Pharmaceutical preparation containing drospirenone for application to the skin

(Description)

Technical field

The invention relates to a pharmaceutical preparation for application to the skin having a content of drospirenone. The amount of drospirenone contained in the preparation in the initial state thereof is not above the saturation solubility, while the saturation solubility of drospirenone is exceeded after application of the preparation to the skin through efflux of solubilizing components.

Prior art

Steroid hormones are even now in large numbers administered transdermally. This takes place either during hormone replacement therapy in men and women or else for contraception in women.

Despite the large number of transdermal pharmaceutical forms, to date only a small number of steroidal active ingredients can be administered in this way: from the group of estrogens this is true of estradiol and ethinylestradiol (e.g. Estraderm, Climara®, Fem7, OrthoEVRA®, EstraDOT), and in the case of progestogens it is levonorgestrel, norethisterone and norethisterone acetate (e.g. Fem7 Combi, CombiPatch), and norelgestromin.

In andrology, testosterone is available in transdermal pharmaceutical forms (e.g. Androderm®, Testoderm®, Testogel®).

The feasibility of transdermal administration is, however, based not on good skin penetration by steroid hormones, but solely on the high potency of their effects. Ethinylestradiol and levonorgestrel display their effect even with daily doses in the range from 20 to 50 µg per day. Norethisterone acetate, with a typical transdermal daily dose of 125-250 µg/d, is one of the substances having weaker activity.

Among the progestogens currently used therapeutically, dienogest and drospirenone are, based on the necessary daily dose, among the less potent substances because they must be administered in the range of typical oral daily doses of 2 to 3 mg in order to display for example their contraceptive effect. In contrast to so-called highly potent progestogens such as, for example, gestodene or norelgestromin, whose daily dose is in the lower two-figure microgram range, it has to date been necessary to regard drospirenone and dienogest as unsuitable for transdermal administration.

The only steroid hormone which can at present be administered transdermally with daily doses in the milligram range is testosterone. However, the commercial patch products Testoderm® and Androderm® are known for their low local tolerability and the low acceptance by patients because of the site of use - on the scrotum (Testoderm®) - and the necessary size of patch of 74 cm^2 (Androderm®, 2 patches applied simultaneously).

On the other hand, the gel product Testogel® is available for transdermal testosterone therapy and likewise permits absorption of about 5-10 mg of testosterone per day with a low local irritation potential and improved convenience of use.

The patent literature discloses a large number of pharmaceutical preparations for application to the skin having a content of progestogens.

WO 97/11680 A1 describes a dispenser for administration of progestogens and estrogens.

DE patent 199 06 152 A1 claims at the outset reservoir systems in which the active ingredient is dissolved in volatile solvents such as ethanol. The transdermal administration of active ingredients by means of adhesive matrix system is described.

WO 99/15156 A1 describes a process for producing a transdermal administration form, where the active ingredient(s) may be steroidal hormones and the latter are present in the matrix on the support in the saturated or supersaturated state.

Description of the invention

It is an object of the invention to find transdermal administration forms for application to the skin for less potent progestogens.

The object is achieved according to the invention by a pharmaceutical preparation for application to the skin having a content of drospirenone, in which the amount of drospirenone contained in the preparation in the initial state thereof is not above the saturation solubility,
and the saturation solubility of drospirenone is exceeded after application of the preparation to the skin through efflux of solubilizing components from the preparation.

It is possible according to the invention for the saturation solubility of drospirenone to be exceeded in

the preparation during application by a factor of at least 5, preferably by a factor of at least 10.

It is also possible for the saturation solubility of drospirenone to be exceeded in the preparation during application by a factor of at least 2, preferably by a factor of at least 5, after only 1 hour.

The pharmaceutical preparation may have a content of ethanol or isopropanol.

The pharmaceutical preparation may according to the invention comprise a crystallization-inhibiting addition and/or a content of at least one permeation promoter in relation to drospirenone.

It has been found that the crystallization-inhibiting addition takes the form of a soluble polyvinyl-pyrrolidone.

The pharmaceutical preparation may be a semisolid preparation in the form of an alcohol-containing gel or a liquid, alcohol-containing preparation in the form of a lotion, of a foam or of a spray.

It is also possible for the liquid or semisolid, alcohol-containing preparation to form part of a transdermal patch of the reservoir system type.

It has further been found that the saturation solubility of drospirenone is exceeded in the preparation during application by a factor of at least 1.5, preferably by a factor of at least 2, and that the alcoholic preparation has an alcohol content of at least 60% (m/m), preferably of at least 65% (m/m).

Besides drospirenone, an estrogen may also be present.

