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(54) Titre : ADMINISTRATION A FAIBLE DOSE D'UNE COMPOSITION TOPIQUE
(54) Title: LOW DOSE ADMINISTRATION OF A TOPICAL COMPOSITION

(57) Abrégé/Abstract:
Unexpectedly, the therapeutically required amount of active ingredient in a topical drug delivery product may be significantly reduced by applying the product in a delivery vehicle containing a SEPA® penetration enhancer to the upper arms and shoulders of an individual in need of the active ingredient rather than to the abdomen of the individual.

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(54) Title: LOW DOSE ADMINISTRATION OF A TOPICAL COMPOSITION

(57) Abstract: Unexpectedly, the therapeutically required amount of active ingredient in a topical drug delivery product may be significantly reduced by applying the product in a delivery vehicle containing a SEPA® penetration enhancer to the upper arms and shoulders of an individual in need of the active ingredient rather than to the abdomen of the individual.

Low Dose Administration of a Topical Composition

Cross-Reference to Related Application

[0001] This application claims benefit of U.S. Provisional Application No. 60/679,673 filed May 11, 2005. This application, in its entirety, is incorporated herein by reference.

Field of the Invention

[0002] This invention relates to the field of topical drug delivery and more specifically to the field of improving topical delivery of physiologically active compounds by applying them to the skin of the shoulders and/or upper arms.

Background of the Invention

[0003] The administration of drugs and other biological materials to the bloodstream via a transdermal route of administration has received much attention in recent years. The skin of an average adult covers more than two square meters of surface area and receives about one-third of all blood circulating through the body. It is elastic, rugged, and generally self-regenerating. Human skin consists of two layers: the epidermis (which is a composite of multiple layers including the stratum corneum), and the dermis. The stratum corneum (S.C.) represents the rate-limiting step in diffusion of chemical through the skin. The S.C. is composed of dead, keratinized, metabolically inactive cells which are closely packed together, and embedded in an amorphous matrix of mainly lipoid and nonfibrous protein within which keratin filaments are distributed. The cells of the S.C. generally contain 20% water, while the cells below, in the stratum germinativum, contain 70% water. The S.C. does not become hydrated readily. Thus, transdermal permeation is primarily controlled by diffusion through the S.C.

[0004] There are several major reasons for the interest in transdermal delivery of drugs:

1) elimination of uncertainties of absorption from, and irritation to, the gastrointestinal tract which can arise when drugs are administered orally;
2) bypassing the portal circulation, thereby eliminating first-pass metabolism in the liver; this is extremely important for drugs with short half-lives, or with potential unwanted actions on the liver:
3) localized delivery of medication to the intended target site;

4) delivery of medication directly into the systemic circulation at a constant rate (similar to intravenous infusion);
5) infrequent dosing (daily, weekly or longer) for certain drugs;
6) ease of use and to foster patient compliance.

[0005] Transdermal delivery is generally restricted to those small molecule medications requiring delivery rates less than 10 mg/day. In order to obtain higher blood levels, the rate of drug delivery must be increased. There have been many proposals to accomplish the higher rate of drug delivery via the use of absorption promoters and by the development of prodrugs that can be more readily absorbed. Examples of existing absorption enhancers include dimethyl sulfoxide (DMSO), ethylene glycol, hexanol, fatty acid and esters, alkyl-2-(N,N-disubstituted amino)-alkanoate ester, an (N,N-disubstituted amino)-alkanol alkanoate, or a mixture of these, cyclopentadecalactones, ester sunscreens and pyrrolidone derivatives, among others. One such enhancer compound which has received much attention is Azone (N-dodecyl azacycloheptan-2-one).

[0006] Use of such penetration enhancers has been made for a variety of small molecule drugs as has been demonstrated. Prior art patents of relevance to penetrating enhancers of physiologically active agents include U.S. Pat. Nos. 3,551,554 which describes dimethyl sulfoxide, U.S. Pat. No. 3,989,816 discloses 1-substituted azacycloheptane-2-one; U.S. Pat. No. 4,132,781 discloses a topical antibiotic plus 2-pyrrolidone or an n-lower alkyl-2-pyrrolidone, U.S. Pat. No. 4,017,641 also describes 2-pyrrolidone but with propylene glycol; others of interest are U.S. Pat. Nos. 3,903,256, 4,343,798, 4,046,886, 3,934,013; 4,070,462; 4,130,643, 4,130,667, 4,289,764; 4,070,462; 3,527,864, 3,535,422, 3,598,123, 3,952,099, 4,379,454, 4,286,592; 4,299,826; 4,314,557; 4,343,798; 4,335,115; 3,598,122; 4,405,616, 3,896,238, 3,472,931 and 4,557,934.

[0007] Applicants have previously developed a new class of compounds which are derivatives of 1, 3-dioxanes and 1, 3-dioxolanes for use as skin penetration enhancing compounds. These compounds, which have been made commercially available under the trademark SEPA®, are described in detail in U.S. Pat. No. 4,861,764. Work with the dioxolane enhancers has been described in several literature and patent publications. For example, Samour, et al., Proc. Int. Symp. Control. Rel. Bioact. Mater. 16: 183-184 (1989); Marty, et al., Proc. Int. Symp. Control. Rel. Bioact. Mater. 16:179-180 (1989); Marty, et al., Proc. Int. Symp. Control. Rel. Bioact. Mater. 17:415-416 (1990); Michniak, et al., Drug Delivery 2:117-122

(1995); Marty, et al., Abstract of Paper Presented at American Association of Pharmaceutical Scientists, Washington, D.C., Mar. 26-28, 1990.

[0008] Specific examples of SEPA® enhancers can be found in U.S. Patents 5,976,566 and 5,968,919 where the topical delivery of non-steroidal anti-inflammatory drugs and hormones are demonstrated. Even with penetration enhancement, it can be difficult to deliver sufficient quantities of some small molecule drugs to achieve therapeutic blood levels. An example of this problem can be found in the difficulty associated with delivery of the hormone testosterone. Due to the high serum concentrations required for testosterone, extremely large quantities of topical testosterone formulations, on the order of 5-10 g/day, are required to be applied in order to achieve therapeutic serum levels of testosterone. Methods are needed to reduce the amount of active ingredient required when using topical administration, even with the existing penetration enhancers. Applicants have discovered a method of treatment that allows for a significant reduction in the required dosage of active ingredient when applied topically.

Summary of the Invention

[0009] The present invention has as a principal object to provide an improved method of topical delivery of physiologically active compounds or ingredients by administration to the skin of the upper arms and/or shoulders. In one embodiment, the improved method allows a significant reduction in the dosage of active ingredient required to achieve the same therapeutic effect.

[0010] In one embodiment, a method of elevating total serum testosterone concentration in a testosterone deficient individual includes applying to the upper arm and/or shoulder of the individual a low dosage amount of a testosterone composition that includes a skin penetration enhancing amount of a C_7 to C_{14} - hydrocarbyl substituted 1,3 - dioxalane, 1,3 - dioxane, or acetal thereof.

[0011] In another embodiment, a method of delivering an active ingredient includes applying a composition including the active ingredient and a C_7 to C_{14} - hydrocarbyl substituted 1,3 - dioxalane, 1,3 - dioxane, or acetal thereof to the shoulders and/or upper arms of an individual.

Detailed Description of the Invention

[0012] The compositions used in the invention are intended for topical non-invasive application to the skin, providing improved systemic delivery of the active ingredient, and any other co-active ingredients. The low dose administration of a

composition can be applied as required to the skin of the upper arms and/or shoulders of an individual seeking the therapeutic effect.

[0013] Examples of the active ingredients which are advantageously administered by the topical formulations of this invention include any locally or systemically active agents which are compatible with the dermal penetration enhancers of the present invention and which can be delivered through the skin with the assistance of the dermal penetration enhancer to achieve a desired effect. The amount of the active ingredient used will be dependent on the ability of the active to be incorporated into a delivery vehicle and on the required therapeutic amount. In part, this amount can be dependent on the solubility of the active in specific solvents used in the delivery vehicle. The active agents (grouped by therapeutic class) include:

[0014] Alimentary System:

[0015] Antidiarrhoeals such as diphenoxylate, loperamide and hyoscyamine.

