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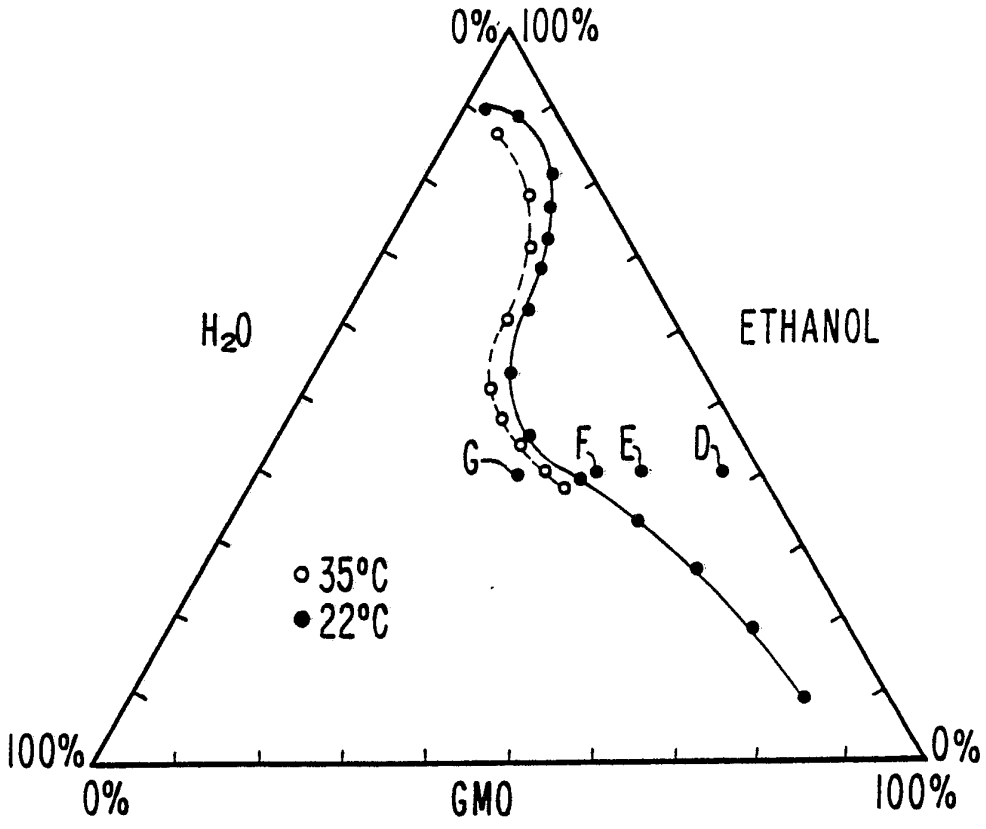

(57) Abstract

Mixtures of ethanol and glycerol monooleate are disclosed for enhancing the permeation of drugs through skin or mucosa.

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PERMEATION ENHANCER COMPRISING ETHANOL AND GLYCEROL MONOOLEATE

FIELD OF THE INVENTION

This invention relates to the transdermal delivery of drugs and other biologically active agents. More particularly, this invention relates to novel methods and compositions for enhancing the percutaneous absorption of drugs when incorporated in transdermal drug delivery systems. Still more particularly, but without limitation thereto, this invention relates to the transdermal delivery of drugs utilizing a mixture of glycerol monooleate (GMO) and ethanol.

BACKGROUND OF THE INVENTION

The transdermal route of parenteral delivery of drugs provides many advantages over other administrative routes and transdermal systems for delivering a wide variety of drugs or other beneficial agents are described in U.S. Patent Numbers 3,598,122; 3,598,123; 4,379,454; 4,286,592; 4,314,557 and 4,568,343, for example, all of which are incorporated herein by reference. In many instances, drugs which would appear to be ideal candidates for transdermal delivery are found to have such low permeability through intact skin that they can not be delivered at therapeutically effective rates from reasonably sized systems.

In an effort to increase skin permeability, it has been proposed to pretreat the skin with various chemicals or to concurrently deliver the drug in the presence of a permeation enhancer. Various materials have been suggested for this purpose as described in U.S. Pat. Nos. 3,472,931, 3,527,864, 3,896,238, 3,903,256, 3,952,099, 4,046,886, 4,130,643, 4,130,667, 4,299,826, 4,335,115, 4,343,798, 4,379,454, 4,405,616 and 4,746,515, all of which are incorporated herein by reference, British Pat. No. 1,001,949 and Idson, Percutaneous Absorption, J. Pharm. Sci., vol. 64, No.b6, June 1975, pp. 901-924 (particularly 919-921).

To be considered useful, a permeation enhancer should have the ability to enhance the permeability of the skin for at least one and preferably a significant number of drugs. More importantly, it

should be able to enhance the skin permeability such that the drug delivery rate from a reasonably sized system (preferably 5-50 cm^2), is at therapeutic levels. Additionally, the enhancer, when applied to the skin surface should be non-toxic, non-irritating on prolonged exposure and under occlusion, and non-sensitizing on repeated exposure. Preferably it should be odorless and capable of delivering drugs without producing burning or tingling sensations.

The present invention greatly increases drug permeability through the skin, and also reduces the lag time between application of the drug to the skin and attainment of the desired therapeutic effect.

While it is known in the art to combine permeation enhancers, this invention utilizes a novel combination of ethanol and GMO; the combined effect of which produces a significant and surprising improvement over use of either GMO or ethanol alone.

SUMMARY OF THE INVENTION

It is an object of this invention to increase the permeability of body surfaces of animals and humans, particularly the skin or by the concurrent application of a drug, ethanol and GMO to the body surface.

BRIEF DESCRIPTION OF THE DRAWING

The invention will be described in further detail with reference to the accompanying drawings wherein:

FIG. 1 is a cross-sectional view of one embodiment of the transdermal drug delivery system according to this invention, utilizing a rate controlling membrane;

FIG. 2 is a cross-sectional view of another embodiment of the transdermal drug delivery system of this invention;

FIG. 3 is a cross-sectional view of still another embodiment of the transdermal drug delivery system according to this invention, utilizing a rate controlling membrane;

FIG. 4 is a cross-sectional view of yet another embodiment of the transdermal drug delivery system of this invention; and

FIG. 5 is a cross-sectional view of another embodiment of the transdermal drug delivery system according to this invention, utilizing an adhesive overlay.

