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(54) Title: METHODS OF DELIVERY OF CETYL MYRISTOLEATE

(57) Abstract

The invention provides novel and advantageous delivery devices for compositions of cetyl myristoleate. The delivery devices include transdermal delivery devices, suppositories, intranasal delivery devices, enteric coatings, and micro-encapsulation. Further provided are methods of treating pain and diseases using the disclosed delivery devices. Diseases that can be treated with the devices include, but are not limited to, diseases associated with the pain or inflammation of tissues, diseases associated with pain or inflammatory conditions affecting joints, autoimmune diseases, and allergies.

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METHODS OF DELIVERY OF CETYL MYRISTOLEATE

This application claims the priority of U.S. Serial No. 09/299,903 filed April 28, 1999 which is incorporated herein in its entirety.

TECHNICAL AREA OF THE INVENTION

The invention relates to novel and advantageous methods of delivery of cetyl myristoleate. The delivery methods are useful in the treatment of pain and several diseases affecting humans and animals.

BACKGROUND OF THE INVENTION

Cetyl myristoleate (CM) is found in and can be isolated from Swiss Albino mice. The compound can also be synthesized in the laboratory using cetyl alcohol and tetradecenoic acid (myristoleic acid). The methods of obtaining CM are described in U.S. Patent Numbers 4,049,824; 4,113,881; and 5,569,676. These patents are incorporated herein in their entirety. The purity of CM isolated by these methods is about 40.0%.

CM can be delivered to animals and humans orally; however, absorption is inhibited because of the "first pass effect" (difficulties caused in the

gastrointestinal tract) *i.e.*, deactivation by stomach acid and digestive pancreatic and liver enzymes.

The administration of lipase digestive enzyme is presently recommended along with oral doses of CM to increase absorption. New methods of delivery of CM that allow for its efficient absorption are needed.

SUMMARY OF THE INVENTION

It is an object of the invention to provide transdermal delivery devices, topical creams, suppositories, enterically coated compositions, intranasal drops and sprays, and micro-encapsulated compositions comprising cetyl myristoleate. It is another object of the invention to provide methods of treatment of various diseases affecting humans and animals by providing cetyl myristoleate compositions to a human or animal in need thereof. These and other objects of the invention are provided by one or more of the embodiments described below.

One embodiment of the invention provides a transdermal delivery device for the delivery of cetyl myristoleate to humans or animals wherein the transdermal delivery device contains 1 mg to 3000 mg of cetyl myristoleate.

Another embodiment of the invention provides an oral medicament comprising cetyl myristoleate and an enteric coating. The coating is resistant to dissolution in the stomach but predisposed to dissolution in the intestine so as to prevent release of the cetyl myristoleate until the composition is in the intestine.

Still another embodiment of the invention provides an oral medicament comprising micro-encapsulated cetyl myristoleate. The micro-encapsulation is

resistant to dissolution in the stomach but predisposed to dissolution in the intestine so as to prevent release of the cetyl myristoleate until the oral medicament is in the intestine.

Even another embodiment of the invention provides a suppository for transrectal, transvaginal, or transurethral delivery comprising cetyl myristoleate in combination with a physiologically acceptable solid carrier that is meltable at human or animal body temperature.

Another embodiment of the invention provides an electrotransport transdermal delivery device for the delivery of cetyl myristoleate to animals or humans comprising 1 mg to 3000 mg of cetyl myristoleate.

Still another embodiment of the invention provides an intranasal delivery device for the delivery of cetyl myristoleate, wherein the intranasal delivery device delivers 0.01 mg/kg/day to 10 mg/kg/day to the nasal mucosa of an animal or human.

BREIF DESCRIPTION OF THE DRAWINGS

Figure 1 demonstrates the hydrolyzer process of making myristoleic acid.

Figure 2 demonstrates the process of making cetyl myristoleate.

DESCRIPTION OF THE INVENTION

Cetyl myristoleate (CM) is a fatty acid ester of the following structure:

$$CH_3(CH_2)_{15}OCO(CH_2)_7\ CH{=}CH(CH_2)_3CH_3$$

The invention provides novel methods of delivery of CM such that improved absorption of the compound is achieved as compared to conventional

delivery methods of CM. These methods include transdermal delivery devices, suppositories, nasal sprays and drops, enteric coatings, and micro-encapsulation.

Manufacture of Cetyl Myristoleate

CM is a carboxylic ester and is made from natural fats and oils. Reacting myristoleic acid (derived from beef tallow) with cetyl alcohol represents one method of manufacturing CM. For example, beef tallow is converted to its neutral salts by use of an alkaline material, such as sodium hydroxide and minor ingredients, such as sodium silicate or magnesium sulfate.

The Making Of Myristoleic Acid

Although the present invention is not limited to any particular process, myristoleic acid is typically made with a hydrolyzer process. A typical hydrolyzer process utilizes continuous hydrolysis for the conversion of tallow into myristoleic acid. This process closely resembles existing techniques of fatty acid extraction used in hydrolysis.

For example, beef tallow is processed with heat and pressure to remove unwanted substances. Glycerin and moisture are then removed through hydrolysis. The resulting product is an esterified waxy ester. This ester is a solid that contains the essential fatty acid group that makes up myristoleic acid.

The steps of a typical hydrolyzing process include (1) hydrolysis, (2) fatty acid distillation, (3) neutralization, (4) myristoleic acid extraction, and (5) glycerin recovery. Development of continuous hydrolysis is the key step toward efficient production. In this reaction, tallow and water are mixed to form a fatty acid and

glycerin mix as follows:

$(RCOO)_3C_3H_5 + 3H_2O$ 3RCOOH + $C_3H_5(OH)_3$ where R is an alkyl of C8 or larger.

This equation represents complete hydrolysis. The reaction takes place in a stepwise fashion, forming intermediate diglyceride, and monoglyceride.

This reaction is accomplished through intimate contact between water and fat molecules. High temperature makes it possible to dissolve an appreciable quantity of water in the fat phase and to obtain intimate contact. At 220°F solubility of water increases up to 25%. High-pressures also are necessary to keep the water from flashing into steam. The required combination of high temperature, high pressure, and continuous glycerin removal can be accomplished in a countercurrent hydrolyzer column.

