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(54) **ESTERS DE LA VITAMINE E POUR APPLICATION LOCALE**

(54) **ESTERS OF VITAMIN E AS PRODUCTS FOR TOPICAL APPLICATION**

(57) Il est possible d'utiliser en tant que tels des esters de la vitamine E, en particulier l'acétate de la vitamine E (ou acétate de d,1-alpha-tocophérol), comme produit cosmétique pour application locale, ayant sur la peau un effet hydratant et un effet de barrière, et comme ingrédient unique pour la production d'un médicament destiné au traitement local des états pathologiques de la peau, tels que le xérosis cutané grave ou le xérosis cutané avec rhagades, la dermite de contact, la dermatite irritative, la chéilite, la kératose pilaire, la kératodermie, les chéloïdes, l'ichtyose et les états ichtyosiformes, la dermatite péri-buccale, la dermatite palmoplantaire juvénile, la dermatite prurigineuse, l'eczéma atopique, la dermatite séborrhéique, l'acné, les démangeaisons, le psoriasis, les piqûres d'insectes, la dystrophie vulvaire, la vestibulite, l'eczéma du conduit auditif, l'eczéma des paupières, la dermatite des paupières liée à une conjonctivite mousseuse, le lichen simplex, la dysidrose, le pityriasis rosé, les cicatrices, l'atrophie cutanée, l'érythème actinique, l'érythème dû aux rayonnements, les érosions cutanées, les brûlures, l'herpès simplex et le prurit cutané, ainsi que pour le traitement des ulcères cutanés, des escarres de décubitus, de la proctite, des hémorroïdes et des rhagades anales, des rhagades du sein, de l'anus humide et de la rhinite atrophique.

(57) Esters of vitamin E, particularly vitamin E acetate (or d,1-alpha-tocopherol acetate) are used as such as a cosmetic product for topical application with a moisturizing effect and a barrier affect on the skin, and as the sole ingredient in the production of a medicament for the topic treatment of pathological skin conditions such as serious skin xerosis or skin xerosis with rhagades, contact dermatitis, irritative dermatitis, cheilitis, pilar keratosis, keratodermy, keloids, ichthyosis and ichthyosiform conditions, perioral dermatitis, juvenile palmoplantar dermatitis, itchy dermatitis, atopic dermatitis, seborrhoeic dermatitis, acne, itchiness, psoriasis, insect stings or bites, vulvar dystrophy, vestibulitis, eczema of the auditory canal, eczema of the eyelid, dermatitis of the eyelid due to foaming conjunctivitis, lichen simplex, dyshidrosis, pityriasis rosea, scars, skin atrophy, actinic erythema, radiation erythema, skin erosions, burns, herpes simplex and skin itchiness, as well as for the treatment of skin ulcers, bed sores, proctitis, haemorrhoids and anal rhagades, breast rhagades, moist anus and atrophic rhinitis.

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(54) Title: ESTERS OF VITAMIN E AS PRODUCTS FOR TOPICAL APPLICATION

(57) Abstract

Esters of vitamin E, particularly vitamin E acetate (or d,l-alpha-tocopherol acetate) are used as such as a cosmetic product for topical application with a moisturizing effect and a barrier affect on the skin, and as the sole ingredient in the production of a medicament for the topic treatment of pathological skin conditions such as serious skin xerosis or skin xerosis with rhagades, contact dermatitis, irritative dermatitis, cheilitis, pilar keratosis, keratodermy, keloids, ichthyosis and ichthyosiform conditions, perioral dermatitis, juvenile palmoplantar dermatitis, itchy dermatitis, atopic dermatitis, seborrhoeic dermatitis, acne, itchiness, psoriasis, insect stings or bites, vulvar dystrophy, vestibulitis, eczema of the auditory canal, eczema of the eyelid, dermatitis of the eyelid due to foaming conjunctivitis, lichen simplex, dyshidrosis, pityriasis rosea, scars, skin atrophy, actinic erythema, radiation erythema, skin erosions, burns, herpes simplex and skin itchiness, as well as for the treatment of skin ulcers, bed sores, proctitis, haemorrhoids and anal rhagades, breast rhagades, moist anus and atrophic rhinitis.

"Esters of vitamin E as products for topical application"

DESCRIPTION

In general, the present invention relates to the use of esters of d,l-alpha-tocopherol, referred to below as vitamin E, with carboxylic acids and, in particular, of vitamin E acetate, in cosmetic and therapeutic skin treatment.

In particular, the present invention relates to the topical application of the aforesaid esters to the skin for cosmetic and therapeutic purposes.

Vitamin E and its derivatives are substances which, by virtue of their presumed properties as antioxidants and removers of free radicals, are widely used in the cosmetics industry in the preparation of formulations for combatting or preventing unsightly skin conditions.

For these reasons, vitamin E and its derivatives are often present in cosmetic formulations, in concentrations variable from 0.5 to 10%, as "active" components with antioxidant and anti-ageing effects.

In fact, the antioxidant and anti-ageing effect of vitamin E at skin level has never been scientifically demonstrated.

Compositions for topical use containing up to 20% by weight (preferably up to 10%) of vitamin E in combination with other active ingredients, emulsifiers and excipients are described in application EP-A-0 158 090. In this application, it is maintained that the aforesaid compositions are useful in the treatment of eczema, skin inflammation and irritation, skin allergies, skin pigmentation, etc., although experimental support is supplied solely for the application of ointments containing 8% of non-esterified vitamin E for the prevention of erythema due to exposure to the sun or to radiation.

The present invention was arrived at in the first place by investigation of the cosmetic properties of the esters of vitamin E when applied topically in the absence of other active ingredients or excipients, particularly those of vitamin E acetate, which is a clear, yellow, viscous liquid, which is insoluble in water, resistant to oxidation by air, by light and by UV rays, and thermally stable.

