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[54] **THERAPEUTIC COMPOSITIONS FOR TOPICAL APPLICATION**
2 Claims, No Drawings

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ABSTRACT: Therapeutic film-forming compositions suitable for topical application which contain medicaments and which dry when applied to the skin to give a flexible, nontacky adherent, substantially water-vapor impermeable film capable of releasing said medicaments to the underlying skin. The preferred film-forming composition comprises an aqueous emulsion of a polyvinylidene chloride and a medicament such as an anti-inflammatory steroid.

THERAPEUTIC COMPOSITIONS FOR TOPICAL APPLICATION

This invention relates to improvements in therapeutic compositions for topical application. More particularly it relates to novel, occlusive film-forming cream bases and topical spray compositions.

Medicaments may be applied to the surface of the skin in solution or suspended in liquid vehicles, as emulsions in the form of lotions or water-miscible creams, as solutions or suspensions in fatty materials in the form of ointments and as dusting powders. Such formulations are widely used for application of topical medicaments and are generally satisfactory. There are, however, certain topical medicaments which are even more effective in their action on certain skin conditions if the site of application is covered by an occlusive dressing immediately after application of the medicament. Occlusive dressings of this nature are thought to operate because there is no loss of water from the site of the application and the skin is made more permeable to the medicament.

Anti-inflammatory steroids are particularly active when applied under an occlusive dressing in this way. The usual occlusive dressings which have been used hitherto include polyethylene film or Saran film (Trade Name), a commercially available occlusive film, the use of which is described by McKenzie and Stoughton, Arch. Derm. 1962, 86, 608. Although the use of such film is reported to give a hundredfold increase in the absorption of the drug, the dressing is cumbersome and areas of skin are unnecessarily covered by the large film wraps.

We have now developed topical film-forming compositions which may contain medicaments and which rapidly dry when applied to the skin to give nonsensitizing, hard-wearing, flexible, substantially water-vapor impermeable films which release medicaments contained therein to the underlying skin.

Broadly speaking, compositions according to the invention comprise a fluid pharmaceutically acceptable carrier and a polymer that will form, on spreading the composition at a temperature below 35° or 40° C., a flexible nontacky adherent film that is substantially water-vapor impermeable, and a medicament, the polymer being present as an aqueous emulsion.

The viscosity of the compositions may vary from a thick paste to a low viscous liquid that can be sprayed. The more fluid compositions may be dispensed from conventional containers such as plastic deformable bottles and mechanical sprays; preferred formulations are in the form of self-propelled, aerosol sprays using compatible propellants. The compositions are generally applied so as to form a thin film and this film must not only be substantially water-vapor impermeable but it must also be adherent and flexible, that is to say it must not crack away from the skin quickly after application.

Most polymeric materials require the inclusion of a plasticizer in order that their films shall be sufficiently flexible. Some polymers can, however, be used without a plasticizer being included. Such polymers are generally copolymers, some grades of the copolymer formed from ethylene and vinyl chloride being an example. When a plasticizer is included in compositions according to the invention it may either be an internal plasticizer or it may be an external plasticizer. Internally plasticized polymers are copolymers containing a small amount of a copolymerized monomer that plasticizes the remainder of the polymer.

The polymers used in compositions according to the invention are generally hydrophobic, and thus do not contain large numbers of hydrophilic groups, such as acetate groups.

A suitable polymeric film-forming agent is polyethylene, which is commercially available in the form of emulsions or self-emulsifying, spray-dried powder. Many grades of polyvinylidene chloride are also suitable and we have obtained the best results with this polymer when it has been internally plasticized especially with a small proportion of acrylamide. Externally plasticized polyvinylidene chloride can also be

used. Other polymeric film-forming agents suitable for use in the topical formulations include polyvinyl chloride, polystyrene, acrylic acid polymers and butadiene polymers.

Some film-forming polymers will only form films at relatively high temperatures; for example, the polyvinylidene chloride polymer emulsion available under the Trade Name Polidene 941 will not form satisfactory films below a temperature of about 80° C. The lowest temperature at which the polymer emulsion will form a film when thinly applied to a surface is defined as the "minimum film-forming temperature." The polymer emulsions which are suitable for preparing the compositions according to the invention have a minimum film-forming temperature which is not appreciably more than, and is preferably less than, the temperature of the body surface. For practical purposes, a minimum film-forming temperature of below 40° and usually below 35° C., is desirable.

