PROSTAGLANDIN COMPOSITIONS AND METHODS OF TREATMENT FOR MALE ERECTILE DYSFUNCTION

RELATED APPLICATIONS

This application is a continuation-in-part of co-pending application Serial No. 09/947,617, filed September 6, 2001, the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD OF THE INVENTION

This invention relates to the compositions and methods for treatment of erectile dysfunction, and more particularly to methods and pharmaceutical compositions for intranavicular administration of vasodilator medicaments to the fossa navicularis of a patient.

BACKGROUND OF THE INVENTION

The term "impotence" has been used to signify the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. The term "erectile dysfunction" has been suggested as a more precise term "to signify an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function." Droller, M. J. et al. Impotence. Consensus Development Conference Statement, National Institutes of Health (1993).

Erectile dysfunction may result from psychological causes (psychogenic erectile dysfunction) or organic causes or a combination of both. Organic causes include physiological, nervous, vascular and hormonal pathologies or a combination thereof.

The normal physiology of an erection involves nerve impulses that signal certain muscles to relax. These muscles, when contracted, restrict blood flow through arteries in the penis. When relaxed, the muscles permit a significant increase in blood flow. The increased blood flow engorges three groups of erectile tissue within the penis with blood and the penis becomes less flaccid. The engorged erectile tissue and the muscle structure of the penis depress adjacent veins, restricting the flow of blood

out of the penis. The restriction of blood flow out of the penis increases and sustains the erection.

Deficiencies of some hormones, such as testosterone, or elevation of others, such as prolactin, can cause erectile dysfunction. Many drugs, such diuretics, antihypertensives, anticonvulsants, narcotics, alcohol, and psychotropic drugs may cause erectile dysfunction as a side effect. Murray, F. T. et al. Amer. J. Medical Sci. 309: 99-109 (1995).

Damage to nerves and blood vessels may also provide an organic cause for erectile dysfunction. Disease processes may involve several aspects. For example, diabetes, which causes damage to both nerves and blood vessels, can cause erectile dysfunction. A significant percent of all diabetic men will suffer from erectile dysfunction.

Methods proposed for the treatment of erectile dysfunction have included external devices, sex therapy, surgical implantation of internal prostheses, injection of drugs directly into the penis and topically applied medications. None of these approaches is entirely effective.

External devices include tourniquets (see U.S. Pat. No. 2,818,855) and externally applied vacuum erection aids. While some clinicians consider externally applied erection aids as a first option for treatment, some patients are unwilling to use such devices. O'Keefe, M., et al. Medical Clinics of North America 79: 415-434 (1995).

Symptomatic sex therapy was originally found to be effective by Masters and Johnson, but later studies have not shown as impressive results. Freudian therapy does not appear to patients to be an attractive alternative. Vickers, M. A., et al. J. Urology 149: 1258-1261 (1993).

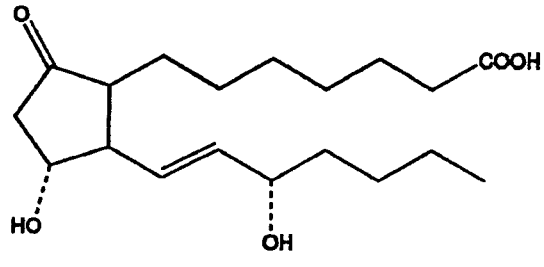
Surgically implanted mechanical devices, such as hinged or solid rods and inflatable, spring driven or hydraulic prostheses have been used for some time.

The administration of erection effecting and enhancing drugs is taught in U.S. Pat. No. 4,127,118 to LaTorre. This patent teaches a method of treating male impotence by injecting into the penis an appropriate vasodilator, in particular, an

adrenergic blocking agent or a smooth muscle relaxant to effect and enhance an erection.

More recently, U.S. Pat. No. 4,801,587 to Voss et al. teaches the application of an ointment to relieve impotence. The ointment consists of the vasodilators papaverine, hydralazine, sodium nitroprusside, phenoxybenzamine, or phentolamine and a carrier to assist absorption of the primary agent through the skin. U.S. Pat. No. 5,256,652 to El-Rashidy teaches the use of an aqueous topical composition of a vasodilator such as papaverine together with hydroxypropyl-β-cyclodextrin.

Prostaglandin E_1 is a derivative of prostanoic acid, a 20-carbon atom lipid acid, represented by the formula:



and is commercially available, e.g., from Chinoin Pharmaceutical and Chemical Works Ltd. (Budapest, Hungary) under the designation "Alprostadil USP."

Prostaglandin E_1 is a vasodilator useful to maintain open blood vessels and therefore, to treat peripheral vascular disease among other ailments. While the potential benefits from transdermal delivery of prostaglandin E_1 have long been recognized, prior efforts at developing a topical composition for prostaglandin delivery have not been fully successful.

In one commercially available form (MUSE®, Vivus, Menlo Park CA), alprostadil is administered in a pellet deposited in the urethra using an applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter (Padma-Nathan, H., et al., N. Engl. J. Med., 336: 1-7 (1997), see especially FIG. 1). In the home treatment portion of the Padma-Nathan et al. study, 32.7% of the patients (10.8% of administrations) receiving MUSE® complained of penile pain and 5.1% experienced minor urethral

trauma, compared to 3.3% and 1.0%, respectively, of the patients receiving placebo. Frequency of report of these side effects has varied in subsequent studies: MUSE® producing penile pain in 17-23.6% of administrations, compared to 1.7% with placebo and minor urethral bleeding reported by 4.8% of patients (Peterson, C.A., et al., J. Urol., 159: 1523-1528 (1998)). In a study on a European population, 31% MUSE® patients reporting penile pain or burning sensations, 4.8% reporting urethral bleeding, and 2.9% reporting severe testicular pain (Porst, H., Int. J. Impot. Res., 9:187-192 (1997)). The percent of patients responding to MUSE® treatment, defined as having at least one erection considered sufficient for intercourse, has been reported to be 43% (Porst, 1997), 65.9% (Padma-Nathan et al., 1997) and 70.5% (Peterson et al., 1998), although published editorial comment has suggested that the percent of patients responding in the latter two studies is more properly reported as 30-40% (Benson, G., J. Urol., 159: 1527-1528 (1998).

In particular, there is presently no commercial source for a topical semi-solid formulation that is useful without a supporting device such as a patch, adhesive strip, and the like. For example, U.S. Patent No. 5,380,760 to Wendel et al. is directed to a topical prostaglandin formulation that includes a pressure-sensitive, adhesive sheet of polyisobutylene.

Working alone, most drugs, prostaglandin formulations included, do not sufficiently permeate the skin to provide drug concentration levels comparable to those obtained from other drug delivery routes. To overcome this problem, topical drug formulations typically include a skin penetration enhancer. Skin penetration enhancers also may be referred to as absorption enhancers, accelerants, adjuvants, solubilizers, sorption promoters, etc. Whatever the name, such agents serve to improve drug absorption across the skin. Ideal penetration enhancers not only increase drug flux across the skin, but do so without irritating, sensitizing, or damaging skin. Furthermore, ideal penetration enhancers should not adversely affect the physical qualities of the available dosage forms (e.g. cream or gel), or the cosmetic quality of the topical composition.

A wide variety of compounds have been evaluated as to their effectiveness in enhancing the rate of penetration of drugs through the skin. See, for example,

Percutaneous Penetration Enhancers, Maibach H. I. and Smith H. E. (eds.), CRC Press, Inc., Boca Raton, FL. (1995), which surveys the use and testing of various skin penetration enhancers, and Büyüktimkin et al., Chemical Means of Transdermal Drug Permeation Enhancement in *Transdermal and Topical Drug Delivery Systems* , Gosh T.K., Pfister W.R., Yum S.I. (Eds.), Interpharm Press Inc., Buffalo Grove, IL. (1997).

A fully successful topical or transmucosal formulation for prostaglandin E_1 has not yet been identified and commercially available. Unfortunately, prostaglandin E_1 is readily transformed by rearrangement and other reactions. This relative instability tends to complicate efforts at formulating composition for intranavicular delivery.

The present invention addresses these problems by providing a method and compositions for the intranavicular delivery of semi-solid, separation- resistant and chemically stable composition for the relatively rapid, sustained delivery of a vasodilator, preferably prostaglandin E_1.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods for the treatment of erectile dysfunction by the intranavicular application of pharmaceutical compositions to the mammalian penis. In another aspect, the present invention provides compositions for the preparation of a pharmaceutical composition for the treatment of erectile dysfunction whereby the pharmaceutical composition is applied in the fossa navicularis of the penis.

The invention provides methods of treating erectile dysfunction comprising the step of placing within the fossa navicularis of the patient an effective erection-inducing amount of a prostaglandin E_1 composition of a semi-solid consistency. The composition comprises a vasodilator, preferably prostaglandin E_1, a penetration enhancer, a shear-thinning polysaccharide, a lipophilic compound, and an acidic buffer system. The penetration enhancer is an alkyl-2-(N-substituted amino)-alkanoate ester, a (N-substituted amino)-alkanol alkanoate, or a mixture of these. The lipophilic compound may be an aliphatic C_1 to C_8 alcohol, an aliphatic C_2 to C_{30} ester, aliphatic C_8 to C_{30} ester or a mixture of these. The composition includes a

buffer system providing a buffered pH value for said composition in the range of about 3 to about 7.4. A preferred pH value is about 3.0 to about 7.4, more preferably about 3.0 to about 6.5, most preferably from about 3.5 to about 6.0.

