Title: COMPOSITION CONTAINING OMEGA 3 AND/OR OMEGA 6 POLYUNSATURATED ACIDS HAVING FROM 12 to 22 CARBON ATOMS

Abstract

The present invention relates to a carrier medium which exhibits therapeutic properties and enhances the transmembranal transport of a medicament. The carrier medium comprises as essential ingredients: 1. one or more physiologically acceptable polyunsaturated acids of the omega-3 and/or omega-6 series containing from 12 to 22 carbon atoms, or a physiologically acceptable derivative or precursor thereof; and at least two ingredients selected from 2. one or more vitamins selected from the series A, B, C, D, or E, or a physiologically acceptable derivative or precursor thereof; 3. one or more physiologically acceptable natural and/or synthetic materials which form a matrix within which the other ingredients of the carrier medium are dispersed; and 4. one or more materials having skin moisturising properties. The invention also provides a method for making such a carrier medium and methods for the treatment of radiation and other burns or damage to the skin using the carrier medium alone or in combination with a medicament.
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COMPOSITION

Composition containing omega 3 and/or omega 6 polyunsaturated acids having from 12 to 22 carbon atoms

BACKGROUND TO THE INVENTION:

Conventional creams or ointments are traditionally designed to deliver an active component only to the epidermal surface of the skin or, at best, to provide limited delivery through the surface skin layers. Most formulations rely on an intimate dispersion or solution of the active component in a suitable oily medium or a water/oil or oil/water emulsion. Thus, a medicament is presented to the epidermal surface in a form likely to penetrate at most only into the outer stratum corneum of the epidermis.

This is considered satisfactory for the treatment of skin conditions where surface involvement is the only consideration, e.g. for infective conditions where repair processes can occur within the skin layers when the surface insult has been removed by a topical treatment.

For deeper/underlying disease states or where it is desired to use the skin as a route for the delivery of medicaments to the systemic circulation, different formulation concepts or the use of penetration enhancers are required to assist transport of the medicament across the barrier of the skin (see for example "Percutaneous Absorption" Eds R.L. Bronaugh & H.I. Maibach, Marcel Dekker N.Y.) for a discussion of these precepts. Thus, for example, it has been proposed in European Patent Application No 0261428 A1 to use a fatty compound in combination with a non-fatty hydroxyl compound as penetration enhancers for a variety of medicaments to be applied topically. The fatty compound is stated to be any
of the essential fatty acids which occur naturally in the form of their glyceride esters in fats and oils. Specific examples of fatty compounds for use as penetration enhancers are oleic or linoleic acids or C₁₃₃ alkyl esters thereof. The acknowledgement of prior art in this application also refers to a number of other types of carrier media which act as penetration enhancers.

It has also been proposed in PCT Application No US92/10673 to use certain specified vegetable oils as penetration enhancers for the topical application of a wide range of medicaments. However, none of the vegetable oils disclosed contain linoleic or linolenic acids or their esters.

In our PCT Application No GB92/01950 we have described an improved hydrogel carrier composition which is based upon the use of certain polyalkylene glycols or ether glycols, a long chain alcohol, an essential oil and a material having skin moisturising properties. That carrier was claimed to exhibit improved transdermal penetration properties and could thus find use in the transdermal application of a wide range of medicaments. However, that carrier composition required the use in combination of a number of ingredients, with resultant complexity and cost in manufacture.

For the treatment of underlying malignant states or of advanced states of malignancy where metastatic or primary disease involves the skin layers or skin surface, radiotherapy is considered to be a useful palliative and, in some cases, beneficial treatment regime.

However, administration of an ionising radiation dose sufficient to halt the growth of or to kill malignant cells within the body also damages normal cell division in the radiation beam paths, despite advances in radiation techniques designed to exploit radio-sensitivity differences between the two types of cell. Damage of normal tissue
cells can lead to highly morbid conditions for the patient and, in some cases, lead to failure to complete worthwhile radiation treatment regimes.

Conventional treatment of, or attempted prevention of, normal tissue damage caused by ionising radiation is currently confined to the application of bland moisturising creams designed only to minimise infection to the damaged site or to prevent itching and subsequent scratching by the patient. Such treatment can at best only offer symptomatic relief and a barrier to assist prevention of secondary infection into the irradiated site.

It has been proposed in European Patent Application No 0416855 A2 to treat or prevent radiation damage to the skin by the topical application of a composition which contains linoleic acid, gamma-linolenic acid and/or dihomo-gamma-linolenic acid to the damaged skin or to the area of the patient to be irradiated. The composition can contain from 0.1 to 20% by weight of the active acid components, optionally in the form of a glyceride ester thereof. The glyceride esters are merely used as a convenient form by which the free acid moieties can be presented to the metabolic chain of the patient.

The active components in EP 0416855 are applied as such or in a conventional cream, oil, gel or lotion carrier medium, which as stated above deliver an active ingredient only to the epidermal surface of the skin. Thus, the proposal in EP 0416855 would present the active components in a form likely to penetrate at most only into the outer stratum corneum of the epidermis.