The human skin behaves as a double barrier, preventing the entry of substances from the outside atmosphere and regulating the passage of water and electrolytes towards the exterior. This barrier function is performed mainly by the cornified layer of the epidermis by means of the corneocyte component which is rich in fibrous proteins (keratin, filagrin, loricrin) and the intercorneocyte lipid component (cholesterol, free fatty acids and ceramides) synthesized by the cells of the granular layer.

At the level of the cornified layer, the ceramides, together with the cholesterol and its esters and the free fatty acids, fill the intercellular space and form a continuous fatty film, defining a barrier to the entry of foreign hydrophilic substances.

Damage to the epidermal barrier function opens the way through the epidermis for electrolytes and chemical substances.

This damage may occur either as a result of the use of toxic or aggressive substances or, more simply, because of too frequent washing due to incorrect habits or to frequent sports or recreational activities.

The consequences of this skin damage may consist of irritative dermatitis or even skin infections.

There is therefore a need to provide a barrier product which offers the skin good protection from attack by irritants and is well-tolerated and easily applied, given that it may be used repeatedly during the day.

An effective barrier product is important in occupational medicine for preventing work-related dermatitis, in the dermatological field for preventing conditions caused by damage to the barrier function (particularly due to irritative or allergy causes), and in the paediatric field, in which skin protection is required basically because the structure of the barrier function is incomplete and the skin is more easily damaged.

To satisfy the aforementioned requirement, the prior art has provided formulations for topical use which can form a kind of barrier on the skin against attack by external agents and can keep the skin moisturized.

These topical formulations are essentially of two basic types: hydrophobic ointments and barrier creams.

A hydrophobic ointment is a single-phase system normally constituted by a semi-solid matrix (Vaseline, paraffin, silicones with high molecular weights), by a liquid consistency regulator (Vaseline oil, vegetable oils, liquid silicones, synthetic esters) and by a stabilizer (beeswax or its synthetic substitutes).

These ointments are used because of their properties of blocking or inhibiting the normal evaporation of water from the skin, causing increased skin moisturization.

However, the aforesaid ointments have the serious disadvantage of leaving the skin greasy and of feeling to the user like a foreign substance generating a need for cleansing.

Moreover, the mineral oils contained in hydrophobic ointments are hydrocarbons derived from petroleum and, although subjected to purification processes, still contain contaminants, particularly polycyclic aromatic hydrocarbons, which are considered responsible for some contact dermatitis and have carcinogenic effects.

Finally, hydrophobic ointments have poor thermal stability.

A barrier cream is an emulsion comprising a lipophilic

phase, generally constituted by 20-30% of Vaseline or paraffin and 60-70% of an aqueous phase, with the addition of stabilizers (surfactants, preservatives) and moisturizers.

These creams are more pleasant to apply than hydrophobic ointments because they are characterized by less greasiness, but are also less effective.

Their barrier effect and their moisturizing effect are in fact due essentially to the lipophilic phase they contain, since the aqueous phase evaporates from the skin almost immediately and the moisturizing components they contain do not have proven effectiveness.

The latter components may be hygroscopic substances such as glycerine, sorbitol, polyethylene glycols and polypropylene glycols, but the effectiveness of these substances is doubtful since they do not modify the water-retention capacity of the cornified layer because they are molecules foreign to the protein and lipid molecules of this layer which have the physiological function of binding water.

Other moisturizing components are constituted by substances which interact chemically with the keratin of the cornified layer, such as urea and the alpha-hydroxy acids; however, these substances, particularly if used in high concentrations, may show keratolytic effects, possibly inducing erythema and/or subjective boring pain sensations.

Finally, substances such as collagen, the glycosaminoglycanes and elastin have been proposed as moisturizing agents and effectively perform a water-retention function in the human skin but, on the skin, can at most perform a humectant function. Some of these substances, particularly if they are of animal origin, like collagen, may contain contaminants and are potentially allergenic.

In conclusion, there is currently no formulation with a

barrier and moisturizing effect which is simultaneously effective, pleasant to apply and safe from the toxicological and allergy points of view.

The problem on which the present invention is based is that of providing a new preparation for topical application with a barrier effect and with moisturizing activity which does not have the disadvantages shown by the preparations of the prior art.

This problem is solved, according to the invention, by the use, for topical application, of an ester of vitamin E with a carboxylic acid of formula R-COOH, in which R is an alkyl, alkenyl or alkynyl radical having from 1 to 19 carbon atoms.

The ester is preferably vitamin E acetate or linoleate. The use of vitamin E acetate is particularly preferred. The term vitamin E is intended to mean both alpha-tocopherol in racemic form (d, l) and the individual enantiomers and mixtures thereof.

It has been found experimentally that vitamin E acetate applied to the skin as such without the addition of any stabilizers, consistency regulators, preservatives, etc., (this product will be referred to below as "pure vitamin E acetate") achieves a barrier effect and a moisturizing effect equal to if not better than those achieved by hydrophobic ointments, without having the disadvantages of the latter.

Pure vitamin E acetate is in fact particularly easy to spread, is absorbed surprisingly quickly, produces no unpleasant thermal sensations, leaves the skin shiny only for a few minutes and then leaves it soft, elastic and not sticky, and resists cleansing with water or detergents.

