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(54) Title: NOVEL TRANSDERMAL ANTI-ANGINAL PHARMACEUTICAL DOSAGE UNIT AND PROCESS FOR ITS ADMINISTRATION

(57) Abstract

Novel transdermal nitroglycerin or other anti-anginal pharmaceutical polymer matrix dosage units have been developed which comprise a backing layer, an adjoining layer of a solid polymer matrix in which the pharmaceutical is microdispersed, and a biologically acceptable adhesive polymer layer which has dispersed one or more skin permeation enhancers. Novel process of administration of the anti-anginal pharmaceutical using the novel polymer matrix dosage units is also provided.

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DESCRIPTION

NOVEL TRANSDERMAL ANTI-ANGINAL PHARMACEUTICAL DOSAGE UNIT AND PROCESS FOR ITS ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. application Ser. No. 06/770,968, filed August 30, 1985, which is a continuation-in-part of U.S. application Ser. No. 06/705/194, filed February 25, 1985, by Yie W. Chien and Chia-Shun Lee.

Technical Field

This invention relates to a novel transdermal nitroglycerin or other anti-anginal pharmaceutical absorption dosage unit comprising a backing layer; an intermediate adjoining layer of solid polymer matrix in which the anti-anginal pharmaceutical is dispersed; and a final biologically acceptable adhesive layer which is in communication with the solid polymer matrix layer and is adapted to adhere to the skin of a subject being administered nitroglycerin or other anti-anginal pharmaceutical, the adhesive layer having dispersed therein an effective amount of one or more skin permeation enhancing compounds for the nitroglycerin or other anti-anginal pharmaceutical dispersed in the polymer matrix layer.

Background Art

It has been found that nitroglycerin and other anti-anginal pharmaceuticals are absorbed to a degree through the skin. This is referred to as transdermal absorption. Anti-anginal pharmaceuticals as used herein mean the nitrate and nitrite esters of mono- and poly-hydric alcohols which are pharmaceutically acceptable, have anti-anginal effectiveness, and are susceptible to transdermal absorption. One means of effecting transdermal absorption of an anti-anginal has been to distribute nitroglycerin within a polymeric disc or a container of a gel, which is brought into contact with an area of the skin of the subject to be treated with the nitroglycerin. Also, ointments or lotions containing nitroglycerin have been applied to an area of the skin of the subject to be treated. Problems encountered in such treatment include inadequate control over the rate and duration of transdermal absorption or the rate can be too slow in the case of certain dosage forms, especially from nitroglycerin-containing discs or nitroglycerin-containing gel container dosage units or pads. Nitroglycerin has been administered using tablet formulations by which the nitroglycerin is absorbed through the sublingual mucosa. Such sublingual mucosa absorption is rapid and effective to treat acute angina attacks, but does not provide sustained, constant blood levels of nitroglycerin together with long-term absorption. It has been found that the transdermal absorption rates of certain pharmaceuticals can be increased by use of absorption promoting compounds (also referred to as skin permeation enhancers) with the pharmaceutical to be

absorbed when compounding in the polymeric disc or the pharmaceutical-containing gel.

It is desired to improve the dosage unit forms or devices by which nitroglycerin or other anti-anginal pharmaceuticals are transdermally absorbed, especially in view of the importance of their administration by this means. Desired transdermal absorption would provide an avoidance of the large, unwanted destruction of anti-anginal pharmaceutical such as nitroglycerin by metabolism in the gastrointestinal tract and "first-pass" hepatic elimination, which is usually about 90 percent or more of orally administered nitroglycerin. The transdermal absorption minimizes inter- and intra-patient variations regarding incompatibilities and metabolisms. By transdermal absorption, it is deemed possible to provide more constant concentration of the anti-anginal pharmaceuticals in the body and to realize a greater pharmaceutical efficiency. It is also possible, by proper transdermal absorption, to reduce the frequency of effective dosing. Transdermal administration provides most of the advantages of intravenous and sublingual dosing without most of the disadvantages of such dosing.

It is desired that improved transdermal nitroglycerin absorption dosage unit forms and processes of transdermal administration be developed. A number of advantages would result.

Summary of Invention

This invention relates to an improved transdermal anti-anginal pharmaceutical containing dosage unit comprising:

a) a backing layer which is substantially impervious to the anti-anginal pharmaceutical to be delivered transdermally;

b) a polymer matrix disc layer which is in contact with said backing layer and which has dispersed therein an amount of nitroglycerin or other anti-anginal pharmaceutical which will provide a dosage amount of the anti-anginal pharmaceutical to be delivered transdermally; and

c) an adhesive layer which is adhered to said anti-anginal pharmaceutical-containing polymer matrix disc layer and which has distributed therein an effective amount of one or more skin absorption enhancers which provide substantial skin absorption enhancement for said anti-anginal pharmaceitucal.

The backing layer is made from materials that are substantially impermeable with regard to the nitroglycerin or other anti-anginal pharmaceutical of the transdermal dosage unit. It can be made of polymers such as polyethylene, polypropylene, polyvinylchloride, polyesters such as poly(ethylene phthalate), and laminates of polymer films with metallic foils such as aluminum foil.

The polymer matrix disc layer is fabricated from biologically acceptable polymers. The polymer matrix disc layer which has the nitroglycerin or other anti-anginal pharmaceutical distributed therein can suitably be made of a

medical-grade silicone polymer such as a polydimethylsiloxane polymer, or a siloxane polymer having methylvinyl siloxane groups. The nitroglycerin or other anti-anginal pharmaceutical is suitably dispersed in the silicone polymer, to which mixture a curing agent is suitably added. The polymer-anti-anginal pharmaceutical mixture is then formed into a layer of an appropriate thickness and is cured. The matrix layer is adhered to the backing layer. Other suitable polymers can be used in the formation of the polymer matrix disc layer are elastomers or thermoplastics. Care must be taken that the polymer selected is compatible with the nitroglycerin or other anti-anginal pharmaceutical, permits its release for transdermal absorption and is free or sufficiently free from any biologically unacceptable components.

Finally, the adhesive layer is applied to the polymer matrix disc layer. The skin permeation enhancer compound is mixed thoroughly with the adhesive polymer which is suitable for adhesion to the skin locus to which the transdermal matrix dosage unit will be applied. The adhesive polymer-skin permeation enhancer layer can be applied to the polymer matrix disc layer by coating or by solvent casting. Alternatively, part of the adhesive skin permeation enhancer layer can be applied to the inner surface of the release liner and the remainder can be applied to the matrix layer surface; the two adhesive-skin permeation enhancer surfaces then are pressed together to form a single layer. The adhesive polymer-skin permeation enhancer layer is desirably thin in the micron-range thickness, suitably 10-300 microns

in thickness, desirably about 20 to 250 microns, and preferably about 50 to 200 microns in thickness.

The transdermal nitroglycerin or other anti-anginal pharmaceutical absorption dosage units of this invention have an Enhancing Factor of at least 1.2, preferably at least 1.3, and more preferably at least about 2.0. Enhancing Factor is defined as the ratio of normalized permeation rate [in mcg/cm^2/hr] of a dosage unit of this invention with skin permeation enhancer/the normalized permeation rate of a corresponding dosage unit without enhancer in the adhesive layer.

The invention also is a process for administering a nitroglycerin or other anti-anginal pharmaceutical transdermally by forming the anti-anginal pharmaceutical-containing polymer matrix disc dosage unit having a polymer matrix disc layer which has the pharmaceutical dosage dispersed therein, to which matrix disc is adhered a skin permeation enhancer-containing adhesive layer and, by applying said dosage unit by way of said adhesive layer to the skin of the subject to be treated, whereby said pharmaceutical is transdermally administered to said subject to achieve desired systemic effects.

Detailed Description of the Invention and the Preferred Embodiments

This invention relates to a transdermal anti-anginal pharmaceutical-containing matrix dosage unit comprising:

a) a backing layer which is substantially impervious to the anti-anginal pharmaceutical to be delivered transdermally;

b) a polymer matrix disc layer which is in contact with said backing layer and which has dispersed therein an amount of the nitroglycerin or other anti-anginal pharmaceutical which will provide a dosage amount of the pharmaceutical to be delivered transdermally; and

c) an adhesive layer which is adhered to said pharmaceutical-containing polymer matrix disc layer and which has distributed therein an effective amount of one or more skin absorption enhancers which provide substantial skin absorption enhancement for said pharmaceutical;

said dosage unit having an enhancing factor of at least 1.2.