It has also been found that during application to the skin there is likewise a transition in the estrogen content from the subsaturated or just saturated state into the supersaturated state.

The estrogen may be ethinylestradiol.

The particularly preferred embodiment of the invention takes the form of a transdermal gel with a content of ethanol and water. The active ingredient drospirenone is present completely dissolved. In order to ensure an adequate solubility of drospirenone with contents of, preferably, 0.2-2% (m/m) particularly preferably 0.5 to 1% (m/m), in the gel, in addition an ethanol content of at least 60% (m/m), particularly preferably even at least 65% (m/m), is provided.

Because of the high alcohol content, suitable gel formers are not only ionic ones based on polyacrylic acid (carbomers or Carbopols, e.g. Carbopol 940,941 or 980) but also gel formers from the group of cellulose derivatives, for example hydroxymethyl-, hydroxyethyl-cellulose or hydroxypropylcellulose.

Further additives which are particularly suitable are permeation promoters, refatting agents and antioxidants.

In order to make it possible for the systems of the invention to be supersaturated with drospirenone during use, it is preferred to employ a group of low molecular weight excipients which, on the one hand have good dissolving capacity for drospirenone, and in addition escape from the preparation under the conditions of use, either through high volatility or else through particularly good skin penetration, thus achieving supersaturation in drospirenone. These preferred

excipients finally also have good toxicological acceptability for use on the skin.

Such substances are preferably, but not exclusively, selected from the group of ethanol, isopropanol (2-propanol), 1,2-propanediol (propylene glycol), dipropylene glycol, 1,3-butanediol, dieethylene glycol monomethyl and monoethyl ethers, propylene carbonate and isopropylidene glycerol, and monoterpene constituents of essential oils.

These solubilizers for drospirenone, which easily escape from the formulation by evaporation or transdermal absorption, may if required be combined with one or more cosolvents which are neither easily vaporizable nor capable of good dermal absorption.

Transdermal systems of the reservoir type are a further preferred embodiment of the present invention.

The same statements apply to the contained semisolid preparation as to transdermal gels.

Reservoir systems can be produced and filled in a known manner.

It has been found that drospirenone on application in a hydroethanolic vehicle permeates through mouse skin in vitro almost as well as testosterone. It can be concluded from this that daily doses of drospirenone in the lower milligram range similar to testosterone can also be achieved on application in humans. This unexpected finding is presumably connected with a very high degree of supersaturation of the active ingredient during drying out of the vehicle on use in conjunction. Although the mechanism of supersaturation through evaporation in particular of the alcohol content from transdermal gels, lotions or sprays is discussed, in

the case of the formulations of the invention unexpectedly high degrees of supersaturation have proved to be expedient and practicable for drospirenone.

Determination of the supersaturation factor occurring during application of the relevant preparation:

- For semisolid gels, lotions, foams and sprays:

To simplify the investigations and, in particular, the analytical sample processing, the determinations of the solubility of drospirenone in these preparations and the residues resulting therefrom by drying out are undertaken on a semitheoretical basis. The semi-theoretical approach consists of taking account only of the liquid ingredients of the formulation for this examination. In the case of gels, lotions and sprays, the content of gel- or film-forming or thickening polymer is usually negligible in terms of quantity, but frequently interferes considerably with the analytical processing of the samples. A test solution composed solely of the liquid ingredients is used in the context of this invention as representative of said preparations.

In the specific case of the formulation from example 2, the following mixture is investigated as representative:

- Test solution example (before drying out)

	Parts (m/m)
isopropyl myristate	1.00
purified water	23.55*
96% ethanol	73.50

* Total of 20.0 g of water plus 3.55 g of water from 3.70 g of 0.1N NaOH (NaOH is not used because this is sensible only in the presence of the polymer, but in

its absence would create a highly alkaline, decomposing medium).

Determination of the solubility of drospirenone in the test solution before drying out is carried out as follows:

Drospirenone is added to about 10 g of weighed test solution while stirring with a magnetic stirrer bar until a clearly visible sediment is formed. This solution is stirred for at least 24 hours, after which the sediment must still be present. Otherwise, further drospirenone is added and the procedure is repeated. After completion of the stirring procedure, about 1.0 ml of test solution is removed and transferred into a 1.5 ml autosampler vial with screw cap. The sample is finally centrifuged at at least 3000 G for 10 minutes in order to deposit the undissolved drospirenone at the bottom of the sample. The concentration of drospirenone is then determined in an aliquot of the resulting supernatant using a suitable HPLC method. The result corresponds to the saturation solubility of drospirenone in the test mixture before drying out ($drospirenone_{s1}$ [mg/ml]).