[0016] Cardiovascular System:

[0017] Antihypertensives such as hydralazine, minoxidil, captopril, enalapril, clonidine, prazosin, debrisoquine, diazoxide, guanethidne, methyldopa, reserpine, trimetaphan. Calcium channel blockers such as diltiazem, felodopine, amlodipine, nitrendipine, nifedipine and verapamil.

[0018] Antiarrhyrthmics such as amiodarone, flecainide, disopyramide, procainamide, mexiletene and quinidine.

[0019] Antiangina agents such as glyceryl trinitrate, erythritol tetranitrate, pentaerythritol tetranitrate, mannitol hexanitrate, perhexilene, isosorbide dinitrate and nicorandil.

[0020] Beta-adrenergic blocking agents such as alprenolol, atenolol, bupranolol, carteolol, labetalol, metoprolol, nadolol, nadoxolol, oxprenolol, pindolol, propranolol, sotalol, timolol and timolol maleate.

[0021] Cardiotonic glycosides such as digoxin and other cardiac glycosides and theophylline derivatives.

[0022] Adrenergic stimulants such as adrenaline, ephedrine, fenoterol, isoprenaline, orciprenaline, rimeterol, salbutamol, salmeterol, terbutaline, dobutamine, phenylephrine, phenylpropanolamine, pseudoephedrine and dopamine. Vasodilators such as cyclandelate, isoxsuprine, papaverine, dipyrimadole, isosorbide dinitrate, phentolamine, nicotinyl alcohol, co-dergocrine, nicotinic acid, glyceryl trinitrate, pentaerythritol tetranitrate and xanthinol.

[0023] Antimigraine preparations such as ergotamine, dihydroergotamine, methysergide, pizotifen and sumatriptan.

[0024] Drugs Affecting Blood and Haemopoietic Tissues:

[0025] Anticoagulants and thrombolytic agents such as warfarin, dicoumarol, low molecular weight heparins such as enoxaparin; streptokinase and its active derivatives. Haemostatic agents such as aprotinin, tranexamic acid and protamine.

[0026] Central Nervous System:

[0027] Analgesics, antipyretics including the opiod analgesics-such as buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, alfentanil, sufentanil, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, codeine and dihydrocodeine. Others include acetylsalicylic acid (aspirin), paracetamol, and phenazone.

[0028] Hypnotics and sedatives such as the barbiturates, amylobarbitone, butobarbitone and pentobarbitone and other hypnotics and sedatives such as choral hydrate, chlormethiazole, hydroxyzine and meprobamate.

[0029] Antianxiety agents such as the benzodiazepines, alprazolam, bromazepam, chlordiazepoxide, clobazam, chlorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, nitrazepam, oxazepam, temazepam and triazolam. Neuroleptic and antipsychotic drugs such as the phenothiazines, chlorpromazine, fluphenazine, pericyazine, perphenazine, promazine, thiopropazate, thioridazine and trifluoperazine and the butyrophenones, droperidol and haloperidol and the other antipsychotic drugs such as pimozide, thiothixene and lithium.

[0030] Antidepressants such as the tricyclic antidepressants amitryptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline, opipramol, protriptyline and trimipramine and the tetracyclic antidepressants such as mianserin and the monoamine oxidase inhibitors such as isocarboxazid, phenelizine, tranylcypromine and moclobemide and selective serotonin re-uptake inhibitors such as fluoxetine, paroxetine, citalopram, fluvoxamine and sertraline.

[0031] CNS Stimulants Such as Caffeine

[0032] Anti-Alzheimer's Agents Such as Tacrine

[0033] Antiparkinson agents such as amantadine, benserazide, carbidopa, levodopa, benztropine, biperiden, benzhexol, procyclidine and dopamine-2 agonists such as S(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetrali- -n (N-0923).

[0034] Anticonvulsants such as phenytoin, valproic acid, primidone, phenobarbitone, methylphenobarbitone and carbamazepine, ethosuximide, methsuximide, phensuximide, sulthiame and clonazepam.

[0035] Musculoskeletal System:

[0036] Non-steroidal anti-inflammatory agents including their racemic mixtures or individual enantiomers where applicable, such as ibuprofen, flurbiprofen, ketoprofen, aclofenac, diclofenac, aloxiprin, aproxen, aspirin, diflunisal, fenoprofen, indomethacin, mefenamic acid, naproxen, phenylbutazone, piroxicam, salicylamide, salicylic acid, sulindac, desoxysulindac, tenoxicam, tramadol and ketoralac.

[0037] Additional non-steroidal anti-inflammatory agents which can be formulated in combination with the dermal penetration enhancers include salicylamide, salicylic acid, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzydamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloide, fluprofen, ibufenac, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, and triflumidate.

[0038] Antirheumatoid agents such as penicillamine, aurothioglucose, sodium aurothiomalate, methotrexate and auranofin.

[0039] Muscle relaxants such as baclofen, diazepam, cyclobenzaprine hydrochloride, dantrolene, methocarbamol, orphenadrine and quinine.

[0040] Agents used in gout and hyperuricaemia such as allopurinol, colchicine, probenecid and sulphinpyrazone.

[0041] Hormones and Steroids:

[0042] Oestrogens such as oestradiol, oestriol, oestrone, ethinyloestradiol, mestranol, stilboestrol, dienoestrol, epioestriol, estropipate and zeranol. Progesterone and other progestagens such as allyloestrenol, dydrgesterone, lynoestrenol, norgestrel, norethyndrel, norethisterone, norethisterone acetate, gestodene, levonorgestrel, medroxyprogesterone and megestrol.

[0043] Antiandrogens such as cyproterone acetate and danazol.

[0044] Antioestrogens such as tamoxifen and epitiostanol and the aromatase inhibitors, exemestane and 4-hydroxy-androstenedione and its derivatives. Androgens and anabolic agents such as testosterone, methyltestosterone, clostebol acetate, drostanolone, furazabol, nandrolone oxandrolone, stanozolol, trenbolone acetate, dihydro-testosterone, 17-α-methyl-19-nortestosterone and fluoxymesterone. 5-alpha reductase inhibitors such as finasteride, turosteride, LY-191704 and MK-306.

[0045] Corticosteroids such as betamethasone, betamethasone valerate, cortisone, dexamethasone, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide.

[0046] Further examples of steroidal antiinflammatory agents for use in the instant compositions include include cortodoxone, fluoracetonide, fludrocortisone, difluorsone diacetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and its other esters, chloroprednisone, clorcortelone, descinolone, desonide, dichlorisone, difluprednate, flucloronide, flumethasone, flunisolide, flucortolone, fluoromethalone, fluperolone, fluprednisolone, meprednisone, methylmeprednisolone, paramethasone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafal, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucloronide, flumethasone pivalate, flunisolide acetate, fluperolone acetate, fluprednisolone valerate, paramethasone acetate, prednisolamate, prednival, triamcinolone hexacetonide, cortivazol, formocortal and nivazol.

[0047] Pituitary hormones and their active derivatives or analogs such as corticotrophin, thyrotropin, follicle stimulating hormone (FSH), luteinising hormone (LH) and gonadotrophin releasing hormone (GnRH).

[0048] Hypoglycaemic agents such as insulin, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide and metformin.

[0049] Thyroid hormones such as calcitonin, thyroxine and liothyronine and antithyroid agents such as carbimazole and propylthiouracil.

[0050] Other miscellaneous hormone agents such as octreotide.

[0051] Pituitary inhibitors such as bromocriptine.

[0052] Ovulation inducers such as clomiphene.

[0053] Genitourinary System:

[0054] Diuretics such as the thiazides, related diuretics and loop diuretics, bendrofluazide, chlorothiazide, chlorthalidone, dopamine, cyclopenthiazide, hydrochlorothiazide, indapamide, mefruside, methycholthiazide, metolazone,

quinethazone, bumetamide, ethacrynic acid and frusemide and pottasium sparing diuretics, spironolactone, amiloride and triamterene.

[0055] Antidiuretics such as desmopressin, lypressin and vasopressin including their active derivatives or analogs.

[0056] Obstetric drugs including agents acting on the uterus such as ergometrine, oxytocin and gemeprost. Prostaglandins such as alprostadil (PGE1), prostacyclin (PGI2), dinoprost (prostaglandin F2-alpha) and misoprostol.

[0057] Antimicrobials:

[0058] Antimicrobials including the cephalosporins such as cephalexin, cefoxytin and cephalothin.