FIG. 6 is a bar chart showing transdermal flux across cadaver skin at 35#C, of hydrocortisone vs. permeation enhancer used;

FIG. 7 is a three component phase diagram showing the soluble and insoluble ranges for ethanol/glycerol monooleate/water mixtures at room temperature (22#C) and at 35#C; and

FIGS. 8 and 9 are plots showing the increased skin permeability obtained from certain embodiments of this invention.

DESCRIPTION OF THE INVENTION

This invention codelivers GMO and ethanol to aid in delivery of drugs across the skin. While both GMO and ethanol are known permeation enhancers, their combined effect according to this invention has been shown to produce dramatic increases (in the order of 10-20 times or even higher) in the permeation of drugs when compared to the use of either ethanol or GMO alone. Improved enhancement of permeation according to this invention can be obtained over a relatively wide range of ethanol/GMO weight ratios. This invention contemplates ethanol/GMO weight ratios in the range of about 5/95 to 97/3 and preferably in the range of 80/20 to 40/60.

This invention finds particular usefulness in enhancing permeability across skin. However, it is also useful in enhancing flux across mucosa. Further, this invention is useful in delivery of both systemically and topically active drugs. According to our invention, ethanol, GMO and the drug to be delivered are placed in drug, ethanol and GMO transmitting relationship to the appropriate body surface, preferably in a pharmaceutically acceptable carrier therefor, and maintained in place for the desired period of time. The drug, ethanol, and GMO are typically dispersed within a physiologically compatible matrix or carrier as more fully described below which may be applied directly to the body as an ointment, gel, cream, suppository or sublingual or buccal tablet for example. When the ethanol and GMO are dispersed in a liquid vehicle for topical application to the skin, greater enhancement of drug flux has been observed when the concentration of ethanol, GMO and the vehicle are selected such that a single liquid phase exists for these components. When used in the form of a liquid, ointment, lotion,

cream or gel applied directly to the skin it is preferable to occlude the site of administration to prevent evaporation of the ethanol and other volatile components such as water. Such compositions can also contain other permeation enhancers such as sucrose monococoate, stablizers such as salicylic acid, dyes, diluents, pigments, stabilizers, vehicles, inert filters, excipients, gelling agents and other components of topical compositions as known to the art.

In other embodiments the drugs and permeation enhancers would be administered from a transdermal delivery device as more fully described below.

In one embodiment, the device administering an excess of drug to the skin and at least one of the ethanol or GMO is coadministered at a controlled, preferably substantially constant rate. The rate of drug administration is determined by the rate of administration of the enhancer whose rate is intentionally controlled.

In this embodiment, the dosage form could comprise a body: (a) having a basal surface.

(i) of area at least about equal to the area of skin to be treated,

(ii) that is adapted to contact the area of skin over the time period, and

(iii) via which the drug and enhancers are presented to the area of skin for the absorption thereby;

(b) containing a supply of the drug that communicates with the basal surface to provide drug at the basal surface over the time period;

(c) containing supplies of GMO and ethanol which communicate with the basal surface so as to provide the enhancers at the basal surface over said time period; and

(d) optionally including means for maintaining the rate at which at least one of the GMO or ethanol is provided at the basal surface.

In one embodiment, the supply of drug is such that over a substantial portion of the time period, the amount of drug provided to the basal surface is in excess of that which the area of treated skin is able to absorb, and the rate at which one of the GMO or

ethanol is provided is substantially constant over a substantial portion of the time period, the rate being:

(i) below the maximum rate the area of skin is able to absorb, and

(ii) sufficient with the coadministration of the other enhancer to substantially increase the permeability of the area of skin to the drug.

The method of this invention comprises:

(a) administering the drug to the area of skin over the time period; and

(b) coadministering GMO and ethanol to the area of skin.

As used herein the term "substantial portion of the time period" means at least about 60% of the time period, preferably at least about 90% of the time period. Correlatively, the term "substantially constant" means a variation of less than about ±20%, preferably less than about ±10%, over a substantial portion of the time period.

It is believed that this invention has utility in connection with the delivery of drugs within the broad class normally delivered through body surfaces and membranes, including skin. As used herein, the expressions "drug" and "agent" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas, including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics and analgesic combinations, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, anti depressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary, anticholinergics, sympathomimetrics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta-blockers, antiarrythmics,

antihypertensives, diuretics, vasodilators, including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, psychostimulants, sedatives and tranquilizers.

We have demonstrated the utility of mixtures of ethanol and GMO as a permeation enhancer for several dissimilar drugs within these classes such as hydrocortizone, tetracaine, lidocaine, PIROXICAM, indomethacin, nisoldipine, nifedipine, nicaradipine and nitrendipine. We also believe the combination to be applicable to an even larger number of drugs. Representative drugs include, by way of example and not for purposes of limitation, scopolamine, isosorbide dinitrate, nitroglycerin, estradiol, clonidine, cortisone, theophylline, phenylephrine, terbutaline, ephedrine, narcodine, quinidine, estradiol diacetate, progesterone, pilocarpine, furosemide, tetracycline, insulin, chlorpheniramine, sulfathiazides, propranolol, testosterone, norgestrel, morphinone, morphine, dihydrocodeine, dihydromorphine, oxycodone, hydrocodone, codeine, norcodeine, hydromorphine, normorphine, norlevorphanol, dihydrothebaine, ouabain, bromocryptine, haloperidol, guanabenz, salbutamol, oxprenolol, dibucaine, verapamil, prazosin, doxazosin, diltiazem, altenol, pindolol and timolol.

The effect of mixtures of GMO and ethanol as a permeation enhancer for any particular drug may be determined by a worker skilled in the art from <u>in vitro</u> permeation measurements performed on cadaver skin or other membranes in conventional diffusional cell tests as verified by <u>in vivo</u> measurements of blood or urine levels, for example.