The backing layer is made from materials that are substantially impermeable with regard to the nitroglycerin or other anti-anginal pharmaceutical of the transdermal dosage unit. It can be made of polymers such as polyethylene, polypropylene, polyvinylchloride; polyesters such as poly(ethylene phthalate), and laminates of polymer films with metallic foils such as aluminum foil.

The polymer matrix disc layer is fabricated from biologically acceptable polymers. The polymer matrix disc layer which has the nitroglycerin, for example, distributed therein can suitably be made of a medical-grade silicone

polymer, such as polydimethylsiloxane polymer or other silicone polymer containing methylvinyl siloxane groups. The nitroglycerin e.g., is suitably dispersed in the silicone polymer to which mixture a curing agent is suitably added. The polymer-nitroglycerin mixture is then formed into an appropriate thickness and cured. The matrix layer is adhered to the backing layer, which can be done directly. Other suitable elastomer or thermoplastic polymers can also be used in the formulation of the polymer matrix disc layer. Care must be taken that the polymer selected is compatible with the nitroglycerin, permits its release for transdermal absorption and is free or sufficiently free from an biologically unacceptable components.

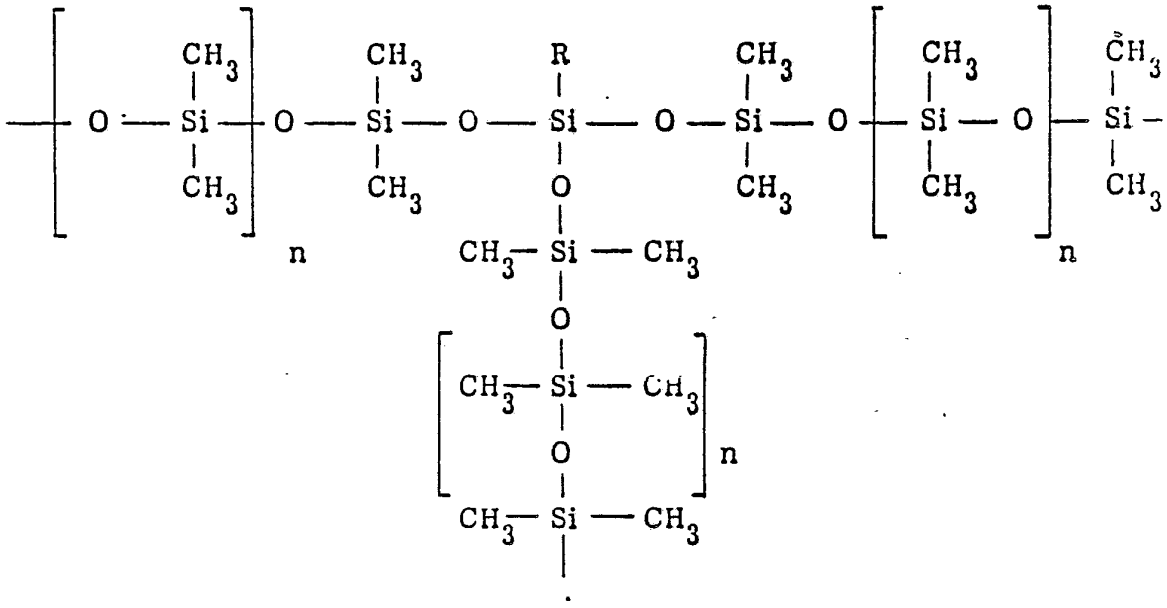
Finally, the adhesive layer is applied to the polymer matrix disc layer. The skin permeation enhancer compound is mixed thoroughly with the adhesive polymer which is suitable for adhesion to the skin locus to which the transdermal matrix delivery dosage unit will be applied. The adhesive polymer-skin permeation enhancer layer can be applied to the polymer matrix disc layer by coating or by solvent casting. Part of the adhesive polymer-skin permeation enhancer layer can be applied to a release liner and combined with the part pplied to the matrix disc layer by application of pressure. The layer is desirably thin, in the micron-range thickness, suitably about 10-300 microns in thickness, desirably about 20 to 500 microns, and preferably about 50 to 200 microns in thickness.

The invention also is a process for administering a nitroglycerin or other anti-anginal pharmaceutical transder-

mally by forming polymer matrix disc delivery dosage unit having a polymer matrix disc which has the anti-anginal pharmaceutical dosage dispersed therein, to which matrix disc is adhered a skin permeation enhancer-containing adhesive layer and, by applying said dosage unit by way of said adhesive layer to the skin of the subject to be treated, whereby said anti-anginal pharmaceutical, such as nitroglycerin, is transdermally administered to said subject to achieve systemic effects.

The backing layer can be made of any suitable material which is impermeable to the nitroglycerin of the polymer matrix layer. The backing layer serves as a protective cover for the matrix layer and provides also a support function. Examples of materials that are suitable are films of high and low density polyethylene, polypropylene, polyvinylchloride, polyesters such as poly(ethylene phthalate) and the like. Preferably, the materials for the backing layer are laminates of such polymer films with a metal foil such as aluminum foil. In such laminates, a polymer film of the laminate will usually be in contact with the polymer matrix layer. The backing layer can overlay the matrix and adhesive layer as desired for protection and to provide the desired pharmaceutical elegance of the final matrix dosage unit form. The protective layer can be any appropriate thickness which will provide the desired protective and support functions. A suitable thickness will be from about 10 to about 200 microns. Desirably, the thickness will be from about 20 to about 150 microns, and preferably be from about 30 to 100 microns. The polymer matrix layer can be

made from silicone elastomers of the general polydimethylsiloxane structure, such as silicone polymers of the following formula:



wherein R is alkyl or alkoxy containing 1-7 carbon atoms, vinyl or phenyl and wherein n is about 100-5000.

The silicone polymers selected preferably are cross-linkable at moderate temperatures such as at room temperature, using cross-linking catalysts which are biologically acceptable in the final polymer matrix and which are compatible with nitroglycerin or other anti-anginal pharmaceutical to be used in making the polymer matrix dosage forms. Some suitable siloxane polymers are crosslinkable copolymers having dimethyl and methylvinyl siloxane which can be cross-linked as by using a suitable peroxide catalyst or a suitable tin or platinum catalyst system. Other cross-linking sites can be present in the polysiloxane elastomers used. Suitable siloxane medical-grade polymers are sold

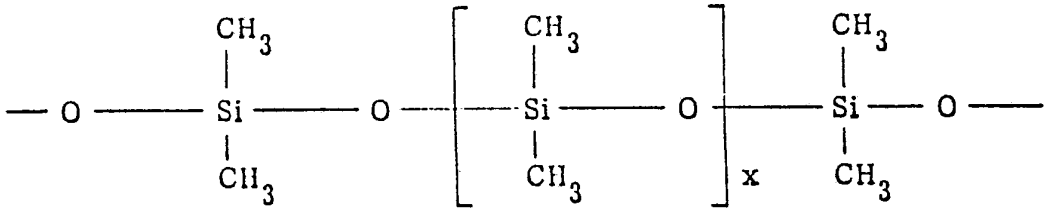
under the designations Silastic 382, Q7-4650, Q7-4665, Q7-4735, Q7-4750, Q7-4765 and MDX-4-4210.

Generally, polymers used to form the biologically acceptable polymer matrix are those capable of forming a thin layer of coatings or a disc of drug-dispersing matrix through which nitroglycerin or other anti-anginal pharmaceutical can pass at a controlled rate. Suitable polymers are biologically-acceptable and compatible with the pharmaceutical, non-allergenic and insoluble in and non-irritating to body fluids or tissues with which the device is contacted. The use of soluble polymers is to be avoided since dissolution or erosion of the matrix would affect the release rate of the nitroglycerin or other anti-anginal pharmaceutical as well as the capability of the dosage unit to remain in place for convenience of removal.

Exemplary materials for fabricating the biologically acceptable polymer matrix include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethylacrylate copolymers, ethylene/vinyl acetate copolymers, silicone elastomers, especially the medical-grade poly-dimethyl-siloxanes, neoprene rubber, chlorinated polyethylene, polyvinyl chloride; vinyl chloride-vinyl acetate copolymer, polymethacrylate polymer (hydrogel), polyvinylidene chloride, poly(ethylene terephthalate), butyl rubber, epichlorohydrin rubbers, ethylene-vinyl alcohol copolymer, ethylene-vinyloxyethanol copolymer; silicone copolymers, for example, silicone-polycarbonate copolymers; cellulose polymers, for example methyl or ethyl cellulose hydroxypropyl methyl cellulose, and cellulose esters; polycarbonates;

polytetrafluoroethylene; and the like. For best results, the biologically acceptable polymer matrix should be selected from polymers with glass transition temperatures below room temperature. The polymer may, but need not necessarily, have a degree of crystallinity at room temperature. Cross-linkable monomeric units or sites can be incorporated into such polymers. For example, cross-linking monomers can be incorporated into polyacrylate polymers, which provide sites for cross-linking the matrix after microdispersing the nitroglycerin or other anti-anginal pharmaceuticals into the polymer. Known cross-linkable monomers for polyacrylate polymers include polymethacrylic esters of polyols such as butylene diacrylate and dimethacrylate, trimethylol propane trimethacrylate and the like other monomers which provide such sites include allyl acrylate, allyl methacrylate, diallyl maleate and the like.