By virtue of these properties, it is also possible to envisage the use of pure vitamin E acetate as an after-sun product and as a topical product after recreational or sports activities which may compromise the integrity

of the cornified layer of the epidermis.
Moreover, since vitamin E acetate is not a molecule foreign to the human organism, it can easily integrate with the lipids present in the cornified layer.
To evaluate the absorption of pure vitamin E acetate, subjective tests were carried out in 20 individuals aged from 25 to 60 years.
The pure vitamin E acetate was pleasant to apply owing to absence of odour, a soft feel of the skin, absence of greasiness, absence of a feeling that a foreign substance had been applied and consequently absence of a need for cleansing, lack of side effects during absorption (no burning of the skin, no boring pain sensation, even with irritated skin).
The application of pure vitamin E acetate, which is very easy per se, can be further facilitated and rendered as uniform as possible by spray dispensers.
In this case, the vitamin E acetate is dissolved in volatile diluents which evaporate instantaneously or within a few seconds after the application of the spray, leaving a film solely of vitamin E acetate on the skin.
Preferably, spray dispensing systems which do not use organic volatile or gaseous compounds as propellants are used, such as, for example, the EP SPRAY SYSTEM® from the Swiss firm EP SPRAY SYSTEM S.A., which uses compressed air.
Two minutes after the application of the pure vitamin E acetate, the skin had no residual greasiness.
The moisturizing effect of the pure vitamin E acetate was evaluated experimentally by corneometry.
Pure vitamin E acetate was applied topically twice a day to 10 healthy subjects aged between 25 and 45 years in two different regions on the skin, of which one was exposed (the back of the left hand) and one was not exposed (the right forearm).
Four measurements were made in each region every hour for

12 hours, for five consecutive days.

From the data obtained it was possible to establish a clear improvement in skin moisturization and, in particular, persistence of the moisturization for at least 12 hours.

Tolerance to pure vitamin E acetate was also tested by patch tests carried out on 20 healthy subjects aged between 25 and 45 years, of whom 2 had positive anamnesis owing to atopy.

None of the subjects examined showed positive reaction to the patch tests.

A comparative test was then carried out to evaluate the moisturizing effect of pure vitamin E acetate in comparison with Vaseline oil and with a commercial cream base, that is, the product IDIBASE®.

The moisturizing effect was evaluated by skin corneometry.

5 female subjects were tested and were asked to apply the vitamin E acetate to the back of the left hand and to the central surface of the left forearm every 12 hours with slight massage.

Vaseline oil was applied in the corresponding regions on the right-hand side and in the same manner. The cream base IDIBASE® was applied to one forearm in a different region.

The subjects were tested for a period of three days; they washed their hands frequently with aggressive soaps, according to their occupation, whereas the forearm was washed only every 24 hours.

The determinations were carried out by means of corneometers, that is, by a special capacitance meter which measures the variations in the capacitance of the skin induced by a greater or lesser water content of the more superficial layers of the epidermis, by means of a skin probe.

Each day a basal measurement (T_o) was made followed by

measurements 3 minutes, 4 hours and 10 hours after application.

The average of the measurements gave the results summarized in Table 1 below.

TABLE 1

(average of corneometric values)

Vitamin E acetate				Vaseline oil				IDIBASE®	
left hand		left forearm		right hand		right forearm		left forearm	
T_o	55	T_o	55	T_o	56	T_o	55	T_o	66
3m	49	3m	39	3m	47	3m	58	3m	69
5h	59	5h	58	5h	57	5h	40	5h	56
10h	61	10h	60	10h	56	10h	57	10h	65

It can be inferred from an analysis of the values given in Table 1 that pure vitamin E acetate brought about a considerable increase in skin moisturization, whereas the products used for comparison did not modify it substantially.

Essentially similar results were obtained by the topical application of vitamin E linoleate.

Finally, the persistence of the pure vitamin E acetate on the skin was measured in order to have an indication of its protective effect.

The same subjects who were subjected to corneometry were also subjected to a sebometric test carried out by means of a sebometer, that is, a device which can determine by a photometric method how much cutaneous fat is deposited on a semitransparent tape with which the device is provided.

The tape is applied to the preselected region for a standard time (30 seconds) with a constant pressure.

The more cutaneous fat is deposited on the tape the more transparent it becomes and the higher will be the values detected by the sebometer.

This type of test is normally used to evaluate the amount of sebum present on the skin; in the case of the present invention it was used to evaluate the persistence of the oily substance applied to the skin, even after the skin had been washed many times.

The results obtained are summarised in Table 2.

TABLE 2

(average of the sebometric values)

Vitamin E acetate				Vaseline oil				IDIBASE®	
left hand		left forearm		right hand		right forearm		left forearm	
T_o	10	T_o	6	T_o	10	T_o	13	T_o	5
3m	340	3m	330	3m	308	3m	304	3m	220
5h	30	5h	60	5h	50	5h	29	5h	7
10h	20	10h	44	10h	22	10h	10	10h	2

The data in Table 2 show a prolonged persistence of the pure vitamin E acetate on the skin even after repeated washing of the hands. It is perceived by the sebometer as a high presence of skin "greasiness" but this greasiness is not in fact perceived by the subject as a troublesome condition, although it represents a valuable protective film.

Substantially similar results were achieved by the topical application of vitamin E linoleate.

It was also surprisingly found that pure vitamin E acetate can also be used as a substance for treating pathological skin conditions in which its moisturizing and protective effect can be of benefit and may help to alleviate symptoms.

Examples of these pathological conditions are: serious skin xerosis or skin xerosis with rhagades, contact dermatitis, irritative dermatitis, cheilitis, pilar keratosis, keratodermy, keloids, ichthyosis and

ichthyosiform conditions, perioral dermatitis, juvenile dermatitis of the sole of the foot, itchy dermatitis, atopic dermatitis, seborrhoeic dermatitis, acne, psoriasis, insect stings or bites, vulvar dystrophy, vestibulitis, eczema of the auditory canal, eczema of the eyelid, dermatitis of the eyelid due to foaming conjunctivitis, lichen simplex, dyshidrosis, pityriasis rosea, scars, skin atrophy, actinic erythema, radiation erythema, skin erosions, burns and herpes simplex.

