Description

The present invention relates to an external adhesive preparation containing steroids. More specifically, the present invention relates to an external adhesive preparation containing steroids which is obtained by incorporating a steroid useful for the treatment of skin diseases into an adhesive gel base comprising as essential components a water-soluble compound water and a water-retaining agent and spreading the resulting composition onto a soft support, said preparation being directly applied to diseased parts on the skin so that the contained steroids are administered to the skin for treatment of the diseases.

Hitherto, for the treatment of allergic skin diseases such as eczema, hives, children's strophulus, contoured exudative erythema, Behcet's syndrome, keratodermia palmeris and psoriasis, there have been used oral preparations, injections and external preparations containing cortisone as an active component.

However, these preparations have some side effects or inconvenience in usage. For example, in case of oral preparations, there is a fear of forgetting taking or an excess administration. In case of injections, patients suffer from pain or stress when administering drugs and further it is difficult to be administered by the patients themselves. External preparations such as ointments or lotions not only stain clothes but also are hard to administer in a fixed-amount. Further, in case of external preparations, patients are forced to be given by a physical stimulus to the diseased parts which are most accompanied with urtication and this stimulus sometimes makes worse symptoms. Therefore, the external preparations are not necessarily suitable. For the purpose of obviating the above-mentioned disadvantages, there have been developed tapes which are produced by incorporating a steroid into a pressure sensitive adhesive comprising a natural gum or a copolymer of acrylic acid ester - acrylic acid. These tapes are more excellent than the conventional external preparations in many respects, i.e. they are expected to have an effect of occlusive dressing technique by applying them to diseased parts and are more easily handled in the treatment. However, the application of these tapes to diseased parts induces occasionally contact dermatitis caused by the adhesive itself, folliculitis caused by bacteria on the skin, or cutaneous inflammation due to stimulus of sweat gland. Furthermore, these tapes are still unsatisfactory in that when these tapes are removed, diseased parts are rather injured or keratin is peeled off and therefore not only it is difficult to apply them succesively but also symptoms are made worse.

US-A-4 008 321 refers to a transparent gelatinous topical composition which is prepared by adding a transparent solution of a steroid in crotamiton and propylene glycol to an aqueous solution of carboxyvinyl polymer and adding thereto an organic amine, which composition forms membranes when applied to the skin.

FR-A-2 229 393 is directed to a composition for topical application to the skin, which forms a film readily removable by water when applied to the skin. The composition of this reference comprises as the essential component an aqueous emulsion of a water insoluble film-forming polymer and a water soluble film-forming polymer which is prepared from a water insoluble polymer, a water soluble polymer and another emulsifier.

EP-A-0 072 251 is directed to a flexible, liquid absorbent, adhesive bandage comprising a solid phase (e.g. natural rubber or synthetic polymer) and a liquid phase (comprising glycerol, propylene glycol, etc).

GB-A-2 177 002 describes an adhesive medical tape for oral mucosa comprising a support layer of intestine soluble polymer and at least one medicament-containing layer of water-soluble polymer which contains a steroid or non-steroid medicament.

As a result of the present inventors' intensive study to obviate defects of these tapes , it has been found that an excellent adhesive preparation without defects as seen in the conventional tapes could be obtained by incorporating a steroid as the active ingredient into an adhesive base comprising as essential components 0.1 to 30 w/w% of a water-soluble compound selected from gelatin, alginic acid, carboxymethyl cellulose, methyl cellulose, polyvinyl alcohol and polyacrylic acid, 10 to 70 w/w% of water, and 5 to 60 w/w% of a water-retaining agent selected from glycerol, sorbitol and 1,3-butanediol, and a soft support on which the pharmaceutical composition is spreaded.

Fig. 1 is a graph showing a cumulative release rate of active agent as to the adhesive preparations of the present invention prepared in Examples 1 and 2 and tapes prepared in Comparative Examples 1 to 3.

The water-soluble compound employed in the external adhesive preparations of the present invention includes gelatin, alginic acid, carboxymethylcellulose, methylcellulose, polyvinyl, alcohol and polyacrylic acid. The above water-soluble compounds are employed alone or in a combination of two or more thereof depending on properties of other materials used in the adhesive gel base and are mixed with the gel base in an amount of from 0.1 to 30 w/w%, preferably from 0.5 to 15 w/w%.