The adhesive layer is suitably made using a silicone adhesive, such as a polydimethylsiloxane adhesive of the following formula:



wherein x shows the unit is repeated to the extent to provide desired properties.

For example, adhesive products sold by Dow Corning under the designation DC-355 are suitable for use in making the adhesive layer. The adhesive polymer must be biologically acceptable and compatible with the nitroglycerin and

skin permeation enhancer used. Certain poly-acrylate adhesive polymers (in the form of an alkyl ester, amide, free acid, or the like) can also be used with anti-anginal pharmaceuticals. Other suitable hypoallergenic pressure-sensitive contact adhesive compositions are also known. A preferred adhesive layer is pressure-sensitive.

The adhesive layer then is finally covered with a releaseable protective layer liner which is made from materials which are substantially impermeable to nitroglycerin or other anti-anginal pharmaceuticals used, the skin permeation enhancer used and any other components of the polymer matrix dosage unit. The polymer materials and metal foil laminates used for the backing layer can be used to make the protective layer, provided the layer is made strippable or releasable such as by applying conventional siliconizing.

In making the nitroglycerin or other anti-anginal pharmaceutical containing polymer matrix disc layer, silicone elastomers such as polydimethylsiloxane of the formula described above can be suitably used. In making nitroglycerin-dispersed polymer matrix disc dosage units, it has been found suitable to use lactose as a dispersing agent to stabilize the nitroglycerin. Other suitable dispersing agents can also be used to replace lactose as long as they can produce a stable dispersion. A dispersing agent might be unnecessary if the anti-anginal pharmaceutical is a solid. Depending upon the drug loading desired, a suitable amount of a dispersing agent has been found to be 1-9 equivalents (by weight) based on the weight of nitroglycerin. The blend of nitroglycerin with dispersing agent then is

added to the polymer used to make the matrix disc layer. The amount of nitroglycerin added depends upon the amount of nitroglycerin dosage desired in each dosage unit and the amount which can be incorporated into the polymer matrix disc to retain suitable structural, diffusion and other properties in the final matrix disc. It has been found, for example, that up to 30 parts of nitroglycerin dispersion can be satisfactorily added to 70 parts of the polyer used in making the matrix disc, such as silicone elastomers. The mixture of the polymer and nitroglycerin/dispersing agent is then thoroughly mixed using a high-torque mixer to form a homogeneous microdispersion of nitroglycerin in the polymer. With continued agitation, an amount of cross-linking catalyst is desirably added together with relatively low molecular weight polymer having a compatible chemical structure. For example, when polydimethylsiloxane is used as the polymer, a relatively low molecular weight polydimethylsiloxane and a cross-linking catalyst is added (such as 10 parts by weight of the low molecular weight polydimethylsiloxane and 30 drops of stannous octanoate per 100g. amount of the final polydimethylsiloxane-nitroglycerin mixture) to the above illustrative composition of 20 parts of nitroglycerin dispersion and 70 parts of polydimethylsiloxane polymer. Again, the mixture is agitated with a high-torgue mixer to form a uniform admixture. After each mixing step, the composition is subjected to vacuum to remove any entrapped air.

It is also desirable to add an amount of dextran to the polymeric mixture used in making the matrix, if it is

compatible with the polymer used. It has been found useful to incorporate about one to about ten parts by weight based on the polymer of dextran, preferably about three to about eight parts by weight, and usually about six parts by weight being a preferable amount depending upon the polymer and anti-anginal pharmaceutical used.

The deaerated mixture is then placed in a device maker and heated to suitable elevated temperature to promote cross-linking. A suitable temperature for cross-linking when the polymer used is polydimethylsiloxane of the above formula and the cross-linking catalyst is stannous octanoate, is from about 10°C to about 200°C, desirably about 20°C to about 100°C. The temperature used should not cause significant degradation of nitroglycerin. The polymer matrix sheet desirably is about 0.05 to 5 mm, preferably about 0.1 to about 3 mm in thickness. The resulting cross-linked polymer matrix sheet is removed from the device maker and can be cut to form discs with desired shapes and sizes. The discs are then attached to a backing sheet, as described above, using an area, suitably about 5 to 100 sq. cm., preferably, about 8 to about 80 sq. cm., generally about 10 to 60 sq. cm. being more preferable. The shape of the discs can vary; they can be circular, square, rectangular, or other desired shapes.

The nitroglycerin-containing polymer matrix disc layer, generally speaking, should contain some excess amount of the dispersed nitroglycerin over the dosage amount desired to be transdermally absorbed by the subject to be treated. Ordinarily, this excess is small, such as less than 2-fold

excess. Generally speaking, an amount of the nitroglycerin used, which is sufficient, is less than 2 to about 10 times the desired dosage to less than 2 to about 5 times, the desired dosage to be transdermally absorbed being adequate, depending upon the physiochemical properties of nitroglycerin, as well as the nature of the polymer of the matrix disc layer and other factors. The amount of nitroglycerin loading in the matrix can be varied, depending upon the polymer used in making the matrix layers, the dosage desired, the skin permeation enhancer system or systems used and the like. Ordinarily, however, in using silicone polymers for making the matrix layer, use of up to about 10 percent loading of nitroglycerin is adequate. It has been observed that a greater loading does not assure a greater transdermal absorption of nitroglycerin and at least at times results in no significant increase.

The adhesive polymer layer containing the skin permeation enhancer is made as by dissolving the enhancer compound in a solvent for the enhancer which is compatible with the adhesive polymer solution used to make the adhesive layer containing the skin permeation enhancer. Any suitable amount of solvent can be used as necessary to dissolve the quantity of enhancer to ber admised with the adhesive polymer solution used. For example, 3 to 10 parts os solvent can be used to dissolve one part of skin permeation enhancer, depending upon the solubility of the enhancer. When using polydimethylsiloxane adhesive solution, it has been found suitable to use 2 to 30 parts of skin permeation enhancer in 20 to 50 parts of solvent (such as acetone,

methyl ethyl ketone, ethyl acetate or other suitable solvent) and add the solution to 100 parts of the adhesive solution. The enhancer-adhesive combination is thoroughly mixed and a coating thereof is applied using a film coating machine to the matrix disk layer or to a strippable release liner, as described above. Preferably, in order to assure adequate adhesion of the adhesive polymer layer to the skin of the subject treated, an enhancer-adhesive polymer solution having a relatively low concentration of enhancer, e.g., 1-2 percent based on the weight of the adhesive polymer is used to apply a coating to the release liner. The thickness of this coating ordinarily is a minor percentage of the thickness of the final adhesive layer, such as 20-40 percent of the total adhesive polymer layer. The remainder of the adhesive polymer layer having a suitable higher concentration of the enhancer is used to coat the matrix disc layer. Suitable higher concentrations of enhancer are usually 10 to about 30 percent based on the adhesive polymer weight, depending on solubility, desired final amount of skin enhancer agent and other factors. The solvent of the respective coatings is removed by evaporation. The respective coatings are combined to make the final adhesive polymer-enhancer agent layer by application of constant pressure.

A suitable release liner being a poly(ethylene phthalate) laminated with aluminum foil. The poly(ethylene phthalate) side to which the adhesive-enhancer coating is applied, is made strippable to conventional siliconizing or by other suitable means, such as fluorocarbon-coating. The

thickness of the adhesive-enhancer layer normally applied is about 10 to about 200 microns, preferably about 30 to about 150 microns. The amount of enhancer in the adhesive layer depends in part on the rapidity at which it is desired that nitroglycerin be absorbed. Generally speaking, about 1 to about 30 percent of skin permeation enhancer based on the weight of the adhesive is suitable depending upon the enhancer, matrix polymer, adhesive and other factors. Desirably, about 2 to 20 percent of skin permeation enhancers are used depending upon the above recited factors. The adhesive layer containing the skin permeation enhancer is applied to the polymer matrix disc surfaces by application of a constant pressure.