Depending on the nature of the polymer used and upon the form of composition that is desired so it may be necessary or desirable to include in the composition various additives, such as pharmaceutically acceptable viscolizers. Other pharmaceutically acceptable ingredients of topical compositions such as buffering agents, opacifying agents and preservatives may be included in the compositions according to the invention.

When the composition is to be a spray it will generally also contain components such as aerosol propellants and suspending agents.

It will be realized that not all components of the carrier need be liquid, but some at least of them must be liquid in order that the carrier as a whole has fluid properties and that a skin shall be formed on spreading. The polymer is mixed with the other components of the composition while the polymer is in the form of an aqueous emulsion, in which event the majority of the liquid carrier is generally made up of the aqueous medium of the emulsion.

The films deposited by compositions according to the invention are nontacky and adherent to the skin and are substantially impermeable to water vapor, but release drugs incorporated therein to the underlying surface. This is surprising since no one has previously been able to incorporate steroids into compositions which could be sprayed on to the skin surface to provide an impermeable film and yet from which the steroid will be released.

Additional ingredients may be included to modify the consistency of the ointments such as polyvinylpyrrolidone or to control the drying time of the ointments after application such as glycerol.

The properties of the creams vary considerably with the nature and concentration of the various ingredients.

Among the preferred polymers we find emulsions of polyvinylidene chloride and its copolymers to be very satisfactory. However, these are generally too free flowing to be used as ointment bases and sprays and so we generally prefer to include in the carrier a pharmaceutically acceptable viscolizer when such an emulsion is used.

The emulsions suitable for preparing the ointment bases according to the invention have been selected by use of the Payne permeability test, the use of which is described in the Paint Research Memorandum No. 234, 1956, 11, 92. Material under test is cast or spread on to a supporting medium, usually filter paper, dried and clamped on to a cup containing a desiccant. The assembly is placed in an atmosphere saturated with water vapor and the gain in weight is followed as a function of time. The permeability of the film is given by the expression $P=(M\times F\times 24)/(10\times T)$ where P = permeability, M = gain of weight of cup in grams in T hours and F = thickness of film in cm. after drying.

The drying temperature for films undergoing this test has been standardized at 40° C. to approximate to body temperature and many polymer emulsions have been tested. Polyvinylidene chloride emulsions were found to be particularly effective and results of the Payne test on commercially available emulsions sold under the Trade Names Daran 210, Polidene 905 and Polidene 941 were as follows:

Emulsion (Trade Name)	Permeability × 10^4 g. days/cm.²
Daran 210	0.10
Polidene 905	0.22
Polidene 941	10.31

Daran is the registered trademark of Scott Bader and Co. Limited of England and Polidene is the registered trademark of W. R. Grace and Co. of Cambridge, Mass.

Polidene 941 has a minimum film-forming temperature of 80° C., and its unsuitability is demonstrated by a relatively high water vapor permeability possibly due to incomplete film formation. Polidene 905 on the other hand, having a film-forming temperature of 10° C., gave an excellent film of extremely low permeability to water vapor Daran 210 also gave an excellent film.

Subsequent tests were mainly carried out on Polidene 905 emulsions; the emulsions have been found to be pharmaceutically acceptable and the dried films release drugs contained therein to underlying skin. These emulsions contain 0.3 percent of acrylamide as copolymer. Polidene 911 emulsions which contain no internal plasticizer have also been used.

For use as ointments it is necessary to add to the emulsions a compatible, pharmaceutically acceptable viscolizer. Suitable viscolizers include finely divided silica, colloidal aluminum magnesium silicate, bentonite, attapulgite, agar, acacia, tragacanth, pectin, gum gatto, gelatin, hydroxyethylcellulose, sodium carboxyethylcellulose, methylcellulose, natural gums of bacterial origin, polyvinyl alcohol, polyvinylpyrrolidone, carboxypolymethylenes, polyethoxy homopolymers and methylvinylether/maleic anhydride copolymers.