Xerosis

Particularly significant results were obtained in skin xerosis (or dryness). Xerosis is a condition suffered by the cornified layer of the epidermis and is manifested by finely exfoliating skin with cracked patches which are dry to the touch and itchy, and is due to a reduction in the water content below the minimum limit of 20%.

Xerotic skin can be caused either by lack of water or by lack of interlamellary lipids. It is usually alteration of the lipid component, for example, by detergents, which induces lack of water in the cornified layer; structural alteration of the corneocyte proteins having the function of binding water, caused, for example, by chemical substances, may induce the same phenomenon.

A defect in the synthesis of the keratinizing proteins or of the interlamellary lipids as occurs in psoriasis, in ichthyosis and as a result of exogenous conditions, may lead to dehydration of the cornified layer.

In children and in the elderly there is a particular predisposition to dry skin owing to a reduced availability of interlamellary lipids.

The production of lipids by the keratinocytes is also subject to genetic, environmental, hormonal (puberty, menopause), vascular and nervous influences.

Chronic exposure to various chemical agents (amongst which are glues, acids, paints, and resins) and

atmospheric agents (wind, sun, cold), repeated physical micro-trauma, senility, deficiency states, and some pathological conditions are thus responsible for xerotic conditions which are sometimes extremely resistant.

Skin xerosis may be more or less marked and may be associated with more significant changes (rhagades, dermatitis). The following conditions are distinguished, according to their predominant causes: xerosis of areas exposed to light (owing to prolonged exposure to sun and wind), xerosis and irritation of the face by shaving of the beard (owing to the action of the razer and of shaving products), xerosis of the hands due to occupational causes and housework, xerosis and hyperkeratosis following immobilization in plaster (reduced trophism), xerosis in uraemics and in patients undergoing substitutive dialytic treatment, xerosis of the lower limbs in carriers of angiodermitis, varicose complex, chronic lymphoedema (owing to ischaemia), xerosis in diabetics (owing to anaphoresis and ischaemia), neonatal xerosis, xerosis in children and in the elderly (owing to lesser production of skin lipids), xerosis of the face, trunk and limbs in young people and adults (owing to genetic influences on the production of skin lipids).

In all of these cases the topical application of pure vitamin E acetate was beneficial, improving moisturization and the general appearance of the skin (softer and more resilient) and alleviating the most troublesome symptoms such as itching or burning sensations.

Surprising results were obtained in 15 cases of skin xerosis of the hands with associated rhagades and irritative contact dermatitis due to occupational causes (3 hairdressers, 2 doctors, 1 dental technician, 1 welfare worker, 1 carpenter, 1 shoe-factory worker) or by repeated use of detergents (6 housewives).

In all cases, the skin of the hands was completely normalized with disappearance of the skin rhagades and of the irritative dermatitis after treatment for one or two weeks.

The vitamin E acetate was applied 4-5 times per day, with a quantity of 0.2-0.4ml each time in order to be able to perform an effective barrier action even during working. When healing had been achieved, continued topical application of vitamin E acetate twice per day was advised.

Ten patients were checked again after 2 months. None had skin xerosis of the hands, rhagades or dermatitis although they continued their occupational activities.

In some cases the xerosis and rhagades had already been present for several years and had responded only transitorily to topical corticosteroid treatment.

The effect of vitamin E linoleate was then checked on another 10 patients suffering from skin xerosis of the hands with associated rhagades and irritative contact dermatitis owing to occupational causes or to repeated use of detergents.

The same favourable effects shown by vitamin E acetate were obtained although complete normalization of the skin of the hands with disappearance of the skin rhagades and of the irritative dermatitis was achieved only after treatment for about 3 weeks.

Atopic dermatitis

Very encouraging results were also obtained in the case of atopic dermatitis which represents a frequently-occurring dermatitis and is sometimes difficult to treat. Pure vitamin E acetate was used as an ointment base with a barrier effect, without interruption of any dietetic and/or pharmacological treatments already in progress, in 200 cases of atopic dermatitis (children aged between 2 months and 12 years), and was applied topically once or

twice per day for a period of from 15 days to several months, according to circumstances.

In all cases, the application of vitamin E acetate (0.2-0.4 ml per dm^2) brought about a significant improvement in skin moisturization lasting for many hours (in the case of dry skin in particular, three applications per day were necessary, especially in the first days of treatment).

The effect on any skin rhagades or chapping present in the folds (elbows, ears, wrists, the backs of the knees) was particularly significant with healing thereof in a period varying from two to seven days.

The effect on inflammatory skin seepage was variable from case to case; in the case of the smallest children (between 2 months and 2 years) a certain percentage of them (60-70%) had relief which was evident after treatment for 7-15 days, although the atopic dermatitis became acute again in the two months following the treatment. Children aged between 2 and 12 years, particularly with limited symptoms (in the folds of the elbows, in the recesses behind the knees, behind the ears, around the lips, on the trunk) which were not particularly intense (erythema, pimples, lichenification, rhagades, abrasions from scratching) but were present chronically, all had a clear improvement and, for 50-60% the skin symptoms disappeared completely in 7-15 days; moreover, with continued application of vitamin E acetate (twice per day) for several months the skin symptoms of atopic dermatitis failed to reappear.

This leads to the conclusion that the repeated application of vitamin E acetate over time in children aged over two years with symptoms which are not very intense can interfere positively with the natural history of atopic dermatitis.