One embodiment of the invention is best understood with reference to FIG. 1, which illustrates a transdermal drug delivery device 10. Device 10 is a multilaminate system comprised of five layers: a top impermeable backing layer 12, a permeation enhancer reservoir layer 14, a permeation enhancer rate controlling membrane 16, a drug reservoir 18, an adhesive layer 20 and a strippable release liner 22. The reservoirs 14 may be comprised of a gel or

polymeric matrix or other carrier having the permeation enhancer or drug to be delivered, dispersed throughout.

Device 10 is held in place by means of an in-line pharmaceutically acceptable contact adhesive 20. An additional loading of the drug, GMO and/or ethanol may also be incorporated into the adhesive layer 20. The composition and thickness of the adhesive layer are preferably selected such that it does not constitute a significant permeation barrier to the drug, GMO or ethanol. During the time interval between the manufacture and use of the system 10, adhesive layer 20 with the other layers will equilibrate and will contain GMO, ethanol and drug in amounts that will depend upon the composition and thickness of layer 20 and the length of the time interval. Contact adhesive compositions that are suitable for use as layer 20 are disclosed in U.S. Pat. Nos. 3,797,494 and 4,031,894. A strippable release liner 22, adapted to be removed prior to application, would normally be included in the packaged product.

Layer 14 may comprise a continuous GMO/ethanol phase, which may also contain one or more covehicles, such as water. Preferably the continuous phase is in the form of a gel that can contain 5% to 75% by weight water. Known gelling agents such as carboxypolymethylene, ethylene maleic anhydride, hydroxyethylcellulose, polyacrylamide, ethylhydroxyethylcellulose, hydroxypropylcellulose, and poly(methylvinylether-maleic anhydride) may also be included in the continuous phase to make it gel. Layer 14 may also include diluents, stabilizers, vehicles, gelling agents, and the like.

The rate controlling membrane 16 may be fabricated from permeable, semipermeable or microporous materials which are known in the art to control the rate of agents into and out of delivery devices. Suitable materials include polyvinylacetate and ethylene vinyl acetate polymers.

The size of the device of this invention can vary from less than 1 cm^2 to greater than 200 cm^2. A typical device however, will have a size within the range of about 5-50 cm^2.

Various materials suited for the fabrication of the various layers are disclosed in the aforementioned patents. The matrix of

the drug reservoir 18 may be an aqueous gel or an anhydrous matrix. Suitable anhydrous materials include, without limitation, natural and synthetic rubbers or other polymeric materials, thickened mineral oil, or petroleum jelly. A preferred embodiment according to this invention is fabricated from an ethylene/vinyl acetate (EVA) copolymer of the type described in U.S. Patent Number 4,144,317, preferably those having a vinyl acetate content in the range of about 28 to 60 weight percent. Particularly good results have been obtained using an EVA copolymer of 40 weight percent vinyl acetate content (EVA 40).

The drug reservoir 18 will contain the drug with an equilibrium concentration of the GMO and ethanol. The amount of drug in the reservoir will depend upon the rate at which the drug is absorbed by the skin from the system and the intended duration of therapy. The reservoir 18 may also include dyes, diluents, pigments, stabilizers, vehicles, inert fillers, excipients, gelling agents, and conventional components of pharmaceutical products or transdermal therapeutic systems as are known in the art.

Certain drugs are highly soluble in the permeation enhancers. In those cases, the permeation enhancer reservoir layer 14 would be initially saturated with drug to insure that the drug contained within matrix 18 will diffuse towards the skin rather than into the permeation enhancer reservoir. The loading of the drug which is ultimately to be delivered will usually be contained within the drug reservoir 18 in excess of saturation.

Embodiments such as device 10 in which the drug and enhancer supplies are separate may be advantageous or necessary in instances where formulation or storage of the drug and enhancers in contact with each other is impractical or undesirable or where separation of the drug and enhancers facilitate selection of the rate controlling membrane.

The initial loading of ethanol and GMO in device 10 will depend upon the rates at which the enhancers are administered to the skin from the system to achieve the desired degree of drug permeability enhancement over the treatment period.

The backing member 12 serves the purpose of both preventing passage of the drug and permeation enhancers through the surface of the gel layer distant from the skin, and also of providing support for the system, where needed. The backing layer can be flexible or nonflexible and suitable materials include, without limitation, cellophane, cellulose acetate, ethyl cellulose, plasticized vinyl acetate-vinyl chloride copolymers, polyethylene terephthalate, nylon, high and low density polyethylene, polypropylene, metalized polyester films, polyvinylidene chloride, coated flexible fibrous backings such as paper and cloth and aluminum foil. Such backings can be in the form of precast films or fabrics which are bonded to the reservoir by heat, adhesives or otherwise or they can be coated onto the reservoir itself. The preferred embodiment utilizes a heat sealable backing membrane, such that the device is sealed around its periphery to prevent evaporation of the ethanol. The heat seal is shown schematically in FIG. 1, by line 24.

In operation, device 10 is applied to a relatively nonhairy area of the skin that is preferably substantially free of wrinkles, creases or folds. Various locations on the torso, such as the flank or shoulder, provide suitable sites for the transdermal system. Once the device is placed on the skin, it will begin coadministering drug, ethanol and glycerol monooleate, to the wearer.

A second embodiment of the invention is shown in FIG. 2. The transdermal drug delivery device 26 comprises a permeation enhancer reservoir 28, backing member 30, drug reservoir 32, adhesive layer 34 and strippable release liner 36. In this embodiment of the invention, the rate controlling membrane has been omitted. As with device 10, device 26 is preferably heat sealed around its periphery, as indicated by line 38.

Another embodiment of the invention is shown in FIGURE 3. Device 40 incorporates the drug and the permeation enhancer into a common reservoir 42 rather than in separate reservoirs. The device has an impermeable backing 44 and a pharmaceutically acceptable in-line contact adhesive 46 which may also contain a specified amount of drug and/or permeation enhancer as a primary dose. Device 40 also has a strippable release liner 48. Device 40 is further

provided with a rate controlling membrane 50. The entire device is sealed along its periphery, as shown by line 52.