The four-layer transdermal nitroglycerin polymer matrix dosage units are excised. The backing layer as desired can be shaped around the sides of the dosage unit including the polymer matrix layer if such protection is desired. The resulting nitroglycerin polymer matrix dosage unit forms are then placed in appropriate storage until they are to be applied in transdermal treatment.

The pharmaceutical nitroglycerin is dispersed in the polymer matrix disc layer. Another type of pharmaceutical may also be dispersed in the polymer matrix disc layer, which includes any pharmaceutical which is capable of being transdermally or topically administered to a subject to be treated and which does not materially interfere with the desired nitrogen absorption and treatment. Such additional pharmaceutical used should have a daily effective dose of less than about 100 mg. With the controlled release of

nitroglycerin and any additional pharmaceutical at a relatively steady-state rate over a prolonged period, typically 24 hours or longer, the patient is provided with the benefit of a steady infusion of the pharmaceutical component over a prolonged period.

It will be appreciated that the nitroglycerin may be added to the above mixture not only in the form of the pure chemical compound, but also in admixture with other pharmaceuticals which may be transdermally applied or with other ingredients which are not incompatible with the desired objective of transdermally administering nitroglycerin to a patient. Thus, it will be suggested to those in the art of nitroglycerin treatment to consider substitution in part or in total other anti-anginal nitrate or nitrite compounds or other pharmaceuticals which have anti-anginal treatment properties. Anti-anginal pharmaceuticals used in this invention are nitrate or nitrite esters of mono-or polyhydric alcohols which are pharmaceutically acceptable, which have anti-anginal effectiveness and which are susceptible to transdermal absorption and can be selected from but are not limited to nitroglycerin, isosorbide dinitrate, pentaerythrityl tetranitrate, erythrityl tetranitrate, amyl nitrite and the like.

The skin permeation enhancers which can be used in carrying out this invention can vary. Ones that give preferred results with the polymer matrix dosage unit form having nitroglycerin can vary. In some instances, the use of permeation enhancer in making a polymer matrix dosage form will result in good or even excellent absorption of

nitroglycerin, might result in relatively low enhancement when another dosage unit form of the invention is used. Use of combinations of two or more of the skin permeation enhancer compounds frequently result in superior results, such as greater transdermal absorption. Some amount of skin permeation enhancer can also be incorporated into the polymer matrix layer, if desired, the amount used in the matrix layer can be varied so long as it is effective, such as an amount equivalent to the amount used in making the adhesive layer or an amount which is 20-80% of the concentration used in the adhesive layer. The skin permeation enhancers can be varied if desired in the respective layers.

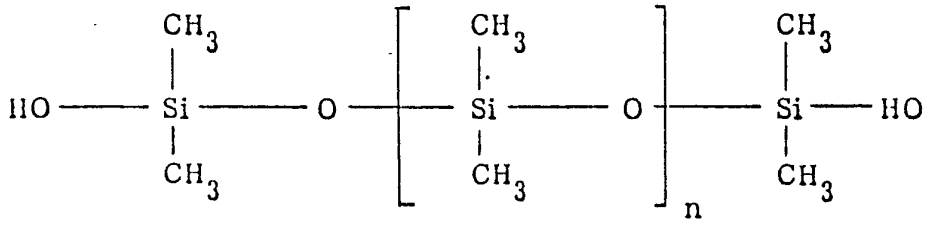
Specific skin permeation enhancers which can be used in making the polymer matrix dosage forms of this invention include saturated and unsaturated fatty acids and their esters, alcohols, monoglycerides, acetates, diethanolamides and N,N-dimethylamides, such as oleic acid, capric or decanoic acid, propyl decanoate, propyl or isopropyl oleate, oleyl acetate, propyl or isopropyl myristate, myristyl alcohol, myristyl N,N-dimethyl amide, stearic acid and stearyl alcohol, propyl stearate monostearin, and combinations of them with, for example, 1-dodecylazacycloheptan-2-one sold under the trademark Azone by Nelson Research and Development; decyl methyl sulfoxide, dimethyl sulfoxide, salicylic acid and derivatives, N,N-diethylm-toluamide, crotamiton, 1-substituted azacycloalkan-2-ones such as disclosed in U. S. Patent 4,316,893 (the 1-substituent having 0-17 carbon atoms, preferably, 1-11 carbon atoms), squalane and various other compounds which are biologically compatible and have

transdermal permeation activity. It has been found useful to incorporate menthol with one or more skin permeation enhancers, even though it is not currently certain whether menthol alone has skin permeation enhancer activity. Ethyl alcohol and other short chain alkanols (with 1-4 carbon atoms) which have substantially the same properties and activity as ethyl alcohol do not come within the definition of skin permeation enhancer as used herein.

The following examples are in illustration of the invention and are not intended to be limiting.

EXAMPLE 1

A dispersion of 10 parts by weight each of pure nitroglycerin oil and lactose is made by using a high-torque mixer (sold by Cole-Parmer Company). The nitroglycerin-lactose dispersion is homogeneously dispersed in 70 parts of silicone elastomer using the high-torque mixer and at about 1,000 rpm. The silicone elastomer is a polydmethylsiloxane polymer sold by Dow Corning Company under the designation Silastic Medical Grade 382 Elastomer. The elastomer is believed to have the following structural formula:



wherein n indicates the number of repeating units.

With continued agitation, 10 parts of DC-360 (silicone medical fluid) and 30 drops (for every 100 g of the mixture)

of a cross-linking agent designated as catalyst M is added, which is stannous octanoate. After each addition of the material, the mixture is thoroughly mixed and is placed under vacuum to remove entrapped air.

The nitroglycerin-polydimethylsiloxane dispersion is placed into a device maker and is cross-linked at room temperature or at an elevated temperature (60° - 100°C) to form a cross linked, medicated polymer sheet, which has a thickness of 0.2-2 mm.

The medicated polymer sheet is removed from the device maker and is cut into circular discs of about 3-20 sq. cm. The discs are attached to a backing layer of heat sealable polyester film which is laminated to aluminum foil. This laminate is sold by 3M Company as Scotchpak 1006. The medicated discs are attached to the backing layer using an adhesive polymer solution, a silicone adhesive polymer sold by Dow Corning as DC-355 or medical-grade adhesive A being suitable. Alternately, the discs can be formed directly on the backing layer and in practice are.

The skin permeation enhancer-adhesive layer is made by dissolving the necessary weight of a skin permeation enhancer in 30 parts of acetone. The acetone solution then is added to 100 parts of a silicone adhesive solution sold by Dow-Corning under the designation DC-355. The mixture is thoroughly mixed to form a homogeneous mixture of skin permeation enhancer and adhesive polymer.

The adhesive polymer layer is formed by making multiple coatings. Desirably, a coating of adhesive polymer solution containing 1-2 percent enhancing agent is applied to the

release liner (a fluorocarbon-coated polyester film). This lower concentration of enhancing agent aids assurance that the surface of the final adhesive layer when applied to skin of the subject treated will satisfactorily adhere. The remaining portion of the adhesive coating necessary to make up the final adhesive layer thickness has a higher enhancing agent content (10-30 percent) and is applied to the matrix layer. The solvent of the respective coatings is removed by evaporation. The release liner so-coated is then applied to the adhesive coated matrix layer under a constant pressure to provide a firmly adhered strip of a four-layered structure as follows:

1. Backing layer
2. Nitroglycerin-containing polymer matrix layer
3. Skin permeation enhancer-adhesive layer (50-200 micron thickness)
4. Release film layer which can be readily removed to permit application to the skin of the subject to receive transdermally the nitroglycerin.

By use of an appropriate cutter, the strip is cut into a suitable shape such as circular to provide the transdermal nitroglycerin polymer matrix dosage units which have an area of about 20 sq. cm.

The above polymer matrix disc dosage units are made using the following skin permeation enhancers as shown in the TABLES.

Use of tert-butyl alcohol did not function as a skin permeation enhancer but rather the dosage units using tert-butyl alcohol resulted in less nitroglycerin absorption than

the absorption from a controlled unit in which no enhancer compound was added to the adhesive layer.

The transdermal absorption of nitroglycerin from the nitroglycerin polymer matrix dosage units of this invention is evaluated by use of skin from a "hairless" mouse or human cadaver by following the procedure described by P. R. Keshary and Y. W. Chien, in Drug Develop. & Ind. Pharm., 10 (6) 883-913(1984).