Intranavicular placement of the vasodilator composition of the present invention, i.e., within in the fossa navicularis, provides a number of advantages over placing such compositions on the skin surface of the penis or depositing a composition within the more proximal "pars spongiosa" portion of the urethra. The fossa navicularis is a natural expanded chamber suitably adapted to receive and retain semisolid medicaments. A semi-solid medicament, such as the composition of the present invention, when placed in the fossa has higher impedance to flow at narrowed exits of this space, the meatus and the urethra. The impedance to flow is proportional to the product of the cross sectional area of the path and the path length.

The lining of the fossa navicularis is a non-keratinized stratified squamous epithelium, thereby providing for enhanced permeability compared to the keratinized epithelium of the surface skin of the outside of the penis.

The use of a short applicator that has a tip that ends within the anatomical limits of the fossa navicularis is less invasive than threading a longer applicator several centimeters up (or proximal) into the penile urethra proper. A suitable applicator is described in U.S. Patent No. 6,224,573 to Yeager et al., which is incorporated herein by reference to the extent relevant. Preferably, the applicator comprises a reservoir containing an erection - inducing amount of a semi-solid prostaglandin E_1 composition. More preferably, the applicator is a single use device and contains a single dose of the semi-solid prostaglandin E_1 composition.

In one embodiment, an amount of the composition of the present invention lacking the active ingredient occupies a position in the applicator between the single dose of the semi-solid prostaglandin E_1 composition and the applicator tip. In such an embodiment, the use of the applicator results in a deposit of composition lacking the active ingredient in the proximal fossa navicularis and the distal portion of the penile urethra proper, physically restricting the single dose of the semi-solid prostaglandin E_1 composition to the fossa navicularis.

The applicator is typically accompanied by instructions for use placed on all or some of the following: on the package containing the applicator, in a package insert and on the outside surface of the applicator itself.

The relatively high glycogen content and bacterial flora within the fossa navicularis provides a naturally lower pH within the space, so that relatively lower pH compositions in the acidic range that provide for enhanced solubility of prostaglandin E_1 can be more easily tolerated without excessive irritation of the tissues.

The fossa navicularis is also a more immunologically protected site than the adjacent pars spongiosa region of the penile urethra proper. Placing the tip of an applicator within the anatomical limits of the fossa navicularis thus presents less of a risk of circumventing the natural barriers to disease by artificially transporting contaminants, e.g., from the surface of the penis, directly into the penile urethra proper.

A pharmaceutical composition suitable for intranavicular application comprises prostaglandin E_1, a penetration enhancer, a modified polysaccharide gum, a lipophilic compound, and an acidic buffer system. The penetration enhancer is an alkyl-2-(N-substituted amino)-alkanoate ester, a (N-substituted amino)-alkanol alkanoate, or a mixture of these. The lipophilic compound may be an aliphatic C_1 to C_8 alcohol, an aliphatic C_8 to C_{30} ester, or a mixture of these. The composition includes a buffer system providing a buffered pH value for said composition in the range of about 3 to about 7.4. If desired, stabilizers, preservatives and emulsifiers may be included.

Compositions of the present invention can take the form of a semi-solid suitable for intranavicular application. In use as a intranavicular agent, these compositions exhibit relatively high prostaglandin penetration into the glans penis and bioavailability without requiring a wasteful overloading prostaglandin concentration. The compositions further exhibit reduced irritation, sensitivity and damage of local tissues. In a preferred embodiment, the compositions are delivered to the fossa navicularis using an suitable single dose applicator.

Other and further aims, purposes, features, advantages, embodiments and the like will be apparent to those skilled in the art from the present specification and the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings,

FIG. 1 is a diagram of the anatomical structure of the human penis in longitudinal section view;

FIG. 2 is a schematic diagram of the anatomical details of the distal portion of the human penis in longitudinal section;

FIG. 3 is a graph of the cumulative prostaglandin E_1 penetration through shed snake skin of seven prostaglandin E_1 compositions prepared according to the present invention; and

FIG. 4 is a comparison graph of the cumulative prostaglandin E_1 penetration through shed snake skin of two prostaglandin E_1 compositions prepared according to the present invention and two comparative compositions.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has been unexpectedly found that that a semi-solid prostaglandin E_1 composition suitable for the treatment of erectile dysfunction can be placed advantageously in a natural enlarged space immediately proximal to the penile meatus, the fossa navicularis.

The fossa navicularis provides a restricted site that is ideally suited for the application of pharmaceutical compositions. The space is lined by a non-keratinized stratified squamous epithelium and is thereby distinguished from the surface skin covering the glans and the rest of the penis as well as from the stratified columnar epithelium of the lining of the urethra proper. It has been found that the administration of the composition of the present invention in the fossa navicularis has unexpectedly high efficacy and low incidence of local side effects.

The fossa navicularis provides a natural space adaptable to the application and retention of pharmaceutical compositions. A semi-solid medicament, such as the

composition of the present invention, when placed in the fossa has higher impedance to flow at narrowed exits of this space, the meatus and the urethra. Thus, a semi-solid medication of suitably chosen viscosity is naturally retained within the fossa, facilitating the absorption of active agents such as vasodilators and the like.

The fossa navicularis is part of the natural defense system that protects the body against infection. The fossa navicularis is a more immunologically protected site than the adjacent pars spongiosa region of the penile urethra proper. Depositing a semisolid medicament within the anatomical limits of the fossa navicularis thus does not circumvent the natural barriers to disease by artificially transporting contaminants, e.g., from the surface of the penis, directly into the penile urethra proper. As noted above, the fossa navicularis naturally supports a bacterial flora that maintains an acid pH.

Referring to FIG. 1, the basic structure of the human penis is illustrated. The fossa navicularis 110 in glans penis 130 is a natural enlargement of the lumen of the male urethra that extends distally to the urethral meatus 128 and proximally to the pendulous region of the urethra 112 (also termed "pars spongiosa" region of the urethra), the portion of the urethra that passes through the corpus spongiosum 134. The bulbar urethra 114 is proximal to the pendulous region of the urethra, and passes through the bulbospongiosus muscle 140. More proximally, the opening 148 in the wall of the urethra of the bulbourethral glands (Cowper's glands) can be seen. More proximally, the urethra passes through the prostate gland 160, where openings of ejaculatory duct 156 and of the prostate utricle 158 are visible in the wall of the urethra.

Referring to FIG. 2, the detailed structure of the fossa navicularis 110 is illustrated. The external opening of the urethral meatus 128 is the distal limit of the fossa navicularis. The external skin of the glans is covered by a keratinized stratified squamous epithelium 186 (Pudney, J., and Anderson, D.J., (1995) Immunobiology of the human penile urethra, Amer. J. Path., 147: 155-165) that is marked by proximally by a sharp transition (dashed line) to the nonkeratinized stratified squamous epithelium without glycogen 184 that is characteristic of the lining of the distal fossa navicularis.

The fossa navicularis widens proximally and the lining changes to a nonkeratinized stratified squamous epithelium with glycogen 182. The glycogen in this region is believed to support a bacterial flora that lowers the pH of the region and contributes to a natural defense against infection. Holstein, A.F., et al., (1991). Different epithelia in the distal human male urethra, Cell Tiss. Res. 264: 23-32. This nonkeratinized stratified squamous epithelium with glycogen is under hormonal control, and increases in extent under increased estrogen levels (Holstein, et al., 1991). The proximal fossa navicularis narrows in width, and is lined by a stratified columnar epithelium 180.

The semi-solid composition of the present invention has a suitably chosen viscosity such that the composition is naturally retained within the fossa navicularis. The semi-solid composition can exhibit Newtonian or non-Newtonian rheological characteristics. In some preferred embodiments, the semi-solid composition of the present invention exhibits non-Newtonian rheological characteristics, i.e. in which the apparent viscosity is dependent on the shear rate applied to the composition. Preferably the composition has "shear-thinning" rheological properties. As used herein, "shear-thinning" refers to a reduction in apparent viscosity (the ratio of shear stress to the shear rate) with increasing shear rate, whether the reduction in apparent viscosity is time independent (pseudoplastic), time dependent (thixotropic) or associated with a yield stress, defined as a stress that must be exceeded before flow starts, (Bingham plastics and generalized Bingham plastics). See, generally, Harris, J., & Wilkinson, W.L., "Non-newtonian Fluid," pp.856-858 in Parker, S.P., ed., McGraw-Hill Encyclopedia of Physics, Second Edition, McGraw-Hill, New York,1993. A suitable viscosity ranges from about 5,000 centipoise (cps) to about 20,000 cps, preferably from about 7,000 cps to about 13,000 cps.

The method of the present invention also provides a relatively non-invasive applicator. When used to place an effective, erection-inducing amount of a prostaglandin E_1 composition within the fossa navicularis, the tip of the applicator does not extend beyond the anatomical limits of the fossa navicularis. Preferably, the tip of the applicator does not extend into the penis more than about two centimeters beyond the meatal opening, more preferably no more than about one centimeter, most

preferably no more than about 0.5 centimeters. Preferably, the applicator comprises a reservoir containing an erection-inducing amount of a semi-solid composition comprising at least one vasodilator, preferably a prostaglandin E_1 composition. More preferably, the applicator is a single use device and contains a single dose of the semi-solid vasodilator composition. The applicator is typically accompanied by instructions for use placed on all or some of the following: on the package containing the applicator, in a package insert and on the outside surface of the applicator itself.

The pharmaceutical composition of the present invention comprises at least one vasodilator, preferably prostaglandin E_1, an alkyl (N-substituted amino) ester, a shear-thinning polysaccharide, a lipophilic compound, and an acid buffer system.

