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(54) Title: TRANSDERMAL PATCH FORMULATIONS FOR DELIVERY OF WATER SOLUBLE DRUGS, PEPTIDES, PROTEINS AND OLIGOSACCHARIDES

![FIGURE 1A]

![FIGURE 1B]

(57) Abstract: The present invention relates to patch formulations for the transdermal delivery of water soluble drugs, peptides, proteins and oligosaccharides. The patch formulations are intended for the delivery of water soluble drugs, peptides, proteins and oligosaccharides across a plurality of pre-formed aqueous microchannels in the skin. The patch formulations contain a water soluble drug, peptides, proteins or oligosaccharide dispersed in a non-adhesive biodegradable polymer and are manufactured via film casting of polymer solutions containing dispersed drug, peptide, protein or oligosaccharide onto a suitable backing material. Both rapid release formulations and prolonged release formulations are disclosed.


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TRANSDERMAL PATCH FORMULATIONS FOR DELIVERY OF WATER
SOLUBLE DRUGS, PEPTIDES, PROTEINS AND OLIGOSACCHARIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 62/086,340 filed December 2, 2014 and U.S. Provisional Application No. 62/081,149 filed November 18, 2014, the entirety of all of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention is in the field of transdermal drug delivery and more particularly in the field of formulations for delivery of water soluble low molecular weight drugs, high molecular weight drugs including peptides and proteins, and oligosaccharides through aqueous microchannels created in the skin.

BACKGROUND OF THE INVENTION

[0003] Transdermal patches are known, including matrix-type patches, multi-laminate type patches, with or without a rate controlling membrane, and monolithic drug-in-adhesive type patches. These traditional transdermal drug delivery systems are used to deliver small molecule (molecular weight usually less than 500 Da) lipophilic drugs. Traditional transdermal drug delivery systems deliver drug through intact skin. Generally, the drug must have significant lipid solubility and correspondingly low water solubility to dissolve in and transport across intact skin.

[0004] Some water soluble drugs, such as certain anesthetic agents, analgesic agents, peptides, proteins, biologic macromolecules, and oligosaccharides such as the low molecular weight heparins enoxaparin and fondaparinux, are administered via bolus intravenous or subcutaneous injection to achieve the intended, rapid therapeutic effect. However, such administration is associated with many drawbacks such as pain, risk of infections, and skin reactions or inflammation at the site of injection.
Transdermal drug delivery technologies have been developed to enable the delivery of water soluble drugs and high molecular weight drugs including peptides and proteins. These technologies include creating microchannels in the outer skin layers to access skin interstitial fluid. The microchannels are created in the skin with an array of microneedles or through ablation of the skin via the rapid application of heat (thermal ablation) or radio frequency energy (RF ablation) or other electrical, mechanical, acoustic or chemical means.

Previously disclosed drug reservoirs designed for placement over the aqueous microchannels range from aqueous solutions and gels containing dissolved drug to dry polymeric films containing the water soluble drug in dispersion. The dry films are preferred since they can maintain a high thermodynamic driving force for drug delivery throughout the patch application duration. This is due to interstitial fluid contacting the reservoir through the microchannels and dissolving a portion of the drug for delivery while the remainder of the dispersed drug dissolves only as the initially dissolved drug is delivered, maintaining a drug saturation concentration condition at the drug film/microchannel interface. In contrast, the aqueous drug reservoirs generally contain drug at a concentration well below the saturation concentration and are characterized by a lower driving force for delivery.

US Patent Publication 2007/0031495 describes dry reservoirs comprised of drug and a non-biodegradable, water insoluble polymer. A primary example of a non-biodegradable base polymer for the drug reservoir matrix is ethylene/vinyl acetate copolymer (40% vinyl acetate) (EVA 40). EVAs are frequently used in medical devices and drug delivery systems and the 40% vinyl acetate monomer content of EVA 40 renders the polymer soluble in some organic solvents commonly used for manufacturing. Frequently, drug reservoirs comprising EVA 40 are cast from solutions of polymer in methylene chloride or other highly polar solvents such as methyl t-butyl ether and methyl ethyl ketone. Methylene chloride is particularly problematic since it is a potential carcinogen and ozone-depleting compound, thus requiring manufacturing controls to limit worker exposure and environmental release. An alternative manufacturing method for EVA 40-based drug reservoirs involves heating the drug/polymer mixture to a temperature where the semi-molten mixture
can be extruded into a film of proper thickness. This approach is not feasible for heat sensitive drugs including many peptides and proteins. Alternatively, the use of water soluble polymers as a base for the drug reservoir matrix is not preferred because the casting process involves dissolution of the drug for casting the film and the subsequent drying of the film may result in drug precipitation or large drug crystal formation with variable crystal size distributions. Such precipitation or irregular crystallization can be problematic by leading to slower dissolution kinetics.

[0008] Other formulations using water insoluble polymers are designed to deliver drug rapidly to mimic the pharmacokinetics of bolus intravenous or subcutaneous injection. The rapid release of drug from these formulations is achieved through use of a high ratio of drug to polymer. However, the difficult manufacturing of these rapid release patches is confounded by the low viscosity of the casting solution. The viscosity of the casting solution is frequently so low that that drug settles out of the solution prior to casting. The result is a film with variable drug content along the length and width of the film, poor manufacturing yield, poor adherence of the film to the backing, and variable drug release kinetics.

[0009] Oligosaccharides are highly water soluble drugs with relatively large molecular weights and are administered to humans in large doses. Enoxaparin is a low molecular weight heparin dosed at 30-40 mg with a molecular weight distribution ranging from less than 2000 Da to greater than 8000 Da (average 4500 Da). Fondaparinux is a synthetic pentasaccharide dosed at 2.5 - 10 mg with a molecular weight of 1728 Da. Therefore, transdermal delivery of oligosaccharides across intact skin at therapeutic levels is not possible.

[00010] WO 2004/039428 describes drug reservoirs for drug delivery through microchannels in the skin utilizing a printing process to place an aqueous solution of drug on the transdermal system backing. The printing process is more suitable for low doses below several hundred micrograms since there are issues controlling the drug layer thickness and uniformity. The variable crystal size and dissolution kinetics issues discussed above may also impact these printed drug reservoirs. Additionally, these reservoirs do not contain polymer to anchor the drug to the backing layer. The
lack of proper anchoring of the drug can cause loss of mechanical integrity of the reservoir prior to use and, as a consequence, poor dose reproducibility patch to patch and potential for loss of drug prior to application to the skin. For example, US Patent Publication 2011/0150976 discloses printed drug reservoirs for delivery of fondaparinux through microchannels in the skin of an animal model. Poor drug bioavailability was observed as compared to subcutaneous injection.

[00011] US Patent Publication 2005/0089554 discloses transdermal delivery of fondaparinux using an array of microneedles coated with the drug. Coated microneedles are often not preferred for transdermal drug delivery due to the limited loading of drug in the coating of the microneedle surface, the inefficient drug transfer from the microneedles into the skin, and the problems inherent in the maintenance of microneedles in the skin.

SUMMARY OF THE INVENTION

[00012] In one aspect, the present invention provides a patch for transdermal delivery of a water soluble drug, wherein the patch comprises (a) a drug/polymer matrix layer, such matrix layer comprising (i) at least one water soluble drug and (ii) one or more biodegradable polymers, and (b) a membrane backing layer, wherein the drug/polymer matrix layer is cast to the membrane backing layer.