The following TABLES show the transdermal absorption of nitroglycerin from the nitroglycerin-containing polymer matrix disc dosage units made by the above procedure:

TABLE I

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY VARIOUS ENHANCERS

Dosage Unit	Agents[1] (1.6 mg/cm²)	Permeation Rate (mcg/cm²/hr ± S.D.)	Enhancing Factors[2]
1.	None	25.72 ± 5.41	1.00
2.	Stearic Acid	27.26 ± 2.53	1.06
3.	Stearyl Alcohol	25.38 ± 0.05	0.99
4.	Stearyl Propyl Ester	42.91 ± 4.81	1.67
5.	Mono-Stearin	36.82 ± 0.01	1.43
6.	Oleic Acid	70.55 ± 11.06	2.74
7.	Oleyl Alcohol	61.74 ± 5.83	2.40
8.	Oley Propyl Ester	62.40 ± 11.12	2.43
9.	Mono-Olein	51.14 ± 10.52	1.99
10.	Myristic Acid	28.04 ± 1.33	1.09
11.	Myristyl Alcohol	45.72 ± 2.33	1.78
12.	Myristyl Propyl Ester	49.46 ± 5.62	1.92
13.	Mono-Myristein	22.54 ± 2.90	0.88
14.	n-Decyl Alcohol	65.59 ± 11.39	2.55
15.	Decyl Acetate	40.01 ± 5.28	1.56
16.	1-Dodecylazacyclo-heptan-2-One	35.83 ± 3.90	1.39
17.	Decyl Methyl Sulfoxide	56.68 ± 1.82	2.20
18.	T-Butanol	22.73 ± 2.02	0.88
19.	1-Propanol	27.56 ± 3.41	1.07
20.	2-Propanol	27.06 ± 4.69	1.05
21.	Triethanolamine	28.62 ± 4.79	1.11
22.	Malonic Acid Diethyl Ester	40.12 ± 2.20	1.56
23.	Maleic Acid Diethyl Ester	30.01 ± 3.83	1.17
24.	Mandelic Acid Ethyl Ester	27.09 ± 0.20	1.05
25.	Glycylglycine	36.94 ± 4.36	1.44

1) Contained in the adhesive layer at a surface concentration of 1.6 mg/cm².

2) Enhancing Factor = $\frac{\text{(Normalized Permeation Rate) Enhancer}}{25.72}$

TABLE II

EFFECT OF LOCATION AND CONCENTRATION OF PROPYL OLEATE, AS SKIN PERMEATION ENHANCER, ON TRANSDERMAL ABSORPTION OF NITROGLYCERIN

Concentration of Enhancer in Polymer Matrix	Concentration of Enhancer in Adhesive Layer	Normalized Permeation Rate ($mcg/cm^2/hr \pm S.D.$)	Enhancing Factor*
0.0%	0.0%	40.33 ± 6.04	1.00
2.5%	-	46.09 ± 5.07	1.14
-	2.5%	59.68 ± 17.34	1.48
2.5%	2.5%	71.00 ± 14.48	1.76
5.0%	-	65.86 ± 22.61	1.63
-	5.0%	87.72 ± 16.31	2.18
5.0%	5.0%	109.58 ± 10.03	2.72
-	10.0%	125.86 ± 12.21	3.12

* Enhancement Factor = $\frac{\text{(Normalized Permeation Rate) Enhancer}}{40.33}$

TABLE III

EFFECT OF SKIN PERMEATION ENHANCER CONCENTRATION IN ADHESIVE LAYER ON THE ENHANCEMENT OF TRANSDERMAL ABSORPTION OF NITROGLYCERIN

Enhancing Conc.	Enhancing Factor							
(mg/cm^2)	A*	B	C	D	E	F	G	H
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.0
0.08	1.16	--	--	--	--	--	--	-
0.20	1.41	--	--	--	--	--	--	-
0.37	1.68	--	--	--	--	--	--	-
0.66	2.41	--	--	--	--	--	--	-
0.80	--	2.59	1.67	1.22	1.69	1.56	1.61	1.3
0.96	1.99	--	--	--	--	--	--	-
1.27	1.41	--	--	--	--	--	--	-
1.59	1.44	4.11	1.92	2.43	2.82	2.58	1.87	2.0
2.40	--	--	--	--	--	--	2.02	-
3.18	1.51	4.41	3.07	3.08	2.65	1.50	--	1.6
4.78	--	--	3.41	3.78	--	1.74	--	1.5
5.00	--	--	--	--	--	--	1.36	--
10.00	--	--	--	--	--	--	1.22	-

*Enhancer A = 1-Dodecylazacycloheptan-2-one
B = Decanoic acid
C = Propyl myristate
D = Propyl oleate
E = Oleyl alcohol
F = 1-monolauroyl-rac-glycerol
G = Decylmethyl sulfoxide
H = Myristic acid, N,N-dimethylamide

TABLE IV

EFFECT OF ENHANCER CONCENTRATION ON SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY COMBINATION OF ENHANCERS

Concentration of Enhancers in Adhesive Layer* (mg/cm²)				Enhancing Factor
A	B	C	D	
1.27	--	--	--	1.41
1.27	1.27	--	--	2.15
1.27	--	1.27	--	1.63
--	1.27	1.27	--	1.28
1.27	1.27	1.27	--	2.37
0.34	3.2	--	--	2.34
0.34	--	3.2	--	2.81
0.34	--	--	2.3	1.87
0.17	1.6	--	--	1.84
0.17	--	1.6	--	1.85
0.17	--	--	1.09	1.35
0.17	0.83	0.83	--	1.87
0.17	0.83	--	0.79	2.83
0.17	--	0.83	0.79	1.78
0.085	0.83	0.83	0.55	2.34

*Enhancer A = 1-Dodecylazacycloheptan-2-one
B = Propyl oleate
C = Propyl myristate
D = Decylmethyl sulfoxide

TABLE V

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY COMBINATION OF ENHANCERS

Enhancers	Conc. (mg/3.14cm²)	Permeation Rate (mcg/cm²/hr + S.D.)	Enhancing Factor A[1]	Enhancing Factor B[2]
None		30.84 ± 1.32	1.00	1.00
1-Dodecylazacycloheptan-2-one	1.0	42.68 ± 3.07	1.38	1.00
+Propyl Myristate	5.0	63.83 ± 2.23	2.07	1.50
	10.0	88.54 ± 1.31	2.87	2.07
+Propyl Oleate	5.0	69.00 ± 2.76	2.24	1.62
	10.0	83.50 ± 3.87	2.71	1.96
+Myristyl Acetate	5.0	116.01 ± 25.71	3.76	2.72
	10.0	103.89 ± 18.41	3.37	2.43
+Oleyl Acetate	5.0	89.71 ± 0.64	2.91	2.10
	10.0	107.03 ± 2.14	3.47	2.51
+Glycylglycine	5.0	47.30 ± 0.90	1.53	1.11
+Decylmethyl Sulfoxide	5.0	81.17 ± 7.11	2.63	1.90
1-Dodecylazacycloheptan-2-one	2.0	46.71 ± 3.39	1.51	1.00
+Propyl Myristate	5.0	71.58 ± 14.57	2.32	1.53
	10.0	82.15 ± 0.05	2.66	1.76
+Propyl Oleate	5.0	50.20 ± 2.62	1.63	1.07
	10.0	79.90 ± 18.95	2.59	1.71
+Salicylic Acid	5.0	52.11 ± 0.40	1.69	1.12
	10.0	41.15 ± 6.80	1.33	0.88

1-Enhancing Factor A = normalized permeation rate with defined skin permeation enhancer content/normalized permeation rate of a corresponding dosage unit with no enhancer.

2-Enhancing Factor B = normalized permeation rate with defined combination of skin permeation enhancer content/normalized permeation rate of a corresponding dosage unit with only the defined amount of the enhancer of the combination, 1-dodecylazacycloheptan-2-one.