Suitable vasoactive agents include, but are not limited to: nitrates such as nitroglycerin, isosorbide dinitrate, erythrityl tetranitrate, amyl nitrate, sodium nitroprusside, molsidomine, linsidomine chlorhydrate ("SIN-1") and S-nitroso-N-acetyl-d,l-penicillamine ("SNAP"); amino acids such as L-arginine; long and short acting α-blockers such as phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, alfuzosin, tamsulosin and indoramin; vasodilative natural herbal compositions and bioactive extracts thereof, such as gosyajinki-gan, Satureja obovata, bai-hua qian-hu, lipotab, saiboku-to, vinpocetine, Gingko biloba, bacopa, Gynostemma pentaphyllum, gypenosides, Evodia rutaecarpa, rutaecarpine, dehydroevodiamine, dan-shen, salviae miltiorrhizae radix, shosaikoto, Zizyphi fructus, ginseng and mixtures thereof (U.S. Patent 6,007,824); ergot alkaloids such as ergotamine and ergotamine analogs, e.g., acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride and terguride; antihypertensive agents such as diazoxide, hydralazine and minoxidil; vasodilators such as nimodepine, pinacidil, cyclandelate, dipyridamole and isoxsuprine; chlorpromazine; haloperidol; yohimbine; trazodone; naturally occurring prostaglandins such as PGE_1, PGA_1, PGB_1, $PGF_{1\alpha}$, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, $PGF_{3\alpha}$; semisynthetic or synthetic derivatives of natural prostaglandins, including carboprost tromethamine, dinoprost

tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone and tiaprost; and vasoactive intestinal peptides. Prazosin, prostaglandin E_1 and prostaglandin E_2 are particularly preferred vasoactive agents for use in conjunction with the present method.

Additionally, simultaneous administration of two or more vasoactive agents may be desirable and may in some cases exhibit a synergistic effect. The combination of prazosin with prostaglandin E_1 has been found to be particularly advantageous in this regard; the latter drug appears to act a permeation enhancer for prazosin, i.e., it increases the rate at which prazosin permeates through the skin or mucosal tissue and enters the bloodstream.

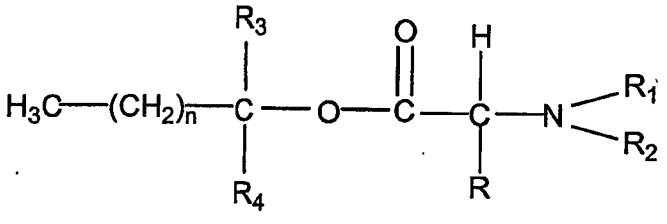
Prostaglandin E_1 is well known to those skilled in the art. Reference may be had to various literature references for its pharmacological activities, side effects, and normal dosage ranges. See for example, *Physician's Desk Reference*, 51st Ed. (1997), *The Merck Index*, 12th Ed., Merck & Co., N.J. (1996), and *Martindale The Extra Pharmacopoeia*, 28th Ed., London, The Pharmaceutical Press (1982). Prostaglandin E_1 as well as other compounds referenced herein are intended to encompass pharmaceutically acceptable derivatives including physiologically compatible salts and ester derivatives thereof.

The quantity of prostaglandin E_1 in the pharmaceutical compositions of the present invention is a therapeutically effective amount and necessarily varies according to the desired dose, the dosage form (e.g., suppository or topical), and the particular form of prostaglandin E_1 used. The term "prostaglandin" as used generically herein refers to the prostaglandin free acid and pharmaceutically acceptable derivatives thereof, including prostaglandin E_1 (PGE_1), pharmaceutically acceptable salts and lower alkyl esters thereof (the term "lower alkyl" as used herein means straight chain or branched chain alkyl containing one to four carbon atoms). The composition generally contains about 0.001 percent to 1 percent prostaglandin E_1, typically contains about 0.05 percent to 1 percent prostaglandin E_1, preferably about 0.1 percent to 0.5 percent, based on the total weight of the composition.

An important component of the present invention is the penetration enhancer. The penetration enhancer is an alkyl-2-(N-substituted amino)-alkanoate, a (N-

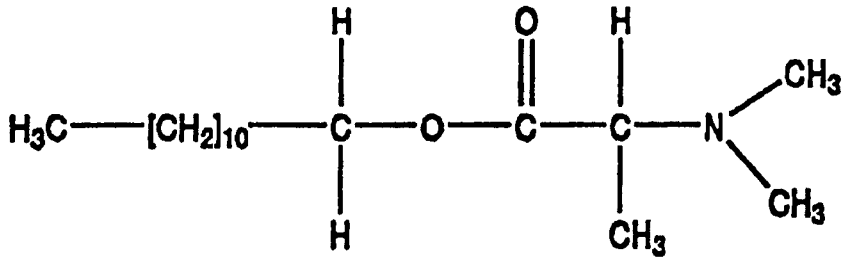
substituted amino)-alkanol alkanoate, or a mixture of these. For convenient reference, alkyl-2-(N-substituted amino)-alkanoates and (N-substituted amino)-alkanol alkanoates can be grouped together under the label alkyl (N-substituted amino) esters.

Alkyl-2-(N-substituted amino)-alkanoates suitable for the present invention can be represented as follows:

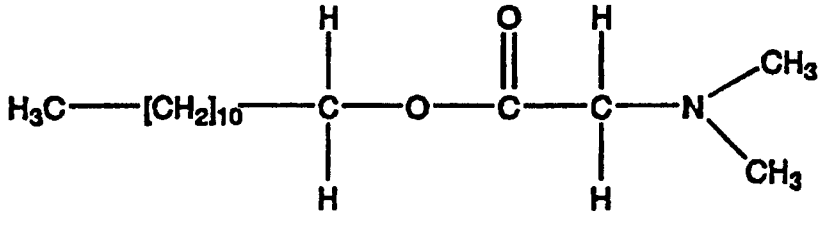


wherein n is an integer having a value in the range of about 4 to about 18; R is a member of the group consisting of hydrogen, C_1 to C_7 alkyl, benzyl and phenyl; R_1 and R_2 are members of the group consisting of hydrogen and C_1 to C_7 alkyl; and R_3 and R_4 are members of the group consisting of hydrogen, methyl and ethyl.

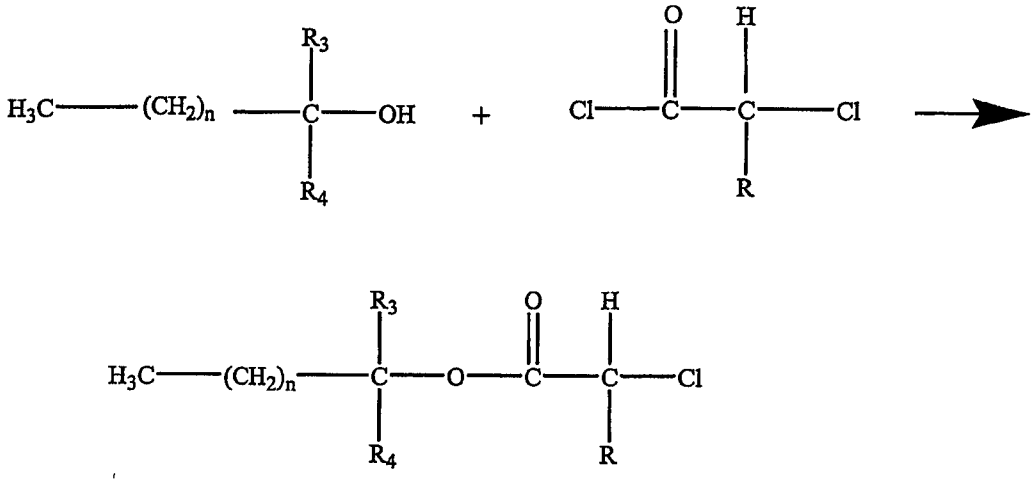
Preferred are alkyl (N,N-disubstituted amino)-alkanoates such as C_4 to C_{18} alkyl (N,N-disubstituted amino)-acetates and C_4 to C_{18} alkyl (N,N-disubstituted amino)-propionates and pharmaceutically acceptable salts and derivatives thereof. Exemplary specific alkyl-2-(N,N-disubstituted amino)-alkanoates include dodecyl 2-(N,N dimethylamino)-propionate (DDAIP);



and dodecyl 2-(N,N-dimethylamino)-acetate (DDAA);

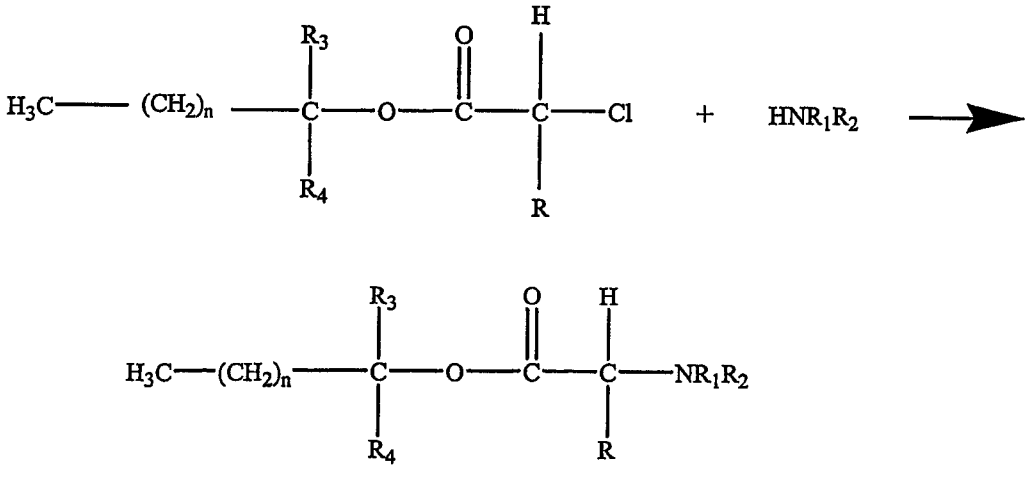


Alkyl-2-(N,N-disubstituted amino)-alkanoates are known. For example, dodecyl 2-(N,N-dimethylamino)-propionate (DDAIP) is available from Steroids, Ltd. (Chicago, IL). In addition, alkyl-2-(N,N-disubstituted amino)-alkanoates can be synthesized from more readily available compounds as described in U.S. Patent No. 4,980,378 to Wong et al., which is incorporated herein by reference to the extent that it is not inconsistent. As described therein, alkyl-2-(N,N-disubstituted amino)-alkanoates are readily prepared via a two-step synthesis. In the first step, long chain alkyl chloroacetates are prepared by reaction of the corresponding long chain alkanols with chloromethyl chloroformate or the like in the presence of an appropriate base such as triethylamine, typically in a suitable solvent such as chloroform. The reaction can be depicted as follows:



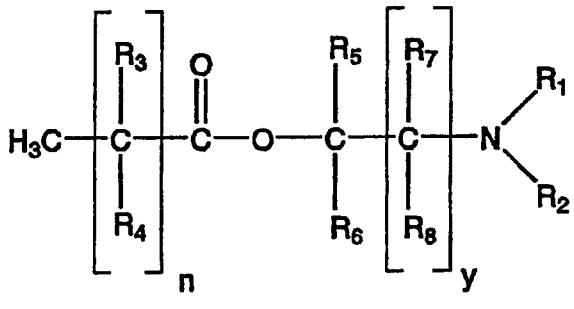
wherein R, R_3, R_4 and n are defined as above. The reaction temperature may be selected from about 10 degrees Celsius to about 200 degrees Celsius or reflux, with room temperature being preferred. The use of a solvent is optional. If a solvent is used, a wide variety of organic solvents may be selected. Choice of a base is likewise not critical. Preferred bases include tertiary amines such as triethylamine, pyridine and the like. Reaction time generally extends from about one hour to three days.

In the second step, the long chain alkyl chloroacetate is condensed with an appropriate amine according to the scheme:



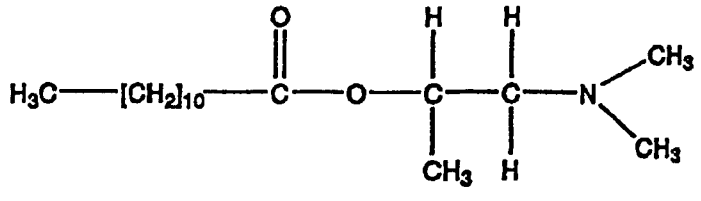
wherein n, R, R_1, R_2, R_3 and R_4 are defined as before. Excess amine reactant is typically used as the base and the reaction is conveniently conducted in a suitable solvent such as ether. This second step is preferably run at room temperature, although temperature may vary. Reaction time usually varies from about one hour to several days. Conventional purification techniques can be applied to ready the resulting ester for use in a pharmaceutical compound.

Suitable (N-substituted amino)-alkanol alkanoates can be represented by the formula:

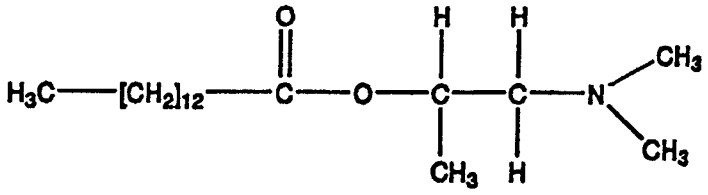


wherein n is an integer having a value in the range of about 5 to about 18; y is an integer having a value in the range of 0 to about 5; and R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are members of the group consisting of hydrogen, C_1 to C_8 alkyl, and C_1 to C_8 aryl; and R_8 is a member of the group consisting of hydrogen, hydroxyl, C_1 to C_8 alkyl, and C_1 to C_8 aryl.

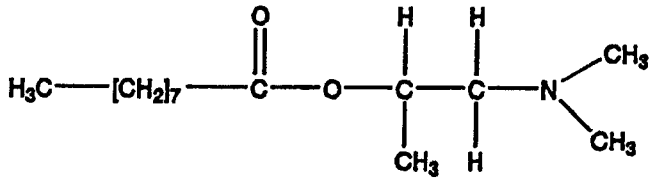
Preferred are (N-substituted amino)-alkanol alkanoates such as C_5 to C_{18} carboxylic acid esters and pharmaceutically acceptable salts thereof. Exemplary specific (N,N-disubstituted amino)-alkanol alkanoates include 1-(N,N-dimethylamino)-2-propanol dodecanoate (DAIPD);



1-(N,N-dimethylamino)-2-propanol myristate (DAIPM);



1-(N,N-dimethylamino)-2-propanol oleate (DAIPO);



The (N,N-disubstituted amino)-alkanol alkanoates are readily prepared by reacting the corresponding aminoalkanol with lauroyl chloride in the presence of triethylamine. A solvent such as chloroform is optional but preferred. For example, 1-(N,N-dimethylamino)-2-propanol can be reacted with lauroyl chloride in chloroform and in the presence of triethylamine to form 1-(N,N-dimethylamino)-2-propanol dodecanoate (DAIPD).

Among the suitable penetration enhancers for the present invention DDAIP is generally preferred.

The penetration enhancer is present in an amount sufficient to enhance the penetration of the prostaglandin E_1 into the tissue. The specific amount varies necessarily according to the desired release rate and the specific form of prostaglandin E_1 used. Generally, this amount is in the range of about 0.5 percent to about 10 percent, based on the total weight of the composition. Preferably, the penetration enhancer is about 2 to about 5 weight percent of the composition.

Natural and modified polysaccharide gums are also an important ingredient of the present composition. Suitable representative gums are those in the natural and modified galactomannan gum category. A galactomannan gum is a carbohydrate polymer containing D-galactose and D-mannose units, or other derivatives of such a polymer. There is a relatively large number of galactomannans, which vary in composition depending on their origin. The galactomannan gum is characterized by a

linear structure of β-D-mannopyranosyl units linked (1→4). Single membered α-D-manopyranosyl units, linked (1→6) with the main chain, are present as side branches. Galactomannan gums include guar gum, which is the pulverized endosperm of the seed of either of two leguminous plants (*Cyamposis tetragonalobus and psoraloids*) and locust bean gum, which is found in the endosperm of the seeds of the carobtree (*ceratonia siliqua*).

Suitable modified polysaccharide gums include ethers of natural or substituted polysaccharide gums, such as carboxymethyl ethers, hydroxypropyl ethers, ethylene glycol ethers and propylene glycol ethers. An exemplary substituted polysaccharide gum is methylcellulose. A preferred modified polysaccharide gum is modified guar gum.

Suitable shear-thinning polysaccharides include, without limitation, guar gums, modified guar gyms, locust bean gums, xanthan gyms carboxymethycellulose, methylcellulose, hydroxypropyl methylcellulose, hydroxygethylcellulose, and hydrocypropylcellulose. Preferred shear-thinning polysaccharides are natural and modified galactomannan gums, including modified guar gums.

Other suitable representative gums include agar gum, carrageenan gum, ghatti gum, karaya gum, rhamsan gum and xanthan gum. The composition of the present invention may contain a mixture of various gums, or mixture of gums and acidic polymers.

Gums, and galactomannan gums in particular, are well-known materials. See for instance, *Industrial Gums: Polysaccharides & Their Derivatives*, Whistler R. L. and BeMiller J.N. (eds.), 3rd Ed. Academic Press (1992) and Davidson R. L., *Handbook of Water-Soluble Gums & Resins*, McGraw-Hill, Inc., N.Y. (1980). Most gums are commercially available in various forms, commonly a powder, and ready for use in foods and topical compositions. For example, locust bean gum in powdered form is available from Tic Gums Inc. (Belcam, MD).

When present, the polysaccharide gums are present in the range of about 0.1 percent to about 5 percent, based on the total weight of the composition, with the preferred range being about 0.5 percent to 3 percent. In one preferred embodiment,

2.5 percent by weight of a polysaccharide gum is present. Illustrative compositions are given in the examples, below.

An optional alternative to the polysaccharide gum is a polyacrylic acid polymer. A common variety of polyacrylic acid polymer is known generically as a "carbomer." Carbomer is a polyacrylic acid polymer lightly cross-linked with polyalkenyl polyether. It is commercially available from the B. F. Goodrich Company (Akron, Ohio) under the designation "CARBOPOL™." A particularly preferred variety of carbomer is that designated as "CARBOPOL 940."

Other polyacrylic acid polymers suitable for use in practicing this invention are those commercially available under the designations "Pemulen™" (B. F. Goodrich Company) and "POLYCARBOPHIL™" (A.H. Robbins, Richmond, VA). The Pemulen™ polymers are copolymers of C_{10} to C_{30} alkyl acrylates and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of sucrose or an allyl ether of pentaerythritol. The POLYCARBOPHIL™ polymer is a polyacrylic acid cross-linked with divinyl glycol.

Where polyacrylic acid polymers are present, they represent about 0.5 percent to about 5 percent of the composition, based on its total weight. Suitable shear-thinning polyacrylic acid polymers include pseudoplastic polyacrylic acid polymers and co-polymers.

Another important component of the present invention is a lipophilic compound. In one embodiment, the lipophilic compound as used herein refers to an agent that is both lipophilic and hydrophilic. The C_1 to C_8 aliphatic alcohols, the C_2 to C_{30} aliphatic esters, and their mixtures can serve as lipophilic compound. Illustrative suitable alcohols are ethanol, n-propanol and isopropanol, while suitable esters are ethyl acetate, butyl acetate, ethyl laurate, methyl propionate, isopropyl myristate and isopropyl palmitate. As used herein, the term "aliphatic alcohol" includes polyols such as glycerol, propylene glycol and polyethylene glycols. A mixture of alcohol and ester is preferred, and in particular, a mixture of ethanol and ethyl laurate is preferred.

