
characterized in that the administration form is a hydroalcoholic gel.

3. The semisolid or liquid transdermal administration form as claimed in claim 1 or 2,
characterized in that the partition coefficient(s) [log P] of the UV absorber(s) is/are either greater than 3.0 or less than 1.0, preferably greater than 5.0 or less than 0.0.

4. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims,
characterized in that the molar mass of the UV absorber(s) is/are greater than 250 $gmol^{-1}$, preferably greater than 500 $gmol^{-1}$.

5. The semisolid or liquid transdermal administration form as claimed in one or more of the preceding claims,
characterized in that the UV absorber(s) is present in a proportion of 1-10%, preferably 2-5%, based on the sum of the mass of the non-readily volatile vehicle constituents.

6. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims,
characterized in that the substance(s) absorbing in the UV range is/are selected from the group which comprises p-aminobenzoic acid and aminobenzoic acid derivatives, 3-benzylidenebornan-2-one and benzylidenebornan-2-one

derivatives, preferably 3-(4')methylbenzylidene-bornan-2-one, 3-(4-sulfo)benzylidenebornan-2-one, 3-(4'-trimethylammonium)benzylidenebornan-2-one methylsulfate, polymer of N-[2(and 4)-(2-oxoborn-3-ylidenemethyl)benzyl]acrylamide, and also salicylic acid derivatives.

7. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims,

characterized in that at least one substance essentially absorbing in the UVA range is present, from the group which comprises 2,4,6-trianiline-p-[carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine, dioctyl butamido triazine, bisethylhexyloxyphenol, methoxyphenyltriazine, 3-imidazol-4-ylacrylic acid, 2-phenylenebenzimidazole-5-sulfonic acid and its K, Na and triethanolamine (= TEA) salts, 2,2'-(1,4-phenylene)bis(1H-benzimidazole-4,6-disulfonic acid, monosodium salt), methylenebisbenzotriazolyltetramethylbutylphenol, drometriazole trisiloxane, 2-cyano-3,3-diphenylacrylic acid, terephthaloylidenedicamphorsulfonic acid, butylmethoxydibenzoylmethane, and also benzophenone or benzophenone derivatives, preferably benzophenone-3, benzophenone-4, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone-5,5'-disodium sulfonate.

8. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims,

characterized in that at least one hormone is contained as a photosensitive pharmaceutical active ingredient.

9. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims,

characterized in that the pharmaceutical active ingredient is a gestagen, preferably gestodene or levonorgestrel.

10. The semisolid or liquid transdermal administration form as claimed in at least one of claims 1 to 8,

characterized in that the pharmaceutical active ingredient is an estrogen, preferably ethinylestradiol.

11. The semisolid or liquid transdermal administration form as claimed in claims 9 and 10, characterized in that two active ingredients is in a combination of gestagen and estrogen, preferably gestodene and ethinylestradiol.

12. The semisolid or liquid transdermal administration form as claimed in at least one of claims 1 to 8, characterized in that the pharmaceutical active ingredient is an androgen, preferably testosterone, methyltestosterone, methylnortestosterone (MENT) or 7α-methyl-11β-fluoro-19-nortestosterone (ef-MENT).

13. The semisolid or liquid transdermal administration form as claimed in at least one of the preceding claims, characterized in that the system is colorless and transparent.