Surprisingly, we have now found that the glyceride esters of unsaturated acids of the omega-3 and omega-6 series, notably those of linoleic and/or gamma-linolenic acids, are remarkably effective in the transdermal transport of a wide
range of medicaments when used as a carrier medium in combination with at least two other ingredients selected from Vitamins of the A to E series, gel matrix forming materials and skin moisturisers. Furthermore, we have also found that such carrier media alone or in combination with other medicaments are remarkably effective in the treatment of skin damage, notably radiation or burn damage.

SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a carrier medium suitable for the transmembranal application of a medicament to a mammal or for topical application to the actual or intended locus of damage to the skin of the mammal, for example by ionising radiation treatment, which carrier medium comprises as essential ingredients:

1. one or more physiologically acceptable polyunsaturated acids of the omega-3 and/or omega-6 series containing from 12 to 22 carbon atoms, or a physiologically acceptable derivative or precursor thereof; and

at least two ingredients selected from

2. one or more vitamins selected from the series A, B, C, D, or E, or a physiologically acceptable derivative or precursor thereof;

3. one or more physiologically acceptable natural and/or synthetic materials which form a matrix within which the other ingredients of the carrier medium are dispersed, notably natural or synthetic waxes, greases, polyalkylene ether glycols or alkylene glycols or fatty acid esters thereof and/or fatty acid esters of long chain alcohols or glycols; and

4. one or more materials having skin moisturising properties.

The invention further provides a method for enhancing the transmembranal administration of a dermatologically and/or
pharmaceutically active component to a mammal, which method comprises applying the active component in a carrier medium of the invention to a locus on the mammal.

The invention further provides a method for the manufacture of a transmembranally administerable dermatological and/or pharmaceutical composition containing an active component, which method comprises the incorporation of the active component in a carrier medium of the invention.

The composition can contain a wide range of dermatologically and/or pharmaceutically active components and these can be present in a wide range of amounts. In view of the enhanced penetration of the active component achieved by the carrier medium of the invention, the invention offers the ability to apply medicaments transdermally in effective amounts and also to use lower concentrations, for example from 0.1 to 2%, of the medicament, which is of advantage where large areas of the skin are to be treated. However, where localised application of the medicament is required, for example in the treatment of a small skin cancer, higher proportions, for example from 5 to 10% by weight, of the active component may be used if desired and acceptable.

Preferably, the carrier medium provides more than 50% by weight of the total composition. However, the combination of the essential ingredients of the carrier medium possesses surprisingly great dermatological and skin repair properties in its own right and it may therefore not be necessary to incorporate an additional active medicament in the carrier medium to achieve useful therapeutic results. In such cases, the carrier medium can provide up to 100% of the overall composition.

The essential ingredients 1 for use in the carrier medium of the invention are conveniently those obtained from a marine and/or vegetable seed oil which contain gamma-3 and/or
gamma-6 forms of eicosapentaenoic acids, notably those containing linoleic and/or linolenic glyceride esters or mixed esters. It is preferred that ingredient 1 contain a glyceride ester of linoleic and/or linolenic acid containing at least two acid moieties, preferably a mixed ester of linoleic and gamma-linolenic acids. A particularly preferred ester for present use is the di-linoleoyl-mono-

10 gamma-linoleyl ester of glycerol (DGLA). Preferably, ingredient 1 used in the present invention contains at least 15% by weight of the DGLA, and levels of 25% or more of DGLA in ingredient 1 can readily be achieved when a synthetic product is used.

Suitable materials containing ingredients 1 for present use can be obtained by the pressing or other extraction of fish or vegetable seeds to provide an oil which can be used in its commercially available form or can be purified or treated further to extract the desirable ingredient 1. Suitable fish oils include purified oils derived from fish livers or from fatty fish, for example tuna, herring, mackerel, cod and commercially available blends thereof. Suitable vegetable seed oils are those natural oils extracted, for example by pressing and subsequent purification, from evening primrose seeds (Oenothera sp), borage seeds (Borago sp), blackcurrants, oil rape seeds and brassica seeds. Such materials may be used in their commercially available forms and purity and mixtures of the fish and vegetable seed oil may be used. Alternatively, ingredients 1 esters may be synthetic materials prepared using the appropriate conventional starting materials and techniques.

A particularly preferred ester for present use is the mixture of the linoleoyl and gamma-linoleyl acid esters in oil of evening primrose, which may be used in its commercially available form and purity. For convenience, the invention will be described hereinafter in terms of the
use of oil of evening primrose (OEP).

The carrier medium preferably contains from 20 to 95%, preferably 2.5 to 50%, notably 5 to 25%, by weight of ingredient 1. Typically, ingredient 1 will provide from 3 to 23% by weight of DGLA in the carrier medium.