The reaction is reversible. In order to make the reaction proceed to the right, the proportion of water to fat can be increased or glycerin can be used as the reaction-forcing method.

Fat stocks (tallow) can be blended with 3% dry zinc oxide that acts as a catalyst. The mixture is maintained at about 212°F (100°C) to ensure dryness and to keep the zinc in solution. Hot water for the hydrolysis reaction is put under high pressure by, for example, piston-type feed pumps with adjustable drives so that the rates and proportions of fat to water can be accurately controlled. The fat and water are heated to the hydrolyzing temperature by

direct steam injection or by heat exchangers. The fats are pumped into the column near the bottom, and the water enters near the top. Thus, a countercurrent flow of water downward pushes the fatty material upward. See Figure 1.

The hydrolysis occurs in a two-phase reaction system. The fats and fatty acids flow continuously with droplets of water falling through them. Glycerin from hydrolysis is dissolved in the excess water falling through the column. The rate-limiting factor is the transfer of glycerin into the water droplets. Zinc oxide catalyzes the reaction that increases the glycerin transfer across the oil-water interface. Fresh water entering the column at the top reduces the glycerin to the lowest possible point, while a glycerin-water seat maintained at the bottom of the column (where the glycerin content is highest) prevents fat from washing out.

The fatty material passes upward through the column with about 99% completeness in splitting. The fatty acids, saturated with water, are discharged through an orifice into a flash tank. The dissolved water vaporizes, cooling the fatty acids and blanketing them with steam. A typical fatty acid mix contains the following:

Octanoic (Caprylic)	0.46%
Decanoic (Capric)	1.86%
Dodecanoic (Lauric)	3.14%
Tetradecanoic (Myristic)	51.3%
Tetradecenoic (Myristoleic)	8.23%
Pentadecanoic	2.75%
Hexadecanoic (Palmitic)	16.8%
Hexadecenoic (Palmitoleic)	3.32%
Octadecenoic (Stearic)	3.21%
Octadecenoic (Oleic)	3.28%
Waste Material	5.65%
Total	100%

The column, pumps, and piping in contact with the hot fatty acid are made from, for example, corrosion-resistant stainless steel. The column can be a hollow vessel, containing no baffles, trays, or packing material. The quality of the hydrolyzing operation is determined by the degree of split obtained on the fat. The fatty acid stream should contain very little free glycerin, if any.

The Making Of Cetyl Myristoleate

CM is a rare naturally occurring ester of tetradecanoic acid. It was first discovered in the blood of the Swiss Albino Mouse by Harry W. Diehl, (see U.S. patent numbers 4,049,824; 4,113,881; and 5,569,676).

CM can be produced synthetically by, for example, combining cetyl alcohol and tetradecanoic acid as follows. Equal portions of cetyl alcohol and tetradecanoic acid are combined with 16.6% p-toluenesulfonic acid monohydrate and 6.6% benzene. See Figure 2. The resulting mixture is then continuously stirred and heated to 100°C for a minimum of four hours. The resulting solution is then washed with a 10% sodium hydroxide solution. The resulting benzene

layer is then recovered and dried in vacuo. This procedure yields approximately 81% CM by volume.

Transdermal Delivery Devices

CM can be delivered through intact skin or organ surfaces by either passive processes such as diffusion or by active processes such as electrotransport. "Passive transdermal delivery" is the passage of an agent, such as CM, through a body surface, such as skin, mucous membrane or nails, in the absence of an applied electrical circuit. Typically, passive transdermal delivery devices have a CM-filled reservoir. The device is placed in contact with a body surface for a period of time and CM is allowed to diffuse from the reservoir into the body of the patient. The primary driving force for passive CM delivery is the concentration gradient of CM across the skin. CM reaches the blood stream by diffusion through the dermal layers of the body. "Transdermal electrotransport" is the delivery of CM through a biological membrane which is induced or aided by application of an electrical potential.

Passive Transdermal Delivery Devices

The passive transdermal delivery devices of this invention include matrix or monolithic-type laminated structures. Such transdermal delivery devices are well known in the art. Cleary, Cosmetics and Toiletries, (1991) 106:97-109. Transdermal delivery devices comprise a matrix layer of CM, permeation enhancer, or other components of a CM pharmaceutical composition admixed with a pressure sensitive adhesive and a backing layer. The matrix serves as a reservoir for CM and as the means of affixing the transdermal delivery devices

to the skin. Alternatively, the adhesive can be provided in a layer separate from the matrix. The transdermal delivery devices preferably comprise a release liner layer that is removed prior to use.

The virtually impermeable backing layer provides the top face of the transdermal delivery device and is the side furthermost away from the skin. The backing layer protects the transdermal delivery device and prevents the escape of CM, adhesive, permeation enhancer or other components of a CM pharmaceutical composition contained within the transdermal delivery device.

The backing layer is preferably made of a material that is inert and incapable of absorbing CM, adhesive, permeation enhancer, or other components of a CM pharmaceutical composition contained within the transdermal delivery device. The backing layer may be comprised of dermatologically acceptable films such as polyesters, polyurethanes, polyethylenes, polypropylenes, polyether amides, polyvinylchloride, polyvinylidene chloride, polyolefins, rubbers, synthetic resins, cloth, foils, and various laminates of these materials. This layer may be pigmented, metallized, or provided with a matte finish suitable for writing. The backing layer may be occlusive (impermeable to gases and liquids) providing for skin hydration, or non-occlusive (allowing moisture to pass through) providing for less skin hydration.

An adhesive layer is used to achieve contact between the transdermal delivery device and skin. Preferably, the adhesive layer provides instantaneous adhesion of the transdermal delivery device to the skin while allowing for easy

removal from the skin. The matrix layer can contain a pressure sensitive adhesive. Alternatively, an adhesive layer can be independent of the matrix layer. Materials used in pressure sensitive adhesives include, but are not limited to natural rubber, styrene-butadiene-rubber polymers, styrene-butadiene-styrene or styrene-isoprene block copolymers, polyisoprene, polyisobutylene, butyl rubber, polyacrylates, silicone pressure-sensitive adhesives, polyisobutylene, and vinyl ether polymers.