The condition applying to preparations of the invention is $drospirenone_{init}$ less than/equal to $drospirenone_{s1}$, where $drospirenone_{init}$ [mg/ml] is the initial concentration of drospirenone in the preparation.

- Determination of the solubility of drospirenone in the liquid test mixture after drying out is carried out as follows:

The test solution is spread in a layer thickness of about 50 µm on a flat, inert support and dried out for a defined period at about 32°C (skin surface temperature) under ambient conditions without covering.

The period depends on the intended duration of use; it corresponds to 24 hours for a single daily application. A shorter period may also be chosen if, for example, the degree of drying out is to be ascertained for an earlier period than the end of application. The layer thickness of 50 µm is defined for the range of validity of this invention as standard layer thickness for the transdermal application of gels, lotions or sprays. In the case of the commercial Testogel for example 5 ml of gel are applied to the upper arm. With the standard layer thickness of 50 µm defined herein, the theoretical application area for 5 ml is about 90 cm^2 (assumed density of the gel about 0.9 g/cm^3), thus achieving an adequate approximation to application in vivo.

In the case of the above test solution example, about 4.36 g of test solution, weighed accurately (weight = W_{T1}), are spread out in a weighed Petri dish with a diameter of 10 cm (corresponding to 78.53 cm^2), resulting in a layer thickness of about 50 µm.

This batch is dried out at about 32°C on a hotplate over a period of 24 hours (corresponding to once a day application). The amount of test solution and the diameter of the dish are exemplary and nonlimiting. The values may be varied within the relationship described. The test mixture is not mechanically agitated or mixed, but left to stand at rest, during the test. No special circulation of air over the sample is undertaken.

At the end of the test, the weight of the dried-out residue of the test solution is ascertained (weight = W_{T2}).

The drying factor of the test solution is calculated from the resulting values by equation 1:

Equation 1: $F_D = W_{T1}/W_{T2}$

About 250.0 g, weighed accurately (weight = W_{R1}), of the test solution in the composition before drying out are introduced into a weighed 500 ml wide-neck flask.

This batch is then concentrated in a Rotavapor at 32°C under reduced pressure until the ratio by weight of the amount is the same as that found after drying out in a Petri dish over a defined period, i.e. until the amount by weight (weight = W_{R2}) remaining in the flask satisfies equation 2:

Equation 2: $W_{R2} = W_{R1}/F_D$

The enlarged batch of the test solution in the Rotavapor is used to obtain a sufficiently large amount of residue for the subsequent determination of the solubility of drospirenone. Operations are once again carried out at 32°C in order to reproduce the evaporation conditions on the skin surface in quantitatively expedited but qualitatively minimally falsified form.

1.0 g* is removed from the amount of residue finally obtained in the flask and is transferred into a 1.5 ml autosampler vial with screw cap. 100 mg of drospirenone are added to this residue. This mixture is subsequently treated in an ultrasound bath for one hour. The sample is then left to stand under ambient conditions for 24 hours. The sample is finally centrifuged at at least 3000 G for 10 minutes in order to deposit the undissolved drospirenone at the bottom of the sample. The concentration of drospirenone is then determined in an aliquot of the resulting supernatant using a suitable HPLC method. The resulting value corresponds to the saturation solubility of drospirenone in the dried-out test solution (drospirenone$_{S2}$ [mg/ml]).

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* in the event that less than 1 gram can be removed, typically when F_D is > 200, the batch in the Rotovapor can be correspondingly enlarged, or the final determination is reduced for example to 50 mg of drospirenone in 0.5 g of dried-out test solution.

The supersaturation factor F_{SS} based on drospirenone in the test solution during drying out is calculated by equation 3, with the initial concentration of drospirenone in the preparation being entered as $drospirenone_{init}$ [mg/ml]:

Equation 3:

F_{SS} = $drospirenone_{init}$ [mg/ml] × F_D/ $drospirenone_{S2}$ [mg/ml]

Reference is made in the claims of this patent application to the supersaturation factor F_{SS} found in this way.

A value of 5 for Fss means for example that the saturation solubility of drospirenone is exceeded by a factor of 5 during use of the preparation.

- For reservoir-type transdermal patches:

The solubility of drospirenone in the formulation of the active ingredient reservoir is considered.

The semitheoretical approach of investigating a test solution solely composed of the liquid ingredients as representative of the semisolid reservoir formulation applies once again.
The saturation solubility in the reservoir preparation is determined on this basis in analogy to the determination of $drospirenone_{S1}$ [mg/ml] in gels, lotions and sprays, as above.