TABLE VI

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY COMBINATION OF 1-DODECYLAZACYCLOHEPTAN-2-ONE WITH OTHER SKIN PERMEATION ENHANCERS

Concentration of Enhancers in Adhesive Layer* (mg/cm²)							Enhancin Factor
A	B	C	D	E	F	G	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.00
0.34	--	--	--	--	--	--	1.18
0.34	0.8	--	--	--	--	--	2.61
0.34	1.6	--	--	--	--	--	4.43
0.34	--	1.6	--	--	--	--	3.82
0.34	0.8	0.8	--	--	--	--	4.38
0.34	0.8	1.6	--	--	--	--	3.61
0.34	--	0.8	0.8	--	--	--	3.05
0.34	--	--	--	1.6	--	--	2.47
0.34	0.8	--	--	0.8	--	--	4.33
0.34	0.8	--	--	1.6	--	--	4.31
0.34	--	0.8	--	--	0.8	--	2.69
0.34	0.8	--	--	--	--	0.8	2.22

*Enhancer A = 1-Dodecylazacycloheptan-2-one
B = Decanoic acid
C = Decanol
D = Oleic acid
E = Oleyl alcohol
F = Lauric acid
G = Decyl methyl sulfoxide

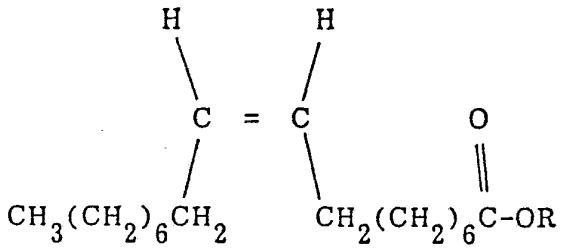
TABLE VII

SKIN PERMEATION ENHANCEMENT BY VARIOUS GLYCERIDES

Glycerides (1.6 mg/cm²)	Skin Permeation Rate (mcg/cm²/hr) With	Without	Enhancing Factor
1-Monolauroyl-RAC-Glycerol	88.02 ± 19.71	34.1 ± 1.62	2.58
1-Monomyristoly-RAC-Glycerol	29.88 ± 3.84	34.1 ± 1.62	0.88
1-Monopalmitoyl-RAC-Glycerol	29.39 ± 1.76	34.1 ± 1.62	0.86
1,2-Dimyristoyl-RAC-Glycerol	40.64 ± 4.27	39.4 ± 4.32	1.03
1,3-Dimyristoyl-RAC-Glycerol	32.13 ± 6.94	34.1 ± 1.62	0.94
1,2,3-Trimyristoyl-RAC-Glycerol	32.36 ± 4.61	39.4 ± 4.32	0.82

TABLE VIII

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY UNSATURATED FATTY ACID ESTERS



Enhancers (1.6 mg/cm²)	R	Normalized Permeation Rate* (mcg/cm²/hr±S.D.)	Enhancing Factor
Methyl Oleate	CH_3	77.56 ± 3.54	2.62
Ethyl Oleate	CH_3CH_2	68.48 ± 9.77	2.31
Propyl Oleate	$CH_3CH_2CH_2$	71.96 ± 12.82	2.43
Butyl Oleate	$CH_3CH_2CH_2CH_2$	61.00 ± 3.22	2.06
Oleyl Acetate	CH_3C	69.05 ± 8.88	2.33

*Normalized Permeation Rate Without Enhancer = 29.66 ± 0.83 for Nitroglyceri

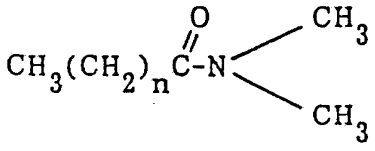
TABLE IX

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY UNSATURATED FATTY ACID PROPYL ESTERS

Enhancing Agents	Skin Permeation Rate (mcg/cm²/hr± S.D.)		Enhancing Factor
	With	Without	
Monoenoic Acid			
Oleic Acid Propyl Ester	72.81 ± 12.97	30.01 ± 4.29	2.43
Dienoic Acid			
Linoleic Acid Propyl Ester	73.89 ± 16.03	30.01 ± 4.29	2.46
Tetraenoic Acid			
Arachidonic Acid Propyl Ester	70.71 ± 31.76	30.01 ± 4.29	2.30

TABLE X

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY SATURATED FATTY ACID AMIDE



Enhancers (1.6 mg/cm²)	n	Normalized Permeation Rate* (mcg/cm²/hr±S.D.)	Enhancing Factor
N-Caproic Acid N,N-Dimethylamide	4	33.49 ± 4.12	1.21
Lauric Acid N,N-Dimethylamide	10	47.33 ± 1.76	1.71
Myristic Acid N,N-Dimethylamide	12	55.83 ± 7.39	2.02

*Normalized Permeation Rate Without Enhancer = 27.65 ± 2.47 for Nitroglycerin.

TABLE XI

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY VARIOUS MYRISTYL DERIVATIVES

Myristyl Derivative	Skin Permeation Rate (mcg/cm²/hr± S.D.)		Enhancing Factor
	With	Without	
Myristic Acid	31.24 ± 1.48	28.66 ± 2.72	1.09
Myristate Sodium	36.28 ± 4.06	39.38 ± 4.32	0.92
Myristyl Esters:			
Methyl	63.36 ± 8.66	32.52 ± 3.52	1.95
Ethyl	52.40 ± 1.47	28.66 ± 2.72	1.83
Propyl	67.77 ± 7.70	35.24 ± 1.75	1.92
Isopropyl	61.29 ± 4.49	35.24 ± 1.75	1.74
Myristyl	40.30 ± 0.03	28.86 ± 0.91	1.40
Myristyl Alcohol	51.30 ± 2.62	28.86 ± 0.91	1.78
Myristyl Acetate	58.54 ± 3.88	28.86 ± 0.91	2.03
Myristyl N,N-Dimethylamide	57.87 ± 7.66	28.86 ± 2.72	2.02

TABLE XII

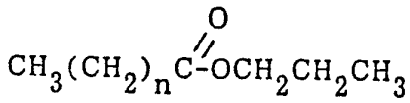
ENHANCEMENT IN TRANSDERMAL ABSORPTION OF NITROGLYCERIN BY SATURATED FATTY ACIDS

$$CH_3(CH_2)_nC(=O)-OH$$

Enhancers (1.6 mg/cm²)	n	Normalized Permeation Rate (mcg/cm²/hr±S.D.)	Enhancing Factor
Butanoic acid	2	34.98 ± 0.48	0.89
Hexanoic acid	4	36.00 ± 1.93	0.92
Octanoic acid	6	101.80 ± 25.9	2.60
Decanoic acid	8	159.12 ± 75.5	4.07
Dodecanoic acid	10	114.67 ± 13.7	2.93
Tetradecanoic acid	12	42.64 ± 2.02	1.09
Octadecanoic acid	16	41.44 ± 3.85	1.06

TABLE XIII

SKIN PERMEATION ENHANCEMENT OF NITROGLYCERIN BY SATURATED FATTY ACID PROPYL ESTERS



Enhancers (1.6 mg/cm²)	n	Normalized Permeation Rate* (mcg/cm²/hr±S.D.)	Enhancing Factor
Hexanoic acid propyl ester	4	43.67 ± 3.90	1.43
Octanoic acid propyl ester	6	49.69 ± 3.12	1.62
Decanoic acid propyl ester	8	69.02 ± 12.54	2.26
Dodecanoic acid propyl ester	10	58.59 ± 2.95	1.92
Tetradecanoic acid propyl ester	12	57.58 ± 6.54	1.88
Hexadecanoic acid propyl ester	14	48.11 ± 5.97	1.57
Octadecanoic acid propyl ester	16	51.02 ± 5.72	1.67

*Normalized Permeation Rate Without Enhancer = 30.58 ± 1.71 for Nitroglycerin

EXAMPLE 2

Following generally the procedure of Example 1, 15 percent W/W of nitroglycerin is incorporated into a polydimethylsiloxane sold under the designation Silastic Medical Grade 382 Elastomer to provide nitroglycerin containing matrix layer units. Also, following generally the procedure of Example 1, 15 percent W/W of nitroglycerin is incorporated into a polymethylvinylsiloxane sold under the designation Silastic Medical Grade MDX4-4210 to form nitroglycerin containing matrix layer units using a two-stage platinum catalyst for crosslinking. Skin permeation enhancers are incorporated into the adhesive compositions used to form the adhesive layer in the manner described in Example 1. The concentration of skin permeation enhancer used are shown in the following TABLES. As described in Example 1, the adhesive layer is formed by making multiple coatings. At times, the adhesive coating solution (10-20%) is further diluted with regard to the skin permeation enhancer content by adding further adhesive polymer, which composition is applied to the release liner. The release liner surface with the adhesive coating then is applied to the adhesive layer which has been applied to the matrix surface to result in a unitary adhesive layer. When the release liner is removed when the final dosage unit is being prepared for application to the subject being treated, the thin coating of the adhesive having low content of skin permeation enhancer (usually no more than 1-2 percent enhancer) adheres satisfactorily to the skin of the subject being treated. The thickness of this layer is typically about 100 microns.