[00013] In another aspect, the present invention provides a method of transdermal delivery of a water soluble drug through the skin of a patient, comprising treating an area of the skin of a patient to generate a plurality of microchannels in the skin of the patient, and affixing a patch for transdermal delivery of a water soluble drug, wherein the patch comprises (a) a drug/polymer matrix layer, such drug/polymer matrix layer comprising (i) at least one water soluble drug and (ii) one or more biodegradable polymers, and (b) a membrane backing layer, wherein the drug/polymer matrix layer is cast to the membrane backing layer.

[00014] In a third aspect, the invention provides a method of preparing a transdermal patch, comprising (a) dispersing the water soluble drug in a solution of a biodegradable polymer in a solvent to prepare a dispersion, (b) casting the dispersion
on a backing layer to form a drug/polymer matrix layer, and (c) drying the
drug/polymer matrix layer.

BRIEF DESCRIPTION OF FIGURES

Figure 1A is a schematic of a cross-sectional view of one embodiment of the invention.

Figure 1B is a schematic of a cross-sectional view of one embodiment of the invention.

Figure 2 shows the in vitro drug release kinetics for a rapid release and prolonged release patch formulations of prilocaine hydrochloride in accordance with the invention.

Figure 3 shows the in vitro drug release kinetics for a rapid release formulation of exenatide in accordance with the present invention using PDLLA as the matrix polymer.

Figure 4 shows the in vitro drug release kinetics for a rapid release formulation of exenatide in accordance with the present invention using polycaprolactone as the matrix polymer.

Figure 5 is a chart showing the Anti-Factor Xa activity versus time plots for a fondaparinux pharmacokinetic study in rats with a formulation in accordance with the present invention.

Figure 6 is a chart showing the Anti-Factor Xa activity versus time plots for a fondaparinux pharmacokinetic study in rats with a formulation in accordance with the present invention.

Figure 7 is a chart showing normalized A/Amax plots for a fondaparinux pharmacokinetic study in rats with a formulation in accordance with the present invention.

Figure 8 is a chart showing the Anti-Factor Xa activity versus time plots for an enoxaparin pharmacokinetic study in rats for with a formulation in accordance with the present invention.
DETAILED DESCRIPTION OF THE INVENTION

[00015] The present invention relates to patch formulations for the transdermal delivery of water soluble drugs via aqueous microchannels formed in the skin of a mammal, including a human. In one embodiment, drug delivery using patch formulations of the present invention is characterized by rapid release including high bioavailability and pharmacokinetic profile similarity as compared to delivery of the same drug via bolus intravenous or subcutaneous injection. In another embodiment, drug delivery using patch formulations of the present invention is characterized by prolonged or delayed release, or a combination of rapid and delayed release, as compared to delivery of the same drug via extended release oral formulations or long-acting depot subcutaneous injection or other topical administration routes.

[00016] Microchannels can be created in the skin by treating skin using any of the physical, chemical, thermal, electrical, mechanical or acoustic means known in the art. Such means include the use of an array of microneedles or through ablation of the skin via the rapid application of heat (thermal ablation) or radio frequency energy (RF ablation), or other electrical, mechanical, acoustic or chemical means. As used herein, the phrase "treated skin", "treated area" and the like means the area of skin where the microchannels are created. In one embodiment, the microchannels are created in the skin by treating the skin prior to application of the patch. In another embodiment, the microchannels are created in the skin by treating the skin while the patch is in place.

[00017] The patch formulations of the present invention are particularly useful for delivery of water soluble drugs. As used herein, the term "drug" includes any small molecule, oligosaccharide, peptide, protein or other large molecule or substance which has a physiological effect when ingested or otherwise introduced into the body. In particular, as used herein, the phrase "water soluble drug" means a drug that is capable of being dissolved in water. Although the specific solubility of each drug may vary, the skilled artisan can readily ascertain whether a drug is a water soluble drug. In certain embodiments, the water soluble drug has a solubility in water of at least 10 mg/mL. In another embodiment, the water soluble drug is a drug that is not
soluble in the solvent used to dissolve the polymer(s) in the drug/polymer matrix. Water soluble drugs include both low and high molecular weight drugs. Low molecular weight drugs may be sufficiently water soluble in a non-ionized form or may be ionizable salt forms of the drug free base or free acid. High molecular weight drugs include peptides, oligosaccharides, proteins and other biologic macromolecules.

[00018] Water soluble drugs suitable for the formulations of the present invention include anesthetic agents, analgesic agents, and combinations thereof. In certain embodiments, the anesthetic can be a local anesthetic agent and can be a cocaine analogue. In particular embodiments, the local anesthetic agent is an aminoamide, an aminoester, or combinations thereof. Representative examples of aminoamides or amide-class anesthetics include articaine, bupivacaine, carticaine, cinchocaine, etidocaine, levobupivacaine, mepivacaine, prilocaine, ropivacaine, and trimecaine. Representative examples of aminoesters or ester-class anesthetics include amyllocaaine, benzocaine, butacaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine, hexylcaine, larocaine, meprylcaine, metabutoxycaaine, orthocaine, piperocaine, procaine, proparacaine, propoxycaine, proxymetacaine, risocaine, and tetracaine. These local anesthetics typically are weak bases and may be formulated as a salt, such as a hydrochloride salt, to render them water-soluble, although the anesthetics also can be used in free base or hydrate form. Other anesthetics, such as lontocaine, also may be used. The drug also can be an antimuscarinic compound that exhibits an anesthetic effect, such as oxybutynin or propiverine. The drug also may include other drugs described herein, alone or in combination with a local anesthetic agent. Representative examples of other suitable analgesic agents include salicyl alcohol, phenazopyridine hydrochloride, acetaminophen, acetylsalicylic acid, flufenisal, ibuprofen, indoprofen, indomethacin, and naproxen.

[00019] In other embodiments of this invention, the water soluble drugs are anxiolytic compounds. Anxiolytic drugs may be benzodiazepines such as alprazolam, chlordiazepoxide, clobazepam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, and midazolam. The anxiolytic drugs may be selective serotonin reuptake inhibitors such as citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine, and sertraline. An additional anxiolytic drug is buspirone.
Drugs such as peptides, proteins and other large biologic macromolecules are used to treat a variety of diseases and disorders including rheumatoid arthritis and other autoimmune disorders, anemia, thrombocytopenia, and metabolic diseases such as diabetes. These drugs are large molecules with high molecular weight (>1000 Da) that are typically administered via injection. In one embodiment of the invention, the water soluble drug is a peptide or protein. Injectable drugs for the treatment of diabetes include insulin and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists). A representative list of GLP-1 drugs includes exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and taspoglutide. Examples of other peptides, proteins and biologic macromolecules include, but are not limited to, oxytocin, vasopressin, adrenocorticotropic hormone, parathyroid hormone, epidermal growth factor, prolactin, luliberin or luteinising hormone releasing hormone, growth hormone, growth hormone releasing factor, follicle stimulating hormone, insulin, somatostatin, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastroine, secretin, calcitonin, enkephalins, endorphins, angiotensins, renin, bradykinin, bacitracins, polymixins, colistins, tyrocidin, gramicidines, and synthetic analogues, modifications and pharmacologically active fragments thereof, monoclonal antibodies and soluble vaccines. In certain embodiments, the water soluble drug is a GLP-1 receptor agonist.