In a significant percentage of cases (60-70%) there was a marked reduction or even disappearance of the itching

associated with the symptoms of atopic dermatitis.
The attenuation of itching is an effect of considerable importance since itching makes children with atopic dermatitis irritable, sometimes causing crying crises, disturbing the daily activity of the child and family interactions as well as night-time sleep with alteration of the sleeping-waking rhythm.
It is important to stress that none of the patients treated showed allergy to tocopherol acetate, in spite of the presence of skin lesions, prolonged topical use, and often positive familiarity owing to atrophy.
Moreover, since pure vitamin E acetate is a food product, its application to subjects of paediatric age is absolutely safe, even should they ingest it by bringing the part treated to their mouths.

Perioral dermatitis

Another condition typical of the paediatric age in which the topical application of vitamin E acetate may be used effectively is perioral dermatitis.
Vitamin E acetate was applied to 10 children aged between 4 months and 6 years, suffering from perioral dermatitis as a result of irritation caused by the prolonged use of a dummy or by prolonged contact with food residues, particularly during weaning.
The regular application of vitamin E acetate (0.2ml), 3-4 times per day in the case of the use of a dummy or half an hour before meals in the case of irritation by contact with foods, achieved a marked attenuation or even complete resolution of the perioral dermatitis in 7 days of treatment.

Dyshidrosis

A positive effect of vitamin E acetate has also been found in dyshidrosis. Pure vitamin E acetate was used in 4 patients aged between 25 and 50 years suffering from

dyshidrosis of the hands and feet. These patients had dyshidrosis symptoms in the same period each year (spring-summer) with a duration of from one month to a few months (up to the autumn). The regular application of vitamin E acetate (twice per day 0.2-0.4 per dm^2) brought about disappearance of the dyshidrosis symptoms in 15 days.

Once healing had been achieved, in cases in which the dyshidrosis symptoms lasted for several months in previous years, the use of vitamin E acetate was continued for several months and there was no reappearance of the dyshidrosis.

Insect stings or bites

The effect shown by vitamin E acetate applied to insect bites is particularly surprising.

The application of vitamin E acetate in 100 cases of mosquito bites both in adults and in children caused the itching to disappear within about 30-60 seconds after application; the itching did not reappear and the pimple reaction to mosquito bites did not develop.

In 8 cases out of 10 of wasp stings the pain disappeared within about 30-60 seconds after the sting and the local erythema-hardening reaction was resolved in about 1-2 hours.

The erythema-hardening reaction caused by intramuscular injection treatment was also inhibited or at least attenuated by the topical application of vitamin E acetate.

Psoriasis

Pure vitamin E acetate was also tested in the treatment of psoriasis in 5 adult patients (aged 40-60 years) and in 5 paediatric patients (aged 10-14 years).

Pure vitamin E acetate was applied twice a day for one month, in an amount of 0.2-0.4 ml per dm^2.

After treatment for 7 days, a marked decrease in exfoliation which disappeared in certain cases, as well as a marked decrease in skin erythema were noted.
The reduction in the erythema was documented by dermospectrophotometer.
After treatment for one month, the decrease in erythema and exfoliation persisted but no modification of the dermic dilated tortuous capillaries which are pathognomonic of psoriasis was noted.
Vitamin E acetate was also used in two cases of psoriasis of the scalp, characterized by multiple intensely exfoliating and itchy patches. The vitamin E acetate was applied directly to the patches (0.1-0.2 ml twice per day), obtaining in 7 days the disappearance of the itching and the normalization of the dyskerathosis, with the presence of less erythematous and non-exfoliating patches.
The effect on the skin exfoliation was particularly evident in 5 cases of marked chronical psoriasis at hands (which was present during the whole year, without remission, with associated onychopathy): in all cases a marked reduction, up to disappearance, of skin exfoliation (which is the most annoying aspect for the patient, from an aesthetical point of view) was obtained in 7 days of treatment, with the persistence of only erythematous and less pronounced patches.

Acne

Another dermatological complaint in which vitamin E acetate has been used advantageously is acne.
Pure vitamin E acetate was used in 50 patients (30 female and 20 male) aged between 10 and 40 years, suffering from slight acne of the face. The manifestations of acne were constituted mainly by blackheads with or without slight inflammation of the pilosebaceous units. The blackheads were mainly open. The vitamin E acetate was applied

twice per day in small quantities (0.2-0.4 ml) so as to achieve complete absorption in about 1-2 minutes without the use of any other product for topical application and with the skin of the face being washed daily with normal commercially-available soap.

In all of the patients, an improvement in the acne was observed with a marked reduction or disappearance of the blackheads within 4-7 days and a reduction in the phlogosis in the inflamed blackheads. The skin was cleaner and less greasy both upon objective examination and according to the patients' subjective perception.

Vitamin E acetate therefore seems to have a sebo-regulatory effect which, up to now, has never been described and which is of considerable benefit in the case of slight acne. In addition, vitamin E acetate also displays an inhibiting activity on the proliferation of the bacteria (in particular Propionibacterium acnes) which are present on the face skin and which are involved in the pathogenesis of acne.

Seborrhoeic dermatitis

The aforementioned sebo-regulatory effect is probably also responsible for the beneficial effects found in 10 cases of infantile seborrhoeic dermatitis in the first months of life in clinical areas varying from cradle cap limited to the scalp to seborrhoeic dermatitis extending over the whole face. In the cases treated, the skin affected was normalized within a week.

Pityriasis rosea

Pure vitamin E acetate was used for one month (0.2-0.4 ml per dm^2 3-4 times per day) in 5 patients with extremely itchy pityriasis rosea (persistent itching, particularly at night, in spite of antihistamines taken per os and the application of various emollient creams). In all of the patients, the use of vitamin E acetate caused

disappearance or marked attenuation of the itching for several hours and was the only treatment which gave appreciable benefit for this symptom.

Skin atrophy

A favourable effect of vitamin E acetate applied topically has also been found in skin atrophy.