The Vitamin essential ingredients 2 for use in the carrier medium of the invention are selected from those in the series Vitamins A, B, C, D and E and their salts, esters and precursors thereof, notably D-pantothenol as a precursor for Vitamin B5 and carotenoids as precursors for Vitamin A. Preferred Vitamins for present use are Vitamins A, B5 and E.

The Vitamins will often be available in mixed stereoisomeric forms and these may be used if desired. However, it is preferred to isolate specific isomers to enhance the desired activity of the Vitamin. Thus, in the case of Vitamin A, it is preferred to use an all trans form of the Vitamin and its carotenoid precursors or derivatives; in the case of Vitamin E, it is preferred to use the DL-alpha form of the Vitamin.

The Vitamins or their precursors or derivatives for present use can be obtained from natural sources or may be synthetic or semi-synthetic and are commercially available. As stated above, it may be desired to isolate specific stereoscopic isomers from a commercially available mixture of isomers in order to enhance the desired activity of the Vitamin. Such isolation and transformation into a desired isomer form may be achieved using conventional techniques.

The Vitamins, when present, provide a total weight of vitamins in the carrier medium of from 0.1 to 20%, typically 1 to 5%, by weight of the carrier medium. It is also preferred to provide the individual Vitamins in the carrier medium in amounts of from 1 to 5% by weight of Vitamin E or Vitamin E acetate, 0.1 to 5% by weight of Vitamin A and from
1 to 5% by weight of D-pantothenol or Vitamin B5.

Ingredients 3 are natural or synthetic animal or vegetable type materials which have film forming and occlusive properties so as to form a matrix within which the other materials of the carrier medium are dispersed. Such materials include waxes or greases, preferably those in which at least part of the ester groupings present have been saponified, either before incorporation into the carrier media of the invention and/or during the adjustment of the pH of the carrier media at described below. Thus, the waxes or greases can be used in the form of a partial alkali metal, alkaline earth metal salt or salt of a strong physiologically acceptable organic base thereof. Typical suitable materials are lanolin, bees wax, carnauba wax, Japan waxes, candelilla wax and hydrocarbon resins or waxes, for example Emulsifying wax BP or USP NF wax, polawax or synchrowaxes.

The polyalkylene ether glycols or alkylene glycols may also be used to provide ingredient 3 and typically have a molecular weight in the range 100 to 600,000, preferably 200 to 6000. We have found that such ether glycols and glycols provide the carrier with occlusive properties as well as providing matrix forming and solvent and transdermal properties. Their inclusion in the carrier medium is especially preferred when the carrier medium is to be used to administer a medicament over a prolonged period where drying out of the skin could occur. The ether glycols and glycols also provide a stable viscous gel consistency to the composition. Where the ether glycol or glycol has a short chain, for example 2 to 5 carbon atoms, the ether glycol or glycol may also serve as a solvent or co-solvent for other components of the carrier medium.

The polyalkylene-ether-glycol for use as ingredient 3 are preferably those of the empirical formula HO-(C₆H₄O)n-OH,
where \( n \) has an average value of from 2 to 6 and \( m \) has an average value of from 2 to 30 or more, in which the alkylene groups can be straight or branched chain, saturated or unsaturated, and in which the hydroxyl groups can be primary, secondary and/or tertiary. Ingredient 3 may also be a physiologically acceptable alkylene-glycol, notably one of the empirical formula HO-(C₆H₄O)₉-OH, where \( q \) has a value of from 2 to 6 and \( g \) has an average value of from 1 to 30, in which the alkylene groups can be straight or branched, saturated or unsaturated, and the hydroxyl groups can be primary, secondary and/or tertiary; or mixtures of such polyalkylene ether glycols and/or alkylene glycols.

Ingredient 3 may also be provided by a fatty acid ester of the above glycols or ether glycols, notably esters with saturated or unsaturated acids containing from 12 to 24 carbon atoms, for example stearic, myristic or palmitic acids or the esters of such acids with long chains alcohols, notably straight or branched chain alkanols containing from 8 to 18 carbon atoms.

The wax, grease, polyalkylene ether glycols, alkylene glycols and/or fatty acids esters, when present, are typically present in a total amount of from 0.25 to about 30% by weight of the total carrier medium, preferably 1 to 25%, and mixtures of waxes, greases, glycols, ether glycols and esters may be used.

Ingredient 4 is a physiologically acceptable material having skin moisturising properties, i.e. it is a compound or mixture of compounds which maintains or increases the hydration of the stratum corneum of the skin. In some cases this property may be possessed by ingredient 1 and part of ingredient 1 may provide at least part of ingredient 4.

A number of other materials are known to possess this property and specific examples include: urea; lactic, ascorbic or glycollic acids and salts and esters thereof;
cholesterol; liposomes and niosomes; pyrrolidone carboxylic acid and salts thereof; mono- and poly-aminosaccharides; chitins and chemically modified chitins which contain ether and extra alkyl groups; hyaluronic acid; and lower alkyl glycols and glycerol. Mixtures of such skin moisturising agents may be used for ingredient 4, if desired.