The drug will be present in the reservoir 42 either wholly in solution or in both dissolved and undissolved form dispersed uniformly through the reservoir. The initial loading of drug in layer 42 will depend on its solubility in the continuous phase and the intended lifetime of system 40. Layer 42 may include diluents, stabilizers, vehicles, gelling agents and the like, in addition to the drug and enhancers. This layer may also contain one or more covehicles, such as water, to alter the solubility of the drug in said phase. Correlatively, the loading of enhancers in the reservoir will depend upon the rate at which the enhancers are administered to the skin from the system to achieve the desired degree of drug permeability enhancement over the treatment period.

Rate controlling membrane 50 may be made of a dense or microporous polymer film that has the requisite permeability to the drug and enhancers. This membrane controls the rate at which at least one of the enhancers or the drug, is administered to the skin. The respective fluxes of the drug and enhancers through layer 50 will depend upon the thickness of the layer and the permeabilities of the drug and the enhancers through the layer. Preferably the rate controlling membrane 50 is substantially impermeable to other components of layer 42. Examples of the types of polymer films that may be used to make layer 50 are disclosed in U.S. Pat. Nos. 3, 797,494 and 4,031,894, both of which are incorporated herein by reference.

FIGURE 4 illustrates still another embodiment of the invention, system 54, where the drug, GMO and ethanol are incorporated into a common reservoir 56. As with system 40, system 54 is comprised of an impermeable backing 58, an in-line contact adhesive 60 and a strippable release liner 62. System 54 is preferably heat sealed around its periphery, as illustrated by line 64. In this embodiment, the rate controlling membrane has been omitted.

FIGURE 5 illustrates a system 66 which provides for an adhesive overlay 68 to maintain the system on the skin 70. Means 68 for adhering the system to the skin may be fabricated together with or

separately from the remaining elements. The multilaminate system 66 is comprised of a GMO/ethanol gel layer 72, a rate controlling membrane 74 and a drug reservoir 76.

In some instances, an adhesive overlay is preferable to an in-line contact adhesive particularly when components of the system which may adversely affect the adhesive properties of an in-line adhesive. For this reason, impermeable backing layer 78 is preferably sized slightly larger than the ethanol reservoir 72 to provide a peripheral area around the reservoir 72, which would be free of any material which may seep from under the base of reservoir 72 and adversely interact with the adhesive in overlay 68. A strippable release liner would also be provided with the system 66, to be removed prior to use.

EXAMPLE I

Several test samples were made to measure the hydrocortisone flux (lg/cm^2-hr) from donor vehicles containing an excess over saturation of hydrocortisone. The donors were water alone, ethanol alone, GMO alone, and ethanol and GMO combined, in a weight ratio of 40/60 with varying amounts of water as set forth below:

	WT % H_2O/GMO/ETOH
A	100/-/-
B	-/-/100
C	-/100/-
D	5/57/38
E	15/51/34
F	20/48/32
G	30/42/28

Transdermal fluxes were obtained using human epidermis skin at 35#C in standard diffusion cells. Samples using water, ethanol and GMO separately all produced an in vitro drug flux through cadaver skin significantly less than 5 lg/cm^2-hr whereas samples using mixtures of GMO and ethanol according to this invention achieved a hydrocortisone flux of more than 30 lg/cm^2-hr. The data obtained are presented graphically in FIGURE 6.

As can be seen, the GMO/ethanol permeation enhancer according to this invention produces fluxes substantially greater than obtained from the use of GMO and ethanol alone.

A suitable formulation for the delivery of hydrocortisone would be comprised of about 42-76 wt% of GMO and about 17-38 wt% ethanol in water containing an excess of hydrocortisone dispersed therethrough. Such formulations are capable of providing hydrocortisone fluxes within the range of 5-33 lg/cm^2-hr, when applied directly to the skin.

Fig. 7 is a phase diagram of the water/GMO/ethanol system at room temperature (22#C) and 35#C on which compositions D, E, F and G have been plotted. As can be seen, compositions D,E and F all fall within the portion of the diagram in which the composition exists as single phase solution and they all produced fluxes that were higher than that obtained from composition G which exists as 2 phase composition. To obtain the greatest increase in flux from the compositions of this invention, the compositions can be selected such that they fall within the portion of their phase diagram in which the compositions exist as a single phase.

EXAMPLE II

A transdermal device fabricated as shown in FIGURE 1 for the delivery of hydrocortisone would have the following composition: a MEDPAR backing layer 12; permeation enhancer reservoir 14 comprised of an ethanol gel 98 w% of 95% ethanol and 2 w% of hydroxypropylcellulose; an EVA 9% VA rate controlling membrane 16; a polymeric drug reservoir 18 comprised of 30 w% hydrocortisone, 30 w% glycerol monooleate and 40 w% EVA 40% VA; a pharmaceutically acceptable in-line contact adhesive 20 and a strippable release liner 22. During storage all of the components will achieve a state of equilibrium so that there will be an equilibrium concentration of ethanol in the drug reservoir 18 and an equilibrium concentration of GMO in the permeation enhancer reservoir 14.

EXAMPLE III

Various ethanol/glycerol monooleate donor compositions were tested with hydrocortisone to measure their effect upon the drug flux across human epidermis at 35#C into an aqueous sink. Test data were obtained using a 2.2 cm^2 horizontal flux cell with 2.5 ml donor solutions and 21 ml receptor solutions.

Solution Composition (wt%) Ethanol	GMO	Average Drug Flux $\mu g/cm^2$-hr
0	100	1
80	20	25
100	0	11

The flux was also measured with 20/80, 40/60 and 60/40 ethanol/GMO ratios. It was found that the hydrocortisone flux from the ethanol/GMO compositions increased as the amount of ethanol increased. Additionally, the effect of the inclusion of water in the donor composition was also studied. Lower hydrocortisone fluxes were observed when the donor compositions had separated into two phases. On the other hand, water content did not significantly affect the drug flux from single phase donor compositions.