In other embodiments, the water soluble drug is an oligosaccharide. Oligosaccharides are highly water soluble drugs with large molecular weights that are typically given in large doses to human patients. For example, Enoxaparin is a low molecular weight heparin dosed at 30-40 mg with a molecular weight distribution ranging from less than 2000 Da to greater than 8000 Da (average 4500 Da). Fondaparinux is a synthetic pentasaccharide dosed at 2.5 -10 mg with a molecular weight of 1728 Da. Representative examples of oligosaccharides suitable for use in the present invention include, but are not limited to, low molecular weight heparins such as enoxaparin and fondaparinux.

In further embodiments, the water soluble drug is selected from one or more anti-infectives such as antibiotics and antiviral agents; anorexics; antihelminthics;
antiarthritis; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antiangiogenic drugs; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta-blockers, alphasblockers, and antiarrhythmics; antihypertensives; diuretics and antidiuretics; vasodilators including general coronary, peripheral, and cerebral; central nervous system stimulants; vasoconstrictors; cough and cold preparations, including decongestants; hypnotics; muscle relaxants; parasympatholytics; psychostimulants; sedatives; tranquillizers; antifibromyalgia drugs; anti-psoriasis drugs; bone resorption inhibitors; agents that build bone strength; agents that reduce bone fragility; anti-incontinence drugs; anti-incontinence drugs; anti-acromegaly drugs; anti-edema drugs; anti-obesity drugs; anesthetics; anti-anxiety drugs; sedatives; muscle relaxants; acetylcholinesterase inhibitors; ACE inhibitors; anti-coagulants; narcotics; anti-obssessional; anti-bulimic; anti-emetic; antirheumatics; hypothyroidism drug treatments; NMDA receptor antagonists; NMDA receptor agonists; partial NMDA receptor agonists; ADHD treatments, anti-spasmodic drugs, anti-convulsant drugs, migraine prophylaxis drugs; benign prostatic hypertrophy drugs; sedatives; opiates; pulmonary arterial hypertension drugs; hypnotics; osteoporosis drugs; anti-inflammatory drugs; diabetic glycemic control drugs; multiple sclerosis drugs; thrombocytopenia drugs; and myeloid reconstitution drugs.

[00023] Cross-sectional diagrams of patch formulations according to certain embodiments of the invention are shown in Figures 1A and IB. In Figure 1A, the patch formulation generally consists of a drug/polymer matrix or drug film layer consisting of a biodegradable matrix polymer containing dispersed drug (1). In one embodiment, the drug/polymer matrix may contain plasticizers and thickening agents useful for increasing the viscosity of the casting solution used to make the drug/polymer matrix layer and may contain preservatives or stabilizers to maintain drug potency and for microbiological control. In addition to the drug/polymer matrix layer, the patch formulation contains an occlusive or semi-permeable membrane backing layer (2) that serves to maintain drug and interstitial fluid from the
microchannels at the drug film/skin interface by preventing evaporation of the interstitial fluid. The formulation optionally may have a protective liner covering the exposed side of the matrix (3) which is discarded prior to use and an adhesive layer consisting of an acceptable skin adhesive layer (4) and a backing layer (5) to anchor the patch to the skin. In an alternative embodiment, in Figure 1B, there is an adhesive free zone (6) in the adhesive layer (7) that extends beyond the drug film layer (1).

[00024] Suitable materials for the backing layers for both the drug/polymer matrix and the adhesive layer include metal foils, metalized polymer films, composite foils or films containing polyester such as polyester terephthalate, aluminized polyester, polytetrafluoroethylene, polyether block amide copolymers, polyethylene methyl methacrylate block copolymers, polyurethanes, polyvinylidene chloride, nylon, styrene, styrene-butadiene and styrene-isoprene copolymers, polyethylene, and polypropylene. A thickness of about 0.0005 to 0.01 inch can, for example, be used. Useful adhesives for anchoring the patch to skin include, for example, acrylics (e.g., polyacrylates including alkyl acrylates), tackified polyvinylacetates, natural and synthetic rubbers, tackified ethylene/vinylacetate copolymers, polysiloxanes, polyurethanes, plasticized polyether block amide copolymers, plasticized styrene-butadiene rubber block copolymers, and mixtures thereof.

[00025] In one embodiment, the base polymer for the matrix is a water insoluble biodegradable polymer that can be cast from a safe, environmentally acceptable organic solvent. The polymer should be a good film former, should have low solubility for water soluble drugs, should be biodegradable, and should be non-adhesive to skin. Such polymers include polyorthoesters, polyanhydrides, polycaprolactone, poly(d,l lactide - co-glycolide), poly(d,l lactide - co-caprolactone) and poly(d,l lactide) (PDLLA). In certain embodiments of the invention, the polymer is PDLLA. PDLLA is soluble in common, relatively non-toxic solvents such as acetone and toluene. PDLLA is amorphous, a good film former, and has a glass transition temperature between 50 and 60 °C. Although the glass transition temperature is above body temperature, thin films of PDLLA are sufficiently conformable to create a uniform, pliant interface with the treated skin area. If a more compliant matrix is desired, PDLLA can be plasticized to a glass transition
temperature well below body temperature through incorporation of non-toxic plasticizers such as triethyl citrate, poly(ethylene glycol), glucose monoesters and partial fatty acid esters. In other embodiments of the invention, the biodegradable polymer is polycaprolactone. Polycaprolactone is a semi-crystalline polymer with a low melting point of around 60°C, is a good film former and has a glass transition temperature of -60°C. Without being bound by any particular theory, the low melting point of polycaprolactone may allow oligosaccharide-containing films to consolidate during solvent drying at temperatures above the melting point resulting in reduced film friability. The use of plasticizers such as triethyl citrate, poly(ethylene glycol), glucose monoesters and partial fatty acid esters may be used to further reduce the friability of the film. In certain embodiments, the patch of the present invention further comprises a plasticizer.

[00026] The patch formulations of the present invention contain drug dispersed in a biodegradable polymer and are manufactured via film casting of polymer solutions containing dispersed drug onto a suitable backing material. The biodegradable polymer is selected to be non-adhesive to skin and to be soluble in low toxicity organic solvents such as toluene or acetone. Both rapid drug release formulations and prolonged drug release formulations are disclosed.

[00027] For the patch formulations of the present invention, the kinetics of drug release can be varied by alteration of the ratio of drug to polymer. Generally, the drug release kinetics become more rapid as the drug to polymer ratio is increased. The total drug content in each patch is determined primarily by the patch size or drug film area as well as the dried drug film thickness, maintaining a fixed ratio of drug to polymer so as to maintain the desired drug release kinetics.