The skin moisturising agent ingredient 4, when present, is present in an amount of up to about 10%, for example from 0.1 to 5%, preferably from 0.1 to 2% by weight of the carrier medium.

We have found that the above ingredients of the carrier medium often interact with one another synergistically to enhance the transmembral transport property of the carrier medium. This effect is particularly marked when the carrier medium contains all four of the essential ingredients. Thus, it is preferred that the carrier medium contain from 20 to 95% of ingredient 1; from 0.5 to 20% of ingredient 2; from 0.25 to 30% of ingredient 3; and from 0.1 to 5% of ingredient 4; all percentages being by weight of the active component in each ingredient based on the weight of the carrier medium, the remainder of the carrier medium typically being water or a water based gel or matrix having the other ingredients uniformly distributed throughout it.

The essential ingredients of the carrier medium may provide the sole ingredients of the carrier for an active medicament component which is dissolved, emulsified, dispersed or suspended therein. However, it is preferred that the carrier medium contain other ingredients to assist the performance of the carrier and the active components.

Typical of such other ingredients are:

5. one or more materials having anti-bacterial and/or anti-fungal properties; and
6. a long chain alcohol.
The ingredient 5 can be selected from a wide range of materials which exhibit anti-fungal and/or anti-bacterial properties. Preferably, it is a plant extract and the plant extract also exhibits preservative properties at dosage rates of the ingredient which are physiologically acceptable. That is, the plant extract exhibits physiologically useful effects at a dosage rate similar to the rate at which the other ingredients are applied to the skin in the overall composition. Thus, the amount of the plant extract required to achieve useful effects does not imbalance the overall composition.

Suitable ingredients 5 include essential oils as defined at page 670 of Martindale, The Extra Pharmacopoeia, 28th edition. Such essential oils include those derived from the foliage of plants and trees and are typified as containing terpenoid compounds. These may be hydrocarbon terpenes or oxygen containing compounds, for example terpene alcohols, ketones or oxides. Specific preferred terpene compounds include a-pinene, a-terpinene, limonene, 1,8-cineol, gamma-terpinene, p-cymene, 1-terpinen-4-ol, aromadendrene, a-terpineol, and mixtures thereof. The terpene compounds for present use may be synthetic or naturally occurring, as when a eucalyptus type tree oil is used, notably the oil from Melaleuca alternifolia tree, known as Tea Tree Oil.

Ingredient 5 may also or in addition be a natural vegetable oil, for example a saturated or mono- or polyunsaturated oil as specified in PCT Application No US92/10673, or a synthetic oil.

Ingredient 5 may be used as the naturally occurring mixture of materials containing the active ingredient, or may be used in the form of an isolated and refined extract containing a raised proportion of the active ingredient or as an individual synthetically prepared single compound or mixture of isomers.
Ingredient 5, when present, is typically present in up to 15\%, for example from 0.1 to 10\%, preferably 0.5 to 5\%, notably from 0.5 to 2.5\%, by weight of active ingredient based on the weight of the carrier medium and serves primarily as a penetration assistant and preservative against bacterial contamination of the composition and also to confer skin disinfecting properties on the carrier medium.

The long chain alcohol ingredient 6 is preferably a physiologically acceptable straight chain aliphatic alcohol containing from 9 to 24 carbon atoms, for example a C₉-C₁₄ aliphatic monohydric alcohol, notably a C₉-₁₂ alcohol. Specific examples of alcohols for use as ingredient 6 are lauryl or dodecyl alcohol, which latter may be derived from propylene tetramer. The alcohol serves as a lubricant to aid direct application of the composition to the skin and also assists transdermal penetration of the medicament. The presence of the long chain alcohol is therefore preferred when the composition would otherwise be excessively viscous and is particularly desirable when the polyalkylene ether glycol or alkylene glycol ingredient 3 is also present.

The long chain alcohol ingredient 6, when present, is present in an amount of up to about 30\%, for example from 1 to 25\%, preferably 1 to 10\%, by weight of the carrier medium.

The carrier medium may contain other ingredients normally present in topically applied compositions. Typically these will provide less than 50\%, for example from 0.1 to 35\%, by weight of the total carrier medium. Such other ingredients include for example solvents or co-solvents, such as water, low molecular weight alcohols, eg. ethyl or propyl alcohols or glycols, and liquid silicones, eg. cyclomethicone; hydrocarbon resin thickeners or cellulose derivative gelling agents; and penetration enhancers, such as long chain acids,
esters, glycols or saccharide derivatives. The presence of long chain fatty acids and derivatives, notably esters thereof, is especially preferred since they aid formation of stable gels when all four of the specified essential ingredients are present and may form part of ingredient 3. Particularly preferred fatty acids and esters thereof for present use are those of the empirical formula Alk-OOC-Acid where Alk denotes a straight or branched alkyl group containing from 2 to 18 carbon atoms and Acid denotes a saturated or unsaturated straight or branched chain alkyl group which may carry one or more Alk-OOC- substituents. Typical of such fatty acid esters are C₂ to C₁₈ alkyl esters of oleic acid or oleic acid itself.