We prefer to add viscolizers to give a product having a viscosity range of 10–50 poises and especially 25–35 poises at a shear rate of 125 sec.$^{-1}$; we particularly prefer to use hydroxyethylcellulose. The concentration of hydroxyethylcellulose in the ointment base may vary within the range of 0.25–1.5 percent w/w.

Aerosol compositions according to the invention may be propelled by conventional gaseous propellants such as nitrous oxide, nitrogen and carbon dioxide which are compatible with the polymeric base and the active ingredients. The spray compositions contain one or more viscolizers of the types already described but at a lower concentration than used in the creams.

The ointment bases and topical spray bases according to the invention may be used for applying topically any drug which is compatible with the bases and which has an improved activity when the skin is in a very moist condition. The bases are especially advantageous for the topical application of anti-inflammatory steroids such as hydrocortisone, prednisolone, triamcinolone, triamcinolone acetonide, fluocinolone acetonide, betamethasone, dexamethasone, flurandrenolone, flumethasone, 6α-methylprednisolone, fluperolone, beclomethasone, fluocortolone and 21-desoxyprednisolone. Organic and inorganic esters of the above compounds which may also be used as active ingredients include hydrocortisone 21-acetate prednisolone 21-pivalate, prednisolone 21-phosphate, betamethasone 17α-valerate, flumethasone 21-pivalate, fluperolone 21-acetate, 6α-methylprednisolone 21-acetate, beclomethasone 17α,21-dipropionate, fluocortolone 21-caproate and 17α-esters of 21-desoxyprednisolone, especially 21-desoxyprednisolone 17α-propionate.

In addition to the steroid component, such topical compositions may include other compatible, active ingredients including antibiotics such as gramicidin, neomycin, kanamycin, the tetracyclines, chloramphenicol, polymixin, amphomycin, framycetin, gentamycin, bacitracin and nystatin. Other antibacterial and antifungal agents may be included such as iodochlorhydroxyquinoline, coal tar fractions, di-iodohydroxyquinoline, phenylmercuric dinaphthylmethane disulphonate, chlorphenesin, salicylic acid, buclosamide, halquinol, hexachlorophane, clemizole, chlorquinaldol, cetrimide, cetylpyridinium chloride, benzalkonium chloride and domiphen bromide. Local anesthetic agents such as dibucaine hydrochloride, amethocaine and amylocaine may also be included in the compositions according to the invention.

External plasticizers for use with aqueous polyvinylidene chloride emulsions include dimethyl phthalate, diethyl phthalate, dibutyl phthalate, di-isopropyl adipate, diethyl sebacate, isopropyl palmitate, hexylene glycol, benzyl alcohol and hexadecyl alcohol but these are not to be construed as limiting.

It is to be understood that some active ingredients may be less stable at the natural pH of the composition than at other pH levels. Accordingly pharmaceutically acceptable buffers may also be included in the compositions according to the invention. Citric acid and its salts are particularly valuable as buffering agents as they have the advantage of being antioxidants and may stabilize the compositions by two distinct mechanisms.

Additional ingredients may be included to modify the consistency of the ointments such as polyvinylpyrrolidone or to control the drying time of the ointments after application such as glycerol.

The topical sprays according to the invention may be applied to the skin surface by conventional methods, e.g., from squeeze-bottles, mechanical sprays or by self-propelled aerosol sprays. It is important that in the case of aerosol sprays the propellant should have no solvent effect on the film-forming polymer or the characteristics of the formulation may be adversely affected. For this reason it is preferred that compatible gaseous propellants such as nitrous oxide, nitrogen and carbon dioxide be used.

The ointments according to the present invention are not applied to the skin in the same way as are conventional ointments or creams. Conventional formulations are either massaged into the skin when no dressing is to be used, or are spread on the skin and covered by a dressing in order to prevent the soiling of clothes or removal of the ointment by contact with external objects. The compositions of the present invention are spread or sprayed thinly on the surface of the skin and allowed to dry to give a thin film. The film is non-tacky, flexible and will stay on the skin for 2–5 days if not washed. Washing with soap and water easily removes the film when required. If too thick a layer of film-forming cream or spray is applied to the skin the resultant film will crack and tend to peel off.

The following nonlimitative examples illustrate the invention.