[0059] Penicillins such as amoxycillin, amoxycillin with clavulanic acid, ampicillin, bacampicillin, benzathine penicillin, benzylpenicillin, carbenicillin, cloxacillin, methicillin, phenethicillin, phenoxymethylpenicillin, flucloxacillin, meziocillin, piperacillin, ticarcillin and aziocillin.

[0060] Tetracyclines such as minocycline, chlortetracycline, tetracycline, demeclocycline, doxycycline, methacycline and oxytetracycline and other tetracycline-type antibiotics.

[0061] Aminoglycosides such as amikacin, gentamicin, kanamycin, neomycin, netilmicin and tobramycin.

[0062] Quinolones such as nalidixic acid, cinoxacin, ciprofloxacin, enoxacin and norfloxacin. Sulphonamides such as phthalylsulphthiazole, sulfadoxine, sulphadiazine, sulphamethizole and sulphamethoxazole.

[0063] Sulphones such as dapsone.

[0064] Other miscellaneous antibiotics such as chloramphenicol, clindamycin, erythromycin, erythromycin ethyl carbonate, erythromycin estolate, erythromycin glucepate, erythromycin ethylsuccinate, erythromycin lactobionate, roxithromycin, lincomycin, natamycin, nitrofurantoin, spectinomycin, vancomycin, aztreonam, colistin IV, metronidazole, timidazole, fusidic acid and trimethoprim; 2-thiopyridine N-oxide; halogen compounds, particularly iodine and iodine compounds such as iodine-PVP complex and diiodohydroxyquin; hexachlorophene; chlorhexidine; chloroamine compounds; benzoylperoxide.

[0065] Antituberculosis drugs such as ethambutol, isoniazid, pyrazinamide, rifampicin and clofazimine.

[0066] Antimalarials such as primaquine, pyrimethamine, chloroquine, hydroxychloroquine, quinine, mefloquine and halofantrine.

[0067] Antiviral agents such as acyclovir and acyclovir prodrugs, famciclovir, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, saquinavir, indinavir, ritonavir, n-docosanol, tromantadine and idoxuridine.

[0068] Anthelmintics such as mebendazole, thiabendazole, niclosamide, praziquantel, pyrantel embonate and diethylcarbamazine.

[0069] Cytotoxic agents such as plicamycin, cyclophosphamide, dacarbazine, fluorouracil and its prodrugs [described, for example, in International Journal of Pharmaceutics 111, 223-233 (1994)], methotrexate, procarbazine, 6-mercaptopurine and mucophenolic acid.

[0070] Metabolism:

[0071] Anorectic and weight reducing agents including dexfenfluramine, fenfluramine, diethylpropion, mazindol and phentermine.

[0072] Agents used in hypercalcaemia such as calcitriol, dihydrotachysterol and their active derivatives or analogs.

[0073] Respiratory System:

[0074] Antitussives such as ethylmorphine, dextromethorphan and pholcodine.

[0075] Expectorants such as acetylcysteine, bromhexine, emetine, guaiphenesin, ipecacuanha and saponins.

[0076] Decongestants such as phenylephrine, phenylpropanolamine and pseudoephedrine.

[0077] Bronchospasm relaxants such as ephedrine, fenoterol, orciprenaline, rimiterol, salbutamol, sodium cromoglycate, cromoglycic acid and its prodrugs [described, for example, in International Journal of Pharmaceutics 7, 63-75 (1980)], terbutaline, ipratropium bromide, salmeterol and theophylline and theophylline derivatives.

[0078] Allergy and Immune System:

[0079] Antihistamines such as meclozine, cyclizine, chlorcyclizine, hydroxyzine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine, diphenylamine, doxylamine, mebhydrolin, pheniramine, tripolidine, azatadine, diphenylpyraline, methdilazine, terfenadine, astemizole, loratidine and cetirizine.

[0080] Neuromuscular blocking agents such as suxamethonium, alcuronium, pancuronium, atracurium, gallamine, tubocurarine and vecuronium.

[0081] Smoking cessation agents such as nicotine, bupropion and ibogaine.

[0082] Nutritional agents, such as vitamins, essential amino acids and essential fats.

[0083] Keratolytics such as the alpha-hydroxy acids, glycollic acid and salicylic acid.

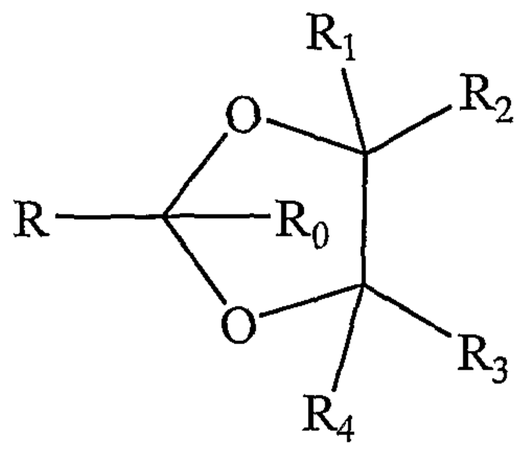
[0084] Psychicenergisers, such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

[0085] Anticholinergic agents, which are effective for the inhibition of axillary sweating and for the control of prickly heat. The antiperspirant activity of agents such as methatropine nitrate, propantheline bromide, scopolamine, methscopolamine bromide, and the new class of soft antiperspirants, quaternary acyloxymethyl ammonium salts [described, for example, by Bodor et al, J. Med. chem. 23, 474 (1980) and also in United Kingdom Specification No. 2010270, published Jun. 27, 1979].

[0086] Other physiologically active peptides and proteins, small to medium-sized peptides, *e.g.*, vasopressin and human growth hormone.

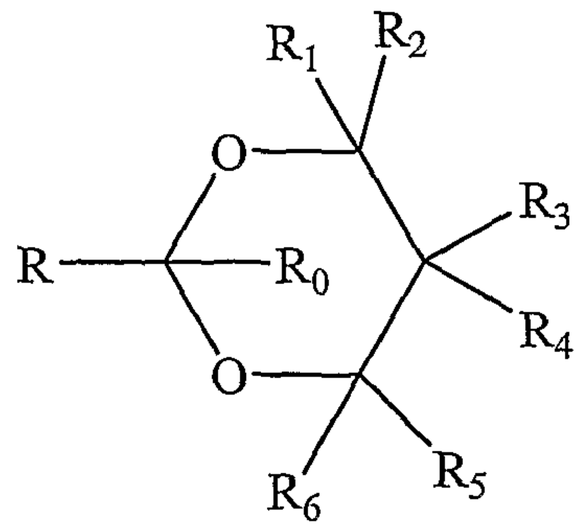
[0087] The penetration of the active ingredient through the skin is preferably enhanced to an acceptable level by including in the composition an effective amount of a skin penetration enhancing compound in the form of a skin modifying agent of the substituted 1,3-dioxacyclopentane and substituted 1,3-dioxacyclohexane types disclosed in U.S. Pat. No. 4,861,764, the disclosure of which is incorporated herein in its entirety by reference thereto, or the corresponding substituted acetal compound. Representative examples of the skin penetration enhancing compounds include:

2-substituted 1,3-dioxolanes of the formula (I):



(I)

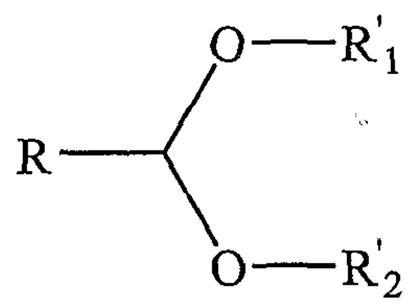
2-substituted 1,3-dioxanes of the formula (II):



(II)

and

substituted-acetals of the formula (III):



(III)

[0088] In the above formulas (I), (II) and (III), R preferably represents a C_7 to C_{14} hydrocarbyl group, R_0, R_1, R_2, R_3, R_4, R_5, and R_6, each, independently, represent hydrogen or a C_1 to C_4 alkyl group. R'_1 and R'_2, each, independently, represent C_1 to C_4 alkyl group.