In one embodiment, the C_2 to C_{30} aliphatic esters, and their mixtures comprising the lipophilic compound include C_8 to C_{30} aliphatic esters of glycerol

selected from the group consisting monoglycerides, diglycerides, triglycerides, and mixtures thereof. Suitable aliphatic esters include glyceryl esters of saturated fatty acids, unsaturated fatty acids and mixtures thereof. Suitable saturated fatty acids include caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid and lignoceric acid. Suitable unsaturated fatty acids include oleic acid, linoleic acid and linolenic acid. Suitable glyceryl esters include glyceryl monooleate, triolean, trimyristin and tristearin, perferably trimyristin.

The concentration of lipophilic compound required necessarily varies according to other factors such as the desired semi-solid consistency and the desired skin penetration promoting effects. Suitably the concentration of lipophilic compound is in the range of 0.5 percent to 40 percent by weight based on the total weight of the composition. The preferred topical composition contains lipophilic compound in the range of 7 percent to 40 percent by weight based on the total weight of the composition.

Where a mixture of aliphatic alcohol and aliphatic ester are employed, the suitable amount of alcohol is in the range of about 0.5 percent to 10 percent. In one preferred embodiment, the amount of alcohol is in the range of about 5 percent to 15 percent, while that of aliphatic ester is in the range of about 2 percent to 15 percent (again based on the total weight of the composition). In another preferred embodiment, the amount of alcohol is in the range of about 0.5 percent to 10 percent, while that of aliphatic ester is in the range of 0 percent to 10 percent (again based on the total weight of the composition).

An optional, but preferred, component of the present invention is an emulsifier. Although not a critical factor, a suitable emulsifier generally will exhibit a hydrophilic-lipophilic balance number greater than 10. Sucrose esters, and specifically sucrose stearate, can serve as emulsifiers for the topical composition of the present invention. Sucrose stearate is a well-known emulsifier available from various commercial sources. When an emulsifier is used, sucrose stearate present up to about 2 percent, based on the total weight of the composition, is preferred. The preferred amount of sucrose stearate emulsifier can also be expressed as a weight

ratio of emulsifier to polysaccharide gum. A ratio of 1 to 6 emulsifier to gum is preferred, and a ratio of 1 to 4 is most preferred to generate the desired semi-solid consistency and separation resistance.

Other emulsifiers are also suitable and include polyoxyethylene sorbitan esters, long chain alcohols, preferably cetostearyl alcohol, and fatty acid glycerides. Suitable polyoxyethylene sorbitan esters include the monolaurate (Tween 20, Span 20) the monopalmitate (Tween 40), the monostearate (Tween 60), and the monooleate (Tween 80) and mixtures thereof. Preferred fatty acid glycerides include glyceryl monooleate, triolean, trimyristin and tristearin.

The present invention further includes an acid buffer system. Acid buffer systems serve to maintain or buffer the pH of compositions within a desired range. The term "buffer system" or "buffer" as used herein means a solute agent or agents which, when in a water solution, stabilize such solution against a major change in pH (or hydrogen ion concentration or activity) when acids or bases are added thereto. Solute agent or agents which are thus responsible for a resistance to change in pH from a starting buffered pH value in the range indicated above are well known. While there are numerous other suitable buffers, such as acetate buffers, potassium phosphate monohydrate has proven effective for compositions of the present invention. Suitable buffer concentrations range from about 0.005M to about 1.0M. Preferred buffer concentrations range from about 0.05M to about 0.2M. In several preferred embodiments the buffer concentration is 0.1M.

The final pH value of the pharmaceutical composition of the present invention may vary within the physiologically compatible range. Necessarily, the final pH value is not irritating to human skin. Without violating this constraint, the pH may be selected to improve prostaglandin E_1 stability and to adjust consistency when required. In one embodiment, the preferred pH value is about 3.0 to about 7.4, more preferably about 3.0 to about 6.5, most preferably about 3.5 to about 6.0.

The remaining component of the composition is water, which is necessarily purified. The composition contains water in the range of about 50 to about 90 percent, based on the total weight of the composition. The specific amount of water

present is not critical, however, being adjustable to obtain the desired consistency and/or concentration of the other components.

Additionally, known transdermal penetration enhancers can also be added, if desired. Illustrative are dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA), 2-pyrrolidone, N,N-diethyl-m-toluamide (DEET), 1-dodecylazacycloheptane-2-one (Azone™, a registered trademark of Nelson Research), N,N-dimethylformamide, N-methyl-2-pyrrolidone, calcium thioglycolate, oxazolidinone, dioxolane derivatives, laurocapram derivatives, and macrocyclic enhancers such as macrocyclic ketones.

Prostaglandin E_1 stabilizers, coloring agents, rheological agents, and preservatives can be added to the extent that they do not overly limit prostaglandin E_1 skin penetration or adversely affect the desired semi-solid consistency.

Contemplated dosage forms of the semi-solid pharmaceutical composition of the present invention are creams, gels, ointments, colloidal suspensions and the like, also including but not limited to compositions suitable for use with transdermal patches and like devices.

The ingredients listed above may be combined in any order and manner that produces a stable composition comprising a prostaglandin E_1 evenly dispersed throughout a semi-solid formulation. One available approach to preparing such compositions involves evenly dispersing the polysaccharide gum (or polyacrylic acid) in a premixed water/buffer solution and then thoroughly homogenizing (i.e. mixing) the resulting mixture ("Part A"). When present, the emulsifier is added to the water/buffer solution before dispersing the polysaccharide gum. Any suitable method of adjusting the pH value of Part A to the desired level may be used, for example, by adding concentrated phosphoric acid or sodium hydroxide.

Separately, the prostaglandin E_1 is dissolved with agitation in the lipophilic compound, which itself may be a mixture of alcohols, esters, or alcohol with ester. Next, the penetration enhancer is added. Alternatively, when the lipophilic compound includes both an alcohol and an ester, the prostaglandin E_1 can be dissolved in the alcohol before adding the penetration enhancer followed by the ester. In either case, the resulting mixture is a mixture that contains prostaglandin E_1 ("Part

B"). The final step involves a relatively slow addition (e.g. dropwise) of Part B into Part A under constant mixing.

The resulting topical composition, when compared to exhibits the advantageous properties described above, including improved prostaglandin E_1 permeation and bioavailability without drug overloading, reduced skin damage and related inflammation, and increased flexibility in available dosage forms. These compositions can be used for prolonged treatment of peripheral vascular disease, male impotency and other disorders treated by prostaglandin E_1, while avoiding the low bioavailability and rapid chemical decomposition associated with other delivery methods. Application of prostaglandin E_1 in a topical composition of the present invention to the skin of a patient allows a predetermined amount of prostaglandin E_1 to be administered continuously to the patient and avoids undesirable effects present with a single or multiple administrations of larger dosages by injection. By maintaining a sustained dosage rate, the prostaglandin E_1 level in the patient's target tissue can be better maintained within the optimal therapeutic range.

In one embodiment, the present invention provides a composition comprising about 0.01 percent to about 5 percent modified polysaccharide gum; about 0.001 percent to about 1 percent of a prostaglandin selected from the group consisting of PGE_1, pharmaceutically acceptable salts thereof, lower alkyl esters thereof and mixtures thereof; about 0.5 percent to about 10 percent DDAIP or salts thereof; about 0.5 percent to about 10 percent of a lower alcohol selected from the group consisting of ethanol, propanol, isopropanol and mixtures thereof; about 0.5 percent to about 10 percent on an ester selected from the group consisting of ethyl laurate, isopropyl myristate, isopropyl laurate and mixtures thereof; based on the weight of the composition, and an acid buffer. Preferably the composition also comprises up to about 2 percent sucrose stearate.

Optionally the composition also contains up to about 5 percent emulsifier, preferably, up to about 2 percent emulsifier. Suitable emulsifiers include glyceryl monooleate, triolean, trimyristin and tristearin. A preferred emulsifier is trimyristin.

The practice of the present invention is demonstrated in the following examples. These examples are meant to illustrate the invention rather than to limit its

scope. Variations in the treating compositions which do not adversely affect the effectiveness of prostaglandin E_1 will be evident to one skilled in the art, and are within the scope of this invention. For example, additional ingredients such as coloring agents, anti-microbial preservatives, emulsifiers, perfumes, prostaglandin E_1 stabilizers, and the like may be included in the compositions as long as the resulting composition retains desirable properties, as described above. When present, preservatives are usually added in amounts of about 0.05 to about 0.30%. Suitable preservatives include methylparabens (methyl PABA), propylparabens (propyl PABA) and butylhydroxy toluene (BHT). Suitable perfumes and fragrances are known in the art; a suitable fragrance is up to about 5 percent myrtenol, preferably about 2 percent myrtenol, based on the total weight of the composition. The compositions of the present invention can also include a small amount, about 0.01 to about 4% by weight, of a topical anesthetic, if desired. Typical topical anesthetics include lidocaine, dyclonine, dibucaine, pharmaceutically acceptable salts and mixtures thereof. In one preferred embodiment, the topical anesthetic is about 0.5 percent dyclonine, based on the weight of the composition.

Unless otherwise indicated, each composition is prepared by conventionally admixing the respective indicated components together.