[00028] Weight ratios of polymer to drug range from about 100:1 to about 1:5, although more specific ratios are employed depending upon the desired release profile. In addition, drug/polymer matrix film thickness can range from about 5 µm to about 250 µm, but can be altered based upon the desired release profile.
[00029] For drug delivery in a sustained dosing manner, for example to maintain relatively constant blood drug concentration for an extended time period of several hours to several days, the concentration of drug in the matrix layer is reduced relative to the concentration of polymer. Sustained delivery kinetics are associated with formulations where the concentration of polymer is greater than that of drug with drug delivery becoming more sustained as the ratio of polymer to drug concentration is increased. Generally the sustained delivery formulations are characterized by a polymer to drug weight ratios of about 1:1 to about 100:1. In preferred embodiments, the sustained delivery formulations have polymer to drug weight ratios of about 2:1 to about 50:1. At a given polymer to drug concentration ratio, a more sustained pattern of drug release can be obtained through an increase in the drug/polymer matrix layer thickness.

[00030] For transdermal delivery of water soluble drugs to match the pharmacokinetics of a bolus dose of the same drug, such as the pharmacokinetics of a subcutaneous injection of the drug, it is desired to have rapid release of the drug from the patch matrix upon contact with the interstitial fluid exposed at the treated skin site. This is achieved through use of matrix formulations with a high fractional drug content in which the drug is the continuous phase and the base polymer serves primarily to anchor the drug to the membrane backing layer of the patch. In one embodiment, the polymer to drug weight ratios are from about 1:1.1 to about 1:5. In another embodiment, the polymer to drug weight ratios are from about 1:2 to about 1:5. In certain embodiments, especially embodiments wherein the drug is an oligosaccharide, the polymer to drug weight ratios are from about 1:2.5 to about 1:3.5. If very low drug content is desired for a particular formulation while maintaining rapid drug release, a water soluble bulking agent such as mannitol, lactose, sorbitol, or polyvinylpyrrolidone can be used as a substitute for a portion of the drug. In these embodiments, the drug portion of the polymer to drug ratio is the sum of the amounts of drug and water soluble bulking agent.

[00031] In one embodiment, the patch formulation of the present invention provides for a bioavailability of the water soluble drug that is greater than 50 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection. In
another embodiment, the patch provides for a bioavailability of the water soluble drug that is greater than 75 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection. In a further embodiment, the patch provides for a bioavailability of the water soluble drug that is greater than 90 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection.

[00032] PDLLA and polycaprolactone are preferred choices of base polymer for these high drug content formulations because they are biodegradable. Use of high drug content matrices may result in small fragments of the base polymer detaching from the matrix and migrating into the microchannels. If non-biodegradable polymer fragments migrate into the skin they may remain in the skin long after patch removal with unknown long-term side effects. If a biodegradable base polymer such as PDLLA or polycaprolactone is used, any fragments that detach from the matrix would degrade into well-known and safe products to be cleared from the skin site and body.

[00033] Fabrication of high drug content reservoirs can be challenging. Casting solutions that have a very high drug to polymer ratio tend to have low viscosities (essentially the same viscosity of the casting solvent). During the film casting process, the drug can settle out of the casting solution before the film is formed resulting in variable drug content along the length and width of the film. In one embodiment, the high drug content reservoir formulations further comprise a thickening agent to increase casting solution viscosity to facilitate fabrication of uniform films. Prior to dissolution of the polymer and suspension of the drug, the viscosity of the solvent can be increased through the addition of a thickening agent such as colloidal silicon dioxide or bentonite clay. The increased casting solution viscosity retards settling of the drug allowing the formation of uniform films. Additionally, even for formulations with a relatively high polymer to drug concentration ratio, the use of a thickening agent may result is reduced drug settling in the solution, more uniform drug/polymer matrix layers, and improved process yield.

[00034] Highly polar solvents such as methyl t-butyl ether and methyl ethyl ketone have been used for EVA 40-based drug film layers but the casting solution used to create such layers cannot be thickened using colloidal silicon dioxide as their high
hydrogen bonding potential prevents the required formation of an interconnected silicon dioxide particle network. Therefore, non-polar solvents such as toluene can be used instead. Toluene is a good solvent for both PDLLA and polycaprolactone, has relatively low volatility with a boiling point of 110°C, is relatively non-toxic, and can be thickened with colloidal silicon dioxide. In certain embodiments, the solvent for preparing the drug/polymer matrix is a non-polar solvent. In preferred embodiments, the solvent is toluene.

[00035] The dried films of the drug/polymer matrix can be cut into individual patches of any desired shape and area. In certain embodiments of the invention, sustained transdermal drug delivery is desired for periods of several hours to several days. In these embodiments, prolonged drug delivery at a given drug to polymer ratio can be achieved by designing a patch with a drug film area greater than the area of the treated skin site. For patches larger than the treated skin site, drug delivery can be prolonged due to the additional time required for interstitial fluid to wet the full thickness of the patch and the area of the patch outside of the treated skin area and for the drug to transport through the wetted matrix to the treated skin site. In certain embodiments of sustained delivery formulations, the ratio of drug film area to treated skin area is from about 1.0 to about 2.0. In preferred embodiments, the ratio of drug film area to treated skin area is about 1.0 to about 1.5.

[00036] In other embodiments of the invention, rapid transdermal delivery of the entire patch drug content to match the dose and pharmacokinetics of bolus drug administration via injection is desired. For these embodiments, rapid drug delivery at a given drug to polymer ratio can be achieved via design of a patch wherein the drug film area is less than the area of the treated skin site. For drug film areas smaller than the treated skin site, interstitial fluid at the treated skin site can wet the drug matrix very quickly as it spreads over the entire treated area allowing delivery of the total applied drug dose in a rapid manner. In embodiments using an adhesive layer to attach the patch to the skin for which the drug film area is less than the treated skin area, the patch design should include spacing without adhesive, or an adhesive free zone around the patch to prevent the adhesive from contacting the treated skin area and interfering with drug delivery. In one embodiment, the ratio of drug film area to
pretreated skin area is less than 1.0. For certain embodiments, the ratio of drug film area to treated skin area is from about 0.3 to about 0.99. In preferred embodiments, the ratio of patch drug matrix area to treated skin area is from about 0.5 to about 0.8.

[00037] The rate and extent of drug delivery through the microchannels in skin can be modulated by variation in the number of microchannels in a given area of skin. Use of a greater density of microchannels can yield rapid drug delivery and rapid rates of rise in circulating blood drug concentration. A lower microchannel density can slow the initial rate of drug delivery and associated rise in blood drug concentration. Modulation of the microchannel density can be useful in matching the transdermal blood drug concentration profile to that of subcutaneous injection of the drug. Useful microchannel densities for this invention range from 10 microchannels per square centimeter of skin surface to 1000 microchannels per square centimeter of skin surface. The preferred range of microchannel density is 50 to 500 microchannels per square centimeter of skin surface.

[00038] The following examples are merely illustrative of certain embodiments of the present invention and should not be considered as limiting the scope of the invention in any way. These examples and equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure and the accompanying claims.