The matrix layer contains CM and may also contain adhesive, permeation enhancer, or other components of a pharmaceutical composition. The most simple transdermal delivery device design comprises the incorporation of CM into an adhesive matrix covering the backing layer. CM may be dissolved or dispersed in the adhesive matrix, or bound to a non-soluble absorbent in the adhesive matrix. Alternatively, a porous pad soaked with an adhesive gel or liquid containing CM can be used.

The matrix may include other additives depending upon the particular adhesive and CM formulation used. For example, polyvinyl pyrrolidone (PVP) which inhibits drug crystallization, hygroscopic agents that improve the duration of wear, or additives that improve the physical (*e.g.* cold flow) or adhesive (*e.g.* tack cohesive strength) properties of the matrix can be added.

The matrix may also be non-adhesive. A non-adhesive matrix comprises CM, permeation enhancer or other components of a CM pharmaceutical composition dissolved or dispersed in a matrix or bound to a non-soluble absorbent in the matrix. Suitable matrix materials include, but are not limited to,

polysaccharides such as starch, cellulose, hyaluronic acid, pectin, seaweed gums, polypeptides such as casein, albumin, keratin and collagen, thermoplastics such as unvulcanized elastomers, nylon, polyethylene, polyurethane, acrylic resins, cellulose resins, polypropylene, polyethylene glycols, polyvinylacetates, polyvinyl alcohols, and polyvinylpyrrolidones. In these peripheral adhesive systems the non-adhesive matrix is lined with a separate adhesive layer. The peripheral adhesive system may also comprise a porous pad filled with non-adhesive gel or liquid and equipped with peripheral adhesive.

Additionally, in contrast to homogeneous bulk concentrations of CM in the matrix, a bulk concentration gradient of CM may be established. Such gradients comprise drug adsorbents located in the deeper layers of the matrix only. The gradients provide for uniform release rates. Further, a textured matrix or matrix and adhesive layer may be used to provide for a timed release of CM.

The transdermal delivery device may include a release liner or peel strip. The release liner covers the surface of the adhesive during storage and protects the adhesive and matrix, and maintains CM stability. The release liner may be made from any impermeable film including, but not limited to, those materials specified for the backing layer. Preferably, the release layer is comprised of silicone-coated polyester.

Electrotransport Transdermal Devices

There are several types of electrotransport processes. Electromigration or iontophoresis involves the electrically induced transport of charged ions.

Electroosmosis involves the flow of a liquid under the influence of an electric field wherein the liquid contains the beneficial agent to be delivered. Electroporation involves the formation of transiently-existing pores in a biological membrane by the application of an electric field. In any given electrotransport process, more than one of these processes may be simultaneously occurring along with passive transport (*i.e.*, transport without electrical assistance). Therefore, the use of the term "electrotransport" includes the electrically induced or enhanced transport of at least one agent, which may be charged, uncharged, or a mixture of charged and uncharged species, regardless of the specific mechanism or mechanisms by which the agent actually is transported.

The electrotransport devices of the invention comprise at least two electrodes that are in electrical contact with some portion of the skin, nails, mucous membrane, organ surfaces, or other surface of the body. The "donor" or "active" electrode, is the electrode from which the agent is delivered into the body. The second electrode is the "counter" or "return" electrode which serves to close the electrical circuit through the body. For example, if the agent to be delivered is positively charged, *i.e.*, a cationic agent ion, then the anode is the active or donor electrode, which the cathode serves to complete the circuit. Alternatively, if an agent is negatively charged, *i.e.*, an anion, the cathode is the donor electrode. Additionally, both the anode and cathode may be considered donor electrodes if both anionic and cationic agent ions, or if uncharged agents are to be delivered.

The electrodes may be composed of any materials which are sufficiently electrically conductive, including, for example, silver, silver chloride, zinc, carbon, and stainless steel. The electrodes may be present in a variety of forms including a metal foil or screen, a polymer film having an electrically conductive coating or a polymer matrix containing an electrically conductive filler, *e.g.*, powdered carbon or metal, formed by conventional processes such as extruding, calendering, film evaporation, or spray coating.

The donor and counter electrodes are positioned adjacent to, and in electrical contact with the donor reservoir and counter reservoir, respectively. The donor reservoir contains a solution of CM, while the counter reservoir contains a solution of a biocompatable electrolytic salt such as sodium chloride or optionally another beneficial agent or more CM. An electrical insulator may be positioned between the donor electrode and the donor reservoir and the counter electrode and the counter reservoir. The insulator may be an air gap or a material with conducts neither electrons nor ions to a substantial extent, such as vinyl acetate, and prevents the device from short-circuiting though a path which does not include the body surface to which the device is applied. The device optionally includes a backing layer composed of a liquid-impermeable non-conducting material. The backing protects the electrodes form exposure and prevents leakage of the drugs or other system components. It can also provide support for the system, where needed. The backing member can be flexible or non-flexible and may be comprised of, for example, cellophane, cellulose acetate, ethylcellulose, plasticized vinyl acetate-vinyl acetate-vinyl

chloride copolymers, polyethylene terephthalate, polyethylene terephthalate/ethylene vinyl acetate, nylon, high and low density polyethylene, polypropylene, polyester, polycarbonate, polyurethane or other polyester films, polyvinylidene chloride and coated flexible fibrous backing such as paper or cloth.

The electrotransport devices of the invention further comprise one or more reservoirs or sources of CM to be delivered to the body. The donor reservoir can be a pouch, cavity, porous sponge or pad, hydrophilic polymer, or a gel matrix. The donor reservoir or reservoirs are electrically connected to, and positioned between, the anode electrode or cathode electrode and the body surface, to provide a fixed or renewable source of CM.

Electrotransport delivery devices of the invention also comprise an electrical power source such as one or more batteries. Polymeric, flexible, and other types of electrochemical cells can also be used as the electrical power source. Typically, one pole of the power source is electrically connected to the donor electrode, which the opposite pole is electrically connected to the counter electrode. The electrotransport devices may further comprise an electrical controller that controls the current applied to the electrodes, thereby regulating the rate of agent delivery. Other components of the electrotransport devices may comprise passive flux control membranes, adhesives for maintaining device contact with a body surface, insulating members, and impermeable backing members.