EXAMPLE 1: Topical Prostaglandin E_1 Composition A

Composition A was prepared as follows. Part A of the composition was formed by dissolving 0.4 parts by weight prostaglandin E_1 (Alprostadil USP) in 5 parts by weight ethyl alcohol. Next, 5 parts by weight dodecyl 2-(N,N-dimethylamino)-propionate were mixed into the alcohol-prostaglandin E_1 solution, followed by 5 parts by weight ethyl laurate.

Part B was prepared starting from a pH 5.5 water/buffer solution. The water/buffer solution was prepared by adding sufficient potassium phosphate monohydride to purified water to create a 0.1 M solution. The pH of the water/buffer solution was adjusted to 5.5 with a strong base solution (1 N sodium hydroxide) and a strong acid (1 N phosphoric acid). The buffer solution represented about 80 parts of the total composition. All parts specified herein are parts by weight.

Ethyl laurate, 0.5 parts by weight, was added to the buffer solution. Next, the locust bean gum (in powder form) was dispersed in the buffer solution and homogenized using a homogenizer. TABLE 1, below, contains a list of the ingredients.

The resulting composition was a spreadable, semi-solid preparation suitable for application to the skin without the need for supporting devices such as patches and adhesive strips. The composition was both homogenous in appearance and resistant to separation.

Additional exemplary compositions B – H were prepared in the same manner using the components listed in Table 1. As noted above, in other embodiments, such as Composition H, the composition may include a modified polysaccharide gum, suitably a modified galactomannan gum, such as a guar gum. Alternatively, a polyacrylic polymer may be used instead of the polysaccharide gum.

Composition A was evaluated for skin penetration using shed snake skin as a model barrier. Shed snake skin was obtained from the Animal Care Unit of the University of Kansas. With head and tail sections removed, the skin was randomly divided into test sections and then hydrated by soaking.

The samples were then evaluated using Franz-type Diffusion Cells (surface area 1.8 cm^2). Specifically, skin pieces were mounted on top of a receptor cell of a vertical diffusion cell assembly in which a small magnetic bar was inserted and filled with an isotonic buffer. A seal was placed on top of the skin section followed by a donor cell. The two cells were clamped together. Known amounts of the formulations were applied on the bottom of a small capped vial (weight 0.5 grams) which fits exactly to the donor cell to ensure uniform distribution. The vials were placed on the skin in the donor cell. To reduce the evaporation of the ingredients, the donor cell and vial were taped together with a water-resistant adhesive band. The cells were transferred to a stirred water bath (32 degrees Celsius). Samples were withdrawn from the cells each hour for four hours and analyzed for the concentration of prostaglandin E_1, with changes in concentration indicating the amount penetrating. Tests with multiple skin samples yielded data that were averaged.

For a discussion of the use of shed snake skin in the evaluation of drug penetration, see U.S. Patent No. 4,771,004 to Higuchi, which is incorporated here by reference to the extent pertinent.

The prostaglandin E_1 penetrated quickly at a relatively sustained rate for four hours. The results of the penetration study are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 2: Topical Prostaglandin E_1 Composition B

Composition B was prepared using the ingredients listed in TABLE 1, below. Composition B contained more prostaglandin E_1 than Composition A. Despite this increased drug loading, Composition B exhibited a similar semi-solid consistency and homogenous appearance. The penetration of prostaglandin E_1 was measured according to the technique described in Example 1. Composition B provided a relatively fast, sustained delivery of prostaglandin E_1. The results are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 3: Topical Prostaglandin E_1 Composition C

Composition C was prepared using the ingredients listed in TABLE 1, below. Composition B contained more prostaglandin E_1 than either Composition A or B. The increased drug loading had little or no effect on the consistency or appearance, which substantially matched that of Compositions A and B. The penetration of prostaglandin E_1 was again measured according to the technique described in Example 1. According to this test, Composition C also provided a relatively fast, sustained delivery of prostaglandin E_1. The results are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 4: Topical Prostaglandin E_1 Composition D

Composition D was prepared using the ingredients listed in TABLE 1, below. The level of prostaglandin E_1 was again increased without substantially affecting the favorable consistency and separation resistance. The penetration of prostaglandin E_1

was again measured according to the technique described in Example 1. The results are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 5: Topical Prostaglandin E_1 Composition E

Composition E was prepared using the ingredients listed in TABLE 1, below. To assess the repeatability of compositions according to the present invention, the recipe of Composition D was again applied for Composition E. Repeatability was substantially confirmed by Composition E's favorable, semi-solid consistency and separation resistance. The penetration of prostaglandin E_1 was again measured according to the technique described in Example 1. The prostaglandin E_1 delivery from Composition E was again relatively fast and sustained. The results are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 6: Topical Prostaglandin E_1 Composition F

The level of prostaglandin E_1 was again increased for Composition F. The specific ingredients are listed in TABLE 1. The favorable consistency and separation resistance was undiminished. The results of a penetration analysis are presented in TABLE 2, below, and in FIG. 3.

EXAMPLE 7: Topical Prostaglandin E_1 Composition G

Composition G was prepared using the ingredients listed in TABLE 1. For Composition G, the recipe of Composition F was repeated except that the ester component (ethyl laurate) was omitted and the level of ethanol was increased a corresponding amount. The resulting composition was also a spreadable, semi-solid having a homogenous appearance and resistance to separation. The results of a penetration analysis are presented in TABLE 2, below, and in FIG. 3. While still favorable, these results reflect the relative benefit to compositions of the present invention from a lipophilic compound that includes both an ester component and an alcohol component.

TABLE 1: Topical Prostaglandin E_1 Compositions

	Ingredient (wt%)	A	B	C	D	E	F	G	H
Part A:	prehydrated locust bean gum	3	3	3	3	3	3	3	-
	prehydrated modified guar gum	-	-	-	-	-	-	-	3
	water/buffer (pH 5.5)	81	81	81	81	81	81	81	81
	sucrose stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	-
Part B:	prostaglandin E_1	0.1	0.2	0.3	0.4	0.4	0.5	0.4	0.3
	DDAIP	5	5	5	5	5	5	5	2.5
	ethanol	5	5	5	5	5	5	10	5
	ethyl laurate	5	5	5	5	5	5	-	3

EXAMPLE 8: Comparison of Penetration Profiles

TABLE 2 shows the cumulative amount of prostaglandin E_1 penetrating each hour for 4 hours for each example composition according to the present invention. These data demonstrate the ability of the present invention to deliver prostaglandin E_1 drugs transdermally.

FIG. 3 is a graph generated from the data presented in TABLE 1. Significantly, and as represented in graphical form, compositions according to the present invention deliver effective skin penetration relatively fast and at a sustained rate. Cumulative penetration increased with increased prostaglandin E_1 loading of the source composition.

TABLE 2: Cumulative Prostaglandin E_1 Penetration ($\mu g/cm^2$)

Hour	A	B	C	D	E	F	G
1	1.96	3.37	5.47	7.20	7.09	10.38	3.03
2	5.49	9.72	18.06	21.26	16.6	25.03	8.17
3	11.25	18.18	30.34	35.53	28.24	42.18	12.93
4	13.98	23.48	38.49	47.98	41.1	52.13	18.71

To further assess the effectiveness of compositions according the present invention, comparative example compositions were prepared. A first comparative example (Comparative Example 1) was prepared with the same recipe as Compositions D and E except that the DDAIP penetration enhancer was omitted. For a second comparative example (Comparative Example 2), the DDAIP was again omitted, but the level of ethanol was increased a corresponding amount. The specific ingredients used are listed in TABLE 3, below.

TABLE 3: Comparative Examples

	Ingredient (parts by weight)	Comparative Composition 1	Comparative Composition 2
Part A:	prehydrated locust bean gum	3	3
	water/buffer (pH 5.5)	86	. 81
	sucrose stearate	0.5	0.5
Part B:	prostaglandin E_1	0.4	0.4
	Ethanol	5	10
	ethyl laurate	5	5

The penetration of prostaglandin E_1 was evaluated according to the technique described in Example 1. The results are presented in TABLE 4, below.

TABLE 4: Comparative Examples
Cumulative Prostaglandin E_1 Penetration ($\mu g/cm^2$)

Hour	Comparative Composition 1	Comparative Composition 2
1	2.64	1.55
2	4.46	3.69
3	6.59	6.63
4	9.67	11.05

The data of TABLE 4 are compared graphically to the example compositions having the same prostaglandin E_1 loading, Compositions D and E in FIG. 4. The penetration data demonstrate that compositions according to the present invention benefit greatly from the presence of the DDAIP penetration enhancer.

EXAMPLE 9: Single Use Double Blind and Open Label Clinical Trials

The safety and efficacy of a 0.4% weight prostaglandin E_1 (prostaglandin E_1 or alprostadil) topical composition (composition D of Example 4 and Table 1, above) was evaluated in a total of 143 men at three study sites. This study consisted of a double-blind, placebo controlled and cross-over portion and an open-label portion.

The double-blind placebo controlled portion of the study was entered and completed by 64 men (Table 5, below). Seventy-nine (79) men entered and completed the open-label portion of the study (Table 5, below). Summarized below are discussions on the results of the clinical studies.

Inclusion Criteria

1. Males, ages 21-70 years, inclusive.

2. Documented history of erectile dysfunction, defined as the inability to achieve and maintain an erection of sufficient rigidity for sexual intercourse due to psychogenic, neurogenic or vasculogenic causes during the previous 6 months. This includes patients who may still have some erections sufficient for intercourse but not consistently, which is the typical complaint of the age onset, mild to moderate impotent man. The diagnosis of erectile dysfunction was based on medical history and physical examination.

Exclusion Criteria

1. History of urethral stricture or obstruction.

2. Any combination of findings from history, physical examination or screening studies which indicate pre-existing impairment of heart, liver and/or kidney function (such as congestive heart failure, unstable angina or recent acute myocardial infarction, uncontrolled diabetes, for erectile dysfunction of hormonal origin) which in the investigator's opinion could influence the outcome of the study.