The water-retaining agent includes glycerol,sorbitol, and 1,3-butanediol. These are employed alone or in combination of two or more thereof and are mixed with the gel base in an amount of from 5 to 60 w/w%, preferably from 10 to 50 w/w%. Also there may be employed highly absorptive compounds, selected from starch - acrylonitrile graft copolymer, starch - acrylic acid graft copolymer, starch - styrenesulfonic acid graft copolymer, starch - vinylsulfonic acid graft copolymer, cellulose - acrylonitrile graft copolymer, cellulose - styrenesulfonic

acid graft copolymer, a cross-linked product of carboxymethylcellulose, a cross-linked product of polyvinyl alcohol, a saponification product of acrylic acid - vinyl acetate, a cross-linked product of polyacrylate, a saponification product of polyacrylonitrilic polymer and a cross-linked product of polyethylene glycol diacrylate. These are employed in an amount of from 0.01 to 10.0 w/w%, preferably from 0.05 to 7.0 w/w%.

One of the characteristics of the adhesive gel base employed in the present invention is that it contains water, thereby enhancing an absorption of steroids as an active component. The water content is in the range of from 10 to 70 w/w%, preferably from 20 to 50 w/w%.

The steroids which are an active component of the external adhesive preparations of the present invention include, for example, deprodone propionate, fluocinolone acetonide, triamcinolone acetonide, dexamethasone, methylprednisolone, prednisolone, hydrocortisone, paramethasone, betamethasone, betamethasone sodium phosphate, dexamethasone acetate, cortisone acetate, hydrocortisone acetate, methylprednisolone acetate, clobetasol propionate, hydrocortisone butyrate, fluocinonide, fluorometholone, fludroxycortide, flumethasone pivalate, beclomethasone propionate, betamethasone valerate, and methylprednisolone acetate. These steroids are incorporated into the adhesive gel base in an amount of from 0.001 to 1 w/w%, preferably from 0.005 to 0.5 w/w%, more preferably from 0.01 to 0.25 w/w%.

In order to improve a solubility or a dispersibility of the above steroids in water, the gel base may contain oil components and surfactants such as crotamiton, benzyl alcohol, isopropyl myristate, ethylene glycol, diethyl sebacate-2-ethyl-5-pyrrolidone.

Further, if necessary, known stabilizing agents, antioxidants, pH controling agents or inorganic fillers may also be added. The stabilizing agents and antioxidants include, for example, disodium edetate, tetrasodium edetate, sodium metabisulfite, dibutylhydroxytoluene (BHT), butylhydroxyanisol (BHA), ascorbic acid, sodium ascorbate, erythorbic acid, sodium erythorbate, sodium sulfite, d-α-tocopherol, tocopherol acetate, gualacum resin, nordihydro guaiaretic acid, and propyl gallate, which may be used alone or in combination of two or more thereof. These are mixed usually in an amount of from 0.005 to 1.0 w/w%, preferably from 0.01 to 0.5 w/w%.

A support employed in the present invention is preferably such a soft one as being able to follow a movement of a human body and includes various woven fabrics, non-woven fabrics, and flannels. The external adhesive preparations of the present invention are expected to have an effect of occlusive dressing technique since the adhesive gel base layer is a continueous phase. However, when more powerful effect of occlusive dressing technique is desired, the above-mentioned support may be laminated by ethylene vinyl acetate, polyethylene, polyvinyl chloride and polyurethane.

The external adhesive preparation of the present invention has less side effects such as cutaneous inflammation and further less injury of diseased parts or peeling off of keratin when the preparations are removed as compared with the conventional tapes, and hence, the present preparation can be used succesively. Moreover, when the external adhesive preparation of the present invention is applied to diseased parts on the skin, not only an effect of occlusive dressing technique is expected as in the case of the conventional tapes but also more excellent treatment effect can be obtained through increased absorption of the main component steroid, which is induced by an active hydration of keratin layer owing to water contained in the external adhesive preparation of the present invention.

In order to exhibit the medical effects by applying the external adhesive preparation to cutaneous diseased parts, it is necessary that the active ingredient is released from the base and transferred into the cutaneous diseased part. It is known that an affinity between the active ingredient and the base is related to the above and has an influence on the medical effects. The affinity is influenced by various factors such as a solubility, a diffusion coefficient, a thermodynamic activity and the like of the base or active agent in the base. In case of the external adhesive preparation of the present invention, these factors are controllable by varying a combination of the base components to enable to adjust an optimum concentration of each active ingredient, and thereby, the desired excellent treatment effects can be more effectively exhibited as compared with the other conventional preparations.

The present invention is more specifically illustrated by the following Examples and Experiments. In the Examples, "part" means a part by weight.