The drying factor F_D appears here for the determination of the concentration factor F_C, because the reservoir dries out through transdermal permeation of liquid ingredients.

The active ingredient-delivering area of the reservoir system is covered with this film, and the reservoir system is weighed in this arrangement (W_{RS1}). The reservoir system is then exposed to pure water as acceptor liquid at a temperature of 32°C over the intended period. The intended period is 24 hours for a system for once daily application.

The system is then weighed (W_{RS2}).

The drying factor F_D in the reservoir preparation is obtained from the weight loss found by equation 4:

Equation 4: $F_D = W_{RF}/(W_{RF}-(W_{RS1} - W_{RS2}))$,

where W_{RF} is the weight of the amount of active ingredient-containing reservoir formulation contained in the reservoir system before the test.

The saturation solubility of drospirenone in the concentrated reservoir formulation (drospirenone$_{S2}$) and the supersaturation factor F_{SS} are determined in analogy to the statements concerning gels, lotions and sprays from equation 1 onwards, with F_C appearing instead of F_D.

Exemplary embodiments

Example 1 - Hydroethanolic gel

	Parts (m/m)
drospirenone	1.0
Testogel®	99.0

Drospirenone is mixed directly with the commercially available Testogel and completely dissolved therein.

Testogel corresponds in its composition to Androgel®:

100 g of gel contain	testosterone	1.0 g
	Carbopol 980	0.90 g
	isopropyl myristate	0.50 g
	0.1N NaOH	4.72 g
	ethanol (95% w/w)	72.5 g*
	purified water	to 100 g

* equivalent to 67 g of ethanol.

Example 2 - Polyacrylate-based hydroethanolic gel

	Parts (m/m)
drospirenone	1.0
ethinylestradiol	0.1
isopropyl myristate	1.0
Carbopol 940	0.7
0.1N NaOH	3.7
purified water	20
96% ethanol	to 100.0

Preparation takes place in the manner known to the skilled worker by dissolving/mixing all the components and finally neutralizing the gel former with dilute sodium hydroxide solution, whereupon gel formation starts. Isopropyl myristate serves as refatting agent on the skin.
Drospirenone becomes supersaturated during application through evaporation of ethanol.

Example 3 - Cellulose-based hydroethanolic gel with crystallization-inhibiting addition

	Parts (m/m)
drospirenone	0.5
ethyl oleate	2.0
Collidon 12 PF	0.5
hydroxyethylcellulose	1.0
water	30.0
96% ethanol	to 100.0

Preparation takes place in the manner known to the skilled worker by mixing the gel former methylcellulose with water and alcohol and finally adding the excipients and active ingredients.

Ethyl oleate serves as permeation promoter.

Drospirenone becomes supersaturated during application through evaporation of ethanol.

Example 4 - Reservoir system-type transdermal patch

drospirenone	5.0 mg*
96% ethanol	about 196 µl
Androderm	1 × 2.5 mg patch

The protective cover is removed from a previously accurately weighed Androderm patch and, with the now exposed membrane lying on top, the contents are allowed to evaporate under ambient conditions until about 180 mg of the contents have evaporated. The reservoir is then covered again with the protective film. This pretreatment is necessary in order to create sufficient space in the reservoir for the subsequently described addition of drospirenone solution.

100 mg of drospirenone are dissolved in 4 ml of ethanol 96% by exposure to ultrasound. About 500 µl of this solution are drawn into a 1 ml disposable syringe with fitted steel needle (0.9 × 40 mm).

The reservoir of the Androderm patch is then punctured with this syringe, and about 200 µl of solution are injected into the reservoir. This is made possible by piercing an additional ventilation hole at the place where the air bubble is present in the semisolid reservoir.

A piece of tesa film is then stuck over the two puncture sites. The contents of the reservoir are mixed by cautious kneading with the fingers for some minutes. The system is equilibrated under ambient conditions for at least 24 hours before use for the experiment.

Drospirenone becomes supersaturated during application of the system substantially through the transdermal absorption of ethanol, which proceeds considerably more quickly than that of drospirenone.

Example 5 - Transdermal spray

	Parts (m/m)
drospirenone	0.5
ethinylestradiol	0.1
oleyl alcohol	1.0
1,2-propanediol	0.5
96% ethanol	60.0
dimethyl ether	to 100.0

Drospirenone becomes supersaturated during application substantially through evaporation of ethanol. Dimethyl ether serves as propellant for the spray.

Example 6

The formulation of example 1 was investigated for in relation to the permeation of drospirenone compared with testosterone through mouse skin - see figure 1.

About 200 mg of the preparation of example 1 were applied to nude mouse skin which was fixed as permeation membrane in modified Franz permeation cells.