The skin permeation enhancer concentrations of the adhesive compositions making up the adhesive layers are shown in the following TABLES:

TABLE XIV

SYNERGISTIC EFFECT IN SKIN PERMEABILITY ENHANCEMENT OF NITROGLYCERIN[1)]

Enhancers composition (mg/cm²)			Enhancement Factor	
(+) menthol	capric acid	3rd enhancer	MDX4-4210	DC-382
1.6	--	--	0.93	--
0.8	0.8	--	3.40	--
--	0.8	--	2.26	2.80
0.8	0.8	Decanol 0.8		6.74
0.8	0.8	Decanol 1.6	7.49	7.76
0.8	0.8	Oleyl alcohol 0.8	6.13	5.29
0.8	0.8	Oleyl alcohol 1.6	6.34	4.61
0.8	0.8	Salicylic acid 0.8	4.01	3.47
0.8	0.8	Methyl Salicylate 0.8	2.50	3.36

1) 15% W/W in either MDX4-4210 or DC-382 type silicone matrix.

TABLE XV

SYNERGISTIC EFFECT IN SKIN PERMEABILITY

ENHANCEMENT OF NITROGLYCERIN[1)]

Enhancers combination[3)] (mg/cm²)						Enhancement Factor	
A	B	C	D	E	F	MDX4-4210[2)]	DC-382
1.0	1.0	--	--	--	--	1.72	--
1.0	--	1.0	--	--	--	3.32	2.96
1.0	--	--	1.0	--	--	3.10	3.45
1.0	1.0	--	--	1.6	--	2.40	3.37
1.0	--	1.0	--	1.6	--	16.68	7.24
1.0	--	--	1.0	1.6	--	12.39	--
1.0	--	--	--	1.6	--	--	2.09
--	1.0	--	--	1.6	1.0	4.04	--
--	--	0.8	--	1.6	0.8	--	5.80

1) Drug loading = 15% W/W

2) Contains 6% dextran

3) A = Decylmethyl sulfoxide
B = Octanol
C = Decanol
D = Oleyl alcohol
E = Squalane
F = Capric acid

TABLE XVI

EFFECT OF ENHANCER LOCATION ON SKIN PERMEABILITY AND ENHANCEMENT OF NITROGLYCERIN BY PROPYL OLEATE

Enhancer Concentration		Permeation Rate	Enhancement Factor
Matrix	Adhesive	(mcg/cm²/hr)	
0%	0%	40.33 ± 6.04	1.00
2.5%	--	46.09 ± 5.07	1.14
--	2.5%	59.68 ± 17.34	1.48
2.5%	2.5%	71.00 ± 14.48	1.76
5.0%	--	65.86 ± 22.61	1.63
--	5.0%	87.72 ± 16.31	2.18
5.0%	5.0%	109.58 ± 10.03	2.72
--	10.0%	125.86 ± 12.21	3.12

TABLE XVII

SYNERGISTIC EFFECT IN SKIN PERMEABILITY

ENHANCEMENT OF NITROGLYCERIN[a)]

Enhancers Composition		Enhancement Factor[b)]
menthol[c)] (mg/cm^2)	capric acid (mg/cm^2)	
(-) menthol		
1.6	--	0.90
0.8	0.8	2.29
(+) menthol		
1.6	--	0.93
0.8	0.8	3.40
(±) menthol		
1.6	--	1.01
0.8	0.8	3.01
--	0.8	2.26

a) 10% W/W in MDX4-4210-type silicone matrix.

b) Skin permeation rate for control device = 30.33 ± 0.2 $mcg/cm^2/hr$.

c) Menthol has been reportedly used to relieve local irritation or for counterirritant purposes.

TABLE XVIII

SILICONE ELASTOMER COMPOSITION ON SKIN

PERMEATION RATE OF NITROCLYCERIN

Drug Loading	Skin Permeation Rate (mcg/cm²/hr)	
(% W/W)	DC-382[a)]	MDX-4-4210[b)]
10	37.79 ± 8.12	33.28 ± 4.77
15	33.05 ± 0.99	37.60 ± 11.87
20	30.14 ± 1.19	33.40 ± 4.44

a) Tin-catalyzed 2-part system

b) Platinum-catalyzed 2-part system

EXAMPLE 3

Dosage units are made using polymethylvinylsiloxane sold by Dow Corning under the designation MDX 4-4210 by following the general procedure described in Example 1. The polymer matrix layers have a nitroglycerin content of 12 percent and 6 percent of dextran based on the weight of the silicone polymer. The adhesive layer (thickness of about 300 microns) applied to the matrix layer has 3 percent squalane, 2.2 percent decylmethyl sulfoxide and 2.2 percent oleyl alcohol, based on the adhesive polymer weight. It is made by first applying to a release liner and then applying the coating to the matrix surface. The outer adhesive layer is applied to the release liner of the final dosage unit has 2 percent squalane, 1 percent decylmethyl sulfoxide and 1 percent oleyl alcohol; it has a thickness of about 100 microns. A laminating machine is employed to apply the respective adhesive layers to make the final matrix dosage unit. The dosage units show retention of nitroglycerin skin permeation rate after storage for one week at 25°, 37°, and 45°, respectively.

EXAMPLE 4

Examples 1-3 are essentially repeated using effective dosage amounts of isosorbate dinitrate, pentaerythrityl tritranitrate, erythrityl tetranitrate, and amyl nitrite respectively, instead of nitroglycerin.

WHAT IS CLAIMED IS:

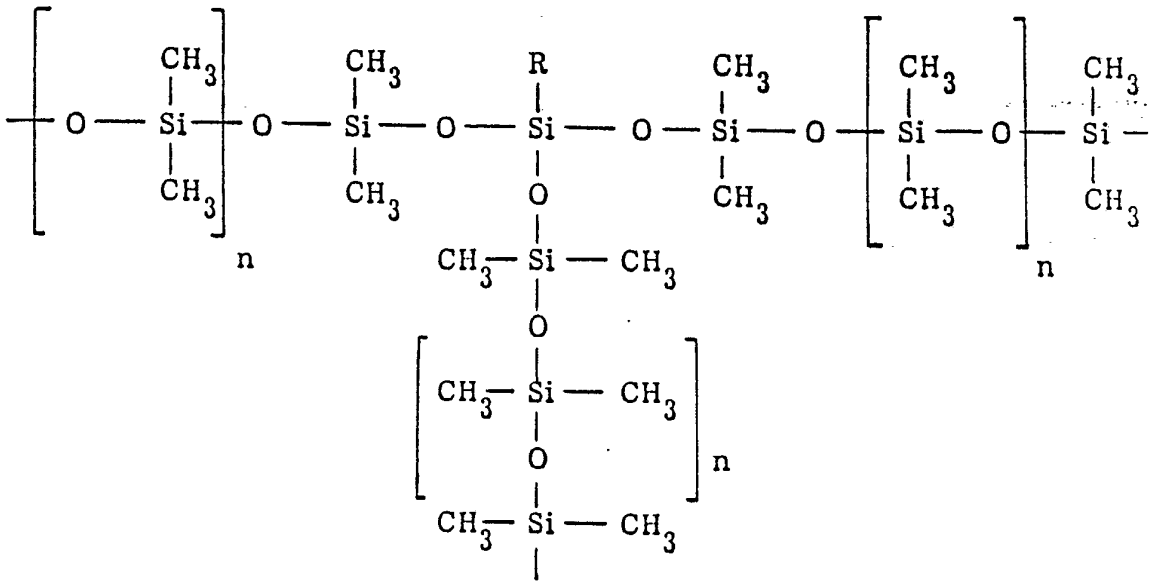
1. A transdermal nitroglycerin or other anti-anginal pharmaceutical polymer matrix dosage unit comprising:

a) a backing layer which is substantially impervious to the pharmaceutical to be delivered transdermally;

b) a polymeric matrix disc layer which is adhered to said backing layer and which has microdispersed therein an amount of the pharmaceutical which will provide a dosage amount of the pharmaceutical to be delivered transdermally; and

c) an adhesive layer which is adhered to said pharmaceutical containing polymeric matrix disc layer and which has distributed therein an effective amount of one or more skin permeation enhancers which provide substantial skin absorption enhancement for said pharmaceutical; said dosage unit having an enhancing factor of at least 1.2.

2. A transdermal nitroglycerin or other anti-anginal pharmaceutical polymer matrix dosage unit of claim 1 wherein the polymer matrix disc layer is a cross-linked polysiloxane polymer of the following formula:



wherein R is alkyl or alkoxy having 1-7 carbon atoms, vinyl, phenyl or combination thereof; and wherein n is about 100 to about 5,000.