EXAMPLE 1

A film-forming cream was prepared containing the following ingredients:

Thiomersal	0.02% w/w
Sodium citrate	0.2% w/w
Citric acid	0.3% w/w
Hexachlorophane	1.0% w/w
Disodium edetate	0.1% w/w
Hydroxyethylcellulose	0.75% w/w
21-Desoxyprednisolone 17α-propionate	0.2% w/w
Water	5.0% w/w
Polidene 905 emulsion	to 100% w/w

Similar creams were prepared but replacing the 0.2 percent of 21-desoxyprednisolone 17α-propionate with 0.5 percent w/w of prednisolone, 1.0 percent w/w of hydrocortisone, 0.2 percent w/w of 21-desoxyprednisolone 17α-isobutyrate or 0.2 percent w/w of 21-desoxyprednisolone 17α-butyrate.

EXAMPLE 2

A film-forming cream was prepared containing the following ingredients:

Thiomersal	0.01% w/w
Sodium citrate	0.1% w/w
Citric acid	0.12% w/w
Cetylpyridinium chloride	0.5% w/w
Hydroxyethylcellulose	0.75% w/w

21-Desoxyprednisolone 17α-propionate	0.2% w/w
Polidene 905 emulsion	to 100% w/w

EXAMPLE 3

A film-forming cream containing external plasticizer was prepared containing the following ingredients:

Chlorocresol	0.1% w/w
Benzyl alcohol (external plasticizer)	0.05% w/w
Citric acid	0.24% w/w
Sodium citrate	0.2% w/w
Hydroxyethylcellulose	0.8% w/w
21-Desoxyprednisolene 17α-propionate	5.0% w/w
Water	5.0% w/w
Polidene 911 emulsion	to 100% w/w

EXAMPLE 4

A film-forming cream containing the following ingredients was prepared:

Bronopol	0.05% w/w
Sodium lauryl sulfate	0.1% w/w
Citric acid	0.24% w/w
Sodium citrate	0.2% w/w
Hexachlorophane	1.0% w/w
Hydroxyethylcellulose	0.8% w/w
Water	5.0% w/w
21-desoxyprednisolone 17α-propionate	0.2% w/w
Polidene 905 emulsion	to 100% w/w

EXAMPLE 5

A film-forming cream was prepared contianing the following ingredients:

Paraffin wax	10.0% w/w
Chlorinated paraffin wax	5.0% w/w
Poly (ethylene-vinyl chloride) copolymer	10.0% w/w
Sodium lauryl sulfate	1.0% w/w
Polyoxyethylene 20 sorbitan mono-oleate	0.5% w/w
Sodium citrate	0.2% w/w
Citric acid	0.24% w/w
Hexachlorophane	1.0% w/w
Chlorocresol	0.2% w/w

21-Desoxyprednisolone 17α-propionate	0.2% w/w
Hydroxyethylcellulose	1.0% w/w
Water	to 100% w/w

EXAMPLE 6

A film-forming cream was prepared containing the following ingredients:

Hydroxyethylcellulose	0.75% w/w
Thiomersal	0.02% w/w
Sodium citrate	0.2% w/w
Citric acid	0.3% w/w
Hexachlorophane	1.0% w/w
Disodium edetate	0.1% w/w
Ephedrine hydrochloride	0.25% w/w
Lignocaine hydrochloride	0.5% w/w
Allantoin	0.5% w/w
Water	5.0% w/w
Polidene 905 emulsion	to 100% w/w

EXAMPLE 7

A film-forming spray was prepared which contained:

Hydroxyethylcellulose	0.25% w/w
21-Desoxyprednisolone 17α-propionate	0.2% w/w
Polidene 905 emulsion	to 100% w/w

This lotion (96 parts) was filled into pressurized containers and nitrous oxide (4 parts) was added as propellant.

We claim:

1. A pharmaceutical composition for topical application to the skin comprising an anti-inflammatory steroid and a fluid pharmaceutically acceptable carrier therefor, which carrier comprises an aqueous emulsion of a polyvinylidine chloride which has a minimum film-forming temperature of less than 35° C. and which when applied to the skin dries readily to give a flexible, nontacky, adherent, substantially water-vapor impermeable film which releases said anti-inflammatory steroid to the underlying skin.

2. A composition as claimed in claim 1 in which said steroid is 21-desoxyprednisolone 17α-propionate.

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