Vitamin E acetate was applied (0.2 ml) twice per day for two months to 5 patients suffering from skin atrophy on the face. The skin affected was extremely delicate and bled easily at the slightest trauma. The use of vitamin E acetate had a clear protective effect with improvement in skin trophism and consequent better resistance to trauma and less easy bleeding.

Herpes simplex

A complaint in which the topical application of vitamin E acetate has achieved surprising results is herpes simplex.

Vitamin E acetate was used for topical application by 100 patients affected by herpes simplex of the lips (herpes labialis) (aged between 3 and 45 years).

In 95 cases out of 100 a marked clinical improvement was achieved by the application of vitamin E acetate at least three times per day with quantities of 0.2-0.4ml each time.

When the vitamin E acetate was applied at the first sign of the complaint (itching, paraesthesia, or a burning sensation localized on the lip, initial blister) the blisters failed to appear (if initially absent) or developed to the scabby stage in 1 day (if initially present) with a clear acceleration of healing (which normally takes place in 8-10 days).

When the vitamin E acetate was applied to already apparent herpetic conditions (multiple blisters present for 1-2 days) the appearance of further blisters and the

increase in the size of the lesions was stopped with accelerated development to the scabby stage (1 or 2 days).

Moreover, immediately after application, the subjective symptoms of a burning sensation and/or itching associated with the herpes symptoms disappeared.

In only 2 cases, the application of vitamin E acetate did not modify the normal course of the herpes symptoms and did not lead to attenuation of the subjective symptoms associated therewith.

In 3 cases lack of clinical response to the application of vitamin E acetate appeared to be connected with insufficiently frequent application since an increase in the number of applications within a day (up to 6 times per day) brought about an acceleration in healing.

Keratodermy

The topical application of vitamin E acetate also showed beneficial effects in keratodermy. Vitamin E acetate was applied to 10 patients suffering from keratodermy of the sole of the foot twice per day for one month (0.2-0.4ml per dm^2). In all cases a progressive reduction in hyperkeratosis was achieved with a reduction and regularization of the thickness of the cornified layer of the epidermis or even normalization thereof within the period of one month.

This surprising effect suggests a normalizing effect of vitamin E acetate on the altered keratinization process; the average turnover of the epidermis cells (that is, the average time necessary for the cells of the basal layer to reach the cornified layer) is in fact 28 days, which corresponds to the time necessary for the vitamin E acetate to normalize the epidermis in cases of keratodermy.

Keloids

Vitamin E acetate was also used in the treatment of patients suffering from keloids. Ten patients of ages varying from 3 to 40 years suffering from keloids which had arisen recently (one month at the maximum) on surgical wounds or on 2nd-3rd degree burns were treated by the topical application of vitamin E acetate (0.1-0.4 ml per application).

The keloids were erythematous and intensely itchy and projected up to 2 centimetres from the surrounding skin. From the first occasion, the application of vitamin E acetate brought about disappearance or marked attenuation of the itching in all cases; in some cases a marked decrease in erythema and clear flattening of the keloid relative to the surrounding skin was already noted after the first week of treatment.

Skin ulcers

The effect of vitamin E acetate applied topically in 30 patients suffering from ulcers of vascular origin (arterial, venous or capillary owing to arteriopathy, phlebopathy or vasculitis) which were on the lower limbs and were of a chronic nature, having been present for more than two months, and which were resistant to known treatments, was also checked.

In 15 cases, the vitamin E was applied for 15 days (1-2 ml once per day) to the skin around the ulcer and to the edges thereof which were undermined, seeping and moist. In all cases a marked clinical improvement was already achieved in the first days; the edges of the ulcer became clean, neither secerning nor seeping and no longer undermined but flat and the skin around the ulcer (particularly in venous ulcers) previously affected by dermitis and hypodermitis in all cases became of normal eutrophic appearance.

In 15 cases, vitamin E acetate was applied directly to

the skin ulcers (1-2 ml once per day). In half of the cases an acceleration of the healing of the ulcers was achieved and in the rest of the cases no clear improvement was observed. In one case, a capillary ulcer (due to immunologically-based vasculitis) which is usually very difficult to heal, was healed in 15 days. In all of the treated cases a significant antiseptic activity of vitamin E acetate was remarked.

Bed sores

The application of vitamin E acetate also achieved beneficial effects in bed sores.

Vitamin E acetate was applied to 10 adult or elderly patients suffering from bed sores of limited size (3-4 cm) in the sacral region. The application took place 3-4 times per day and in any case after each cleaning or washing of the area. In all cases re-epithelialization was achieved in 7-15 days.

Anal rhagades

The positive effect achieved by the topical application of pure vitamin E acetate is particularly noteworthy in the case of anal rhagades which represent a pathology which is difficult to treat and which, in the current state of knowledge, does not benefit from any medical treatment.

Patients suffering from single anal rhagades with or without inflammation of the mucous membrane of the edges or of the haemorrhoidal plexus were treated with pure vitamin E acetate applied topically.

Two applications (0.2-0.4 ml at a time) per day were carried out for one or two months.

In all of the patients, healing of the subjective symptoms relating to the rhagades and objective disappearance of the lesion were achieved.

Complete healing was confirmed upon programmed checking

three months after the suspension of the treatment with pure vitamin E acetate.

Haemorrhoids

Patients suffering from symptomatic haemorrhoids (heavy feeling and irritation, itching, pain and bleeding) were also treated with pure vitamin E acetate with two applications (0.2-0.4 ml at a time) per day for 15 days. In all of the patients, the beneficial effect on the symptoms was immediate with disappearance or marked attenuation thereof from the very first application and cessation of bleeding after treatment for a few days. A significant reduction (about 50%) in the size of the haemorrhoids was also observed.