The electrotransport devices utilize an electrical circuit to connect electrically the power source and the electrodes. In simple electrotransport devices, the circuit is merely an electrically conductive wire used to connect the battery to an electrode. Typically, an electronic circuit layer is relatively thin and comprised of electronically conductive pathways with are printed, painted or otherwise deposited on a thin, flexible substrate such as, for example, a film or polymeric web. The electronic circuit layer is for example, a printed flexible circuit. In addition to the power source the electronic circuit layer may also include one or more electronic components with control the level, waveform shape, polarity, and timing of the electric current applied by the device. For example, the circuit layer may contain one or more elements of control circuitry such as a current controller, *e.g.*, a resistor or a transistor-based current control circuit, an on/off switch, or a microprocessor adapted to control the current output of the power source over time. Other electrotransport devices of the invention may further comprise a variety of electrical components to control the amplitude, polarity, time, and waveform shape of the electric current supplied by the power source. The electrical components of the electrotransport delivery devices of the invention can be miniaturized and may be in the form of either integrated circuits such as microchips or small printed circuits.

The passive and electrotransport transdermal delivery devices of the invention may further be comprised of permeability enhancers to improve the permeability of the skin. A permeation enhancer may cause a reduction of electrical or diffusional resistance. Such compounds include, but are not limited

to dimethylsulfoxide, dimethylformamide, decylmethylsulfoxide, 2-pyrrolidone, N-methyl-2-pyrrolidone, 1-dodecylazacylcloheptan-2-one, propylene glycol, oleic acid, lactate ester of $C_{12}C_{18}$ aliphatic alcohol, lauryl lactate, N,N-dimethylacetamide, polyethylene glycol monolaurate, glycerol monolaurate, lecithin, lower C_2-C_4 alcohols, higher alcohols such as C_6-C_{14} alcohols, surfactants such as sodium laurylsulfate, fatty acids such as oleic acid and combinations thereof. The amount of permeation enhancer included in the matrix will depend upon the particular enhancer or enhancers used, the strength of the enhancer, the desired increase in skin permeability, and the amount of drug to be delivered. In most cases the permeation enhancer will constitute 0.01 to 20% by weight of the matrix or reservoir. The drug reservoir may further comprise buffering agents, antioxidants, antimicrobial agents and agents that further increase the conductivity of the body surface or its permeability.

The amount of CM incorporated in a transdermal delivery device will vary depending upon on the dosage required, the permeability of the pressure-sensitive adhesive materials, the thickness of the pressure-sensitive adhesive layer, and the length of time the transdermal delivery device is to remain on the skin.

The transdermal delivery devices of the invention may be fabricated using procedures known in the transdermal delivery devices art. In general, the matrix is formulated (*i.e.* the adhesive, CM, permeation enhancer, and any additives are mixed). The matrix is coated on the backing or release liner layer, the solvent is removed from the matrix, and the backing or release layer is added.

Conventional coating and laminating techniques and equipment are known to those skilled in the art and can be used to make the transdermal delivery devices of the invention. Transdermal delivery devices can be fabricated by techniques including, but not limited to, solvent evaporation film casting, melt extrusion, thin film lamination, and die cutting.

Suppositories

CM may also be delivered via a transrectal, transvaginal, or transurethral suppository. Typical carriers used in standardized suppositories are solid and meltable at human or animal body temperature. Examples of carriers include, but are not limited to, beeswax, cocoa butter, natural fatty acid bases, glycerol and glycerin or combinations thereof.

Other components that may be included in the transdermal delivery device and suppository CM drug formulations of the invention include carriers such as water, azone, and propylene glycol, tackifers, pigments, dyes, and other additives that do not adversely affect the mechanical or adhesive properties of the formulation.

Intranasal Delivery

The invention provides methods of intranasal administration of CM in the form of nose drops or nasal spray. Formulations suitable for intranasal administration can consist of (a) liquid solutions, such as an effective amount of CM dissolved in diluents, such as water, or saline; (b) suspensions in an appropriate liquid; and (c) suitable emulsions, all of which can be administered in suitable ways, including nose drops and nasal sprays. Formulations can also

include gels, ointments and the like, containing, in addition to the active ingredient, such excipients as are known in the art, all of which can be administered in suitable ways, including by painting on the nasal mucosa, or squirting into the nose. Preferably, CM is administered intranasally in liquid form, most preferably in a physiological saline solution.

CM, alone or in combination with other suitable components, can also be made into aerosol formulations to be administered via a nasal spray or nasal inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They may also be formulated as pharmaceuticals for non-pressured preparations such as in a nebulizer or an atomizer.

A nasal spray dosage formulation typically also contains pH adjusters, emulsifiers or dispersing agents, buffering agents, preservatives or wetting agents as are known to those skilled in the art.

Oral Administration

Another aspect of the invention provides for the effective oral administration of CM such that the drug is released when it reaches the small intestine. Release of CM into the small intestine is desirable because significantly better absorption of CM occurs in the small intestine as compared to the stomach. CM may be delivered to the small intestine using an enteric coating or micro-encapsulation.

Enterically Coated Formulations

Enteric coatings are used to deliver drugs to the small intestine and to protect drugs from inactivation by gastric, pancreatic and liver enzymes or low pH. Targeted delivery is based upon the pH differences between these two parts of the alimentary canal. Enteric coatings are selectively insoluble substances that are insoluble in a low pH medium typically having a value less than about 5.5, but are soluble in a higher pH medium typically having a value greater than about 5.5. Preferably, an enteric coating is soluble at a pH of 7 or greater.

The coatings provide an impermeable barrier which will not readily dissolve or disperse at the low pH of the gastric juices of the stomach or duodenum. However, at the higher pH of the intestinal fluids the enteric coating will dissolve or disperse allowing for absorption of the drug.

CM is provided in an enterically coated, delayed release formulation. To prepare the delayed release enterically coated formulations of CM, pharmaceutical preparations of CM are either formed into a tablet or put into a capsule, and the tablet or capsule is coated with an enteric-coating material which dissolves at a pH of approximately 5.5 or greater. Suitable materials for enteric coatings include, but are not limited to methacrylic acid copolymers, formaldehyde cross-linking of gelatin, cellulose acetate phthalate, cellulose acetate succinate, and styrol maleic acid co-polymers, polymethacrylic acid/acrylic acid copolymer, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate, hydroxyethyl ethyl cellulose phthalate, hydroxypropyl methyl

cellulose acetate succinate, cellulose acetate tetrahydrophtalate, acrylic resin, cellulose acetate, timellitate, and phthalate or polyphthalate esters of film-forming polymers such as those listed above.