[0089] The hydrocarbyl group for R may be a straight or branched chain alkyl, alkenyl or alkynyl group, especially alkyl or alkenyl. Preferably, R represents a C_7 to C_{12} aliphatic group; especially C_7 to C_{10} aliphatic group. Examples of suitable alkyl groups include, for example, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, 2-methyl-octyl, 4-ethyl-decyl, 8-methyl-decyl, and the like. The straight chain alkyl groups, such as n-heptyl, n-octyl, n-nonyl and n-decyl, are especially preferred. Examples of alkenyl groups include, for example, 2-hexenyl, 2-heptenyl, 2-octenyl, 2-nonenyl, 2',6'-dimethyl-2',6'-heptadienyl, 2',6'-dimethyl-2'heptaenyl, and the like. The R group may also be substituted by, for example, halo, hydroxy, carboxy, carboxamide and carboalkoxy.

[0090] The C_1 to C_4 alkyl group may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and the like. The preferred alkyl groups for R_0, and for R_1 to R_6 and for R'_1 and R'_2 are alkyl having 1 or 2 carbon atoms, most especially ethyl. R_0, and R_1 to R_6 may also, preferably, all be hydrogen.

[0091] Specific skin modifying agents include, for example, 2-n-pentyl-1,3-dioxolane, 2-n-heptyl-1,3-dioxolane, 2-n-nonyl-1,3-dioxolane, 2-n-undecyl-1,3-

dioxolane, 2-n-nonyl-1,3-dioxane, 2-n-undecyl-1,3-dioxane, 2-n-heptylaldehyde-acetal, 2-n-octyl-aldehyde-acetal, 2-n-nonylaldehyde-acetal, 2-n-decylaldehyde-acetal, 3,7-dimethyl-2,6-octadienal (citral), citronal and the like. 2-n-nonyl-1,3-dioxolane is especially preferred and is commercially available from MacroChem Corporation of Lexington, Mass., under the trademark SEPA®.

[0092] Examples of other skin penetration enhancers and co-solvents that may be added in addition to the skin modifying agent include dimethyl sulfoxide (DMSO), polyethylene glycol monolaurate, ethylene glycol, alkyl lactams, long chain amides, hexanol, fatty acids and their esters, and pyrrolidone derivatives.

[0093] The solubilizing and/or absorption-promoting agents that can be used in the present invention means an agent which can dissolve the active or actives or their pharmaceutically acceptable salts with a concentration of at least 0.01% relative to the total weight of the composition, and further promote the absorption of the active(s) or their pharmaceutically acceptable salts through skin. In other words, the solubilizing and/or absorption-promoting agent affords solubilizing and absorbing abilities to the active(s) or their pharmaceutically acceptable salts. Examples of absorption promoters and/or solubilizers include: alkane dicarboxylic esters such as alkane dicarboxylic dialkyl esters (dimethyl adipate, diethyl adipate, diisopropyl adipate, diethyl pimelate, diethyl sebacate, dipropyl sebacate etc.); and higher alkane carboxylic alkyl esters (isopropyl myristate, ethyl myristate, etc.).

[0094] The amount of the skin modifying agent is selected to provide the desired delivery rate for the active compound by taking into consideration such additional factors as, product stability, side effects, carrier system and the like, while minimizing the dosage size. Generally, depending on the particular active compound and other vehicles, amounts of the skin modifying agent in the range of from about 2.0 to 25%, preferably from about 2 or 3 or 4 or 5% to 10 or 12 or 15 or 20 percent, especially from about 5 to 10 percent, of the composition, will provide optimal flux rate and 24 hour payload of the active ingredient. Usually, for gel formulations the amount of enhancer compound may be lower than for cream formulations, such as from about 2 to 10 percent of the formulation.

[0095] In addition to the active ingredient and the penetration enhancer, the amount of the delivery vehicle can comprise the balance of the composition. Accordingly, the delivery vehicle or vehicles may comprise up to about 98%, for example, from about 50 to about 98%, for example, from about 70 to about 95%, for example, from about 70 to about 90% by weight of the composition.

[0096] The compositions may be formulated as gels, especially aqueous-alcoholic gels, lotions, creams, mousses, aerosols, ointments, lubricants, lacquers, patches, solutions, tinctures, and the like, may be used so long as when applied to the affected area of the skin the formulation will stay in place, i.e., without run-off, for sufficient time, to permit an individual to spread and retain the composition over and on the affected area.

[0097] The vehicle for any of the forms of the compositions of the invention may also include glycol, e.g., propylene glycol, butylene glycol, hexylene glycol, etc. (except in the case of the third embodiment described above), lower alcohol, e.g., ethanol, isopropanol, and, usually, water. In addition, of course, the skin penetration enhancing dioxolane, dioxane or acetal is included in the formulations in an amount effective to enhance the penetration of the active ingredient through the skin, including the stratum corneum.

Vehicle Components

[0098] The composition used according to the invention may also comprise a solid, semi-solid or liquid pharmaceutically acceptable vehicle, to help the active agent and skin penetration enhancer to be conveyed to the skin or other membrane, such as the nasal or oral mucosa, at an appropriate concentration and amount. The nature of the vehicle will depend upon the method chosen for topical administration of the composition.

[0099] The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition.

[00100] It should be explained that vehicles are compositions which may include diluents, dispersants, or solvents for the active agent and penetration enhancer which therefore ensure that they can be applied to and distributed evenly over an appropriate area of the skin.

[0100] Compositions according to this invention can include water as a vehicle, and/or at least one pharmaceutically acceptable vehicle other than water.

[0101] Vehicles other than water that may be used in compositions according to the invention include solids or liquids such as emollients and moisturizers, solvents, humectants, thickeners, preservatives, colorants, fragrances, propellants and solid additives. Examples of types of such additives, which can be used singly or as mixtures, are as follows.

[0102] Emollient materials may also serve as cosmetically acceptable additives. These may be in the form of silicone oils and synthetic esters. The emollient material

may be a silicone oil, an ester or a mixture of these. Amounts of the emollients may range anywhere from 0.1 to 20%, such as between 1 and 5% by weight of the final composition.

[0103] Silicone oils may be divided into the volatile and non- volatile variety. The term "volatile" as used herein refers to those materials which have a measurable vapour pressure at ambient temperature. Volatile silicone oils are preferably chosen from cyclic or linear polydimethyl siloxanes containing from 3 to 9, preferably from 4 to 5 silicon atoms. Linear volatile silicone materials generally have viscosities less than about 5 centistokes at 25° C., while cyclic materials typically have viscosities of less than about 10 centistokes.

[0104] Non-volatile silicone oils useful as an emollient material include polyalkyl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers. The essentially non-volatile polyalkyl siloxanies useful herein include, for example, polydimethyl siloxanes with viscosities of from about 5 to about 25 million centistokes at 25° C.

[0105] Silicone emulsifying agents can include dimethicone copolyols. These can include polydimethylsiloxanes modified to include polyether side chains. Other modifications to the side chains can result in nonionic, anionic, cationic, amphoteric, and zwitterionic pendant moieties.

[0106] Among the ester emollients are:

1. Alkenyl or alkyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include isoarachidyl neopentanoate, isononyl isononanoate, oleyl myristate, oleyl stearate, and oleyl oleate;
2. Ether-esters such as fatty acid esters of ethoxylated fatty alcohols;
3. Polyhydric alcohol esters; ethylene glycol mono and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly- fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters;
4. Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate and arachidyl behenate; and

5. Sterol esters of which cholesterol fatty acid esters are examples thereof.

[0107] Representative emollients and moisturizers, include, for example, stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate,propane-1, 2-diol,butane-1, 3-diol, mink oil, cetyl alcohol, ispropyl isostearate, stearic acid, isobutylpalmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropylpalmitate, isopropyl stearate, butyl stearate, polythylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate.

[0108] Representative propellants include, for example, trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoromethane, trichlorotrifluoroethane, propane, butane, isobutane, carbon dioxide.

[0109] Representative solvents include, for example, lower alchols, polyols, polyehters, oils, esters, alkyl ketones, and the like. For instance, mention may be made of ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran. The solvent may be selected for its ability to dissolve the active agent, and the SPE compound or SPE compounds, and one of ordinary skill in the art would understand which solvents would be suitable for such purposes, or how to determine which solvents would be appropriate.

[0110] Representative humectants include, for example, glycerin, sorbitol, sodium 2- pyrrolidone-5-carboxylate, soluble collagen, gelatin, may be used in embodiments according to the invention.