Other ingredients which may also be present include, for example, a pH controlling agent such as sodium, potassium, ammonium or an alkaline-earth metal hydroxide, or an organic base of the primary, secondary or tertiary amine type, to give a final pH in the range 4.5 - 9.0 and more preferably 6.5 - 7.5.

The ingredients in the carrier media of the invention may be used in the form of the free active ingredients. However, they may also be used in the form of a physiologically acceptable salt, ester or other derivative, metabolite or precursor thereof. Thus, the ingredients may be present in the form of an alkyl ester, acetate or acyl derivative, an alkali or alkaline earth metal salt or an amine salt or complex thereof. Specifically, ingredient 1 may be present in the form of a salt or ester thereof, notably a mono-, di or triglyceride ester which may contain mixed acid moieties as is the case with the preferred ingredient 1 DGLA.

All weights and percentages of the ingredients are therefore given in terms of the free active ingredient.

It will be appreciated that some ingredients are capable of
providing more than one effect, for example ingredient 1 may provide some moisturising effect and the essential oil ingredient 5 may also provide anti-pruritic effect, in which case the amount of one or more of the other ingredients may be appropriately reduced. Furthermore, the oils containing ingredients 1 and 5 are often obtained from natural materials and will therefore differ in composition and be a mixture of the desired ingredient with other materials. Such mixtures may be used without the need to isolate the specified ingredient and the percentages given above are in terms of the desired active ingredient in such mixtures, where the mixture contains large amounts of physiologically acceptable other components, these may themselves provide beneficial other properties, for example fragrance, to the composition.

Surprisingly, we have found that the essential ingredients of the carrier medium, with or without other pharmaceutically active components, often interact synergistically to achieve a greater than expected effect in preventing or reducing the effects of ionising radiation on normal tissue cells and in repairing other damage to the skin. Notably, we have found that, in laboratory in vivo experiments using areas of irradiated pig skin, the prevention of desquamation and the acceleration of healing of desquamated skin is generally more pronounced with compositions containing one or more ingredients 1, Vitamins and ingredients from at least three of the other groups 3 to 6, than with formulations which omit more than one of the ingredients from groups 1 to 4.

We have also found that the carrier media of the invention are remarkably effective in their own right, notably when containing ingredients 1, 2 and 3, in aiding repair to cuts, abrasions, open wounds or other traumatisations of the skin and in the treatment of other disorders of the skin, such as dermatitis, eczema, psoriasis and a wide range of types of
damage to the dermis and are indicated as potentially effective in the treatment of some skin cancers; and to a lesser extent, the sub-dermal layers of the skins, for example due to viral and other infections or to metastatic disease.

Thus, the invention also provides a method for the treatment of or the prophylaxis of damage to normal tissue cells by ionising, photo- or UV radiation, open wound type trauma to the skin, or of viral and other infections of the skin, which method comprises applying a pharmaceutically effective amount of a carrier medium of the invention to the known or expected site of the damage to the skin of a mammal.

The carrier medium of the invention may be used as such in the repair of skin damage or in the treatment of radiation and other burns. However, the carrier media of the invention find widespread use in the topical application of a wide range of medicaments in the treatment of a wide range of skin and other conditions. As indicated above, the compositions find use in the treatment of skin conditions such as the treatment of wounds, sores, burns, lesions and abrasions of the skin, particularly in the prevention or treatment of burns caused by ionic or UVA or UVB radiation. The carrier media of the invention also find use in the administration of drugs which are to be transported across the skin and act systemically throughout the body of a patient. Since many of the essential oils which can be used as ingredient 5 exhibit preservative as well as antibacterial properties, compositions containing such essential oils may be self preserving and assist the prevention of infection in open wounds or abrasions due to these properties of the essential oil ingredient.

Specific examples of suitable medicaments include radiation protectors, for example thiol compounds such as N-acetylcysteamine, N-acetylcysteine and glutathione;
radiation repair agents, for example methylsulphonyl methane, bisabolol and chamazulene; benzocaine, lidocaine, tetracaine as local anaesthetics; benzydamine, naproxen, ibuprofen, ketoprofen, indomethacin, diclofenac, fenclofenac, piroxicam as anti-inflammatory agents or mild analgesics; allantoin as an enhancer of skin repair regrowth; and tranquillisers and sedatives of the phenothiazine or butyrophenone type.

The invention may also be applied to precursors of the active medicaments, for example an acetate or acyl derivative, an alkali metal salt or an amine salt or complex thereof.

For convenience, the term medicament will be used herein to denote in general terms a active ingredient of a medicament, its analogues and precursors thereof, whether alone or in admixture with one another.