Example 1

A mixture of 31 parts of water, 5.0 parts of gelatin, 0.1 part of methyl p-hydroxybenzoate, 0.2 part of citric acid, 0.2 part of deprodone propionate, 1.0 part of crotamiton, 20 parts of sorbitol, 30 parts of glycerol and 4.0 parts of polyacrylic acid is stirred with heating in a kneader to give a solution, and thereto is added a solution of 0.5 part of aluminum potassium sulfate in 8 parts of water, and the mixture is stirred well to give an adhesive gel base. This adhesive gel base is applied and spread on a release paper in an amount of 200 g/m² in a conventional manner, and then transferred to polyurethane-laminated nonwoven fabric made of rayon, which is

cut in a desired size to give an external adhesive preparation containing 40 μg/cm² of deprodone propionate.

Example 2

A mixture of 25 parts of water, 10 parts of polyacrylic acid, 5 parts of zinc white, 6 parts of polyvinyl alcohol, 3.0 parts of benzyl alcohol, 0.2 part of deprodone propionate, 0.1 part of propyl p-hydroxybenzoate, 8.0 parts of carboxymethylcellulose sodium, 20 parts of glycerol and 20 parts of sorbitol is dissolved in a kneader in the same manner as in Example 1, and thereto is added a solution of 0.2 part of dihydroxyaluminum aminoacetate in 2.5 parts of water, and the mixture is well stirred to give an adhesive gel base. Using this base, the procedure of Example 1 is repeated to give an external adhesive preparation containing 40 μg/cm² of deprodone propionate.

Example 3

Except that 0.025 part of deprodone propionate is employed, the procedure of Example 1 is repeated to give an external adhesive preparation containing 5 μg/cm² of deprodone propionate.

Example 4

Except that 0.05 part of deprodone propionate is employed, the procedure of Example 1 is repeated to give an external adhesive preparation containing 10 μg/cm² of deprodone propionate.

Example 5

Except that 0.1 part of deprodone propionate is employed, the procedure of Example 1 is repeated to give an external adhesive preparation containing 20 μg/cm² of deprodone propionate.

Example 6

Except that 0.4 part of deprodone propionate is employed, the procedure of Example 1 is repeated to give an external adhesive preparation containing 80 μg/cm² of deprodone propionate.

Comparative Example 1

A four-necked flask is charged with a mixture of 7.0 parts of acrylic acid, 68 parts of 2-ethylhexyl acrylate, 25 parts of vinyl acetate, 0.2 part of azobisisobutyronitrile and 150 parts of ethyl acetate under nitrogen. The mixture is stirred with heating at 65 - 70°C to conduct polymerization to give an acrylic adhesive agent having 40% of a solid content. To 99.6 parts (in solid content) of the adhesive agent is added 0.4 part of deprodone propionate, and the mixture is applied to in an amount of 100 g/m² (in dry state) in a conventional manner, which is laminated on polyethylene film to give an acrylic adhesive tape containing 40 μg/cm² of deprodone propionate.

Comparative Example 2

Fifty parts of raw rubber is dissolved in 203 parts of toluene and therein are dissolved with stirring 10 parts of polybutene, 38 parts of ester gum and 2.0 parts of dibutylhydroxytoluene to give a natural gum adhesive agent having 33% of a solid content. Then, after 0.4 part of deprodone propionate is added to 99.6 parts (in solid content) of the adhesive agent, the procedure of Comparative Example 1 is repeated to give a natural gum adhesive tape containing 40 μg/cm² of deprodone propionate.

Comparative Example 3

A mixture of 29 parts of styrene-isoprene-styrene copolymer, 47 parts of an alicyclic saturated hydrocarbon petroleum resin, 10 parts of a liquid polyisoprene rubber, 12.6 parts of a liquid paraffin and 1.0 part of an antioxidant is dissolved with heating at 160°C in a kneader. After stirring, the mixture is cooled to 120°C and thereto is added 0.4 part of deprodone propionate, and the mixture is applied to a release paper with a coator in an amount of 100 g/m². After cooling, the mixture is transferred to a polyethylene vinyl acetate film, which is cut in a desired size to give a hot-melt type adhesive tape containing 40 μg/cm² of deprodone propionate.

Experiment 1

The vasoconstrictor test was carried out as to the adhesive preparations prepared in Examples 1-6, the tapes prepared in Comparative Examples 1-3, a commercially available acrylic adhesive tape containing 4 μg/cm² of fludroxycortide and a commercially available acrylic adhesive tape containing 8 μg/cm² of fluocinolone acetonide to compare effects of these preparations or tapes.