3. History of penile surgery, including penile implant, prostatectomy or cancer of the prostate, penile trauma including paraplegia or quadriplegia.

4. Any condition which might predispose towards priapism, such as sickle cell anemia, multiple myeloma, or leukemia.

5. Hypertension, (sitting diastolic pressure >90 or systolic >150) requiring treatment with other than angiotensin converting enzyme inhibitors (ACE inhibitors).

6. Presence of a sexually transmitted disease as determined by physical examination.

7. Use of a cavernosal injection or external erectile device within 4 weeks prior to entering into this study.

8. Peyronie's Disease or any palpable fibrous scar or plaque on the penis, evidence of curvature during tumescence and rigidity stimulation or an anomaly of the penis skin or mucosa of the glans.

9. Any concomitant medication which are known to interfere with sexual activity such as antidepressants, some antihypertensives, sedatives hormones and some allergy medications.

10. Received any investigational treatment within 30 days of entering into this study.

11. Inability or unwillingness to give informed consent.

The patient population in this study consisted of men in the age range of 49 - 70 years old.

Table 5. Patient Enrollment by Study Sites

	Patients Enrolled On Study Sites			
Portion	No. 1	No. 2	No. 3	Total
Double-Blind	30	34	0	64
Open Label	32	8	39	79

Clinical efficacy was evaluated from patient history and patient evaluation questionnaires both before and after medication using a six-point classification scale (Table 6). Each patient was given one (1) placebo and one (1) active dose in a crossover manner with a 5 to 7 day wash-off period in the double-blind portion of the study. In the open-label portion the patients were given only one (1) active dose. The clinical supply was packaged in single-dose containers each containing 250mg (net weight) of cream and 1.0 mg prostaglandin E_1.

The efficacy response rate was determined as the number of men that had erections sufficient for intercourse out of the total number of men. To be considered a success, a score of 8 to 10 must be achieved after administration of the dose or the patient must have had intercourse.

Statistical analysis compared before and after response scores using a paired t-test. A statistically significant difference ($P < 0.001$) between all before and after dosing scores was found for each group of patients receiving active medication

whether in the double-blind portion of the study or the open label portion of the study. Also, a statistical significance was seen between the active and placebo groups per study site.

Table 6. Six-Point Classification Scale for Assessing the Severity of Male Erectile Dysfunction (Impotence)

Classification	Definition
0	Severe impotence with no function
2	Severe impotence with very little function
4	Severe impotence with some function
6	Mild to moderate impotence
8	Not impotent but has some loss of function
10	Not impotent with full function

Table 7. Patient Enrollment by Impotence Classification

	Severe	Mild to Moderate	Not Impotent	
Double-Blind	39	25	0	64
Open Label	63	16	0	79
Total Patients	102	41	0	143

The topical prostaglandin E_1 composition was found to be safe and effective in impotent men with the moderate to severe impotence. The efficacy rate was 64.7% (66/102 patients) in severely impotent men and 100% (41/41 patients) in mild to moderately impotent men. The overall clinical efficacy rate for the study is 74.8% (107/143 patients) as shown in Table 8, below.

Table 8. Overall Clinical Efficacy Rates

	Double-Blind Portio	Open-Label Portion	Combined Overall Rat
Placebo	4.7% (3/64)	-	4.7% (3/64)
Active	87.5% (56/64)	64.6% (51/79)	74.8% (107/143)
	P<0.001		P<0.001

The prostaglandin E_1 topical composition was extremely effective (100%) in the mild to moderate impotent patient population. The mild to moderate impotence class is the most prevalent class and is estimated to represent 70% of all erectile dysfunction complaints. The product was also very effective (64.7%) in the severely impotent study population.

A placebo efficacy response was seen in only 3 of 64 (4.7%) patients studied in the double-blind portion of the study. This is far below the expected rate of approximately 10% as reported in other clinical studies. This low rate is perhaps due to the fact that the majority (63%) of the patients enrolled in the double-blind portion of the study were classified with severe impotence. While 17 of 64 (26.6%) patients showed improvement with the placebo, only three (3) of those patients had sufficient improvement to be assessed as efficacious (8 or 10 on the classification scale).

Table 9. Clinical Efficacy Rates by Impotence Classification

		Study Sites			
	Portion	**No. 1**	**No. 2**	**No. 3**	**Combined Efficacy**
Severely Impotent	**Double-Blind**	85.7% (24/28)	63.6% (7/11)	No Patients Entered	79.5% (31/39)
	Open Label	72.2% (13/18)	33.3% (2/6)	51.3% (20/39)	55.6% (35/63)
Mild to Moderate Impotence	**Double-Blind**	100% (2/2)	100% (23/23)	No Patients Entered	100% (25/25)
	Open Label	100% ((14/14)	100% (2/2)	No Patients Entered	100% (16/16)

The open label efficacy rate was lower than the double-blind efficacy rate (Table 9). This was primarily due to the enrollment of a relatively high number of severely impotent men in the open-label portion of the study as compared to the double-blind portion. (Table 8) Of the men enrolled in the open label portion of the study, 79.7% (63/79) were assessed as severely impotent while only 60.9% (39/64) were assessed as severely impotent on entering the double-blind portion. The efficacy rate among the severely impotent population is expected to be lower because by definition these men have little or no function. Practically, it is expected to be more difficult to move the impotence classification from 0, 2 or 4 up to 8 or 10. While most of the severely impotent men showed significant improvement, 36 men (36/102 or 35.3%) did not have sufficient improvement to be classified as efficacious.

Adverse events observed in this study were mild transient burning or tingling at the application site. No systemic toxic side effects were observed. Also, none of

the spouses involved in the studies reported adverse events. None of the patients dropped out of the study or were lost to follow-up

EXAMPLE 10: Multiple Use Open Label Clinical Trial

The safety and efficacy of a 0.4% prostaglandin E_1 topical composition (composition D of Example 4 and Table 1, above) was evaluated in an additional study of a total of 56 men at three study sites. Fifty-six (56) male patients with organic erectile dysfunction entered and completed the study. Patients were classified into groups based on their responses to the International Index of Erectile Dysfunction (IIEF) and the pre dose Sexual Encounter Profile (SEP). Forty-nine (49) patients were classified as having mild to moderate erectile dysfunction and 7 patients were classified as having severe erectile dysfunction. Each patient was asked to use from 3 to 10 doses of medication over a four week period in a multiple use, in-home study. The overall efficacy rate for the mild to moderate group was 75%. The results of this study were consistent with the combined overall efficacy rate reported above in Example 9. None of the patients dropped out of this multiple use study and no severe adverse events were noted.

Inclusion Criteria

1 Males, ages 21-70 years, inclusive.

2. Documented history of erectile dysfunction, which is defined as the inability to achieve and maintain an erection of sufficient rigidity for sexual intercourse due to psychogenic, neurogenic or vasculogenic, causes during the previous 6 months. This includes patients who may still have some erections sufficient for intercourse but not consistently, which is the typical complaint of the age onset, mild to moderate impotent man. The diagnosis of erectile dysfunction will be based on medical history and physical examination.

Exclusion Criteria

1. History of urethral stricture or obstruction.

2. Any combination of findings from history, physical examination or screening studies which indicate pre-existing impairment of heart, liver and/or kidney function (such as congestive heart failure, unstable angina or recent acute myocardial infarction, uncontrolled diabetes, for erectile dysfunction of hormonal origin) which in the investigator's opinion could influence the outcome of the study.

3. History of penile surgery, including penile implant, prostatectomy or cancer of the prostate, penile trauma including paraplegia or quadriplegia.

4. Any condition which might predispose towards priapism, such as sickle cell anemia, multiple myeloma, or leukemia.

5. Hypertension, (sitting diastolic pressure >90 or systolic >150) requiring treatment with other than angiotensin converting enzyme inhibitors (ACE inhibitors).

6. Presence of a sexually transmitted disease as determined by physical examination.

7. Use of a cavernosal injection or external erectile device within 4 weeks prior to entering into this study.

8. Peyronie's Disease or any palpable fibrous scar or plaque on the penis, evidence of curvature during tumescence and rigidity stimulation or an anomaly of the penis skin or mucosa of the glans.

9. Any concomitant medication which are known to interfere with sexual activity such as antidepressants, some antihypertensives, sedatives hormones and some allergy medications.

10. Received any investigational treatment within 30 days of entering into this study.

11. Inability or unwillingness to give informed consent.

The patient population in this study consisted of men in the age range of 49-70 years old.

Table 10. Patient Enrollment by Study Sites

Patients Enrolled On Study Sites			
No. 1	**No. 2**	**No. 3**	**Total**
22	13	21	56

Clinical efficacy was evaluated from patient history and patient evaluation questionnaires both before and after medication using the International Index of Erectile Function (Table 11) and the Sexual Encounter Profile (SEP) six-point classification scale (Table 12). Each patient was given 10 active doses and asked to take the medication home and attempt intercourse as many times as possible over a 4 week period. The medication was packaged in a specially designed single dose applicator.

Table 11. International Index of Erectile Function

Classification	Definition
<12	Severe impotence with no function
12-18	Mild Impotence with very little function
18-24	Moderate Impotence with some function
24+	No dysfunction

The efficacy response rate was determined as the number of intercourse successes out of the total number of intercourse attempts. To be considered a success, a SEP score of 8 to 10 must be achieved after administration of the dose or the patient must have had satisfactory sexual intercourse. Statistical analysis compared before and after response scores using Chi Square statistics. A statistically significant difference ($P < 0.001$) between before and after dosing scores was found for each group of patients receiving active medication.