The composition of the invention thus finds widespread use in the treatment of a wide range of conditions for which the medicaments have been indicated, eg. in the application of methotrexate in the treatment of proliferative skin disorders including: psoriasis; primary malignant disease, for example squamous cell carcinoma, basal cell carcinoma, malignant melanoma, Kaposi sarcoma etc.; and secondary deposits in the skin and neoplasms due to or associated with warts, herpes simplex, human papilloma virus etc..

Where a medicament is also present, this will typically be present in from 0.1 to 10% by weight of the total composition.

The carrier media and the compositions of the invention can be prepared using a wide range of techniques, for example by admixing and stirring together the desired amounts of the various ingredients to form a cream, paste or gel. If
desired, the ingredients can be pre-dissolved or suspended in one or more of the other ingredients, for example in a propylene glycol solvent, to aid formation of a stable gel or emulsion. In some cases it may be desirable to subject the carrier medium at some stage during its preparation to high speed shear working, taking care to avoid entrainment of air, notably where a resin thickener or cellulose derivative is used as a gelling agent. Where necessary, the pH of the carrier medium can be adjusted by the addition of a suitable pH regulator after the other ingredients have been incorporated and before the final carrier medium has been achieved.

The carrier media of the invention with or without the presence of a medicament are applied to the affected area of, or the predicted area of radiation or other damage to, the skin of a mammal, for example of horse, pig, cattle or human being, by applying the carrier medium or total composition as a coating over the affected area. Alternatively, where the medicament is one which is to be absorbed through the skin and is to act systemically elsewhere in the body, the composition can be applied at any convenient locus on the skin. This can be achieved by applying the carrier or composition directly in the required amount as a cream, paste or gel to the skin. Alternatively, the carrier or composition can be applied as a spray, foam, mousse or gel from a pressurised dispenser having an appropriate valved spray outlet. The carrier or composition can then be spread over and/or massaged into the skin. The carrier or composition may also be applied to an adhesive plaster, pad, gauze or other backing support member, which is then applied over the treated area.

The coating of the composition on the skin or on the support member can have applied thereto a vapour barrier film, for example a plastic film or a spray on film-forming resin, for example a synthetic skin type composition, which serves to
retain water and other fluids in the composition and the skin. However, where a polyalkylene ether glycol or alkylene glycol ingredient 3 is present in sufficient amounts in the carrier medium, this may impart sufficient occlusive properties for the use of a vapour barrier membrane not to be necessary.

The compositions of the invention also find use where it is desired to apply a medicament across other membranes than the skin. Thus, for example, the compositions can be ingested to apply the active ingredient across the buccal mucosa and other portions of the gastrointestinal tract.

The amount of the composition applied will be sufficient to apply the biologically effective amount of the active ingredient(s) therein to the affected area of the skin or to achieve the desired therapeutic effect or dosage application. This amount will vary according to the treatment required and the content of active ingredient in the composition. The optimal amount required to achieve the desired biological effect can readily be established as is known from a knowledge of these.

DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION:

The invention is illustrated by the following Examples, in which all parts and proportions are given by metric weight and volume units unless stated otherwise.

Example 1
A mixture of stearic acid (9 parts by weight), oil of evening primrose (ingredient 1, 20 parts), pola wax GP 200 (4 parts) and synchrowax BB4 (2 parts) (ingredients 3) was melted together at 70°C with mechanical stirring. Separately, polyethylene glycol 1500 (ingredient 3) was warmed to 70°C and then added to the mixture. A solution of sodium hydroxide (1.12 parts), a polyaminosaccharide
condensate skin moisturising agent (ingredient 4, 1 part by weight) in deionised water (33 parts by volume) was slowly added with stirring. The mixture was slowly cooled to 30°C with high shear mixing without entrainment of air to give a viscous white cream. The cream was mixed with a solution of Tea Tree oil in ethanol (ingredient 5, 1 part oil in 10 parts ethanol) and, as a lubricant to aid preparation of the mixture and application of the composition to the skin, an emollient ester of polypropylene glycol and myristic acid (5 parts by weight, ingredient 3). The mixture was stirred continuously for one hour to give a creamy base and packed into a sealed container until used (Formulation I).

By way of further example, compositions were prepared as in Example 1, but using other active ingredients as follows:

Example 2: as Example 1, but including 5% by weight of Vitamin E acetate.

Example 3: as Example 1, but including 1% by weight methylsulphonylmethane.

Example 4: as Example 2, but including 1% by weight of methylsulphonylmethane.

Example 5: as Example 1 but also containing 0.02% by weight Vitamin A, 5% by weight Vitamin E acetate and 0.5% alphabisabolol.

Example 6: as Example 1 but also containing 3% by weight of benzydamine hydrochloride.

Example 7: as Example 2, but containing 1% by weight of benzydamine hydrochloride.