The results in figure 1 are the averages of n = 7 experiments.

Skin: nude mouse skin, HsdCpb NMRI-nu/nu, Harlan Bioservice, Walsrode

Acceptor medium for the Franz cells:

potassium chloride	0.6 g
potassium dihydrogen phosphate	0.09 g
sodium chloride	10.905 g
sodium hydrogen phosphate dihydrate	0.09 g
HEPES	8.94 g
gentamicin sulfate	0.075 g
γ-cyclodextrin	7.5 g
Aqua purificata	to 1500 g

Samples each of 100 µl were taken from the acceptor medium of the Franz cells by an automatic sampling system at times 3, 6, 9, 12, 15 and 18 hours and injected into an automatic HPLC.

HPLC method:

column	LiChrospher 100 RP 18, 5 µm, 125 × 3 mm
mobile phase	acetonitrile/H2O (40/60)
flow rate	1 ml/min
temperature	40°C
vol. injected	100 µl
detection wavelength (UV):	244 nm (testosterone), 261 nm (drospirenone)

Example 7:

The formulation of example 1 was investigated for in relation to the permeation of drospirenone compared with testosterone on human skin (female abdominal skin from cosmetic reduction, dermatomized to about 450 µm layer thickness) - see figure 2.

Tab. 1: Permeation of testosterone from example 1 through human skin:
Average cumulative permeation [$\mu g/cm^2$] of 1% testosterone in Testogel (K2053) through dermatomized human skin

Time [h]	Average	SD	RSD [%]
0	0.00	0.00	-
3	3.62	1.24	34
7	7.72	2.21	29
10	10.70	2.34	22
24	26.57	6.72	25
30	33.31	7.06	21
48	44.35	10.03	23

Tab 2: Permeation of drospirenone from example 1 through human skin:
Average cumulative permeation [$\mu g/cm^2$] of 1% drospirenone in Testogel (K2053) through dermatomized human skin

Time [h]	Average	SD	RSD [%]
0	0.00	0.00	-
3	0.87	0.34	39
7	2.04	0.68	33
10	2.86	0.75	26
24	8.67	2.19	25
30	12.13	2.64	22
48	19.23	4.03	21

It can be concluded from these data that on application to human skin the permeation of drospirenone is up to 40% of that of testosterone. Since Testogel is authorized for administering 5 to 10 mg per day, it can

be concluded that about 3-5 mg/d drospirenone can also be administered transdermally in this form. The transdermal application of contraceptively effective amounts of drospirenone is thus made possible.

Claims

1. A pharmaceutical preparation for application to the skin having a content of drospirenone, characterized in that the amount of drospirenone contained in the preparation in the initial state thereof is not above the saturation solubility, while the saturation solubility of drospirenone is exceeded after application of the preparation to the skin through efflux of solubilizing components from the preparation.

2. The pharmaceutical preparation as claimed in claim 1, characterized in that the saturation solubility of drospirenone in the preparation during application is exceeded by a factor of at least 5, preferably by a factor of at least 10.

3. The pharmaceutical preparation as claimed in claim 2, characterized in that the saturation solubility of drospirenone in the preparation during application is exceeded by a factor of at least 2, preferably by a factor of at least 5, after only 1 hour.

4. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that it has a content of ethanol or isopropanol.

5. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that a crystallization-inhibiting addition in relation to drospirenone is present.

6. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that the crystallization-inhibiting addition is a soluble polyvinylpyrrolidone.

7. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that it has a content of at least one permeation promoter.

8. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that it is a semisolid preparation in the form of an alcohol-containing gel.

9. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that it is a liquid, alcohol-containing preparation in the form of a lotion, of a foam or of a spray.

10. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that it is a liquid or semisolid, alcohol-containing preparation as constituent of a transdermal patch of the reservoir system type.

11. The pharmaceutical preparation as claimed in claim 10, characterized in that the saturation solubility of drospirenone in the preparation during application is exceeded by a factor of at least 1.5, preferably by a factor of at least 2.

12. The pharmaceutical preparation as claimed in any of claims 9 to 11, characterized in that the alcoholic preparation has an alcohol content of at least 60% (m/m), preferably of at least 65% (m/m).

13. The pharmaceutical preparation as claimed in one or more of the preceding claims, characterized in that an estrogen is present in addition to drospirenone.

14. The pharmaceutical preparation as claimed in claim 13, characterized in that during application to the skin there is likewise a transition in the estrogen content from the subsaturated or just saturated state

into the supersaturated state.

15. The pharmaceutical preparation as claimed in claim 13 or 14, characterized in that the estrogen is ethinylestradiol.