[0111] In some compositions which are in the form of a gel, a thickening agent, such as hydroxypropyl cellulose, can be included as a gelling agent. However, any other pharmaceutically acceptable thickening/gelling agent may be used. For example, mention may be made of other cellulosic ethers, polymeric thickening agents, e.g., acrylic acid polymers, Carbopol.RTM. thickeners, etc., xanthan gum, guar gum, and the like, as well as inorganic thickeners/gelling agents. The amount of the thickening agent is not particularly critical and can be selected to provide the desired product consistency or viscosity to allow for easy application to the skin but which will not be too watery or loose so that it will stay where applied. Generally,

depending on its molecular weight, amounts of thickening agent up to about 5%, such as, for example, from 0.1 to about 2%, of the composition will provide the desired effect.

[0112] As is well known in this art, it is possible to include other ingredients in the formulations for particular aesthetic and/or functional effects. For example, the formulations may, optionally, include one or more moisturizers for hydrating the skin and emollients for softening and smoothing the skin. Glycerin is an example of such a suitable moisturizing additive. When present the additive will usually be incorporated in an amount of up to about 5 percent by weight of the composition, for example, from about 0.1 to 5%.

[0113] Hydrophobic or lipophilic components of the formulation can be fatty acid material. "Fatty acid material" may include blends of fatty acids, typically containing fatty acid moieties with chain lengths of from C8 to C30. The fatty acid material may also contain relatively pure amounts of one chain length fatty acid moiety. Suitable fatty acids from which fatty acid/nonionic surfactant base mixtures may be derived include pelargonic, lauric, myristic, palmitic, stearic, isostearic, oleic, linoleic, ricinoleic, arachidic, behenic and erucic acids. Although normally saturated, suitable fatty acid materials may contain unsaturated fatty acid moieties, and may contain fatty acid moieties having a degree of substitution, such as e.g. hydroxy fatty acids. The chain length of the components of the fatty acid material also determines the rheological properties of the resultant skin composition base. A fatty acid material mix containing relatively high proportions of stearic and palmitic acid moieties has been found to be particularly suitable for use for manufacturing skin creams and lotions which may be used in temperate to hot climates, while fatty acid material mixtures containing relatively high amounts of lower chain length fatty acid moieties (*e.g.* more than 50% of the fatty acid moiety having a chain length of C8-C14) may also be suitable for the preparation of skin compositions for use in relatively cold climates.

[0114] Additional additives in the compositions can include skin care actives which are acidic in aqueous solution, such as for example fatty acids, such as alpha hydroxy fatty acids including lactic acid and glycolic acid; as well as peroxides such as hydrogen peroxide, vitamins such as vitamin B3, and polysaccharides such as chitosan; particularly preferred alpha hydroxy fatty acids are lactic acid and glycolic acid.

[0115] Representative solid additives include, for example, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, tetra alkyl and/or trialkyl aryl

ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymers, hydroxyalkylated cellulosics, sodium carboxymethyl cellulose.

[0116] The compositions of the present invention may be prepared and formulated as emulsions. Emulsions are typically heterogenous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter. (Idson, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 199; Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245; Block in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 2, p. 335; Higuchi et al., in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising of two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be either water in oil (w/o) or of the oil in water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase the resulting composition is called a water in oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase the resulting composition is called an oil in water (o/w) emulsion. Emulsions may contain additional components in addition to the dispersed phases and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed. Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil in water in oil (o/w/o) and water in oil in water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous provides an o/w/o emulsion.

[0117] Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may broadly be classified into four categories: synthetic surfactants, naturally occurring

emulsifiers, absorption bases, and finely dispersed solids (Idson, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 199).

[0118] Useful oils can include vegetable and hydrogenated vegetable oils including safflower oil, castor oil, coconut oil, cottonseed oil, menhaden oil, aplm kernel oil, palm oil, peanut oil, soybean oil, jojoba oil, linseed oil, rice bran oil, pine oil, sesame oil, and sunflower seed oil and their hydrogenated varieties. Additional useful oils can include animal fats and oils such as cod liver oil, and lanolin and its derivatives, mineral oil and petrolatum.

[0119] Synthetic surfactants, also known as surface active agents, can be used in the carrier in forming emulsions and have been reviewed in the literature (Rieger, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 285; Idson, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants used may be classified into different classes based on the nature of the hydrophilic group into: nonionic, anionic, cationic, zwitterionic and amphoteric (Rieger, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 285).

[0120] Common nonionic surfactants are polyoxyethylene ester and ether surfactants, a specific example of which is Tween 60. Other suitable nonionic surfactants are described in McCutcheons "Detergents and emulsifiers", North American edition (1986), published by Allured Publishing Corporation, the contents of which are specifically incorporated herein by reference. Examples of common nonionic surfactants can be derived from condensation reactions between long chain alcohols (C8-C30) with sugar or starch polymers. Other useful nonionic surfactants are the condensation products of alkylene oxides with fatty acids (alkylene oxide esters of fatty acids, or alkylene oxide diesters of fatty acids), or the condensation products of alkylene oxides and fatty alcohols (alkylene ethers of fatty alcohols).

[0121] Other useful nonionic emulsifying agents include sugar esters, poly esters, alkoxylated sugar esters and polyesters, C1-C30 fatty acid esters of C1-30 fatty alcohols, alkoxylated derivatives of C1-C30 fatty acid esters of C1-30 fatty alcohols, alkoxylated ethers of C1-30 fatty alcohols, polyglyceryl esters of C1-C30 fatty acids, C1-C30 esters or ethers of polyols, alkyl phosphate, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates and mixtures thereof.

[0122] Exemplary cationic emulsifying agents are those disclosed in McCutheon's, Detergents and Emulsifiers, North American Edition (1986), the contents of which are hereby incorporated by reference in their entirety. Useful cationic surfactants include cationic ammonium salts such as quaternary ammonium salts and amino-amides.

[0123] Useful anionic emulsifying agents include alkoxyl isethionates, alkyl and alkyl ether sulfates and salts thereof, alky and alkyl ether phosphates and salts thereof, alkyl methyl taurates and soaps of fatty acids.

[0124] An ionic polyamide polymer containing acrylamidopropanesulfonic acid (AMPS) and/or its salts as a comonomer may be used as an ionic polymeric stabilizing agent. These polymers can be formed from a variety of monomers including acrylamide and methacrylamide, which may be unsubstituted or substituted with one or two alkyl groups (preferably C1 to C5), or N-vinyl pyrrolidone. In one embodiment the acrylate amide and methacrylate amide are monomers in which the amide nitrogen is unsubstituted, or substituted with one or two C1 to C5 alkyl groups (preferably methyl, ethyl, or propyl), for example, acrylamide, methacrylamide, N-methacrylamide, N-methylmethacrylamide, N,N-dimethylmethacrylamide, N-isoproprylacrylamide, N-isopropylemthacrylamide, and N,N-dimethylacrylamide. In another embodiment the polyacrylamide-AMPS copolymer is the product given the CTFA designation polyacrylamide (and) isoparrafin (and) laureth-7, available under the Trade name Sepigel 305 from Seppic Corporation (Fairfield, N.J.). In another embodiment a copolymer of ammonium AMPS and N-vinylpyrrolidone, commercially under the trade name Aristoflex®, can be used. In a particular embodiment a mixture containing sodium AMPS (also known as acryloyldimethyltaurate) copolymer, isohexadecane, and polysorbate 80, commercially available under the trade name Simulgel 600 is used. Mixtures of two or more ionic polymeric stabilizing agents may also be used.

[0125] The ionic stabilizing agents are included in an amount sufficient to prevent visible separation of the composition. The stabilizers are generally present in a concentration of about 0.1 to about 10% by weight. One of skill in the art will also recognize that the amount of ionic polymeric stabilizing agent necessary will depend upon the hydrophobic and hydrophilic phases, intended use, intended storage, and use conditions, and other optional ingredients which maybe used within the composition as well as the mixing conditions and mixing apparatus used to prepare the emulsion or dispersion.

[0126] The ionic polymeric stabilizing agents of the present invention allow for the formation of a stable composition at lower concentrations of alcohol than compositions without these ionic stabilizing agents. In one embodiment, the ionic polymeric stabilizing agent is present from between about 1 and about 10 percent, for example, from about 2 to about 8 percent by weight of the composition.