EXAMPLE IV

Various ethanol/glycerol monooleate donor compositions were tested with tetracaine to measure their effect upon the drug flux across human epidermis at 35#C. Test data were obtained using a 1.13 cm^2 wet-wet horizontal flux cell with 2.5 ml donor solution and 10 ml receptor solutions (pH 4.5 acetate buffer, 0.05 M).

Donor Solution Composition wt% EtOH	GMO	Water	Tetracaine (wt%)	Avg. Tetracaine Flux $\mu g/cm^2$-hr
--	100	--	8	10
15	74	11	8	55
45	30	25	8	60
72	18	10	8	35
100	--	--	8	3
15	74	11	20	100
45	30	25	20	100
72	18	10	20	30

EXAMPLE V

Use of the ethanol/GMO permeation enhancer compositions of this invention provides for the rapid onset of therapeutic effect. This is very beneficial when an anesthetic is being transdermally administered prior to a painful procedure such as injection, venipuncture, or minor surgery. A topical anesthetic which can be used for such purpose, is tetracaine, the topical application of which has been found to require at least one hour to achieve adequate anesthesia. Incorporation of the GMO/ethanol enhancer of our invention into a tetracaine gel however dramatically reduces the time of onset of anesthesia to about 30 minutes after placement on the skin.

Double blind testing was done on 10 subjects. An active gel formulation was placed on each subject's right antecubital fossa and a placebo was simultaneously positioned on the left. The gels (0.6 gm) were placed in 5 cm^2 PVC cups covered with two polyester cloth discs and had the following composition (wt%):

Component	Active	Placebo
Tetracaine Base	20 %	0 %
Glycerol Monooleate	21.90 %	27.90 %
Ethanol (95%)	32.85 %	41.85 %
Purified Water	18.25 %	23.25 %
Phenethyl Alcohol	7 %	7 %

The gels were left in place for 30 minutes. Anesthesia was evaluated by standard venipuncture technique using a 22 gauge needle without drawing blood at each site, within 5 minutes after removal of the formulations. The subjects were then asked whether they felt no pain, slight/mild pain (like a pinprick) or moderate pain (like venipuncture). At the active sites, five subjects reported no pain, three reported slight/mild pain and the remaining two reported moderate pain. At the placebo sites, two subjects reported no pain, three reported slight/mild pain and the remaining five reported moderate pain. Six hours after removal, eight subjects continued to feel anesthesia at the active sites, and all subjects felt no anesthesia at the placebo sites.

EXAMPLE VI

A transdermal device fabricated as shown in FIG. 2 for the delivery of tetracaine comprises a MEDPAR backing layer 30; permeation enhancer reservoir 28 comprised mainly of an ethanol gel 98 w% of 95% ethanol and 2 w% of hydroxypropylcellulose; a polymeric drug reservoir 32 comprised of 30 w% tetracaine 30 w% GMO and 40 w% EVA 40; a pharmaceutically acceptable in-line contact adhesive 34 and a strippable release liner 36. During storage all of the components will achieve a state of equilibrium so that there will be an equilibrium concentration of ethanol present in the drug reservoir and an equilibrium concentration of GMO present in the permeation enhancer reservoir 28.

EXAMPLE VII

Lidocaine is a topical anesthetic which can be used in conjunction with minor surgical procedures. When a topical ointment containing lidocaine (EMLA) is applied to the skin, it has been reported that about 1 hour is required to achieve significant levels of local anesthesia. A vehicle composition according to this invention comprising 41.6 wt% ethanol, 30 wt% GMO (Myverol brand available from Eastman Kodak) and 28.4 wt% water was prepared, to which was added 34 wt% lidocaine base. 0.5 g of the mixture so formed was absorbed into a 0.75 in. diameter foam pads, applied to facial cheek skin on human volunteers and maintained in place by means of 1.625 in. diameter adhesive overlay for 15 minutes and 30

minutes. The sites were checked for pain by needle penetration. No pain was detected on some of the punctures and pain was observed at a penetration of 2 mm, primarily at the periphery of the site. No difference between the quality of anesthesia at 15 and 30 minutes was observed.

EXAMPLE VIII

The lidocaine fluxes from various ethanol/GMO compositions according to this invention through cadaver skin into an aqueous sink at 35#C were compared to the flux obtained from other vehicles and the results are shown in Figs. 8 and 9. The compositions identified as A, B, C and D had the following formulations to which were added sufficient lidocaine to maintain the samples saturated with lidocaine throughout the experiment:

A. 40 wt% sucrose monococoate (SMC) in ethanol/water

B. 60 wt% ethanol, 40 wt% GMO

B′ 60 wt% ethanol, 40 wt% Myverol

C. 27.5 wt% GMO, 41.25 wt% ethanol, 22.5 wt% water, 8.75 wt% phenethyl alcohol

D. mineral oil

E. 5.4 ml of C + 2.5 ml of A

F. 40 wt% A + 60 wt% B′

G. 50 wt% A + 50 wt% B′

H. 60 wt% A + 40 wt% B′

I. 70 wt% A + 30 wt% B′

The results of one set of experiments is shown in Figs. 8 and 9. As can be seen, the highest overall lidocaine flux was obtained from compositions C and B. Significant improvement in permeation was also observed from various mixtures of compositions B, B′ and A (which contains another known permeation enhancer, SMC). This illustrates that the use of other permeation enhancers in combination with the ethanol/GMO permeation enhancer of this invention is also contemplated according to this invention.

EXAMPLE IX

A transdermal device according to FIG. 5 delivery of a therapeutic agent would comprise: a MEDPAR backing layer 44; an enhancer/drug reservoir 42 which would be comprised mainly of single phase solution of 95% ethanol and GMO having an excess of the drug to be delivered dispersed therethrough; an EVA 9 rate controlling membrane 50; a pharmaceutically acceptable in-line contact adhesive 46; and a strippable release line 48.

This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A composition of matter for application to a body surface or membrane to administer a drug by permeation through a body membrane comprising in combination; the drug to be administered and a permeation enhancing amount of a mixture of GMO and ethanol.