The treatment, which continued for several months in all of the patients, maintained the reduction in the volume of the haemorrhoids by 2° to 3° (prolapsed) without reappearance of bleeding of the haemorrhoids and almost complete control of the symptoms was achieved.

Moist anus

Positive effects connected with the topical application of vitamin E acetate were also found in the pathological condition known as moist anus.

Moist anus is a pathological condition characterized by a secerning, inflamed anus with associated cracking of the skin-mucous membrane and intense pain (such as to interfere with regular night-time sleep) which may arise after haemorrhoidectomy or owing to reduced tonicity of the anal sphincter or allergic diathesis thereof.

Vitamin E acetate was used (0.2-0.4 ml 3 times per day) in 3 patients (aged 30-45 years) suffering from moist anus. In all cases disappearance of the cracking and of the inflammation was achieved after treatment for one month and the beneficial effect on the symptoms (pain, burning sensation) was immediate from the very first day

of treatment.

Aspecific proctitis

Pure vitamin E acetate was used for one month (2 applications per day, each of 0.2-0.4 ml) in 20 patients with aspecific symptomatic proctitis present for a period varying from a few days to a few years. The symptoms were characterized by itching, irritation, a heavy feeling in the anus and sometimes slight bleeding upon defecation associated with exacerbation of the symptoms. The use of vitamin E acetate brought about a rapid benefit in all cases (from the very first application) with marked attenuation of the symptoms and of the proctitis (70%) or even complete disappearance thereof with clinical healing of the proctitis in a certain percentage of cases (30%).

In 30% of cases in which healing was achieved, the treatment with vitamin E acetate was suspended after the initial month with no reappearance of the symptoms or proctitis in subsequent months.

In the remaining 70% of cases, the clinical and symptomatological benefit was maintained only by continuation of the treatment with vitamin E acetate beyond the initial month with cessation of the benefit upon suspension of the treatment.

Superficial skin erosions

Another skin complaint in which the application of vitamin E acetate has shown a favourable effect is constituted by superficial skin erosions.

Superficial skin erosions may occur in various situations, and have, as a common denominator, the presence of individual or repeated physical micro-trauma (rubbing, pressure, removal of patches or adhesive pouches) or chemical micro-trauma (contact with irritants). For example, children may have superficial

skin erosions in the perigenital area due to the application of sterile disposable nappies, or in the perianal area due to irritation by acid faeces.
Vitamin E acetate was used (0.2-0.4 ml per dm^2 twice a day) in 50 patients suffering from superficial skin erosions which were predominantly perianal. In all cases an immediate beneficial effect on the symptoms (burning sensation, pain) was noticed and re-epithelialization took place on average in 48 hours.

Vulvar dystrophy and vestibulitis

Patients suffering from vulvar dystrophy and vestibulitis also benefitted from the application of vitamin E acetate.
Vitamin E acetate was applied for one month (0.2-0.4 ml 3 times per day) at the vulvar level by 10 women suffering from vulvar dystrophy. In 6 patients the itching disappeared from the very first applications and the vulvar skin was normalized after treatment for 3 weeks. In another two patients the vulvar skin was normalized in 3 weeks but persistence of the itching was reported. In the remaining 2 patients both the itching and the skin changes persisted.
Vitamin E acetate was also used (0.2-0.4 ml 3 times per day) in 20 patients suffering from aspecific vulvitis or vestibulitis. In all cases the symptoms (itching, burning sensation, pain) disappeared from the very first application and in 7 days the inflammation was resolved in the vulva and in the vestibule.

Eczema of the auditory canal

Another complaint characterized by intense itching is eczema of the auditory canal.
In this case, the application of vitamin E acetate (0.2 ml twice a day) in 10 patients suffering from eczema of the auditory canal with intense associated itching also

led to the disappearance of the itching from the very first applications and to normalization of the skin of the canal in 7 days of treatment.

Eczema of the eyelid

Vitamin E acetate was used (0.2 ml applied twice a day) in 10 patients suffering from eczema of the eyelid of various origins. From the very first applications there was a marked attenuation of the associated symptoms (itching, pain, irritation) and a significant reduction or even disappearance of the eczema in 7-10 days.

Dermatitis of the eyelid from foaming conjunctivitis

Foaming conjunctivitis is always associated with irritative dermatitis of the eyelid owing to the dense and foamy conjunctival secretions with associated rhagades of the outer edge of the eyelid. Vitamin E acetate was used (2-3 times per day, 0.2 ml per application) in 10 patients with dermatitis of the eyelid caused by foaming conjunctivitis for 10 days. In all cases an effective and protective barrier effect with a marked reduction or even disappearance of the changes in the eyelid skin associated with conjunctivitis was noted.

Lichen simplex

Vitamin E acetate was used (0.2-0.4 ml per dm^2) twice a day for one month in 5 patients with lichen simplex localized on the lower limbs. In all of the patients a marked reduction in hyperkeratosis and erythema was achieved. A marked attenuation or even disappearance of the itching was also achieved for several hours after the application of the vitamin E acetate from the very first application.

Breast rhagades

The effect of vitamin E acetate applied topically in

cases of breast rhagades was particularly surprising. Breast rhagades appear during breast feeding and constitute the main cause for giving up breast feeding. Vitamin E acetate was applied to the nipple (0.2 ml twice a day) starting from the last days of pregnancy in 100 pregnant women. After the birth, the vitamin E acetate was applied to the nipples 15 minutes before each breast feeding of the infant, throughout the first month of breast feeding. In no case was the appearance of breast rhagades observed.

The vitamin E acetate was also used (15 minutes before the baby was put to the breast and after feeding, with a quantity of 0.2 ml each time) in 30 puerperal women with breast rhagades appearing in the first days of breast feeding. In all cases the healing of the rhagades (with disappearance of bleeding and pain) was noted in a minimum period of 2 days and a maximum of 7 days.