[0127] Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

[0128] The compositions used in the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, steroids, local anesthetics or anti-inflammatory agents, skin conditioning agents such as oils and vitamins or may contain additional materials useful in physically formulating various dosage forms of the composition of present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers

[0129] The above-described ingredients can be formulated with the skin penetration enhancer and active agent to form a composition suitable for topical application, including creams, lotions, ointments, gels, sprays, aerosols, and the like. In one embodiment, the active agent and skin penetration enhancer are dispersed within cream bases or ointment bases to form a cream or ointment.

[0130] Topical carriers may include conventional emulsifiers or other excipients including alginates, glyceryl stearate, PEG-100 stearate, cetyl alcohol, propylparaben, butylparaben, sorbitols, polyethoxylated sorbitan, fatty esters(TWEENS), white soft paraffin (petrolatum),triethanolamine, aloe vera extract, lanolin, cocoa butter, and the like. Suitable topical carriers are well known to the skilled artisan.

Preparation and administration

[0131] Traditionally, cosmetic or pharmaceutical creams were limited to oil-in water emulsions which contained more than 50 wt. % of water. According to some embodiments of the present invention, stable creams may include those with less than 50 wt. % water. Such cream formulations have the advantage of being able to

incorporate larger quantities of organic solvents, such as alcohols (*e.g.* , ethanol) while still maintaining acceptable cream properties. Creams which have, in the past, incorporated skin penetration enhancing agents have been typically limited to low concentrations of these compounds (*e.g.*, < 5 wt. %) because higher concentrations of such skin penetration enhancers resulted in either emulsion destabilization, or required more organic solvents, such as alcohols, which will breakdown the cream. Therefore, the cream embodiments of the present invention provide, inter alia, for creams with higher concentrations of skin penetration enhancers, while still maintaining an acceptable cream feel.

[0132] The term "cream" as used herein refers to a composition which is opaque or milky at room temperature and is an oil in water emulsion with a hydrophilic phase in which a hydrophobic phase is emulsified and dispersed, in a micellar structure. Some Cream composition embodiments of the present invention may include those cream compositions which clarify or liquefy when contacted with animal, e. g., human, skin so as to not discolor or otherwise present an unpleasant aesthetic quality to the user. Such "vanishing creams" typically will clarify at temperatures above ambient temperature, for example, above about 30° C, such as above about 33° C, or above about 35° C. These qualities of a vanishing cream are thought to occur by the thermal breakdown of the micellar structure of the cream at elevated temperature, resulting in the separation of the emulsion, and loss of opacity.

[0133] The components of some cream base embodiments of the present invention may include a hydrophobic component and a hydrophilic component. These cream base formulations may further comprise an emulsifying agent and a skin penetration enhancing agent. The active agent of the present invention may be dispersed, dissolved or suspended within the cream base formulation of the present invention, for example, in one or both the hydrophobic or hydrophilic components.

a. Hydrophilic Component

[0134] Some compositions of the present invention include a hydrophilic component, *e.g.*, water and/or other water soluble or water miscible compounds. Suitable water soluble or dispersible ingredients may comprise alcohols, carboxylic acids, diols, triols, polyols, and the like.

[0135] According to one embodiment of the present invention, the hydrophilic component includes water and one or more alcohols. Suitable alcohols in the present invention include: straight or branched chain alkyl, aromatic, or alkylene alcohols. In one embodiment, the alcohol used in the hydrophilic component is a linear alkyl

alcohol containing between 1 and 6 carbon atoms, for example, methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, tert-butnaol, 1-pentanol, or 1-hexananol. In another embodiment, the alcohol is methanol or ethanol. Polyols, including diols and triols may be present in place of or together with the monoalcohol. Representative polyols include, for example, ethylene glycol, propylene glycol, diethylene glycol, butylene glycol, and the like. The amount of alcohol used in the hydrophilic component may be selected to accomplish the emulsions described herein, and may generally comprise between 1 and 99 wt. % relative to the total weight of the hydrophilic component. The alcohol may constitute between about 15 and about 85 wt. % of the hydrophilic component, such as between about 30 and about 70 wt. %, for example between about 35 and about 55 wt.% of the hydrophilic component.

[0136] The amount of the hydrophilic component present will depend on the additional components present in the composition as described herein.

[0137] Some of the compositions of the present invention will include between about 40 and about 90 wt. % relative to the total weight of the hydrophilic component. In one embodiment, the compositions of the present invention will include between about 45 and about 85 wt. % of the hydrophilic component, such as between about 50 and about 80 wt. %, or between about 60 to about 70 wt.%.

[0138] For example, in one embodiment, the hydrophilic phase comprises water in at least about 5 wt. %, for example, at least about 10 wt. %, such at least about 15 wt.%, at least about 20 wt. %, at least about 25 wt. %, at least about 30 wt. %, at least about 40 wt. %, at least about 45 wt. %, at least about 50 wt. %, at least about 55 wt. %, at least about 60 wt. % or least about 70 wt. %, based on the total weight of the composition. The amount of water may be less than about 85 wt. % based on the total weight of the composition, for example, less than about 80 wt. %, such as less than about 75 wt. %, less than about 70 wt. %, less than about 65 wt. %, less than about 60 wt. %, less than about 50 wt. %, less than about 55 wt. %, less than about 50 wt. %, less than about 45 wt. %, less than about 40 wt. % or less than about 35 wt.% water.

[0139] The hydrophilic phase may comprise water between about 15 to about 89 wt. %, for example, between about 20 and about 80 wt. %, or from about 25 to about 70 wt. %, or from about 30 to about 60 wt. % by weight of the composition.

[0140] In one embodiment, ethanol may be present in at least 15 wt. % relative to the total weight of the composition, for example, in at least about 20 wt. %, such as at least about 25 wt. %, at least about 30 wt. %, at least about 40 wt.%, at least about

45 wt. %, at least about 50 wt. %, at least about 55 wt. %, or at least about 60 wt. %. The amount of ethanol may be less than, for example less than about 65 wt. %, such as less than about 60 wt.%, or less than about 55 wt.%, or less than about 50 wt. %, or less than about 45 wt. %, or less than about 40 wt. %, or less than about 35 wt. %.

b. Hydrophobic component

[0141] The hydrophobic component of some of at least one embodiment of the present invention may include one or more oily or fatty components as exemplified above, comprising from about 5 to about 60 wt. % of the total weight of the composition, for example, from about 9 to about 50 wt. % of the total weight of the composition, such as about 12 to about 40 wt. % of the total weight of the composition, such as about 15 to about 30 wt. % of the total weight of the composition.

[0142] The compositions according to the invention are well suited for topical, *e.g.*, transdermal administration and may be prepared, in a conventional manner, by mixing together the various constituents in the chosen proportions. Different active agents may yield different results with different skin penetration enhancers, solvent or carrier systems or other ingredients in the formulation and in light of the present disclosure, the skilled artisan would be able to select an appropriate enhancer with the appropriate system for a given active agent.

[0143] The compositions of the invention may be applied by any means to a predetermined area of skin, for example to an area of between 10 and 100 cm^2, for example 50 cm^2.

[0144] When the pharmaceutical compositions of this invention are in the form of a lotion, cream, emulsion, gel, solution, ointment or similar composition, the compositions may be spread as a film over the selected area of skin and, to this end, do not necessarily require intermediate propellant gases. Alternatively, the topical transdermal composition may also be incorporated into a transdermal delivery device, *e.g.*, a patch.

[0145] In another embodiment of the present invention, the compositions may be administered by direct spraying using a doser pump of a type which is known and marketed for use without the aid of a propellant. If so desired, the compositions of the invention may, however, be administered by spraying from a container fitted with a dose valve, additionally containing a compressed propellant gas such as those mentioned above

[0146] The method of the current invention includes application of a composition comprising one or more of the active ingredients identified in combination with a SEPA® penetration enhancer in a delivery vehicle comprising the components discussed above and that is well known in the art, to the upper arms and/or shoulders of an individual in need of the active ingredient. By applying the composition to the upper arms and/or shoulders of the individual rather than to the abdomen, the required dosage of active ingredient-containing composition can be significantly reduced.