2. The composition of claim 1 further comprising a carrier containing said GMO, ethanol and drug therein.

3. The composition of claims 1 or 2 wherein the ratio of ethanol to GMO is in the range of from about 97/3 to 5/95.

4. The composition claims 1 or 2 wherein the ratio of ethanol to GMO is in the range of about 80/20 to 40/60.

5. The composition of claim 2 wherein said body membrane is skin.

6. The composition of claim 5 wherein said drug is selected from the group consisting of hydrocortisone, tetracaine lidocaine, piroxicam, indomethacin, nisoldipine, nifedipine, nicardipine and nitrendipine.

7. The composition of claim 2 further comprising a material selected from the group consisting of sucrose monococoate and salicylic acid.

8. A dosage form for transdermally administering a drug, glycerol monooleate and ethanol to the skin of a patient,the dosage form comprising:

a) a body containing a supply of drug, glycerol monooleate and ethanol; and

b) means for maintaining said body in drug, glycerol monooleate and ethanol transmitting relationship to the skin.

9. The dosage form of claim 8 further comprising:means for maintaining the rate at which at least one of said drug, ethanol or glycerol monooleate is transmitted to the skin

substantially constant over a substantial portion of the time period.

10. The dosage form of claim 7 wherein said means maintains the rate at which at least one of said ethanol or glycerol monooleate transmitted to the skin said rate is below the maximum rate the skin is able to absorb, and sufficient in combination with the administration rate of other component to substantially increase the permeability of the area of skin to the drug.

11. The dosage form of claim 10 wherein said means maintains the rate at which ethanol is provided to the skin.

12. The dosage form of claim 9 wherein said means maintains the rate at which at said drug is transmitted to the skin below the maximum rate the skin is able to absorb.

13. The dosage form of claims 8, 9, 10, 11, or 12 wherein the supplies of drug, ethanol and glycerol monooleate are admixed within a common reservoir.

14. The dosage form of claims 8, 9, 10, 11 or 12 wherein the supply of at least 2 of said drug and ethanol and glycerol monooleate are contained in separate reservoirs.

15. The dosage form of claims 8, 9, 10, 11 or 12 wherein the ratio of ethanol to GMO is in the range of about 97/3 to 5/95.

16. The dosage form of claims 8, 9, 10, 11 or 12 wherein the ratio of ethanol to GMO is in the range of about 80/20 to 40/60.

17. The dosage form of claim 15 wherein the drug is selected from the group consisting of hydrocortisone, tetracaine, lidocaine, piroxicam, indomethacin, nisoldipine, nifedipine, nicardipine, and nitrendipine.

18. The dosage form of claim 15 wherein said body contains a material selected from the group consisting of sucrose monococoate and salicylic acid.

19. The dosage form of claim 15 wherein the drug is selected from the group consisting of hydrocortisone, tetracaine and lidocaine.

20. A method for administering a drug, glycerol monooleate and ethanol, to a predetermined area of skin of a patient for a predetermined time period comprising:

administering the drug to the area continuously over the time period; and

simultaneously administering ethanol and glycerol monooleate to the area of the skin at rates which are sufficient to substantially increase the permeability of the area of the skin to the drug.

21. The method of claim 20 wherein said drug is administered at a rate in excess of that which the area of skin is able to absorb in the absence of the ethanol and glycerol monooleate.

22. The method of claims 20 or 21 wherein at least one of said ethanol and glycerol monooleate enhancer is administered at a rate which is substantially constant over a substantial portion of the time period, and said rate is below the maximum rate the area of the skin is able to absorb and sufficient in combination with the other component to substantially increase the permeability of the area of the skin to the drug.

23. The method of claim 22 wherein ethanol is delivered at a substantially constant rate.

24. The method of claims 20 or 21 wherein said drug is selected from the group consisting of hydrocortisone, tetracaine,lidocaine, piroxicam, indomethacin, nisoldipine, nifedipine, nicardipine, and nitrendipine.

25. The method of claims 20 or 21 wherein the ratio of ethanol to GMO is in the range of about 97/3 to 5/95.

26. The method of claims 20 or 21 wherein the ratio of ethanol to GMO is in the range of about 80/20 to 40/60.

27. The method of claim 24 wherein the ratios of ethanol to GMO is in the range of about 97/3 to 5/95.

28. The method of claim 22 wherein the ratio of ethanol to GMO is in the range of about 80/20 to 40/60.

29. The method of claim 20 further comprising administering a material selected form the group consisting of sucrose monococoate and salicylic acid.