EXAMPLES

Example 1 - Rapid Release Prilocaine / PDLLA Formulation

[00039] Colloidal silicon dioxide (Cab-O-Sil - M5, Cabot) was dispersed under high shear into toluene at a loading of two weight percent. 133 mg of PDLLA (M_w 75,000-120,000 Da - Sigma Aldrich) and 39.9 mg of triethyl citrate (> 99% - Sigma Aldrich) was added to 3 mL of the toluene/silicon dioxide mixture and mixed on a roller mill until the polymer was dissolved. 400 mg of prilocaine hydrochloride (Sigma) was added to the polymer solution and mixed using a vortex mixer to initially disperse the drug. The resulting casting solution was mixed on a roller mill until uniform. Immediately prior to film casting, the drug dispersion was mixed again using a vortex
mixer. A section of backing material (Scotchpak 1109 - 3M) was taped to a glass plate and a cast of the polymer solution containing dispersed drug was made using a casting knife set to a 10 mil gap. The film was dried in a convection oven at 80°C for 10 minutes. Circular patches with a diameter of 10 mm were punched from the film using an arch punch for testing of drug content and release kinetics. The film was 63.7 weight percent drug and had a prilocaine content of 1.87 ± 0.26 mg/cm² (mean ± one standard deviation; N=10). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute. The drug release kinetics for this example are shown in Figure 2.

Example 2 - Prolonged Release Prilocaine / PDLLA Formulation

[00040] A prilocaine hydrochloride formulation was made in the same manner as Example 1 with the following changes: the mass of drug was 50 mg; the mass of polymer was 500 mg; no triethyl citrate was added; and the casting knife gap was set to 20 mil. The film was 8.3 weight percent drug and had a prilocaine content of 0.84 ± 0.03 mg/cm² (mean ± one standard deviation; N=6). In vitro dissolution testing at 32°C indicated that release of the drug into distilled water was prolonged and occurred over a one hour period. The drug release kinetics for this example are shown in Figure 2.

Example 3 - Prolonged Release Prilocaine / PDLLA Formulation (Extended Profile)

[00041] A prilocaine hydrochloride formulation was made in the same manner as Example 2 with the following changes: the mass of drug was 25 mg and the casting knife gap was set to 25 mil. The film was 4.3 weight percent drug and had a prilocaine content of 0.47 ± 0.01 mg/cm² (mean ± one standard deviation; N=6). In vitro dissolution testing at 32°C indicated that release of the drug into distilled water was prolonged and occurred over a two to three hour period. The drug release kinetics for this example are shown in Figure 2.

Example 4 - Rapid Release Prilocaine / Polycaprolactone Formulation
A film of prilocaine hydrochloride (Sigma) was made in the same manner as Example 1 with the following changes: the matrix polymer was Polycaprolactone (M\textsubscript{w} 80,000 Da - Sigma Aldrich). The film was 63.7 weight percent drug and had a prilocaine content of 2.50 ± 0.14 mg/cm\textsuperscript{2} (mean ± one standard deviation; N=5). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute.

Example 5 - Rapid Release Buspirone / PDLLA Formulation

A film of buspirone hydrochloride (Fermion) was made in the same manner as Example 1 with the following changes: the volume of toluene/silicon dioxide mixture was 3.5 mL and the knife gap setting was 8 mil. The film was 62.8 weight percent drug and had a buspirone content of 1.09 ± 0.17 mg/cm\textsuperscript{2} (mean ± one standard deviation; N=8). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute.

Example 6 - Rapid Release Exenatide / PDLLA Formulation

A film of exenatide (Lonza) was made in the same manner as Example 1 with the following changes: the volume of toluene/silicon dioxide mixture was 2.0 mL, but with addition of 1.5 mL of neat toluene and the knife gap setting was 15 mil. The film was 68.8 weight percent drug and had an exenatide content of 2.58 ± 0.11 mg/cm\textsuperscript{2} (mean ± one standard deviation; N=8). In vitro dissolution testing at 32°C indicated that over 86 percent of the drug is released within 5 minutes. The drug release kinetics for this example are shown in Figure 3.

Example 7 - Rapid Release Exenatide / Polycaprolactone Formulation

A rapid release exenatide film was made by dissolving 1.12 g of polycaprolactone polymer (M\textsubscript{w} 80,000 Da - Sigma Aldrich) in methylene chloride while stirring. To the solution was added 0.112 g of exenatide (Lonza), 0.448 g of mannitol (Fisher), and 2.05 g of disodium citrate (POSY). The mixture was mixed using a vortex mixer to initially disperse the drug. The resulting casting solution was further mixed on a roller mill until uniform. Immediately prior to film casting, the
drug dispersion was mixed again using a vortex mixer. A section of backing material (Scotchpak 1109 - 3M) approximately 4" x 6" was taped to a glass plate and the polymer solution containing dispersed drug was poured onto the backing material and immediately spread using a casting knife set to a 25 mil gap. The film was dried in a convection oven at 40°C for 10 minutes. Circular patches with a diameter of 10 or 18 mm were punched from the film using an arch punch and then tested for drug content and drug release kinetics. The cast film was 5 weight percent drug and had a exenatide content of 0.92 ± 0.12 mg/cm² (mean ± one standard deviation; N=2). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one hour. The drug release kinetics for this example are shown in Figure 4.

Example 8 - Fondaparinux / PDLLA Rapid Release Patch Manufacture for Testing in Rats

[00046] Colloidal silicon dioxide (Cab-O-Sil - M5, Cabot) was dispersed under high shear into toluene at a loading of 2.0 weight percent. PDLLA (33.3 mg; M_w 75,000-120,000 Da - Sigma Aldrich) and triethyl citrate (10 mg; ≥ 99% - Sigma Aldrich) were added to 2 mL of the toluene/silicon dioxide mixture and mixed on a roller mill until the polymer was dissolved. Fondaparinux sodium (100 mg; Apicore) was added to the polymer solution and mixed using a vortex mixer to initially disperse the drug. The resulting casting solution was mixed on a roller mill until uniform. Immediately prior to film casting the drug dispersion was mixed again using a vortex mixer. A section of backing membrane (Scotchpak 1109 - 3M) was taped to a glass plate and polymer solution containing dispersed drug was poured onto the backing and spread using a casting knife set to a 5 mil gap. The film was dried in a convection oven at 90°C for 10 minutes. Circular drug films with a diameter of 9 mm (area 0.636 cm²) were punched from the film using an arch punch for use in drug content/release kinetics testing and animal pharmacokinetic studies. The drug films were 55.2 weight percent drug and had a fondaparinux content of 0.365 ± 0.037 mg (mean ± one standard deviation, N=5). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute.
Example 9 - Fondaparinux / PDLLA Patch Pharmacokinetic Study in Hairless Rats

[00047] A pharmacokinetic study comparing transdermal administration of the fondaparinux patches of Example 8 to the equivalent dose of fondaparinux administered by subcutaneous injection was conducted in a hairless rat model. There were 5 rats per group each receiving 0.8 mg/kg fondaparinux either by transdermal or subcutaneous injection. For the transdermal fondaparinux group, a single 1 cm² skin site was pretreated via thermal ablation to create aqueous microchannels in the outer layer of the skin using a thermal ablation system configured to create 200 microchannels/cm² with a 4 millisecond electrical current pulse. Using the drug films described in Example 8, the ratio of drug film area to treated skin area was 0.636. The patches were placed on the pretreated skin site and covered with polyethylene/acrylic adhesive tape (3M 1521) to keep the patch in contact with the skin. Venous blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 2, and 6 hours and analyzed via a chromogenic method for anti-Factor Xa activity (Aniara - Hyphen BioMed). The pharmacokinetic results are presented in the following table.