To apply an enteric coating onto a dosage form substrate an organic solvent may be used as a vehicle for coating the polymers. Examples of organic solvents include water, formaldehyde, acetone, methanol, ethanol, isopropyl alcohol, ethyl acetate, methylene chloride, or mixtures thereof. Aqueous coating systems such as acrylic enteric polymers in latex form, aqueous dispersions of cellulosic enteric polymers and aqueous ammonium salt solutions of cellulosic enteric polymers may also be used. The coating may be applied by spray coating, fluid bed coating, chemical vapor deposition, rotating pan coating, coascervation tank or any other process known in the art.

An example of enteric coating is formaldehyde induced cross-linking. Cross-linking is accomplished by spraying, for example, a mixture of 10% formaldehyde, 30% water and 60% ethanol on finished gelatin capsules that are being continuously turned in a receiving tray. The capsule gelatin reacts with formaldehyde mixture by causing the initial formation of amine methylols (carbinolamines) on lysine and arginine residues in the gelatin. As the applied solution reacts with the gelatin carbinolamines methylene bridges (cross-links) between lysine and arginine are formed. These bridges change the absorption properties of the gelatin capsule so that it is able to deliver the medicament into the ileum.

When the finished capsule is ingested, studies show that pancreatin, a proteolytic enzyme present in the gastrointestinal tract, depolymerizes the cross-linked gelatin and releases the medicament at a pH of 7.0. This results in the release of CM in the ileum.

Encapsulated Formulations

The formulations of the present invention may also be encapsulated in other time-release delivery systems such as a liposome delivery system (Langer & Kral, Pol. J. Pharmacol. (1991) 51:211; Allen, Drugs. (1997) 54 Suppl.4:8; Taylor & Newton, Br. J. Hosp. Med. (1994) 51:55), polysaccharides exhibiting a slow release mechanism, salistic or other polymer implants or microspheres. In these time release delivery systems, CM is suitably protected with differentially degradable coatings, *e.g.*, by micro-encapsulation and multiple coatings, which effect continual dosing of compositions contained therein.

CM can be coated by micro-encapsulation to provide for release in the small intestine instead of the stomach. Micro-encapsulation advantageously provides for better absorption of CM, taste abatement, and GI tolerability. Coacervation can be used to micro-encapsulate a drug. In coacervation, a hydrophilic substance is added to a solution of colloid. Ranade, Drug Delivery Systems 5A, (1991) J. Clin. Pharmacol. 31:2-16. If a drug is sensitive to water it may still be micro-encapsulated by protecting the drug from the aqueous environment by coating the drug with polymers such as ethylcellulose, cellulose acetate phthalate, or carnauba wax prior to micro-encapsulation. CM formulations may also be micro-encapsulated by spray coating, fluid bed coating,

chemical vapor deposition, rotating pan coating, or any other process know in the art.

Hydrophilic or hydrophobic substances or mixtures thereof may be used in micro-encapsulation. Natural polymers such as starch and other polysaccharides can be employed as well as synthetic polymers and phospholipids. Other materials suitable for use in micro-encapsulation include, but are not limited to, methacrylic acid ester copolymers, polysaccharides and their derivatives of natural or synthetic origin, cellulose derivatives including, but not limited to chitin derivatives, polymers of α-and/or β-hydroxycarboxylic acids, polymers of glycolic acid, polymers of lactic acid, polymers of α-hydroxybutyric acid, polymers of -hydroxyvaleric acid and/or their copolymers, or mixtures of such polymers and/or copolymers. Further, enteric coatings may be used in micro-encapsulation.

The thickness of the micro-encapsulation coat can be adjusted from less than 1 μm to 200 μm by changing the amount of coating material. The micro-encapsulated drug may also be admixed or concentrically coated with other fractions of free or time-released drug. The admixtures may be placed in either capsules or tablets and with other ingredients such as binders, fillers, and lubricants.

Methods of Treatment

CM can be used to treat, prophylactically and therapeutically, pain and diseases in humans and animals such as, but not limited to mice, baboons, chimpanzees, dogs, cats, horses, and livestock. CM is useful in the treatment

of pain, diseases, or symptoms of diseases associated with the inflammation of tissues such as tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

CM is also useful in the treatment pain, diseases, or symptoms of diseases characterized by inflammatory conditions that affect joints such as arthritis, rheumatoid arthritis, juvenile chronic arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis. Diehl and May, (1994) J. Pharm. Sci. 83(3):296-299.

CM can be used to treat pain, diseases, and symptoms of diseases including autoimmune diseases such as autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia can be treated with CM.

CM can also be used in the treatment of pain, diseases, and symptoms of diseases including migraine, emphysema, asthma, myofascial pain, arteriosclerosis, osteoarthritis, and sprains, insulin dependant diabetes, peripheral vascular disease, carpal tunnel syndrome, cardiomyopathy, chronic fatigue immune dysfunction syndrome, Churg-Strauss syndrome, allergies, and psoriasis.

Pharmaceutical Compositions

Delivery devices of the invention comprise CM. Preferably CM is present in a CM base comprising 40 to 95% CM, 5-50% cetyl myristate with any remaining portion representing a mix of cetyl laurate, cetyl palmitate, cetyl palmitoleate and/or cetyl oleate (all less than 5% each). Delivery devices of the invention may also contain glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane. Niacin, potassium, zinc, manganese sulfate and magnesium may be added as cofactors. NADH (Nicotinamide Adenine Dinucleotide) and coenzyme A (Pantothenic acid) may be added as coenzymes. Preferably, the amounts of each of these ingredients range from 1 mg to 1000 mg, preferably, the amounts of each of these ingredients range from 10 mg to 750 mg, even more preferably, the amounts of each of these ingredients range from 50 mg to 500 mg.

The delivery devices may also contain herbal ingredients. Preferably, the herbal ingredients are listed on the USDA GRAS list. Examples of such herbal ingredients include, but are not limited to, licorice root, cat's claw, black cohosh root, boswellia herb, curcumin, ginger root, cinnamon bark, and bromelain. The amount of each of the herbal ingredients ranges from 5 mg to 150 mg, preferably the amount of each of the herbal ingredients ranges from 10 mg to 100 mg, even more preferably the amount of each of the herbal ingredients ranges from 20 mg to 75 mg.