FIG.1

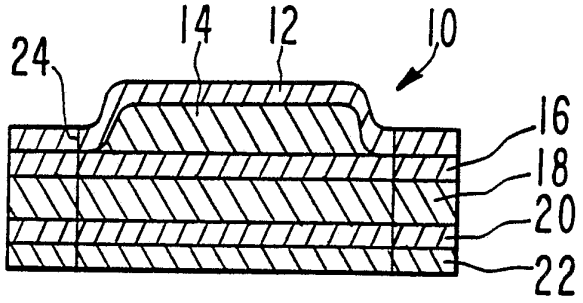


FIG.2

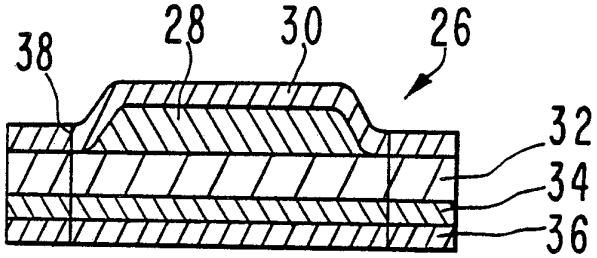


FIG.3

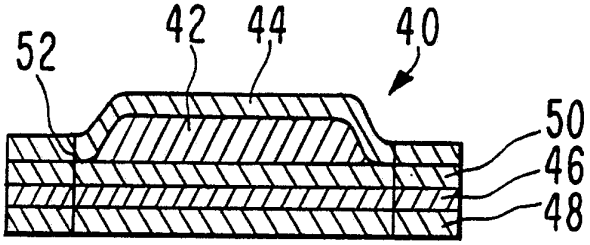


FIG.4

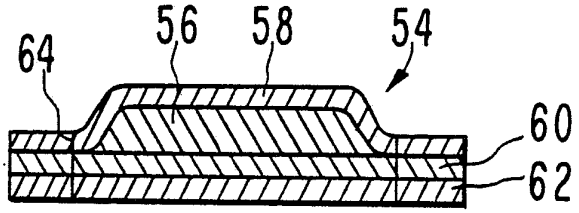


FIG.5

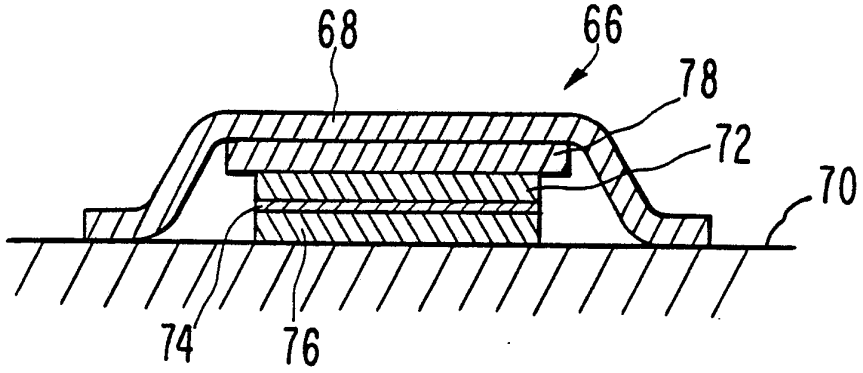
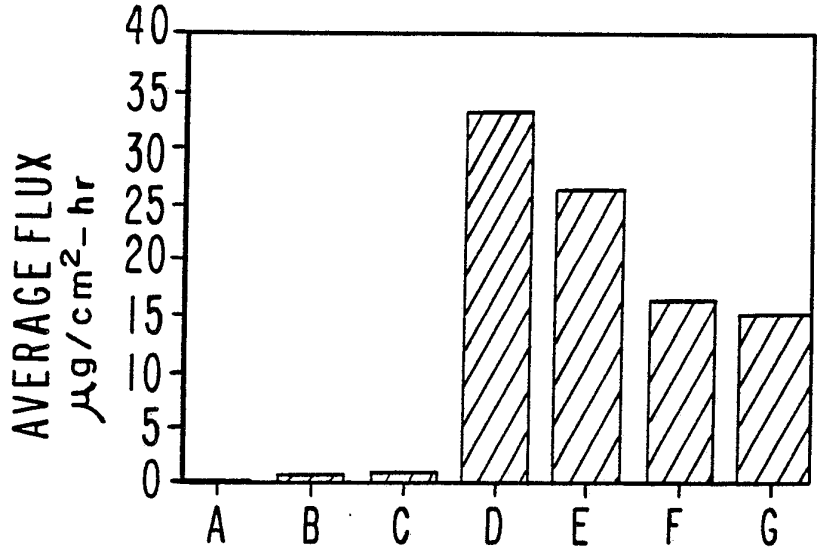


FIG.6


AVERAGE FLUX
μg/cm²-hr
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30
25
20
15
10
5
0
A
B
C
D
E
F
G

FIG.7

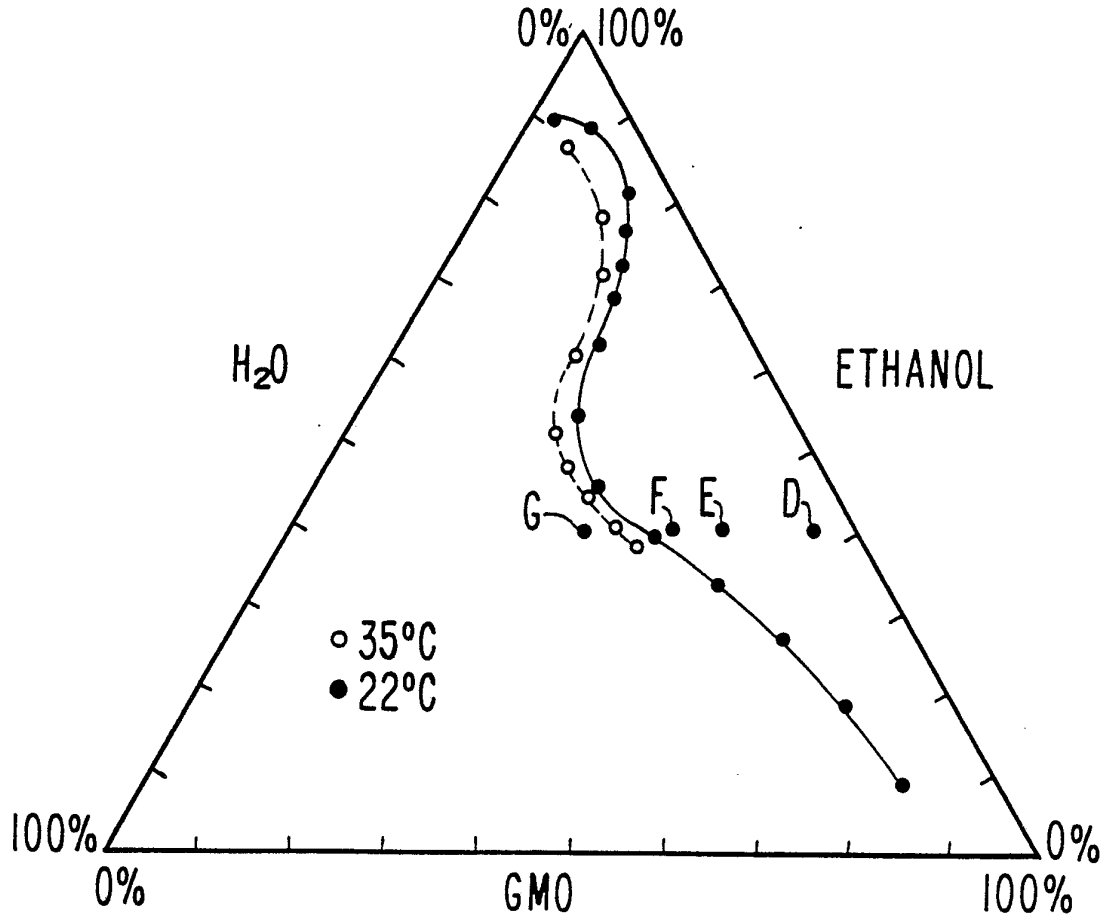
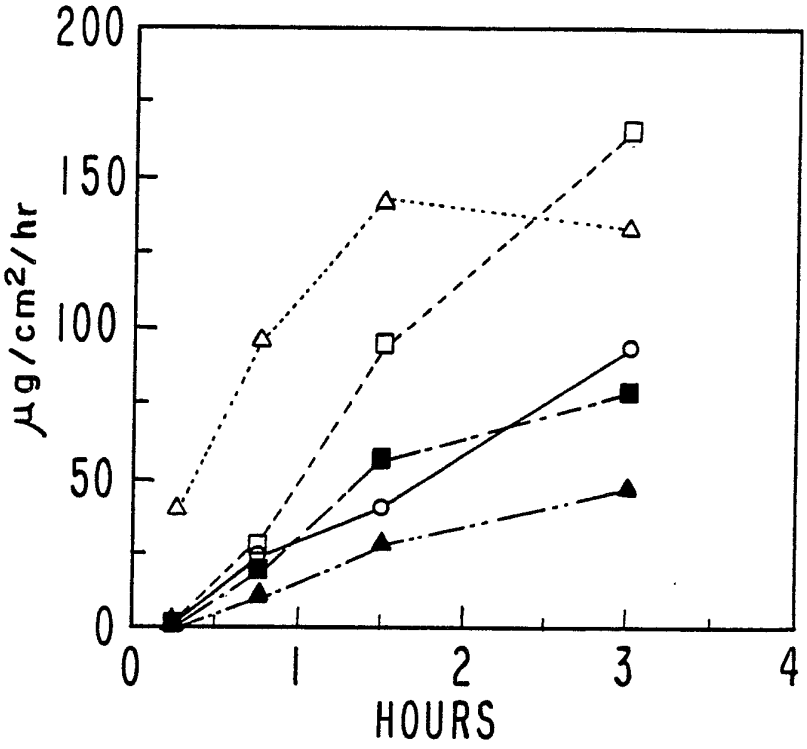