3. A transdermal polymer matrix dosage unit of claim 1 wherein the polymer matrix disc layer has microdispersion compartments and has a cross sectional dimension of from about 10 to about 200 microns.

4. A transdermal polymer matrix dosage unit of claim 2 wherein the polymer matrix disc layer has microdispersion compartments and has a cross sectional dimension of from about 10 to about 200 microns.

5. A transdermal polymer matrix dosage unit of claim 4 wherein R in the polysiloxane formula is selected from alkoxy, alkyl, vinyl, phenyl and combinations thereof.

6. A transdermal polymer matrix dosage unit of claim 4 wherein the adhesive layer is made using a silicone polymer adhesive.

7. A transdermal polymer matrix dosage unit of claim 4 wherein the adhesive layer is made from a pressure-sensitive adhesive and the dosage unit has a releasable protective layer.

8. A transdermal polymer matrix dosage unit of claim 4 wherein the adhesive layer is made using a silicone polymer adhesive and the dosage unit has a releasable protective layer.

9. A transdermal polymer matrix dosage unit of claim 4 wherein the enhancing factor is at least 1.3.

10. A transdermal polymer matrix dosage unit of claim 4 wherein the enhancing factor is at least about 2.

11. A transdermal nitroglycerine or other anti-anginal pharmaceutical polymer matrix dosage unit comprising:

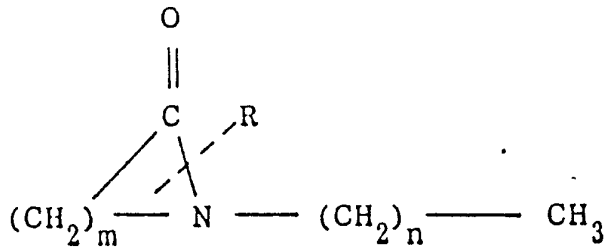
a) a backing layer which is substantially impervious to the pharmaceutical to be delivered transdermally;

b) a polymeric matrix disc layer which has a thickness of from about 0.1 to about 5mm, has microdispersed therein an amount of the pharmaceutical which can be delivered transdermally in a dosage amount, is composed of a cross-linked polysiloxane polymer with the pharmaceutical in microdispersion

compartments, and has a cross sectional dimension of from about 10 to about 200 microns;

c) a polysiloxane adhesive layer which is adhered to said nitroglycerin or other anti-anginal pharmaceutical containing polymer matrix disc layer and has distributed therein from about 1 to about 30 percent of one or more skin absorption enhancers based on the weight of the polysiloxane adhesive, which are effective in the enhancement of the transdermal absorption of the pharmaceutical in the polymer matrix disc layer; said dosage unit having an enhancing factor of at least 1.2.

12. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancement compound is selected from decyl methyl sulfoxide, 1-dodecylazacycloheptan-2-one, a compound of the formula:



wherein R is H or a lower alkyl group, m is 5-7 and n is 0-17;saturated and unsaturated fatty acids in their alkyl esters, alcohols, monoglycerides, diethanolamides, triethanolamine complex, N,N-dimethylamide derivatives, and acetate esters of said alcohol derivatives; propyl or isopropyl myristate; myristyl alcohol;

propyl or isopropyl oleate; oleic acid; oleyl alcohol; oleyl acetate; monoolein; myristyl N, N-dimethyl amide; stearic acid; stearyl alcohol; propyl stearate; monostearin; mono-myristein; salicylic acid and derivatives; glycylglycine; N,N-diethyl-M-toluamide; squalane; capric acid; crotamiton; and combinations thereof.

13. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancer is selected from the group represented by the following formula:

$$CH_3(CH_2)_n\text{-}COOH$$

wherein n is an integer from 6 to 10.

14. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancer is decanoic acid.

15. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancer is a combination of decanoic acid or decanol and 1-dodecylazacycloheptan-2-one.

16. A transdermal polymer matrix dosage unit of claim 11 wherein both the matrix layer and the adhesive layer have effective amount of one or more skin permeation enhancers.

17. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancer is a combination of 1-dodecylazacylcloheptan-2-one, decanoic acid and decanol or oleyl alcohol.

18. A transdermal polymer matrix dosage unit of claim 11 wherein the skin permeation enhancer is a combination of squalane, decylmethyl sulfoxide and oleyl alcohol.

19. A transdermal polymer matrix dosage unit of claim 18 in which the polymer of matrix layer is a polydimethyl-siloxane or polysiloxane having methylvinyl units, has about 1 to about 10 percent based on the polymer weight of dextran and at least about 10 percent by weight of nitroglycerin as the anti-anginal pharmaceutical.

20. A method of administering nitroglycerin transdermally by forming a nitroglycerin-containing polymer matrix disc dosage unit having a polymer matrix disc which has the nitroglycerin dosage microdispersed therein, which matrix disc is adhered to a skin permeation enhancer-containing adhesive polymer layer, and by applying said dosage unit by way of said adhesive layer to the skin of the subject to be treated, whereby said nitroglycerin is transdermally administered in dosage amount systematically effective to said subject.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/01739

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61L 15/03
U.S. : 424/28

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/19, 424/22, 424/28 514/946, 514/947, 514/953 604/890, 604/896, 604/897

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	U.S.,A, 3,742,951 (ZAFFARONI) 3 July 1973, see (Col. 6, lines 54-68, Col. 7, lines 38-63)	1,20
A	U.S.,A, 3,996,934 (ZAFFARONI) 14 Dec.1976, see (Col. 10, line 50 to Col. 11, line 13, & 40)	12,15,17
A	U.S.,A, 4,291,015 (KEITH ET AL) 22 Sept. 1981, see (Col. 3, lines 25 to 34)	1,20
A	U.S.,A, 4,336,243 (SANVORDEKER et al) 22 June 1982 see (Col. 3, lines 12-20, Col. 4, lines 3-7)	12,15,17
A	U.S.,A, 4,405,616 (RAJADHYAKSHA) 20 Sept. 1983 see (Col. 3, lines 34-35)	12,15,17

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
28 Oct. 1986	04 NOV 1986
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Shep K. Rose Shep K. Rose

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 16 with indication, where appropriate. of the relevant passages 17	Relevant to Claim No 18
A	U.S.,A, 4,421,737 (ITO ET AL) 20 Dec. 1983 see (Col. 3, lines 18-21, Col. 4, lines 34-54)	1,20
A	U.S.,A, 4,485,087 (OTSUKA ET AL) 27 Nov. 1984 see (Col. 4, lines 43-45, 60-65)	1,20
A	U.S.,A, 4,486,193 (SHAW ET AL) 4 Dec. 1984 see (Col. 2, lines 51-66, Col. 4, lines 31-45)	12,15,17
A	U.S.,A, 4,505,891 (ITO) 19 Mar. 1985 see (Col. 3, lines 43-60, Col. 3, line 61 to Col. 4, line 6)	12,15,17
A	U.S.,A, 4,533,540 (BLANK) 06 Aug. 1985 see (Col. 6, lines 60-64)	1,20
A,P	U.S.,A, 4,542,013 (KEITH ET AL) 17 Sept 1985 see (Col. 3, lines 15-22)	1,20
A,P	U.S.,A, 4,555,398 (ODA) 26 Nov. 1985	1,20
A,P	U.S.,A, 4,562,075 (RAJADHYAKSHA) 31 Dec. 1985 see (Col. 3, lines 35-36, 62-63)	12,15,17
A,P	U.S.,A, 4,568,343 (LEEPER ET AL) 4 Feb. 1986 see (Col. 3, lines 5,6,16, Col. 4, lines 25,26 Col. 6, lines 6-24)	1,20

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate. of the relevant passages [17]	Relevant to Claim No [18]
A,P	U.S.,A, 4,573,996 (LEEPER ET AL) 4 Mar 1986 see (Col. 10, lines 39-49, Col. 11, lines 43-68)	1,20
A,P	U.S.,A, 4,592,753 (PANOZ) 3 June 1986 see (Col. 3, lines 27,28 57-60, Col. 5, lines 35-40)	1,20
A,P	U.S.,A, 4,608,249 (OTSUKA) 26 Aug. 1986 see (Col. 3, lines 35-45, Col. 4, lines 30-33)	1,20

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	U.S.,A,	4,409,206 (STRICKER) 11 Oct. 1983 see (Col. 4, line 5, Col. 5, lines 27 to 40)	1,20
A	U.S.,A,	4,420,470 (OTSUKA ET AL) 13 Dec. 1983 see (Col. 2, lines 33-34, Col. 4, lines 61-66)	1,20

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.