These adhesive preparations and tapes containing steroids, and further, blank adhesive preparations and tapes which were prepared by removing deprodone propionate from the adhesive preparations in Examples 1-2 and the tapes in Comparative Examples 1-3 (hereinafter, referred to merely as blank of Example 1 were punched in a circular form of 15 mm diameter to give test samples. The samples were adhered to backs of 20 healthy adult men. Application periods were 30 minutes, 1 hour, 2 hours and 4 hours. After removal, the applied portions were wiped with slightly warm water. Two hours later a degree of the vasoconstrictor activity was evaluated. The experiment was carried out by a double blind test.

The results are shown in Table 1. The figures in the table are % of a number having the vasoconstrictor activity in the 20 volunteers.

Table 1 Vasoconstrictor test

Sample name	30 min. application	1 hour application	2 hours application	4 hours application
Example 1	75	85	100	100
" 2	60	90	95	100
" 3	5	15	50	55
" 4	10	30	65	80
" 5	30	55	75	100
" 6	95	100	100	100
Comp. Ex. 1	10	55	70	90
" 2	15	50	75	90
" 3	30	60	85	100
Commercial product 1	5	25	55	60
" 2	5	15	40	65
Example 1	5	5	0	5
" 2	5	0	5	5
Comp. Ex. 1	0	5	0	0
" 2	0	0	0	0
" 3	0	0	5	0

Experiment 2

Employing Franz Diffusion Cell (manufactured by CROWN GLASS Co. Inc.), active agent release patterns

of each adhesive preparation and tape were evaluated. The test samples were punched into 15 mm diameter and adhered to silicone membrane and the amount of deprodone propionate transferred into phosphate buffer of pH 7.4 was measured by HPLC. The measurement was carried out over a period of 6 hours at an interval of 1 hour. A released amount of the active agent was calculated based on the charged amount of the active agent and a cumulative release rate (%) (the release amount/the charged amount x 100) was shown in graph (Fig. 1).

Experiment 3

In the case of the sample adhered for 4 hours in Experiment 1, conditions of cutaneous stimulus were observed immediately, 24 hours and 48 hours after peeling off the sample, and evaluated as 0: no reaction, 0.5: slight erythema, 1: erythema, 2: erythema with edema, 3: small blister, 4: large blister. A mean strength of cutaneous stimulus was calculated by multiplying these figures with a number showing these conditions, which is then divided by a total number of volunteers. The results are shown in Table 2.

Table 2 Strength of cutaneous stimulus

Sample name	immed. after removal	24 hours after removal	48 hours after removal
Example 1	0.075	0.100	0
" 2	0.100	0.075	0
" 3	0.225	0.100	0.075
" 4	0.150	0.100	0
" 5	0.075	0.05	0
" 6	0.05	0.075	0
Comp. Ex. 1	0.25	0.125	0.050
" 2	0.200	0.200	0.075
" 3	0.175	0.125	0.075
Commercial product 1	0.600	0.200	0.150
" 2	0.525	0.225	0.100
Example 1	0.200	0.100	0.050
" 2	0.325	0.100	0.025
Comp. Ex. 1	0.500	0.200	0.050
" 2	0.575	0.100	0.025
" 3	0.375	0.150	0.025

Example 7

A mixture of 31 parts of water, 5.0 parts of gelatin, 0.1 part of methyl p-hydroxybenzoate, 0.2 part of citric acid, 0.1 part of triamcinolone acetonide, 1.0 part of crotamiton, 20 parts of sorbitol, 30 parts of glycerol and

4.0 parts of polyacrylic acid is stirred with heating in a kneader to give a solution, and thereto is added a solution of 0.5 part of aluminum potassium sulfate in 8 parts of water, and the mixture is stirred well to give an adhesive gel base. This adhesive gel base is applied and spread on a release paper in an amount of 200 g/m^2 in a conventional manner, and then transferred to a polyurethane-laminated non-woven fabric made of rayon, which is cut in a desired size to give an external adhesive preparation containing 20 μg/cm^2 of triamcinolone acetonide.

Example 8

A mixture of 25 parts of water, 10 parts of polyacrylic acid, 5 parts of zinc white, 6 parts of polyvinyl alcohol, 3.0 parts of benzyl alcohol, 1.0 part of hydrocortisone, 0.1 part of propyl p-hydroxybenzoate, 8.0 parts of carboxymethylcellulose sodium, 20 parts of glycerol and 20 parts of sorbitol is dissolved in a kneader in the same manner as in Example 7, and thereto is added a solution of 0.2 part of dihydroxyaluminum aminoacetate in 2.5 parts of water, and the mixture is well stirred to give an adhesive gel base. Using this base, the procedure of Example 7 is repeated to give an external adhesive preparation containing 200 μg/cm^2 of hydrocortisone.

Example 9

Except that 0.1 part of dexamethasone acetate is employed, the procedure of Example 7 is repeated to give an external adhesive preparation containing 20 μg/cm^2 of dexamethasone acetate.