0%
100%
H2O
ETHANOL
G
F
E
D
35°C
22°C
100%
0%
GMO
0%
100%

FIG.8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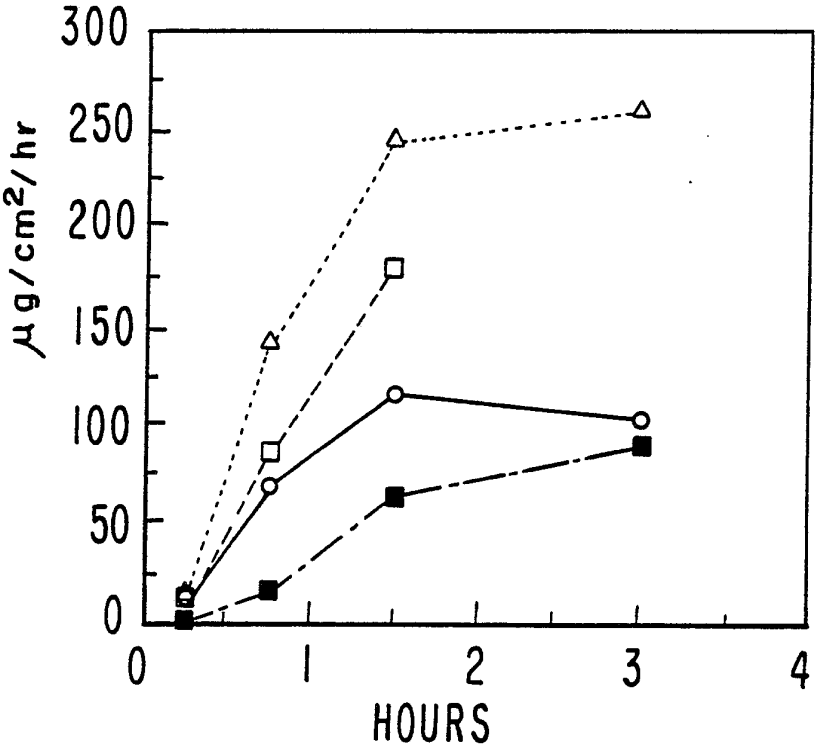
150
100
50
0
μg/cm²/hr
0
1
2
3
4
HOURS

FIG.9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μg/cm²/hr
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1
2
3
4
HOURS

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/02506

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

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

IPC [4]: A 61 K 47/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC [4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,Y	EP, A, 0267617 (THERATECH, INC.) 18 May 1988, see page 3, line 53 - page 4, line 27; page 6, lines 16-29; page 29, formulation VI-JJ; pages 48-57 --	1-6,8-17, 19-28
X	US, A, 4335115 (E.D. THOMPSON) 15 June 1982, see table 2, penetration data 7; see claims cited in the application --	1-5,9-12, 15,16,20-23, 25-28
Y	US, A, 4764379 (H.F. SANDERS) 16 August 1988, see claims; column 3, line 45 - column 4, line 12 ----	1-6,8-17, 19-28

* Special categories of cited documents: [10]

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

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"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	Date of Mailing of this International Search Report
29th September 1989	01. 11. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	T.K. WILLIS

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8902506 SA 29455

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/10/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0267617	18-05-88	JP-A- 63211241	02-09-88
US-A- 4335115	15-06-82	BE-A- 860349	02-05-78
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		DE-A,C 2748399	11-05-78
		FR-A,B 2368949	26-05-78
		GB-A- 1587428	01-04-81
		JP-A- 53094030	17-08-78
		NL-A- 7712005	03-05-78
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		EP-A- 0305026	01-03-89
		JP-A- 1068314	14-03-89
		US-A- 4820720	11-04-89