[0147] By reducing the amount of required composition and active ingredient, the efficiency of the delivery has been increased, while the probability of cross contamination has been reduced. Furthermore, by reducing the amount of composition required, the time needed to apply the dose is reduced. In addition, the lower the possible dose used, the lower the risk of side effects, including blood and liver effects, and other events associated with processing and receiving excess amounts of any active ingredient into the body. Examples of the importance of reducing dosage to lower levels in order to reduce side effects and other events abound, and are well known to those of skill in the art. An example of this is the pharmaceutical sector's experiences with Estrogen replacement therapy.

[0148] In one embodiment the method of the present invention can be a method of elevating to therapeutic levels, the serum levels of an active ingredient by applying to the upper arm and/or shoulder of an individual needing the active ingredient a composition comprising a cream base with a SEPA® enhancer and a reduced amount of active ingredient than that included in traditional topical therapies based on daily dosage. For example in one embodiment, the total serum testosterone concentration in a testosterone deficient individual (individual having a sustained total serum testosterone level below physiological norms, such as below about 280 ng/dl can be elevated to therapeutic/normal levels by applying to the upper arms and/or shoulders of said individual no more than 4.5 grams/day of a testosterone composition comprising a skin penetration enhancing amount of a C_7 to C_{14} - hydrocarbyl substituted 1, 3 - dioxalane, 1, 3 - dioxane, or acetal thereof, while existing comparable topical therapies require application of 5-10 g/day. In another embodiment no more than 3.5 g/day, for example 3.0 g/day or 2.5 g/day of testosterone composition is applied. The testosterone composition can be no greater than 2% testosterone, for example 1.5%, or more prefereably 1% testosterone. The composition can be no less than 0.5% testosterone.

[0149] In at least one embodiment, the individual's total serum testosterone concentration is elevated to a level greater than 280 ng/dl such as 290 ng/dl or more preferably greater than 300 ng/dL, such as 310 ng/dl or 320 ng/dl but not greater than 1500 ng/dL and more preferably not greater than 1000 ng/dL.

[0150] In another embodiment, the low dose topical administration of a composition containing an active ingredient can include application of no greater than 7.5 g/day, for example no greater than 6.0 g/day, 4.0 g/day, 3.5 g/day, or 3.0 g/day of composition to the upper arms and/or shoulders of an individual. In another embodiment, low dose administration of a composition containing an active ingredient can include application of no greater than 2.5 g/day, or 1.0 g/day, or for example 0.5 g/day or even 0.1g/day of composition to the upper arms and/or shoulders of an individual..

[0151] In yet another embodiment, the low dose administration of a composition containing an active ingredient can include application of no greater than 100 mg/day of an active ingredient, for example no greater than 75 mg/day, 60mg/day, 50 mg/day, 40 mg/day, or 30 mg/day of the active ingredient to the upper arms and/or shoulders of an individual. In another embodiment the low dose administration of a composition containing an active ingredient can include application of no greater than 25 mg/day of active ingredient, for example no greater than 15 mg/day, 10 mg/day, 5mg/day, 2.5 mg/day, 1 mg/day or even 0.5 mg/day of the active ingredient to the upper arms and/or shoulders of an individual.

[0152] In one embodiment of the invention, the daily dose of the composition or active ingredient can be administered in no less than 1 application, for example, 2 applications, 3 applications, 4 applications, 5 applications or even 6 applications within the same 24 hour period. In one embodiment, dosing of the composition or active ingredient can occur every 24 hours, or every 12 hours, or every 8 hours, or 6 hours or even 4 hours.

[0153] In another embodiment, a method of delivering an active ingredient includes applying a composition with the active ingredient and SEPA® enhancer to the upper arms and/or shoulders of an individual. The active ingredient can be testosterone. Such a method can treat an individual that is hypogonadal, an individual that has been prescribed testosterone replacement therapy, an individual that has a reduced libido, a male individual, or an individual over the age of 40, or where an individual exhibits HIV –associated muscle wasting. This embodiment of the method can treat a female, such as for anorexia nervosa, or where the individual is ovariectomized, or has female sexual dysfunction. This embodiment can also be

used where the individual is receiving antiepileptic therapy, or opiate therapy, or has hypopituitarism.

[0154] In another embodiment, the same delivery is achieved by applying approximately one-half of the amount of said composition as would be necessary to achieve the same delivery of the active if applied to the individual's abdomen. The delivery can be measured by comparing 24 hour average serum concentration levels of the active ingredient, or by comparing the area under a curves of concentration vs. time plots of the active, or by comparing the maximum serum concentration levels of the active ingredient.

[0155] The effects of the topical compositions according to the invention are further illustrated by way of the following representative examples, which in no way are intended to limit the scope of the invention.

Examples

[0156] A three-way crossover study comparing one 2.5 g dose of Opterone® (1% testosterone in a cream base containing 5% of a SEPA® penetration enhancer) applied to the upper arms and shoulders and 2.5 g of Opterone® and 5.0 g of Opterone® applied to the abdomen between the rib cage and the pubis in hypogonadal adults was conducted. Ten eligible subjects were randomized to receive three different treatment sequences of the study creams. Each subject was evaluated during 3 identical test periods that included pre-dose evaluations, one day of dosing (once/day), followed by a six-day off-treatment (washout) period. Each dose was evaluated over this one week period and then each subject was dosed with the second treatment followed by a six day washout, and then followed by the subject's third treatment and washout period and then a final safety evaluation. There was a ± 3 day window allowed for treatment days. Subjects reported to the clinic at the same time for each visit.

[0157] On Day 1, subjects reported to the clinic and remained there overnight (approximately 24 hours). They received their treatment assignment and whole blood specimens for serum testosterone (total, free and the metabolite DHT) assessments were obtained 30, 15, and 1 minute prior to dosing, and at 1, 2, 4, 6, 8, 12, 16, 18, 20, and 24 hours post-dosing. The blood specimen collected at 30 minutes prior to dosing was also used for measurements of serum estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG). Prior to discharge on Day 2, subjects received a diary and

event log to record any adverse events and/or change in medication. They were instructed not to use any testosterone products and OTC supplements for the duration of the study. This procedure was repeated for the remaining two treatments for each subject. The same schedule and procedures were followed for all three treatment regimens. After a six day wash out period (Week 4, Day 1), subjects were instructed to return to clinic for final blood specimens for serum harvesting and safety assessments at the same time as all other visits.

[0158] Prior to the first application, subjects were informed of the region of application; either the upper arms and shoulders or abdomen that was used for the test article application. The sample cream was applied only on the designated area according to the assigned treatment sequence. The cream was applied so that as much as possible of the designated skin area was covered by the cream.

[0159] All dose application used the same procedures. Before the first dose was applied, the selected area was washed with soap and water and allowed to dry thoroughly. The surface of the abdomen between the rib cage and the pubis or the upper arms including the shoulders was used as the designated application area. When randomized to Treatment 1, 2.5 g of Opterone® was applied to the upper arms and the shoulders as the designated area for that regimen. When Treatment 2 (2.5g), and/or Treatment 3 (5.0 g) were assigned, the test article was applied to the surface of the abdomen between the rib cage and the pubis. A single dose of cream was used per application. For study drug application, the entire contents of one glass jar was removed using the plastic applicator wand (provided by the sponsor) and then applied to the selected region for that treatment sequence. After the dose was applied, the subject gently massaged the cream into the skin over as much of the area as possible of the designated site using two fingers until the test article was no longer visible. Upon completion, hands were thoroughly washed with soap and water while the application site was left open to air dry for a minimum of 10 minutes without clothing and undisturbed by touching. After the test article had dried, the application site remained covered by clothing for at least 12 hours. No showering, bathing, swimming or strenuous activity/exercise that is likely to promote profuse sweating was allowed to take place for at least 6 hours following the application of the test article. Prior to discharge on Day 2, subjects were released with a Patient Diary and Event Log with instruction for completion, and instructed to return to the clinic the following week by 8:00 AM (± one hour). Subjects were to bring their Diary and Event Log to the clinic for review and collection.

Total Testosterone (TTEST) Concentration-Time Data

[0160] Mean total testosterone concentration versus time is provided in Table 1. Total testosterone (TTEST) is an endogenous compound and was detectable in all subjects before receiving the first dose. Descriptive statistics of mean total testosterone concentrations are listed by treatment in Table 1 below.