Example 10

Except that 0.25 part of methylprednisolone is employed, the procedure of Example 7 is repeated to give an external adhesive preparation containing 50 μg/cm^2 of methylprednisolone.

Example 11

Except that 0.5 part of prednisolone is employed, the procedure of Example 7 is repeated to give an external adhesive preparation containing 100 μg/cm^2 of prednisolone.

Example 12

Except that 0.04 part of fluocinolone acetonide is employed, the procedure of Example 7 is repeated to give an external adhesive preparation containing 8 μg/cm^2 of fluocinolone acetonide.

Experiment 4

The vasoconstrictor test was carried out as to the adhesive preparations prepared in Examples 7-12, commercially available acrylic adhesive tapes containing 4 μg/cm^2 of fludroxycortide, 8 μg/cm^2 of fluocinolone acetonide and 6 μg/cm^2 of betamethasone valerate, respectively, to compare effects of these preparations or tapes. These adhesive preparations and the commercially available tapes containing steroids were punched in a circular form of 10 mm diameter to give test samples. The samples were randomly assigned to and adhered to middle backs of 10 healthy adult men. Application periods were 30 minutes, 1 hour, 2 hours and 4 hours. The vasoconstrictor activity was evaluated 2 hours and 4 hours after removal.

The results are shown in Tables 3-6. Table 3 and Table 4 show the results of vasoconstrictor activity when evaluated 2 hours after removal, wherein Table 3 shows a number of positive and Table 4 shows a number of pseud-positive or positive in 10 persons tested. Table 5 and Table 6 show the results when evaluated 4 hours after removal wherein table 5 shows a number of positive and Table 6 shows a number of pseud-positive or positive in 10 persons tested.

Table 3

Sample name	Active ingredient		Application period (h)			
	Name	conc. ($\mu g/cm^2$)	0.5	1.0	2.0	4.0
Ex. 12	Fluocinolone acetonide	8	0	0	3	7
" 7	Triamcinolone acetonide	20	0	3	5	7
" 9	Dexamethasone acetate	20	0	1	4	6
" 10	Methyl-prednisolone	50	0	0	0	5
" 11	Prednisolone	100	0	0	1	5
" 8	Hydrocortisone	200	0	0	1	0
Commerc. product 1	Fludroxycortide	4	0	0	2	4
" 2	Fluocinolone acetonide	8	0	0	0	2
" 3	Betamethasone valerate	6	0	0	1	4

Table 4

Sample name	Active ingredient		Application period (h)			
	Name	conc. ($\mu g/cm^2$)	0.5	1.0	2.0	4.0
Ex. 12	Fluocinolone acetonide	8	0	1	5	9
" 7	Triamcinolone acetonide	20	1	6	9	9
" 9	Dexamethasone acetate	20	1	4	6	10
" 10	Methyl-prednisolone	50	0	1	6	6
" 11	Prednisolone	100	1	1	3	5
" 8	Hydrocortisone	200	1	0	2	6
Commerc. product 1	Fludroxycortide	4	0	2	4	10
" 2	Fluocinolone acetonide	8	0	3	2	6
" 3	Betamethasone valerate	6	1	2	6	8

Table 5

Sample name	Active ingredient		Application period (h)			
	Name	conc. ($\mu g/cm^2$)	0.5	1.0	2.0	4.0
Ex. 12	Fluocinolone acetonide	8	0	1	7	10
" 7	Triamcinolone acetonide	20	1	5	8	9
" 9	Dexamethasone acetate	20	0	5	8	10
" 10	Methyl-prednisolone	50	0	1	2	7
" 11	Prednisolone	100	0	0	1	3
" 8	Hydrocortisone	200	0	0	2	2
Commerc. product 1	Fludroxycortide	4	0	0	3	7
" 2	Fluocinolone acetonide	8	0	0	1	6
" 3	Betamethasone valerate	6	0	0	7	9

Table 6

Sample name	Active ingredient		Application period (h)			
	Name	conc. ($\mu g/cm^2$)	0.5	1.0	2.0	4.0
Ex. 12	Fluocinolone acetonide	8	2	6	8	10
" 7	Triamcinolone acetonide	20	4	8	9	10
" 9	Dexamethasone acetate	20	3	9	9	10
" 10	Methyl-prednisolone	50	0	1	5	9
" 11	Prednisolone	100	1	3	4	9
" 8	Hydrocortisone	200	0	0	6	5
Commerc. product 1	Fludroxycortide	4	2	1	6	9
" 2	Fluocinolone acetonide	8	0	2	3	9
" 3	Betamethasone valerate	6	0	3	7	9