Dosage and Administration

A delivery device of the invention may contain 1 mg to 3000 mg of CM, preferably, the delivery device contains 1 mg to 1000 mg of CM, more preferably the delivery device contains 200 mg to 600 mg of CM, more preferably the delivery device contains 300 mg to 500 mg of CM.

When CM is administered by transdermal delivery device, intranasal delivery device, topical cream or suppository, the effective therapeutic dose is normally in the range of 0.01 mg/kg/day to about 10 mg/kg/day, preferably, from 0.1 mg/kg/day to about 5 mg/kg/day, preferably from 0.2 mg/kg/day to about 1.0 mg/kg/day, and more preferably from 0.4 mg/kg/day to about 0.8 mg/kg/day. These rates may vary depending upon the symptom or symptoms being treated.

A transdermal delivery device may be worn for a period of time ranging from a few hours to 15 days, preferably the transdermal delivery device is worn for 1 to 15 days, more preferably the transdermal delivery device is worn for 3 to 5 days. The length of treatment may vary depending upon the symptom or symptoms being treated. The transdermal delivery devices of the invention will preferably have a basal surface area of 10 to 50 cm^2; however, the surface area may be smaller or larger.

Where electrotransport transdermal delivery devices are used, the current may be initially set at a higher level for fast infusion of CM and then decreased to a lower level for prolonged CM infusion. For electrotransport transdermal delivery devices that are to be used in a series, the first patch used may have a

higher level of current for fast infusion of CM and subsequent patches may have a lower current for prolonged CM infusion.

Where suppositories, topical cream or intranasal delivery devices are used to deliver CM the length of treatment will range from an ongoing daily dose for the span of one's lifetime to shorter treatment regimes lasting 30 to 90 days with re-dosing as necessary. The length of treatment may vary depending upon the symptom or symptoms being treated and health of the patient.

Where CM is administered with an enteric coating or by micro-encapsulation, the effective dose is normally in the range of 0.1 g/kg/day to about 2 g/kg/day, preferably from 0.1 g/kg/day to about 1 g/kg/day, and more preferably from 0.15 g/kg/day to about 0.5 g/kg/day. The length of treatment will from an ongoing daily dose for the span of one's lifetime to shorter treatment regimes lasting 30 to 90 days with re-dosing as necessary. The dosage and length of treatment will vary depending upon the symptom or symptoms being treated and the health of the patient.

The dose administered in the context of the present invention should be an effective amount of CM. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the purity of the CM composition employed, the condition of the patient, the body weight of the patient, as well as the severity of the disease or symptoms. The size of the dose will also be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of CM. The preferred dosage is the amount

that results in signification elimination or eradication of symptoms, without significant side effects.

The following are provided for exemplification purposes only and are not intended to limit the scope of the invention described in broad terms above. All references cited in this disclosure are incorporated herein by reference.

Example 1

A cetyl myristoleate base (CM base) comprised 46.2% cetyl myristoleate, 48% cetyl myristate with the remaining 5.8% representing a mix of cetyl laurate, cetyl palmitate, cetyl palmitoleate and cetyl oleate (all less than 2% each). Transdermal patches contained 500mg CM base, 490mg extra virgin olive oil, and 10mg DMSO. Suppositories contained 500mg CM base and 500 mg cocoa butter. Topical cream contained 490mg CM base, 10mg DMSO, and 490mg hand lotion base (comprising water, glycerin, stearic acid, sunflower seed oil, tocopheryl acetate, urea, collagen amino acids, and sodium sterol lactase) and 10mg trolamine salicylate. Gel-capsules contained 400mg CM base, 550mg extra virgin olive oil, and 50mg lecithin in a gelatin shell. Enteric capsules contained 400mg CM base, 550 mg extra virgin olive oil, and 50 mg of lecithin in a cross-linked gelatin shell. The gelatin shell is cross-linked with formaldehyde. The enteric capsules were designed to release at a pH of 7.0 in the ileum.

CM was delivered to human patients as one transdermal patch, one suppository, one dose of topical cream, two gel-capsules, or two enteric capsules, once a day for three weeks. The amount of free CM in each patient's

blood plasma was measured by gas chromatography flame ionization detection at the end of each week. The amount of CM in each patient's blood serum is shown in Tables 1-5. The average amount of CM in the patients' blood serum for each type of delivery device is shown in Table 6.

The delivery of CM by transdermal patch, suppository, and enterically coated capsules resulted in higher amounts of CM in human blood serum than the delivery of CM by gel-capsule or topical cream.

Table 1.

Gel-Capsule CM mg/dL			
Patient	Week 1	Week 2	Week 3
1	0.67	0.83	1.10
2	0.80	0.93	1.13
3	0.50	0.74	0.85
4	0.74	*	*
5	0.81	0.83	1.12
6	0.68	1.18	1.25

* Patient dropped out of study due to an upset stomach.

Table 2.

Topical Cream CM mg/dL			
Patient	Week 1	Week 2	Week 3
1	0.67	0.92	1.20
2	0.81	1.01	1.25
3	0.69	0.91	1.10
4	0.83	1.05	1.29
5	0.76	0.87	1.02
6	0.74	0.86	1.02

Table 3.

Transdermal Patch CM mg/dL			
Patient	Week 1	Week 2	Week 3
1	0.98	1.87	2.25
2	1.12	1.94	2.29
3	0.98	1.88	2.10
4	1.11	1.25	1.96
5	0.96	1.82	1.99
6	0.96	1.82	2.09

Table 4.

Suppository CM mg/dL			
Patient	Week 1	Week 2	Week 3
1	0.91	1.67	2.09
2	0.95	1.73	2.19
3	0.92	1.68	2.10
4	0.95	1.73	2.20
5	0.92	1.68	2.10
6	0.91	1.67	2.09

5

Table 5.

Enteric Coated Capsule CM mg/dL			
Patient	Week 1	Week 2	Week 3
1	1.25	1.73	2.91
2	1.00	1.70	2.20
3	1.08	1.72	2.25
4	1.10	1.71	2.24
5	1.21	1.70	2.90
6	1.10	1.72	2.29

Table 6.