Female Large White pigs (approx 25 Kg bodyweight) were used and 15 skin sites of approximately 25 mm diameter were
marked out by tattoo using India ink on both flanks of each pig. After a week, each site was irradiated with a single
dose of 35 Gy of beta radiation from a Sr\(^{90}/\gamma^{90}\) plaque at a
dose rate of approximately 3 Gy per minute.

At daily intervals following irradiation, approximately 80mg of each formulation was applied and spread uniformly over
each site. The treatment allocation was randomised to each site and also between two pigs. The treatment with each
formulation was replicated between 6 and 9 times.

The severity of the acute reaction of the skin patches to
the radiation was assessed on a graded score and compared
with untreated sites. Reduction in the severity of
desquamation compared to untreated sites was seen in all
cases and a reduction in the time for healing of moist
desquamation sites was observed in all case. The mean
healing times from 6 to 9 replications for each formulation
being assessed are set out below.

<table>
<thead>
<tr>
<th>Example No</th>
<th>Time to heal desquamation (weeks)</th>
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<tbody>
<tr>
<td>1</td>
<td>2.90</td>
</tr>
<tr>
<td>2</td>
<td>2.90</td>
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<td>3</td>
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<td>2.67</td>
</tr>
<tr>
<td>7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

By way of comparison, untreated sites took 5 weeks or more
to heal.

By way of further comparison, a hydrogel carrier was
prepared as described under Formulation II in Example 1 of
our co-pending PCT Application Number GB92/01950 - Example
8. This hydrogel did not contain any of the Vitamins
(essential ingredient 2 of the carrier medium of the
invention) nor did it contain any oil of evening primrose
(essential ingredient 1). Into samples of this hydrogel were incorporated 5% by weight of Vitamin E acetate (Example 9) and 5% by weight of Vitamin E acetate and 0.5% by weight of alpha-bisabolol (Example 10). A further formulation (Example 11) was prepared using a conventional cream base carrier which contained 20% by weight of oil of evening primrose and other ingredients as in Example 1, but omitted the vitamins and moisturising ingredients 2 and 4 from the formulation.

These comparative compositions were also applied to sites on the skin of the pigs and irradiated as in the above assessments. The results of these further assessments were as follows:

<table>
<thead>
<tr>
<th>Example No</th>
<th>Time to heal desquamation (weeks)</th>
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<tbody>
<tr>
<td>8</td>
<td>4.3</td>
</tr>
<tr>
<td>9</td>
<td>4.8</td>
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<tr>
<td>10</td>
<td>4.3</td>
</tr>
<tr>
<td>11</td>
<td>3.7</td>
</tr>
</tbody>
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These results demonstrate the increase in time to heal resulting from omitting one or more of the essential ingredients from the carrier composition of the invention and the marked improvement in healing achieved by the carrier medium of the invention over a conventional cream or hydrogel carriers.

Furthermore, some delay in the onset of desquamation was also noted in all formulations containing the essential ingredients of the carrier media of the invention, but not in formulations which omitted the essential ingredients, notably the oil of evening primrose.
CLAIMS:

1. A carrier medium suitable for the transmembranal application of a medicament to a mammal or for topical application to the actual or intended locus of damage to the skin of the mammal, which carrier medium comprises as essential ingredients:
   1. one or more physiologically acceptable polyunsaturated acids of the omega-3 and/or omega-6 series containing from 12 to 22 carbon atoms, or a physiologically acceptable derivative or precursor thereof; and
   at least two ingredients selected from
   2. one or more vitamins selected from the series A, B, C, D, or E, or a physiologically acceptable derivative or precursor thereof;
   3. one or more physiologically acceptable natural and/or synthetic materials which form a matrix within which the other ingredients of the carrier medium are dispersed; and
   4. one or more materials having skin moisturising properties.

2. A carrier medium as claimed in claim 1, characterised in that ingredient 1 is a glyceride ester of linoleic and/or linolenic acids.

3. A carrier medium as claimed in claim 2, characterised in that ingredient 1 is the di-linoleoyl-mono-gamma-linoleyl ester of glycerol.

4. A carrier medium as claimed in any one of the preceding claims, characterised in that ingredient 2 is selected from Vitamins A, B5, E and precursors thereof.

5. A carrier medium as claimed in any one of the preceding claims, characterised in that ingredient 3 is a natural
and/or synthetic wax, grease, polyalkylene ether glycol or alkylene glycols or a fatty acid ester of such glycols, and/or a fatty acid ester of a long chain alcohol or glycol.

6. A carrier medium as claimed in claim 5, characterised in that the wax or grease is selected from lanolin, bees wax, carnauba wax, Japan waxes, candelila wax and hydrocarbon resins or waxes.

7. A carrier medium as claimed in claim 6, characterised in that at least part of the ester groupings in the wax or grease have been saponified.