Table 12
Sexual Encounter Profile(SEP): Six-Point Classification Scale for Assessing the Severity of Male Erectile Dysfunction (Impotence)

Classification	Definition
0	Severe impotence with no function
2	Moderate Impotence with very little function
4	Moderate Impotence with some function
6	Mild Impotence
8	Not impotent but has some loss of function
10	Not impotent with full function

The efficacy response rate was determined as the number of intercourse successes out of the total number of intercourse attempts. To be considered a success, a SEP score of 8 to 10 must be achieved after administration of the dose or the patient must have had satisfactory sexual intercourse. Statistical analysis compared before and after response scores using Chi Square statistics. A statistically significant difference ($P< 0.001$) between before and after dosing scores was found.

Table 13. Patient Enrollment by Impotence Classification

	Severe	Mild to Moderate	Total
Patients	7	49	56

Table 14. Efficacy per Patient Group

	Efficacy by Patients		Efficacy by Attempts	
Mild to Moderate	36/49	(74%)	178/239	(75%)
Severe	4/7	(57%)	16/36	(44%)

As previously discussed, the prostaglandin E_1 topical composition was extremely effective (75%) in the mild to moderate impotent patient population. The mild to moderate impotence class is the most prevalent class and is estimated to represent 70% of all erectile dysfunction complaints. The product was less effective (44%) in the severely impotent study population; however, a statistically significant difference was noted between the before and after treatment scores in this group.

Even though all of the men in the severe group were totally without any erectile function before the study, 4 of the 7 men (57%) had successful intercourse from at least 3 out of the 10 doses.

Adverse events observed in this study were mild transient burning or tingling at the application site. No systemic toxic side effects were observed. Also, none of the spouses involved in the studies reported adverse events. None of the patients dropped out of the study or were lost to follow-up.

The results of this clinical study indicate the use of the prostaglandin E_1 0.4% topical composition of the present invention for the treatment of mild, moderate to severe impotence is safe and efficacious.

The foregoing specification is intended as illustrative and is not to be taken as limiting. Still other variations within the spirit and the scope of the invention are possible and will readily present themselves to those skilled in the art.

CLAIMS

We Claim:

1. A semi-solid composition comprising:

a vasoactive prostaglandin;

a skin penetration enhancer which is a member of the group consisting of an alkyl-2-(N-substituted amino)-alkanoate, a (N-substituted)-alkanol alkanoate, a pharmaceutically acceptable salts thereof and a mixture thereof;

a shear-thinning polysaccharide;

a lipophilic compound which is a member of the group consisting of an aliphatic C_1 to C_8 alcohol, an aliphatic C_8 to C_{30} ester, and a mixture thereof; and

an acidic buffer system.

2. The semi-solid composition of claim 1, wherein the vasoactive prostaglandin is selected from the group consisting of PGE_1, PGA_1, PGB_1, $PGF_{1\alpha}$, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, PGF_3 and mixtures thereof.

3. The semi-solid composition of claim 1, wherein the shear-thinning polysaccharide has a viscosity of about 5,000 centipoise to about 20,000 centipoise.

4. The semi-solid composition of claim 1, wherein the shear-thinning polysaccharide has a viscosity of about 7,000 centipoise to about 13,000 centipoise.

5. The semi-solid composition of claim 1, wherein the shear-thinning polysaccharide is a modified galactomannan gum.

6. The semi-solid composition of claim 5, wherein the modified galactomannan gum is a modified guar gum.

7. The semi-solid composition of claim 1, wherein the lipophilic compound is at least one aliphatic C_8 to C_{30} ester.

8. The semi-solid composition of claim 1, wherein the lipophilic compound is at least one glyceryl ester selected from the group consisting monoglycerides, diglycerides, triglycerides, and mixtures thereof.

9. The semi-solid composition of claim 1, wherein the lipophilic compound is at least one glyceryl ester selected from the group consisting of glyceryl monooleate, triolean, trimyristin, tristearin, and mixtures thereof.

10. The semi-solid composition of claim 1, wherein the acidic buffer system provides a buffered pH value for said composition in the range of about 3 to about 6.5.

11. The semi-solid composition of claim 1, wherein the composition further comprises an emulsifier selected from the group consisting of sucrose esters, polyoxyethylene sorbitan esters, long chain alcohols, and glyceryl esters.

12. The semi-solid composition of claim 1, wherein the emulsifier is at least one glyceryl ester selected from the group consisting of glyceryl monooleate, triolean, trimyristin, tristearin, and mixtures thereof.

13. The semi-solid composition of claim 1, wherein the composition further comprises a fragrance.

14. The semi-solid composition of claim 1, wherein the composition further comprises up to about 5 percent myrtenol, based on the total weight of the composition.

15. The semi-solid composition of claim 1, wherein the composition further comprises a preservative.

16. The semi-solid composition of claim 1, wherein the composition further comprises a topical anesthetic.

17. The use of a semi-solid prostaglandin composition comprising a vasoactive prostaglandin;

a skin penetration enhancer which is a member of the group consisting of an alkyl-2-(N-substituted amino)-alkanoate, a (N-substituted)-alkanol alkanoate, a pharmaceutically acceptable salts thereof and a mixture thereof;

a shear-thinning polysaccharide;

a lipophilic compound which is a member of the group consisting of an aliphatic C_1 to C_8 alcohol, an aliphatic C_8 to C_{30} ester, and a mixture thereof; and

an acidic buffer system for the preparation of a pharmaceutical composition for treating erectile dysfunction in a patient needing such treatment, whereby the pharmaceutical composition is applied in the fossa navicularis of the patient.

18. The use in accordance with claim 17, wherein the shear-thinning polysaccharide is a modified galactomannan gum.

19. The use in accordance with claim 18 wherein the modified galactomannan gum is a modified guar gum.

20. The use in accordance with claim 17 wherein the lipophilic compound is at least one aliphatic C_8 to C_{30} ester.

21. The use in accordance with claim 17 wherein the lipophilic compound is at least one glyceryl ester selected from the group consisting monoglycerides, diglycerides, triglycerides, and mixtures thereof.

22. The use in accordance with claim 17 wherein the lipophilic compound is at least one glyceryl ester selected from the group consisting of glyceryl monooleate, triolean, trimyristin, tristearin, and mixtures thereof.

23. The use in accordance with claim 17 wherein the acidic buffer system provides a buffered pH value for said composition in the range of about 3 to about 6.5.

24. The use in accordance with claim 17 wherein the composition further comprises an emulsifier selected from the group consisting of sucrose esters, polyoxyethylene sorbitan esters, long chain alcohols, and glyceryl esters.

25. The use in accordance with claim 17 wherein the emulsifier is at least one glyceryl ester selected from the group consisting of glyceryl monooleate, triolean, trimyristin, tristearin, and mixtures thereof.

26. The use in accordance with claim 17 wherein the composition further comprises a fragrance.

27. The use in accordance with claim 17 wherein the composition further comprises up to about 5 percent myrtenol, based on the total weight of the composition.

28. The use in accordance with claim 17 wherein the composition further comprises a preservative.

29. The use in accordance with claim 17 wherein the composition further comprises a topical anesthetic.

30. A prostaglandin E_1 composition comprising prostaglandin E_1 suitable for administration in the fossa navicularis comprising:

a shear-thinning modified galactomannan gum;

a prostaglandin selected from the group consisting of PGE_1, pharmaceutically acceptable salts thereof, lower alkyl esters thereof and mixtures thereof;

about 0.5 percent to about 10 percent DDAIP or a pharmaceutically acceptable salt thereof, based on the total weight of the composition;

about 0.5 percent to about 10 percent, based on the total weight of the composition, of a lower alcohol selected from the group consisting of ethanol, propanol, isopropanol and mixtures thereof;

about 0.5 percent to about 10 percent of an ester selected from the group consisting of ethyl laurate, isopropyl myristate, isopropyl laurate and mixtures thereof, based on the total weight of the composition; and

an acidic buffer system.

31. The composition of claim 30, further comprising an emulsifier selected from the group consisting of sucrose esters, polyoxyethylene sorbitan esters, long chain alcohols, and glyceryl esters.

32. The composition of claim 30, wherein said emulsifier is a sucrose stearate.

33. The composition of claim 30 wherein the emulsifier comprises at least one glyceryl ester selected from the group consisting of glyceryl monooleate, triolean, trimyristin, tristearin, and mixtures thereof.

34. The composition of claim 30 wherein the composition further comprises a fragrance.

35. The composition of claim 30 wherein the composition further comprises up to about 5 percent myrtenol, based on the total weight of the composition.

36. The composition of claim 30 wherein the composition further comprises composition further comprises a preservative.

37. The composition of claim 30 wherein the composition further comprises a topical anesthetic.

- 3 MAR 2006

PROSTAGLANDIN COMPOSITIONS AND METHODS OF TREATMENT FOR MALE ERECTILE DYSFUNCTION

ABSTRACT

The invention provides methods and compositions for treating erectile dysfunction. The methods include the step of placing within the fossa navicularis of the patient an effective erection-inducing amount of a vasoactive prostaglandin composition of a semi-solid consistency. The composition comprises a vasoactive prostaglandin, a penetration enhancer, a shear-thinning polysaccharide, a lipophilic compound, and an acidic buffer system. The penetration enhancer is an alkyl-2-(N-substituted amino)-alkanoate ester, a (N-substituted amino)-alkanol alkanoate, or a mixture of these enhancers. The lipophilic compound may be an aliphatic C_1 to C_8 alcohol, aliphatic C_2 to C_{30} ester, an aliphatic C_8 to C_{30}, or a mixture of these. The composition includes a buffer system providing a buffered pH value for said composition in the range of about 3 to about 7.4.