Example 13

A mixture of 35 parts of water, 1.5 part of gelatin, 1 part of urea, 0.5 part of methyl benzoate, 0.25 part of d-tartaric acid, 6 parts of polyacrylic acid, 1 part of hydrocortisone, 0.1 part of d-α-tocopherol, 14 parts of sorbitol, 1 part of crotamiton, 10 parts of glycerol, 3 parts of carboxymethylcellulose sodium and 4 parts of sodium polyacrylate is stirred in a kneader with heating to give a solution, and thereto are added 0.55 part of dihydroxyaluminum aminoacetate and 0.15 part of ascorbic acid, and further water is added so as to make a total volume of 100 parts, followed by stirring the mixture well to give an adhesive gel. Using this base, the procedure of Example 1 is repeated to give an external adhesive preparation containing 200 $\mu g/cm^2$ of hydrocortisone.

Example 14

Except that 0.08 part of tetrasodium edetate and 0.1 part of dexamethasone acetate are employed, the procedure of Example 13 is repeated to give an external adhesive preparation conatining dexamethasone acetate.

Example 15

Except that 0.04 part of disodium edetate, 0.15 part of sodium ascorbate and 0.25 part of Methyl-prednisolone, the procedure of Example 13 is repeated to give an external adhesive preparation containing methyl-prednisolone.

Example 16

Except that 0.25 part of prednisolone and 0.15 part of erythorbic acid, the procedure of Example 13 is repeated to give an external adhesive preparation containing prednisolone.

Example 17

Except that 0.04 part of fluocinolone acetonide, 0.05 part of disodium edetate and 0.1 part of BHT, the procedure of Example 13 is repeated to give an external adhesive preparation containing fluocinolone acetonide.

Example 18

Except that 0.1 part of triamcinolone acetonide, 0.05 part of disodium edetate and 0.1 part of sodium metabisulfite, the procedure of Example 13 is repeated to give an external adhesive preparation containing triamcinolone acetonide.

Claims

1. An external adhesive pharmaceutical preparation characterized by comprising a pharmaceutical composition which comprises an effective amount of a steroid in admixture with an adhesive gel base comprising as essential components 0.1 to 30 w/w% of a water-soluble high molecular weight compound selected from gelatin, alginic acid, carboxymethyl cellulose, methyl cellulose, polyvinyl alcohol and polyacrylic acid, 10 to 70 w/w% of water, and 5 to 60 w/w% of a water-retaining agent selected from glycerol, sorbitol and 1,3-butanediol, and a soft support on which the pharmaceutical composition is spreaded.

2. The preparation according to claim 1, wherein the amount of the water-soluble high molecular weight compound in the pharmaceutical composition is in the range of 0.5 to 15 w/w%.

3. The preparation according to claim 1, wherein the amount of water in the pharmaceutical composition is in the range of 20 to 50 w/w%.

4. The preparation according to claim 1, wherein the amount of the water-retaining agent in the pharmaceutical composition is in the range of 10 to 50 w/w%.

5. The preparation according to claim 1, wherein the water-retaining agent in the pharmaceutical composition is in a combination with 0.01 to 10.0 w/w% of a highly absorptive high molecular weight compound selected from starch-acrylonitrile graft copolymer, starch-acrylic acid graft copolymer, starch-styrene-sulfonic acid graft copolymer, starch-vinylsulfonic acid graft copolymer, cellulose-acrylonitrile graft copolymer, cellulose-styrenesulfonic acid graft copolymer, crosslinked product of carboxymethylcellulose, crosslinked product of polyvinyl alcohol, saponification product of acrylic acid-vinyl acetate, crosslinked product of polyacrylate, saponification product of polyacrylonitrilic polymer, and crosslinked product of polyethylene glycol diacrylate.

6. The preparation according to claim 5, wherein the amount of the highly absorptive high molecular weight compound in the pharmaceutical composition is in the range of 0.05 to 7.0 w/w%.

7. The preparation according to claim 1, wherein the steroid in the pharmaceutical composition is contained in an amount of 0.01 to 1 w/w%.

Patentansprüche

1. Externes adhäsives pharmazeutisches Präparat, dadurch gekennzeichnet, daß es eine pharmazeutische Zusammensetzung, die eine wirksame Menge eines Steroids im Gemisch mit einer adhäsiven Gel-Basis, die als wesentliche Komponenten 0,1 bis 30 % Gew./Gew. einer wasserlöslichen Verbindung mit hohem Molekulargewicht, ausgewählt aus Gelatine, Alginsäure, Carboxymethylcellulose, Methylcellulose, Polyvinylalkohol und Polyacrylsäure, 10 bis 70 % Gew./Gew. Wasser, und 5 bis 60 % Gew./Gew. eines wasserrückhaltenden Mittels, ausgewählt aus Glycerin, Sorbit und 1,3-Butandiol, enthält, umfaßt, und einen weichen Träger, auf dem die pharmazeutische Zusammensetzung ausgebreitet ist, enthält.

2. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß die Menge der wasserlöslichen Verbindung mit hohem Molekulargewicht in der pharmazeutischen Zusammensetzung im Bereich von 0,5 bis 15 % Gew./Gew. liegt.

3. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß die Menge an Wasser in der pharmazeutischen Zusammensetzung im Bereich von 20 bis 50 % Gew./Gew. liegt.

Example 16

Except that 0.25 part of prednisolone and 0.15 part of erythorbic acid, the procedure of Example 13 is repeated to give an external adhesive preparation containing prednisolone.

Example 17

Except that 0.04 part of fluocinolone acetonide, 0.05 part of disodium edetate and 0.1 part of BHT, the procedure of Example 13 is repeated to give an external adhesive preparation containing fluocinolone acetonide.

Example 18

Except that 0.1 part of triamcinolone acetonide, 0.05 part of disodium edetate and 0.1 part of sodium metabisulfite, the procedure of Example 13 is repeated to give an external adhesive preparation containing triamcinolone acetonide.

Claims

1. An external adhesive pharmaceutical preparation characterized by comprising a pharmaceutical composition which comprises an effective amount of a steroid in admixture with an adhesive gel base comprising as essential components 0.1 to 30 w/w% of a water-soluble high molecular weight compound selected from gelatin, alginic acid, carboxymethyl cellulose, methyl cellulose, polyvinyl alcohol and polyacrylic acid, 10 to 70 w/w% of water, and 5 to 60 w/w% of a water-retaining agent selected from glycerol, sorbitol and 1,3-butanediol, and a soft support on which the pharmaceutical composition is spreaded.

2. The preparation according to claim 1, wherein the amount of the water-soluble high molecular weight compound in the pharmaceutical composition is in the range of 0.5 to 15 w/w%.

3. The preparation according to claim 1, wherein the amount of water in the pharmaceutical composition is in the range of 20 to 50 w/w%.

4. The preparation according to claim 1, wherein the amount of the water-retaining agent in the pharmaceutical composition is in the range of 10 to 50 w/w%.

5. The preparation according to claim 1, wherein the water-retaining agent in the pharmaceutical composition is in a combination with 0.01 to 10.0 w/w% of a highly absorptive high molecular weight compound selected from starch-acrylonitrile graft copolymer, starch-acrylic acid graft copolymer, starch-styrene-sulfonic acid graft copolymer, starch-vinylsulfonic acid graft copolymer, cellulose-acrylonitrile graft copolymer, cellulose-styrenesulfonic acid graft copolymer, crosslinked product of carboxymethylcellulose, crosslinked product of polyvinyl alcohol, saponification product of acrylic acid-vinyl acetate, crosslinked product of polyacrylate, saponification product of polyacrylonitrilic polymer, and crosslinked product of polyethylene glycol diacrylate.

6. The preparation according to claim 5, wherein the amount of the highly absorptive high molecular weight compound in the pharmaceutical composition is in the range of 0.05 to 7.0 w/w%.

7. The preparation according to claim 1, wherein the steroid in the pharmaceutical composition is contained in an amount of 0.01 to 1 w/w%.

Patentansprüche

1. Externes adhäsives pharmazeutisches Präparat, dadurch **gekennzeichnet**, daß es eine pharmazeutische Zusammensetzung, die eine wirksame Menge eines Steroids im Gemisch mit einer adhäsiven Gel-Basis, die als wesentliche Komponenten 0,1 bis 30 % Gew./Gew. einer wasserlöslichen Verbindung mit hohem Molekulargewicht, ausgewählt aus Gelatine, Alginsäure, Carboxymethylcellulose, Methylcellulose, Polyvinylalkohol und Polyacrylsäure, 10 bis 70 % Gew./Gew. Wasser, und 5 bis 60 % Gew./Gew. eines wasserrückhaltenden Mittels, ausgewählt aus Glycerin, Sorbit und 1,3-Butandiol, enthält, umfaßt, und einen weichen Träger, auf dem die pharmazeutische Zusammensetzung ausgebreitet ist, enthält.

2. Präparat nach Anspruch 1, dadurch **gekennzeichnet**, daß die Menge der wasserlöslichen Verbindung mit hohem Molekulargewicht in der pharmazeutischen Zusammensetzung im Bereich von 0,5 bis 15 % Gew./Gew. liegt.