Table 1 - Rat Study Pharmacokinetic Results, Fondaparinux / PDLLA Patch

<table>
<thead>
<tr>
<th>Administration Route</th>
<th>Fondaparinux Dose (mg/kg)</th>
<th>Mean Maximum Anti-Factor Xa Activity $A_{\text{max}}$ (µg/mL)</th>
<th>Mean AUC$_{0-6\text{ hr}}$ (µg-hr/mL)</th>
<th>Bioavailability Versus Subcutaneous Injection (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>0.8</td>
<td>2.35</td>
<td>6.97</td>
<td>93.7</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>0.8</td>
<td>2.72</td>
<td>7.62</td>
<td>N/A</td>
</tr>
</tbody>
</table>

[00048] A plot of Anti-Factor Xa activity versus time for the transdermal and subcutaneous injection fondaparinux groups is shown in Figure 5.
Example 10 - Fondaparinux / Polycaprolactone Rapid Release Patch Manufacture for Testing in Rats

[00049] Colloidal silicon dioxide (Cab-O-Sil - M5, Cabot) was dispersed under high shear into toluene at a loading of 2.0 weight percent. Polycaprolactone (200 mg; M_w 80,000 Da - Sigma Aldrich) and triethyl citrate (145.5 mg; ≥ 99% - Sigma Aldrich) were added to 7.5 mL of the toluene/silicon dioxide mixture and mixed on a roller mill until the polymer was dissolved. Fondaparinux sodium (500 mg; Apicore) was added to the polymer solution and mixed using a vortex mixer to initially disperse the drug. The resulting casting solution was mixed on a roller mill until uniform. Immediately prior to film casting the drug dispersion was mixed again using a vortex mixer. A section of backing membrane (Scotchpak 1109 - 3M) was taped to a glass plate and the polymer solution containing dispersed drug was poured on the backing and spread using a casting knife set to a 11 mil gap. The film was dried in a convection oven at 90°C for 10 minutes. Circular drug films with a diameter of 10 mm (area 0.785 cm²) were punched from the film using an arch punch for use in drug content/release kinetics and animal pharmacokinetic studies. The drug films were 50.7 weight percent drug and had a fondaparinux content of 0.701 ± 0.027 mg (mean ± one standard deviation, N=8). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute.

Example 11 - Fondaparinux / Polycaprolactone Patch Pharmacokinetic Study in Hairless Rats

[00050] A pharmacokinetic study comparing transdermal administration of the fondaparinux patches of Example 10 to the results of fondaparinux administered by subcutaneous injection (from Example 9) was conducted in a hairless rat model. There were 4 rats in the transdermal group each receiving 2.88 mg/kg fondaparinux. For the transdermal fondaparinux group, two 1 cm² skin sites were pretreated via thermal ablation to create aqueous microchannels in the outer layer of the skin using a thermal ablation system configured to create 200 microchannels/cm² with a 4 millisecond electrical current pulse. Using the drug films described in Example 10, the ratio of drug film area to treated skin area was 0.785. The patches were placed on
the pretreated skin sites and covered with polyethylene/acrylic adhesive tape (3M 1521) to keep the patches in contact with the skin. Venous blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 2, and 6 hours and analyzed via a chromogenic method for anti-Factor Xa activity (Aniara - Hyphen BioMed). The pharmacokinetic results are presented in the following table.

Table 2 – Rat Study Pharmacokinetic Results, Fondaparinux / Polycaprolactone Patch

<table>
<thead>
<tr>
<th>Administration Route</th>
<th>Fondaparinux Dose (mg/kg)</th>
<th>Mean Maximum Anti-Factor Xa Activity $A_{\text{max}}$ (μg/mL)</th>
<th>Mean AUC$_{0-6 \text{ hr}}$ (μg-hr/mL)</th>
<th>Bioavailability Versus Subcutaneous Injection (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>2.88</td>
<td>5.38</td>
<td>18.05</td>
<td>73.8</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>0.8</td>
<td>2.72</td>
<td>7.62</td>
<td>N/A</td>
</tr>
</tbody>
</table>

[00051] A plot of Anti-Factor Xa activity versus time for the transdermal and subcutaneous injection fondaparinux groups is shown in Figure 6. A plot of Anti-Factor Xa activity normalized to the maximum Anti-Factor Xa activity for each group is shown in Figure 7.

Example 12 - Fondaparinux / Polycaprolactone Patch with Increased MicroChannel Density Pharmacokinetic Study in Hairless Rats

[00052] A pharmacokinetic study evaluating transdermal administration of the fondaparinux patches of Example 10 with an increased microchannel density of 400 microchannels/cm$^2$ was conducted in a hairless rat in vivo model. There were 5 rats in the transdermal group each receiving 2.33 mg/kg fondaparinux. For the transdermal fondaparinux group, two 1 cm$^2$ skin sites were pretreated via thermal ablation to create aqueous microchannels in the outer layer of the skin using a thermal ablation system configured to create 400 microchannels/cm$^2$ with a 4 millisecond electrical current pulse. Using the drug films described in Example 10, the ratio of
drug film area to treated skin area was 0.785. The patches were placed on the pretreated skin sites and covered with polyethylene/acrylic adhesive tape (3M 1521) to keep the patches in contact with the skin. Venous blood samples were taken at 0, 0.25, 0.5, 0.75, 2, and 6 hours and analyzed via a chromogenic method for anti-Factor Xa activity (Aniara - Hyphen BioMed). The pharmacokinetic results are presented in the following table.

Table 3 – Rat Study Pharmacokinetic Results, Fondaparinux / Polycaprolactone Patch

<table>
<thead>
<tr>
<th>Administration Route</th>
<th>Fondaparinux Dose (mg/kg)</th>
<th>Mean Maximum Anti-Factor Xa Activity (A_{\text{max}}) (µg/mL)</th>
<th>Mean AUC(_{0-6\text{ hr}}) (µg-hr/mL)</th>
<th>Bioavailability Versus Subcutaneous Injection (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>2.33</td>
<td>5.77</td>
<td>20.0</td>
<td>102.2</td>
</tr>
</tbody>
</table>

Example 13 - Enoxaparin / PDLLA Rapid Release Patch Manufacture for Testing in Rats

[00053] Colloidal silicon dioxide (Cab-O-Sil - M5, Cabot) was dispersed under high shear into toluene at a loading of two weight percent (2% w/w). PDLLA (133 mg; \(M_w 75,000-120,000\) Da - Sigma Aldrich) and triethyl citrate (39.9 mg; \(\geq 99\%\) - Sigma Aldrich) were added to 2 mL of the toluene/silicon dioxide mixture and mixed on a roller mill until the polymer was dissolved. Enoxaparin (400 mg; Sanofi Aventis) was added to the polymer solution and mixed using a vortex mixer to initially disperse the drug. The resulting casting solution was mixed on a roller mill until uniform. Immediately prior to film casting the drug dispersion was mixed again using a vortex mixer. A section of backing membrane (Scotchpak 1109 - 3M) was taped to a glass plate and a cast of the polymer solution containing dispersed drug was made using a casting knife set to a 5 mil gap. The film was dried in a convection oven at 90°C for 10 minutes. Circular drug films with a diameter of 10 mm (area 0.785 cm\(^2\)) were punched from the film using an arch punch for use in drug content/release testing and
animal pharmacokinetic studies. The drug films were 65.6 weight percent drug and had an enoxaparin sodium content of 1.43 ± 0.07 mg (mean ± one standard deviation, N=8). In vitro dissolution testing at 32°C indicated that complete drug release into distilled water occurred within one minute.