Average CM mg/dL			
Delivery System	Week 1	Week 2	Week 3
Gel-Capsule	0.70	0.90	1.10
Transdermal Patch	1.02	1.76	2.11
Suppository	0.93	1.69	2.13
Topical Cream	0.75	0.94	1.15
Enteric Coated Capsule	1.12	1.71	2.47

CLAIMS

We claim:

1. A transdermal delivery device for the delivery of cetyl myristoleate to animals or humans wherein the transdermal delivery device contains 1 mg to 3000 mg of cetyl myristoleate.

2. The transdermal delivery device of claim 1 comprising:

a backing layer; and

a matrix layer underlying the backing layer, the matrix layer comprising a mixture of cetyl myristoleate and a pressure sensitive adhesive.

3. The transdermal delivery device of claim 1 wherein the matrix layer further comprises one or more of the components selected from the group consisting of glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, niacin, potassium, zinc, manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

4. The transdermal delivery device of claim 1 wherein the device contains sufficient cetyl myristoleate to deliver cetyl myristoleate for 1 to 10 days.

5. The transdermal delivery device of claim 1 wherein the device contains sufficient cetyl myristoleate to deliver 0.01 mg/kg/day to 10 mg/kg/day of cetyl myristoleate.

6. A method of treating pain or a disease associated with the inflammation of tissues comprising affixing to the skin of an animal or human the transdermal delivery device of claim 1 wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

7. A method of treating pain or a disease associated with an inflammatory condition that affects joints comprising affixing to the skin of an animal or human the transdermal delivery device of claim 1 wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, Behcet's disease, joint injury, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

8. A method of treating an autoimmune disease comprising affixing to the skin of an animal or human the transdermal delivery device of claim 1 wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

9. A method of treating allergies comprising affixing to the skin of an animal or human the transdermal delivery device of claim 1.

10. An oral medicament comprising cetyl myristoleate and an enteric coating, the coating being resistant to dissolution in the stomach but predisposed to dissolution in the intestine so as to prevent release of the cetyl myristoleate until the composition is in the intestine.

11. The oral medicament of claim 10, wherein the enteric coating is resistant to dissolution in an environment having a pH less than about 5.5.

12. The oral medicament of claim 10 comprising 0.1 g to 1 g of cetyl myristoleate.

13. The oral medicament of claim 10, further comprising one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, niacin, potassium, zinc, manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

14. A method of treating pain or a disease associated with the inflammation of tissues comprising administering to a human or animal oral medicament of claim 10, wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

15. A method of treating pain or a disease associated with an inflammatory condition that affects joints administering to a human or animal the oral medicament of claim 10, wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

16. A method of treating an autoimmune disease comprising administering to a human or animal the oral medicament of claim 10, wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

17. A method of treating allergies comprising administering to a human or animal the oral medicament of claim 10.

18. An oral medicament comprising micro-encapsulated cetyl myristoleate, the micro-encapsulation being resistant to dissolution in the stomach but predisposed to dissolution in the intestine so as to prevent release of the cetyl myristoleate until the oral medicament is in the intestine.

19. The oral medicament of claim 18 comprising 0.1 g to 2 g of cetyl myristoleate.

20. The oral medicament of claim 18 further comprising one or more of the components selected from the group consisting of glucosamine

sulfate, niacin, potassium, zinc, manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A, chondroitin sulfate, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

21. A method of treating pain or a disease associated with the inflammation of tissues comprising administering to a human or animal the oral medicament of claim 18, wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

22. A method of treating pain or a disease associated with an inflammatory condition that affects joints administering to a human or animal the oral medicament of claim 18, wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

23. A method of treating an autoimmune disease comprising administering to a human or animal the oral medicament of claim 18, wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

24. A method of treating allergies comprising administering to a human or animal the oral medicament of claim 18.

25. A suppository for transrectal, transvaginal or transurethral delivery comprising cetyl myristoleate in combination with a physiologically acceptable solid carrier that is meltable at human or animal body temperature.

26. The suppository of claim 25 comprising 1 mg to 3000 mg of cetyl myristoleate.

27. The suppository of claim 25 further comprising one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, niacin, potassium, zinc, manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A , sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane

28. A method of treating pain or a disease associated with the inflammation of tissues comprising administering to a human or animal the suppository of claim 25, wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

29. A method of treating pain or a disease associated with an inflammatory condition that affects joints administering to a human or

animal the suppository of claim 25, wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

30. A method of treating an autoimmune disease comprising administering to a human or animal the suppository of claim 25, wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

31. A method of treating allergies comprising administering to a human or animal the suppository of claim 25.

32. An electrotransport transdermal delivery device for the delivery of cetyl myristoleate to humans or animals wherein the transdermal device contains 1 mg to 3000 mg of cetyl myristoleate.

33. The transdermal delivery device of claim 32 comprising:

(a) at least two electrodes separated from each other by an insulator, each electrode containing a conductive element;

(b) a circuit comprising an electrical power source that is electrically connected to the electrodes at the conductive elements; and

(c) a cetyl myristoleate reservoir in contact with at least one of the electrodes.

34. The transdermal delivery device of claim 32 which further comprises one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, niacin, potassium, zinc, manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

35. The transdermal delivery device of claim 32 wherein the device contains sufficient cetyl myristoleate to deliver cetyl myristoleate for 1 to 5 days.

36. The transdermal delivery device of claim 32 wherein the device contains sufficient cetyl myristoleate to deliver 0.01 mg/kg/day to 10 mg/kg/day of cetyl myristoleate.

37. A method of treating pain or a disease associated with the inflammation of tissues comprising affixing to the skin of an animal or human the electrotransport transdermal delivery device of claim 32 wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

38. A method of treating pain or a disease associated with an inflammatory condition that affects joints comprising affixing to the skin of an animal or human the electrotransport transdermal delivery device of

claim 32 wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

39. A method of treating an autoimmune disease comprising affixing to the skin of an animal or human the electrotransport transdermal delivery device of claim 32 wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

40. A method of treating allergies comprising affixing to the skin of an animal or human the electrotransport transdermal delivery device of claim 32.

41. An intranasal delivery device for the delivery of cetyl myristoleate, wherein the intranasal delivery device delivers 0.01 mg/kg/day to 10 mg/kg/day to the nasal mucosa of an animal or human.