8. A carrier medium as claimed in claim 5, characterised in that ingredient 3 is a physiologically acceptable polyalkylene-ether-glycol of the empirical formula HO- \((C_{n}H_{2n}O)_{m}\)-OH, where \(n\) has an average value of from 2 to 6 and \(m\) has an average value of from 2 to 30 or more, in which the alkylene groups can be straight or branched chain, saturated or unsaturated, and in which the hydroxyl groups can be primary, secondary and/or tertiary; or a physiologically acceptable alkylene-glycol of the empirical formula HO- \((C_{p}H_{2p})_{q}\)-OH, where \(p\) has a value of from 2 to 6 and \(q\) has an average value of from 1 to 30, in which the alkylene groups can be straight or branched, saturated or unsaturated, and the hydroxyl groups can be primary, secondary and/or tertiary; or mixtures of such polyalkylene ether glycols and/or alkylene glycols.

9. A carrier as claimed in claim 8, characterised in that ingredient 3 comprises a fatty acid ester of the polyalkylene ether glycol and/or the alkylene glycol.

10. A carrier medium as claimed in any one of the preceding claims, characterised in that ingredient 4 is selected from urea; lactic, ascorbic or glycollic acids and salts and esters thereof; cholesterol; liposomes and niosones;
pyrrolidone carboxylic acid and salts thereof; mono- and poly-aminosaccharides; chitins and chemically modified chitins which contain ether and extra alkyl groups; hyaluronic acid; and lower alkyl glycols and glycerol.

11. A carrier medium as claimed in any one of the preceding claims, characterised in that it contains ingredients 1 and 2 and one selected from ingredients 3 and 4.

12. A carrier medium as claimed in any one of claims 1 to 11, characterised in that it contains all four of ingredients 1 to 4.

13. A carrier as claimed in either of claims 11 or 12, characterised in that ingredient 1 provides at least part of the requirement for ingredient 4.

14. A carrier as claimed in any one of the preceding claims, characterised in that the carrier medium contains from 20 to 95% of ingredient 1; from 0.5 to 20% of ingredient 2; from 0.25 to 30% of ingredient 3; and from 0.1 to 5% of ingredient 4; all percentages being by weight of the active component in each ingredient based on the weight of the carrier medium, the remainder of the carrier medium being water or a water based gel or matrix having the other ingredients uniformly distributed throughout it.

15. A carrier medium as claimed in any one of the preceding claims, characterised in that it also contains as ingredient 5 one or more materials having anti-bacterial and/or anti-fungal properties.

16. A carrier medium as claimed in claim 15, characterised in that the material is an essential oil.

17. A carrier medium as claimed in any one of the preceding claims, characterised in that it also contains as ingredient
6 a physiologically acceptable straight chain aliphatic alcohol containing from 9 to 24 carbon atoms.

18. A carrier medium as claimed in any one of the preceding claims, characterised in that it also comprises a dermatologically and/or pharmaceutically active component.

19. A carrier as claimed in claim 18, characterised in that the active component is present in from 0.1 to 10% by weight of the total composition.

20. A carrier medium as claimed in claim 1, substantially as illustrated in any one of Examples 1 to 7.

21. A method for making a carrier medium as claimed in any one of the preceding claims, characterised in that the ingredients are mixed together.

22. A method for the manufacture of a transmembranally administerable dermatological and/or pharmaceutical composition containing an active component, which method comprises the incorporation of the active component in a carrier medium as claimed in any one of claims 1 to 17.

23. A method as claimed in either of claims 21 or 22, characterised in that the mixture of at least some of the ingredients is subjected to high speed shear working.

24. A method for enhancing the transmembranal administration of a dermatologically and/or pharmaceutically active component to a mammal, which method comprises applying the active component in a carrier medium as claimed in any one of claims 1 to 17.

25. A method for the treatment of or the prophylaxis of damage to normal tissue cells by ionising, photo- or UV radiation, open wound type trauma to the skin, or of viral
and other infections of the skin, which method comprises applying a pharmaceutically effective amount of a carrier medium as claimed in any one of claims 1 to 17 to the known or expected site of the damage to the skin of a mammal.

26. A method as claimed in claim 25, characterised in that the carrier medium also contains a pharmaceutically and/or dermatologically active component.

27. A method as claimed in claim 26, characterised in that the active component is present in from 0.1 to 10% by weight of the overall composition.

28. A method as claimed in any one of claims 25 to 27, characterised in that the carrier medium is applied to the actual or expected site of a radiation burn to the skin of a mammal.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>DATABASE WPI&lt;br&gt;Week 9114, Derwent Publications Ltd., London, GB; AN 91-099139 &amp; JP,A,3 044 322 (SHISEIDO KK) 26 February 1991 &lt;br&gt;see abstract</td>
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**Special categories of cited documents:**

- **A** document defining the general state of the art which is not considered to be of particular relevance
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- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other mean
- **P** document published prior to the international filing date but later than the priority date claimed

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**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**A** document member of the same patent family

**Date of the actual completion of the international search**

24 January 1995

**Date of mailing of the international search report**

31.01.95

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tdl. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016

**Authorized officer**

Ventura Amat, A
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