Example 14 - Enoxaparin / PDLLA Patch Pharmacokinetic Study in Hairless Rats

A pharmacokinetic study comparing transdermal administration of the enoxaparin patches of Example 10 via microporated skin to an equivalent dose of enoxaparin administered by subcutaneous injection was conducted in a hairless rat model. There were 5 rats per group each receiving 1.4 mg enoxaparin either by transdermal administration or subcutaneous injection. For the transdermal enoxaparin group, a single 1 cm² skin site was pretreated via thermal ablation to create aqueous microchannels in the outer layer of the skin using a thermal ablation system configured to create 400 microchannels/cm² with a 4 millisecond electrical current pulse. The ratio of the drug film area to the area of treated skin was 0.785. The drug films were placed on the pretreated skin sites and covered with polyethylene/acrylic adhesive tape (3M 1521) to keep the patch in contact with the skin. Venous blood samples were taken at 0, 1, 2, 3, 4, 6, and 8 hours and analyzed via a chromogenic method for anti-Factor Xa activity. The pharmacokinetic results are presented in the following table.

Table 4 - Rat Study Pharmacokinetic Results, Enoxaparin / PDLLA Patch

<table>
<thead>
<tr>
<th>Administration Route</th>
<th>Enoxaparin Dose (mg)</th>
<th>Mean Maximum Anti-Factor Xa Activity A_max (IU/mL)</th>
<th>Mean AUC_{0-8 hr} (IU-hr/mL)</th>
<th>Bioavailability Versus Subcutaneous Injection (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>1.4</td>
<td>1.51</td>
<td>5.38</td>
<td>110</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>1.4</td>
<td>1.46</td>
<td>4.90</td>
<td>N/A</td>
</tr>
</tbody>
</table>
[00055] A plot of Anti-Factor Xa activity versus time for each enoxaparin group is shown in Figure 8.

Example 15 - Fondaparinux / PDLLA Rapid Release Patch Manufacture for Human

Clinical Testing

[00056] A fondaparinux formulation is made in the same manner as Example 8 with the following changes: the volume of toluene/silicon dioxide mixture is 5 mL; the mass of drug is 1250 mg, the mass of PDLLA is 333 mg, the mass of triethyl citrate is 100 mg and the casting knife gap is 10 mils. A punch is used to cut the patches to an area of 1.5 cm². The drug films contain 65.6 weight percent drug and have a mean fondaparinux sodium content of 2.5 mg. In vitro dissolution testing at 32°C indicates that complete drug release into distilled water occurs within one minute.

Example 16 - Fondaparinux / PDLLA Patch Pharmacokinetic Study in Human Subjects

[00057] A Phase 1, single-center, single-dose, open label, randomized sequence, two-period crossover pharmacokinetic and safety study comparing transdermal fondaparinux sodium to Arixtra® subcutaneous injection is conducted in healthy volunteers. Subjects receive single doses of 2.5 mg Arixtra® SC injection and transdermal fondaparinux sodium (2.5 mg). Plasma samples are obtained at T = 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 hours and analyzed via a chromogenic method for anti-Factor Xa activity. For the transdermal study leg, a single 2.0 cm² skin site on outer upper arm of 10 subjects is pretreated via thermal ablation to create the aqueous microchannels using a 200 filament per square centimeter porator and a 4 ms current pulse. A transdermal fondaparinux patch of Example 14 containing 2.5 mg fondaparinux sodium is applied to the treated skin area. Each patch contains a drug film area of 1.5 cm². The ratio of drug film area to treated skin area is 0.75. The patch is applied for 4 hours and removed. Arixtra® (subcutaneous fondaparinux sodium) is administered as subcutaneous injection in the abdomen according to the instructions for use. Arixtra® contains 2.5 mg fondaparinux sodium in a 0.5 mL single dose prefilled syringe containing an isotonic
solution of sodium chloride, water for injection, affixed with a 27-gauge x ½-inch needle.

Table 5 - Pharmacokinetic Results for Fondaparinux / PDLLA Patch in Humans

<table>
<thead>
<tr>
<th>PK Parameters (Mean)</th>
<th>Fondaparinux Sodium Transdermal System (FSTS)</th>
<th>Arixtra® fondaparinux sodium subcutaneous injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2.5 mg patch applied for 4 hours to upper arm</td>
<td>2.5 mg injection administered to abdomen skin fold</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Maximum Anti-Factor Xa Activity ($A_{\text{max}}$)</td>
<td>0.30 mg/L</td>
<td>0.34 mg/L</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>2.0 hours</td>
<td>1.7 hours</td>
</tr>
<tr>
<td>AUC$_{0-t}$</td>
<td>4.7 mg-h/L</td>
<td>5.3 mg-h/L</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>6.0 mg-h/L</td>
<td>6.7 mg-h/L</td>
</tr>
<tr>
<td>Half-Life $T_{1/2}$</td>
<td>20 hours</td>
<td>17 hours</td>
</tr>
<tr>
<td>Bioavailability Versus Subcutaneous Injection</td>
<td>90%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Example 17 - Fondaparinux / Polycaprolactone Rapid Release Patch Manufacture for Human Clinical Testing

[00058] A fondaparinux formulation is made in the same manner as Example 10 with the following changes: the volume of toluene/silicon dioxide mixture is 15 mL; the mass of drug is 1000 mg, the mass of PDLLA is 400 mg, the mass of triethyl citrate is 291 mg and the casting knife gap is 13 mils. A punch is used to cut the patches to an area of 1.5 cm$^2$. The drug films contain 50.7 weight percent drug and have a mean
fondaparinux sodium content of 2.5 mg. In vitro dissolution testing at 32°C indicates that complete drug release into distilled water occurs within one minute.

Example 18 - Fondaparinux / Polycaprolactone Patch Pharmacokinetic Study in Human Subjects

[00059] A Phase 1, single-center, single-dose, open label, randomized sequence, two-period crossover pharmacokinetic and safety study comparing transdermal fondaparinux sodium to Arixtra® subcutaneous injection is conducted in healthy volunteers. Subjects receive single doses of 2.5 mg Arixtra® SC injection and transdermal fondaparinux sodium (2.5 mg). Plasma samples are obtained at T = 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 hours and analyzed via a chromogenic method for anti-Factor Xa activity. For the transdermal study leg, a single 2.0 cm² skin site on outer upper arm of 10 subjects is pretreated via thermal ablation to create the aqueous microchannels using a 400 filament per square centimeter porator and a 4 ms current pulse. A transdermal fondaparinux patch of Example 16 containing 2.5 mg fondaparinux sodium is applied to the treated skin area. Each patch contains a drug film area of 1.5 cm². The ratio of drug film area to treated skin area is 0.75. The patch is applied for 4 hours and removed. Arixtra® (subcutaneous fondaparinux sodium) is administered as subcutaneous injection in the abdomen according to the instructions for use. Arixtra® contains 2.5 mg fondaparinux sodium in a 0.5 mL single dose prefilled syringe containing an isotonic solution of sodium chloride, water for injection, affixed with a 27-gauge x ½-inch needle.