3. Präparat nach Anspruch 1, dadurch **gekennzeichnet**, daß die Menge an Wasser in der pharmazeutischen Zusammensetzung im Bereich von 20 bis 50 % Gew./Gew. liegt.

4. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß die Menge des wasserrückhaltenden Mittels in der pharmazeutischen Zusammensetzung im Bereich von 10 bis 50 % Gew./Gew. liegt.

5. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß das wasserrückhaltende Mittel in der pharmazeutischen Zusammensetzung in einer Kombination mit 0,01 bis 10,0 % Gew./Gew. einer hoch absorptiven Verbindung mit hohem Molekulargewicht, ausgewählt aus Stärke-Acrylonitril-Pfropfcopolymer, Stärke-Acrylsäure-Pfropfcopolymer, Stärke-Styrol-Sulfonsäure-Pfropfcopolymer, Stärke-Vinylsulfonsäure-Pfropfcopolymer, Cellulose-Acrylonitril-Pfropfcopolymer, Cellulose-Styrolsulfonsäure-Pfropfcopolymer, quervernetztes Produkt aus Carboxymethylcellulose, quervernetztes Produkt aus Polyvinylalkohol, Verseifungsprodukt von Acrylsäure-Vinylacetat, quervernetztes Produkt von Polyacrylat, Verseifungsprodukt von Polyacrylonitril-Polymerem, und quervernetztes Produkt aus Polyethylenglykoldiacrylat, vorliegt.

6. Präparat nach Anspruch 5, dadurch gekennzeichnet, daß die Menge der hoch absorptiven Verbindung mit hohem Molekulargewicht in der pharmazeutischen Zusammensetzung im Bereich von 0,05 bis 7,0 % Gew./Gew. liegt.

7. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß das Steroid in der pharmazeutischen Zusammensetzung in einer Menge von 0,01 bis 1 % Gew./Gew. enthalten ist.

Revendications

1. Préparation pharmaceutique adhésive externe caractérisée en ce qu'elle comprend une composition pharmaceutique qui comprend une quantité efficace d'un stéroïde en mélange avec une base de gel adhésif comprenant comme composants essentiels 0,1 à 30 % en poids/poids d'un composé hydrosoluble de poids moléculaire élevé choisi parmi la gélatine, l'acide alginique, la carboxyméthylcellulose, la méthylcellulose, l'alcool polyvinylique et l'acide polyacrylique, 10 à 70 % en poids/poids d'eau, et 5 à 60 % en poids/poids d'un agent de rétention d'eau choisi parmi le glycérol, le sorbitol et le 1,3-butanediol, et un support mou sur lequel la composition pharmaceutique est étalée.

2. Préparation selon la revendication 1, dans laquelle la quantité de composé hydrosoluble de poids moléculaire élevé dans la composition pharmaceutique est dans une gamme de 0,5 à 15 % en poids/poids.

3. Préparation selon la revendication 1, dans laquelle la quantité d'eau dans la composition pharmaceutique est dans la gamme de 20 à 50 % en poids/poids.

4. Préparation selon la revendication 1, dans laquelle la quantité d'agent de rétention d'eau dans la composition pharmaceutique est dans la gamme de 10 à 50 % en poids/poids.

5. Préparation selon la revendication 1, dans laquelle l'agent de rétention d'eau dans la composition pharmaceutique est en combinaison avec 0,01 à 10,0 % en poids/poids d'un composé de poids moléculaire élevé très absorbant choisi parmi les copolymères greffés amidon-acrylonitrile, les copolymères greffés amidon-acide acrylique, les copolymères greffés amidon-acide styrènesulfonique, les copolymères greffés amidon-acide vinylsulfonique, les copolymères greffés cellulose-acrylonitrile, les copolymères greffés cellulose-acide styrènesulfonique, les produits réticulés de la carboxyméthylcellulose, les produits réticulés de l'alcool polyvinylique, les produits de saponification d'acide acrylique-acétate de vinyle, les produits réticulés de polyacrylate, les produits de saponification des polymères d'acrylonitrile, et les produits réticulés de poly(diacrylate d'éthylèneglycol).

6. Préparation selon la revendication 5, dans laquelle la quantité de composé de poids moléculaire élevé très absorbant dans la composition pharmaceutique est dans la gamme de 0,05 à 7,0 % en poids/poids.

7. Préparation selon la revendication 1, dans laquelle le stéroïde dans la composition pharmaceutique est contenu en une quantité de 0,01 à 1 % en poids/poids.