42. The method of claim 41 wherein the intranasal device delivers cetyl myristoleate as nose drops.

43. The method of claim 41 wherein the intranasal device delivers cetyl myristoleate as nasal spray.

44. The intranasal delivery device of claim 41 which further comprises one or more of the components selected from the group consisting of glucosamine sulfate, chondroitin sulfate, niacin, potassium, zinc,

manganese sulfate, magnesium, Nicotinamide Adenine Dinucleotide, coenzyme A, sea cucumber extract, hydrolyzed shark cartilage, collagen II, and methylsulfonylmethane.

45. A method of treating pain or a disease associated with the inflammation of tissues comprising administering to an animal or human nasal spray or nasal drops from the intranasal delivery device of claim 41 wherein the disease is selected from the group consisting of tendinitis, tenosynovitis, bursitis, chronic patellar tendinitis, Achilles tendinitis, fibrositis, inflammation of the spine, colitis, bronchitis, polymyalagia rheumatica, Crohn's disease, primary biliary cirrhosis, pericarditis, ulcerative colitis, and Sjogren's syndrome.

46. A method of treating pain or a disease associated with an inflammatory condition that affects joints comprising administering to an animal or human nasal spray or nasal drops from the intranasal delivery device of claim 41 wherein the disease is selected from the group consisting of arthritis, rheumatoid arthritis, chronic arthritis, joint injury, Behcet's disease, ankylosing spondylitis, mixed connective tissue disease, Reiter's syndrome, and synovitis.

47. A method of treating an autoimmune disease comprising administering to an animal or human nasal spray or nasal drops from the intranasal delivery device of claim 41 wherein the disease is selected from the group consisting of autoimmune Addison's disease, autoimmune

hepatitis, Behcet's disease, lupus, asthma, hay fever, antiphospholipid syndrome, multiple sclerosis, and essential mixed cryoglobulinemia.

48. A method of treating allergies comprising administering to an animal or human nasal spray or nasal drops from the intranasal delivery device of claim 41.

49. A method of treating a disease selected from the group consisting of migraine, emphysema, myofascial pain, arteriosclerosis, sprains, insulin dependant diabetes, peripheral vascular disease, osteoarthritis, carpal tunnel syndrome, cardiomyopathy, chronic fatigue immune dysfunction, Churg-Strauss syndrome, psoriasis comprising administering to a human or animal transdermal delivery device of claim 1, the oral medicament of claim 10, the oral medicament of claim 18, the suppository of claim 25, the transdermal delivery device of claim 32, or the intranasal delivery device of claim 41.

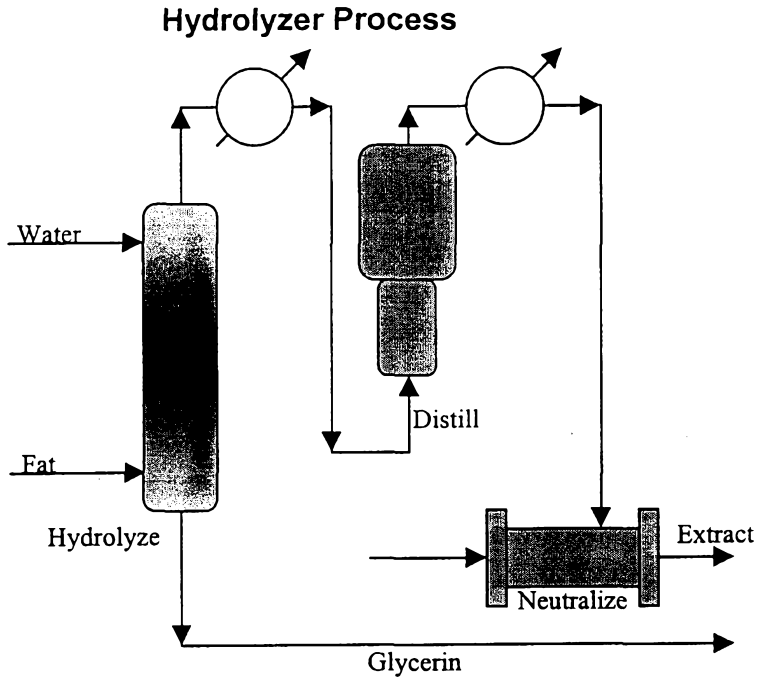
Hydrolyzer Process
Water
Fat
Hydrolyze
Distill
Extract
Neutralize
Glycerin

FIGURE 1

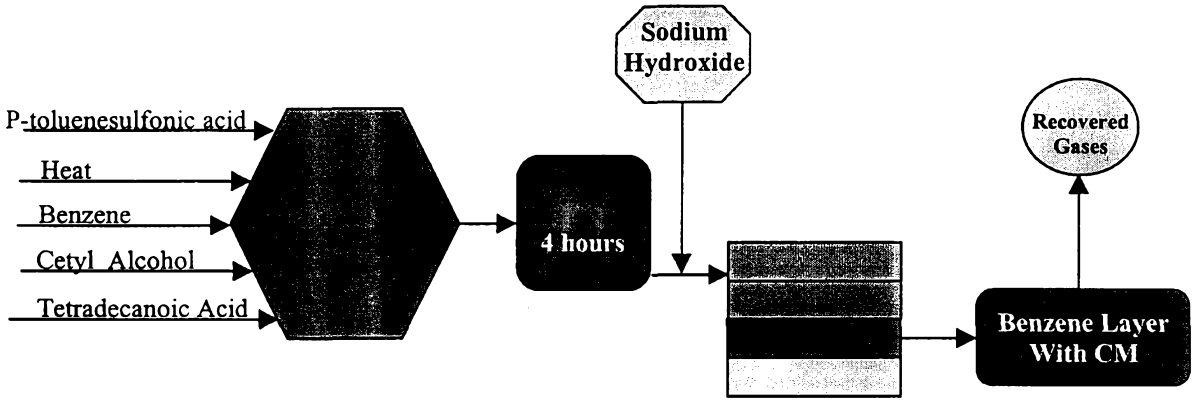
Sodium Hydroxide
P-toluenesulfonic acid
Heat
Benzene
Cetyl Alcohol
Tetradecanoic Acid
4 hours
Recovered Gases
Benzene Layer With CM

FIGURE 2