Table 6 - Pharmacokinetic Results for Fondaparinux / Polycaprolactone Patch in Humans

<table>
<thead>
<tr>
<th>PK Parameters (Mean)</th>
<th>Fondaparinux Sodium Transdermal System (FSTS)</th>
<th>Arixtra® fondaparinux sodium subcutaneous injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2.5 mg patch</td>
<td>2.5 mg injection</td>
</tr>
<tr>
<td></td>
<td>applied for 4 hours to upper arm</td>
<td>administered to abdomen skin fold</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Maximum Anti-Factor Xa Activity ($A_{max}$)</td>
<td>0.34 mg/L</td>
<td>0.34 mg/L</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>1.5 hours</td>
<td>1.7 hours</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$</td>
<td>5.3 mg-h/L</td>
<td>5.3 mg-h/L</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$</td>
<td>6.6 mg-h/L</td>
<td>6.7 mg-h/L</td>
</tr>
<tr>
<td>Half-Life $\gamma_{1/2}$</td>
<td>18 hours</td>
<td>17 hours</td>
</tr>
<tr>
<td>Bioavailability Versus Subcutaneous Injection</td>
<td>99%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
CLAIMS

1. A patch for transdermal delivery of a water soluble drug comprising:
   (a) a drug/polymer matrix layer comprising:
       a. at least one water soluble drug; and
       b. one or more biodegradable polymers, and
   (b) a membrane backing layer,
   wherein the drug/polymer matrix layer is cast to the membrane backing layer.

2. The patch of claim 1, wherein the water soluble drug is an oligosaccharide.

3. The patch of claim 2, wherein the oligosaccharide is selected from the group consisting of fondaparinux and enoxaparin.

4. The patch of claim 3, wherein the oligosaccharide is fondaparinux.

5. The patch of claim 3, wherein the oligosaccharide is enoxaparin.

6. The patch of claim 1, wherein the water soluble drug is a peptide or protein.

7. The patch of claim 6, wherein the water soluble drug is exenatide.

8. The patch of claim 6, wherein the water soluble drug is parathyroid hormone.

9. The patch of claim 6, wherein the water soluble drug is follicle stimulating hormone.

10. The patch of claim 6, wherein the water soluble drug is insulin.

11. The patch of claim 6, wherein the water soluble drug is selected from an anesthetic agent, analgesic agent, and combinations thereof.

12. The patch of claim 6, wherein the water soluble drug is an anxiolytic compound.

13. The patch of claim 12, wherein the anxiolytic compound is buspirone.

14. The patch of any of claims 2 to 13, wherein the patch provides for a bioavailability of the water soluble drug that is greater than 50 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection.

15. The patch of claim 14, wherein the patch provides for a bioavailability of the water soluble drug that is greater than 75 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection.
16. The patch of any of claim 14, wherein the patch provides for a bioavailability of the water soluble drug that is greater than 90 percent of the bioavailability of the same water soluble drug delivered by subcutaneous injection.

17. The patch of any of claims 1 to 16, wherein the weight ratio of polymer to drug is from about 1:5 to about 100:1

18. The patch of claim 17, wherein the weight ratio of polymer to drug is from about 2:1 to about 50:1

19. The patch of claim 18, wherein the weight ratio of oligosaccharide to polymer in the matrix layer is in the range of about 2:1 to about 5:1.

20. The patch of claim 19, wherein the weight ratio of oligosaccharide to polymer in the matrix layer is in the range of about 2.5:1 to 3.5:1.

21. The patch of claim 17, wherein the weight ratio of polymer to drug is from about 1:1.1 to about 1:5.

22. The patch of claim 21, wherein the weight ratio of polymer to drug is about 1:2.5 to about 1:3.5

23. The patch of any of claims 1 to 22, wherein the one or more biodegradable polymers is selected from the group consisting of polyorthoesters, polyanhydrides, polycaprolactone, poly(d,l lactide - co-glycolide), poly(d,l lactide - co-caprolactone) and poly(d,l lactide), and combinations thereof.

24. The patch of claim 23, wherein the one or more biodegradable polymers is selected from the group consisting of polycaprolactone, poly(d,l lactide - co-glycolide), poly(d,l lactide - co-caprolactone) and poly(d,l lactide), and combinations thereof.

25. The patch of claim 23, wherein the one or more biodegradable polymers is polycaprolactone.

26. The patch of claim 23, wherein one or more biodegradable polymers is poly(d,l lactide).

27. The patch of any of claims 1 to 26, further comprising toluene as a solvent.

28. The patch of any of claims 1 to 27, wherein the drug/polymer matrix layer further comprises a plasticizer.

29. The patch of claim 27, wherein the plasticizer is triethyl citrate.

30. The patch of any of claims 1 to 27, wherein the drug/polymer matrix layer further comprises a viscosity increasing agent.
31. The patch of claim 30, wherein the viscosity increasing agent is colloidal silicon dioxide.

32. The patch of any of claims 1 to 31, wherein the patch further comprises an adhesive layer.

33. A method of transdermal delivery of a water soluble drug through the skin of a patient, comprising
   (a) treating an area of the skin of a patient to generate a plurality of microchannels in the skin of the patient; and
   (b) affixing the patch of any of claims 1 to 32.

34. The method of claim 33, wherein the area of the skin treated to generate the microchannels is equal to the area of the drug/polymer matrix layer.

35. The method of claim 33, wherein the area of the skin treated to generate the microchannels is greater than the area of the drug/polymer matrix layer.

36. The method of claim 35, wherein the ratio of the area of the drug/polymer matrix layer to area of skin treated is about 0.3 to about 0.99.

37. The method of claim 33, wherein the area of the skin treated to generate the microchannels is less than the area of the drug/matrix polymer layer.

38. The method of claim 37, wherein the ratio of the area of the drug/polymer matrix to area of skin treated is from about 1.1 to about 2.0.

39. The method of any of claims 30 to 38, wherein the plurality of microchannels in skin is generated by an array of microneedles, by ablation of the skin via the rapid application of heat or radio frequency energy, or by other electrical, mechanical acoustic or chemical means.

40. A method of preparing a transdermal patch comprising:
   (a) dispersing at least one water soluble drug in a solution of a biodegradable polymer in a solvent to prepare a dispersion;
   (b) casting the dispersion on a membrane backing layer to form a drug/polymer matrix layer; and
   (c) drying the drug/polymer matrix layer,

41. The method of claim 40, wherein the method further comprises dispersing colloidal silicon dioxide in the solvent prior to dispersing the water soluble drug in step (a).
42. The method of claim 40 or 41, wherein the solvent is a non-polar solvent.
43. The method of claim 42, wherein the solvent is toluene.
44. The method of any of claims 41 to 43, wherein the colloidal silicon dioxide is dispersed in the solvent using a high sheer mixer.
45. The method of any of claims 40 to 44, further comprising mixing the dispersion prepared in step (a) with a vortex.
46. The method of any of claims 40 to 44, further comprising mixing the dispersion prepared in step (a) with a roller mill.
FIGURE 2
FIGURE 3
FIGURE 4
FIGURE 6