Table 1: Mean Total Testosterone Unadjusted Concentrations Following 2.5 g shoulder (1), 2.5 and 5.0 g abdomen (2 and 3) Doses of Opterone® to Hypogonadal Adult Male Subjects

	Treatment Group Concentrations (ng/dL)		
Hours Postdose	Treatment 1 (2.5g Arm/Shoulder) (n=10)	Treatment 2 (2.5g Abdomen) (n=10)	Treatment 3 (5.0g Abdomen) (n=10)
Day 1 – -0.50 hr	263.80 ± 82.15	264.30 ± 46.79	249.80 ± 69.21
Day 1 – -0.25 hr	271.60 ± 78.22	257.50 ± 50.56	254.50 ± 75.16
Day 1 – -0.01 hr	261.80 ± 86.32	270.60 ± 49.38	260.70 ± 95.25
Baseline – 0 hr	265.73 ± 81.08	264.13 ± 44.44	255.00 ± 77.15
1 hr	349.80 ± 81.96	297.10 ± 52.76	380.70 ± 71.36
2 hr	367.00 ± 28.82	331.40 ± 78.50	453.40 ± 113.69
4 hr	419.90 ± 187.36	317.00 ± 90.99	411.00 ± 108.81
6 hr	417.20 ± 218.05	278.30 ± 76.98	333.30 ± 73.04
8 hr	357.30 ± 72.64	271.80 ± 56.98	331.30 ± 57.22
12 hr	319.70 ± 43.80	291.10 ± 69.13	307.10 ± 108.14
16 hr	372.40 ± 106.04	301.10 ± 71.99	379.90 ± 57.29
18 hr	408.00 ± 112.32 [1]	341.10 ± 59.37	436.60 ± 135.65
20 hr	421.40 ± 122.5	336.60 ± 60.61	374.40 ± 74.52
24 hr	466.90 ± 111.31	357.10 ± 84.62	373.80 ± 99.95

Mean ± SD
[1] n=9

[00172] Descriptive statistics for baseline adjusted total testosterone concentrations are presented by dose level at each measured time point in Table 2.

Table 2: Mean Total Testosterone Baseline Adjusted Concentrations Following Arm/Shoulder 2.5 (1), Abdomen 2.5, and Abdomen 5.0 g Doses of Opterone® to Hypogonadal Adult Male Subjects

	Treatment Group Mean (±SD) Concentrations (ng/mL)		
Hours Postdose	**Treatment 1 (2.5g Arm/Shoulder) (n=10)**	**Treatment 2 (2.5g Abdomen) (n=10)**	**Treatment 3 (5.0g Abdomen) (n=10)**
0 hr	0	0	0
1 hr	84.07 ± 63.28	32.97 ± 46.35	125.70 ± 108.24
2 hr	101.27 ±63.44	67.27 ± 79.79	198.40 ± 151.04
4 hr	154.17 ± 206.98	52.87 ± 80.01	156.00 ± 109.10
6 hr	151.47 ± 248.54	14.17 ± 59.72	78.30 ± 74.20
8 hr	91.57 ± 120.68	7.67 ± 49.03	76.30 ± 76.56
12 hr	53.97 ± 96.49	26.97 ± 50.03	52.10 ± 108.42
16 hr	106.67 ± 104.77	36.97 ± 72.90	124.90 ± 93.81
18 hr	135.63 ± 114.51 [1]	76.97 ± 56.40	181.60 ± 125.65
20 hr	155.67 ± 86.06	72.47 ± 62.57	119.40 ± 71.02
24 hr	201.17 ± 141.78	92.97 ± 66.27	118.80 ± 53.37

[1] n=9

Total Testosterone Pharmacokinetic Parameter Estimates

[00173] The pharmacokinetic non-compartmental analysis was performed on unadjusted total testosterone levels. The TTEST pharmacokinetic parameters were then adjusted to reflect the impact of baseline observations. The baseline adjusted pharmacokinetic parameters were calculated in order to account for differences in baseline total testosterone values across the individual subjects. Mean unadjusted and baseline adjusted TTEST pharmacokinetic parameters are presented in Table 3.

Table 3: Total Testosterone Pharmacokinetic Parameters Following Arm/shoulder 2.5 (1), Abdomen 2.5 (2), and Abdomen 5.0 g (3) Doses of Opterone® to Hypogonadal Adult Male Subjects

Pharmacokinetic Parameter	Dose Group (g) Mean (±SD) Treatment 1 (n=10)	Treatment 2 (n=10)	Treatment 3 (n=10)
Unadjusted Data			
AUC(0-last) (hr*ng/dL)	9186.0 ± 1221.2	7397.4 ± 1237.1	8800.3 ± 1420.1
Cmax (ng/dL)	576.50 ± 192.96	407.90 ± 53.403	533.30 ± 118.76
Cavg (ng/dL)	382.15 ± 50.373	308.31 ± 50.629	366.14 ± 58.686
Tmax† (hr)	19.05 (1.00 – 24.00)	19.03 (2.02 – 24.98)	11.01 (1.97 – 24.23)
Baseline Concentration (ng/dL)	265.73 ± 81.08	264.13 ± 46.439	255.00 ± 77.147
Baseline Adjusted Data			
AUC(0-last) (hr*ng/dL)	2800.6 ± 1923.2	1056.2 ± 893.85	2669.2 ± 1589.1
Cmax (ng/dL)	310.77 ± 221.64	143.77 ± 47.033	278.30 ± 123.74
Cavg (ng/dL)	116.42 ± 79.707	44.172 ± 37.460	111.14 ± 66.313

Mean ± SD

† Time parameters presented as Median (Range)

What is claimed is:

1. A method of elevating total serum testosterone concentration in a testosterone deficient individual comprising, applying to the upper arm and/or shoulder of said individual no more than 4.5 grams/day of a testosterone composition comprising a skin penetration enhancing amount of a C_7 to C_{14} - hydrocarbyl substituted 1,3 - dioxalane, 1,3 - dioxane, or acetal thereof.

2. The method of claim 1, wherein no more than 2.5 g/day of the testosterone composition is applied.

3. The method of claim 1, wherein the testosterone composition contains no more than 2.0 wt.% testosterone relative to the to the total weight of the composition.

4. The method of clam 1, wherein the testosterone composition contains 1.0 wt% testosterone relative to the total weight of the composition.

5. The method of claim 1, wherein a skin penetration enhancing amount comprises no less than 2% by total weight of the composition.

6. The method of claim 1, wherein the composition comprises a skin cream.

7. The method of claim 1, wherein said individual's total serum testosterone concentration is elevated to a level greater than 280 ng/dL.

8. The method of claim 7, wherein said individual's total serum testosterone concentration is elevated to a level no greater than 1500 ng/dl.

9. A method of delivering an active ingredient comprising, applying a composition comprising said active ingredient and a C_7 to C_{14} - hydrocarbyl substituted 1,3 - dioxalane, 1,3 - dioxane, or acetal thereof to the shoulders and/or upper arms of an individual.

10. The method of claim 9, wherein the active ingredient is testosterone.

11. The method of claim 10, wherein the individual is hypogonadal.

12. The method of claim 10, wherein the individual has been prescribed testosterone replacement therapy.

13. The method of claim 10, wherein the individual has a reduced libido.

14. The method of claim 10, wherein the individual is a male.

15. The method of claim 10, wherein the individual is over the age of 40.

16. The method of claim 10, wherein the individual exhibits HIV-associated muscle wasting.

17. The method of claim 10, wherein the individual is female.

18. The method of claim 10, wherein the composition is used to treat anorexia nervosa.

19. The method of claim 17, wherein the individual is ovariectomized.

20. The method of claim 17, wherein the composition is used for female sexual dysfunction.

21. The method of claim 10, wherein the individual is receiving antiepileptic therapy.

22. The method of claim 10, wherein the individual is receiving antiopiate therapy.

23. The method of claim 10, wherein the composition is used for hypopituitarism.

24. The method of claim 9, wherein the individual needs the active ingredient.

25. The method of claim 9, wherein the same delivery of said active is achieved by applying approximately one-half of the amount of said composition as would be necessary to achieve the same delivery of said active if applied to said individual's abdomen.

26. The method of claim 25, wherein delivery is measured by comparing 24 hour average serum concentration levels of the active ingredient.

27. The method of claim 25, wherein delivery is measured by comparing the areas under the curves of concentration vs. time plots of the active ingredient.

28. The method of claim 25, wherein delivery is measured by comparing the maximum serum concentration levels of the active ingredient.

29. The method of claim 9, wherein the composition comprises a skin cream.