Burns

A beneficial effect of vitamin E acetate at skin level was also found in cases of first degree burns characterized by skin erythema, burning sensation and pain.

Vitamin E acetate was applied (0.2-0.4 ml per dm^2 twice a day) to first degree burns resulting from accidental contact with hot liquids or pots in 20 female patients. The burns had a maximum area of one square decimeter and were localized on the upper limbs.

In all cases the application of vitamin E acetate brought about immediate disappearance of the symptoms (burning sensation, pain) and the disappearance of the skin erythema in 24 hours.

Actinic erythema

Vitamin E acetate was used for topical application (0.2-0.4 per dm^2 twice a day) by 20 patients with actinic

erythema (due to exposure to the sun) on the face or on the shoulders. In all cases the symptoms (burning sensation, itching) disappeared immediately and the erythema disappeared in 24 hours.

Radiation erythema

Another type of erythema in which the use of vitamin E acetate was effective is radiation erythema which is a reaction to certain electromagnetic radiation and which often occurs as a result of radiotherapy treatments.

Vitamin E acetate was applied topically (0.2-0.4 ml per dm^2) in 10 women with actinic erythema resulting from radiotherapy for metastatic breast cancer. In all cases there was disappearance or marked attenuation of the symptoms associated with the radiation erythema (burning sensation, pain, itching).

The anti-itching effect constantly exhibited by pure vitamin E, regardless of the cause of the itching, is clear from the clinical trials reported above relating to its use in a number of skin conditions.

The anti-itching effect of vitamin E acetate seems very distinct with disappearance of the symptoms for several hours or even without returning in insect bites, particularly mosquito bites.

The anti-itching effect is also marked in herpes simplex and in local reactions to intramuscular treatment. In these situations, vitamin E also seems clearly to interfere in a positive sense with normal clinical development.

In cases of more significant, non-self-limiting, chronic skin conditions of variable seriousness (e.g. atopic dermatitis, pityriasis rosea, lichen simplex) the effect on the itching seems even more significant, but for a shorter time (a few hours at most).

The effect on itching is also shown markedly at the level of the skin-mucous membrane (anus-anal canal, vaginal

vestibule).

Scars

An intense effect on the itching symptom was also shown in the case of scars.

Vitamin E acetate was used (0.2-0.4 ml) twice a day for a period varying from 7 to 30 days in 20 patients with surgical scars, starting from the seventh day after the surgical operation. Its use was suggested by the protective barrier and anti-itching effect of vitamin E acetate.

All of the patients benefitted from the treatment and in no case did the formation of keloids occur.

Vitamin E acetate was also used (0.2-0.4 ml) twice a day in 10 patients with old, itchy surgical scars. In all patients the application of vitamin E acetate stopped the itching from the very first applications and the treatment was therefore suspended 2-4 days after it started.

Atrophic rhinitis

Finally, a beneficial effect was found in connection with the application of vitamin E acetate to the nasal mucous membrane in 5 cases of atrophic rhinitis.

Atrophic rhinitis is associated with a particular dryness of the nasal mucous membrane which is extremely irritating for the patient and may lead to ulceration of the mucous membrane.

Vitamin E acetate was applied (0.2-0.4 ml twice a day) for one month to the nasal mucous membrane of 5 patients suffering from atrophic rhinitis with disappearance of the nasal dryness from the very first applications. It can probably be assumed that continuous use of vitamin E acetate would prevent the ulceration which occurs with the development of the disease.

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CLAIMS

1. Use of vitamin E acetate as ~~such as~~ the sole ingredient of an ointment for the topical cosmetic treatment of the human skin.

2. A method for the cosmetic treatment of human skin consisting of the topical application of a cosmetically effective quantity of vitamin E acetate, free of any other substance.

3. A method according to Claim 2, characterized in that the application is carried out at least twice a day.

4. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of the following pathological skin conditions: serious skin xerosis or skin xerosis with rhagades, contact dermatitis, irritative dermatitis, cheilitis, pilar keratosis, keratodermy, ichthyosis and ichthyosiform conditions, perioral dermatitis, juvenile palmoplantar dermatitis, itchy dermatitis, atopic dermatitis, vulvar dystrophy, vestibulitis, lichen simplex, dyshidrosis, skin atrophy, skin erosions, insect bites, radiation erythema from radiotherapy treatment.

5. Use according to claim 4, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of said pathological skin conditions.

6. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of proctitis, anal rhagades, moist anus.

7. Use according to claim 6, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of proctitis, anal rhagades, moist anus.

8. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of herpes simplex.

9. Use according to claim 8, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of herpes simplex.

10. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of skin ulcers and bed sores.

11. Use according to claim 10, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of skin ulcers and bed sores.

12. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of atrophic rhinitis.

13. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of skin itchiness.

14. Use according to claim 13, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of skin

medicament may be used for the topical treatment of skin itchiness.

15. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the prevention and topical treatment of breast rhagades.

16. Use according to claim 15, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the prevention and topical treatment of breast rhagades.

17. Use of vitamin E acetate as the sole ingredient in the manufacture of a medicament for the topical treatment of haemorrhoids.

18. Use according to claim 17, wherein the medicament is in a package together with a notice indicating that the medicament may be used for the topical treatment of haemorrhoids.

19. A method of treating pathological human skin conditions consisting of the topical application of a therapeutically effective quantity of vitamin E acetate free of any other substance.

20. A method according to Claim 26, characterized in that the application is carried out at least twice a day with quantities variable from 0.1 to 0.4 ml per dm^2 of skin.

21. A method according to claim 2, wherein the topical application is carried out by spray dispensers.

22. Use according to any one of claims ~~4, 6, 8~~ 4 to 18, wherein the medicament is applied by spray dispensers.