(54) Title: AGENTS FOR CONTROLLING BIOLOGICAL FLUIDS AND METHODS OF USE THEREOF

(57) Abstract: Therapeutic formulations adapted for positive-pressure application for controlling biological fluid at a desired site in a subject, absorbent articles comprising therapeutic formulations, and anti-infective devices coated with therapeutic formulations, said formulations comprising about 25 % to about 99 % by weight liquid-crystal forming compound and 0 % to about 75 % by weight solvent. In addition, methods of using said formulations including methods for controlling biological fluid at a desired site in a subject, methods for controlling blood loss, and methods for facilitating effective closure of a vascular wound or incision site at a desired site in a subject are disclosed, the methods comprising administering particular formulations comprising liquid-crystal forming compounds and solvents that are described herein.
Agents for Controlling Biological Fluids and Methods of Use Thereof

Technical Field and

The present invention relates to compositions which are hydrophobic or amphiphilic and liquid crystalline formulations and methods for use as surgical adjunctive therapies, hemostatic agents, and as primary treatment modalities for hard and soft tissue wounds as well as the basis for cosmetic medical devices.

Background Art

The use of hemostatic agents and devices is a common practice in modern surgery. The general field ranges from the use of agents exhibiting local action by the physical presence of the agent such as astringents (aluminum and magnesium salts), hydrolyzed gelatin (Gelfoam® - Pharmacia) and oxidized cellulose (Surgicel® - Johnson & Johnson) to products seeking to exploit physiologic mechanisms such as thrombin- and fibrin-based systems. However, the field is plagued with formulations of limited efficacy and systems that ultimately expose patients to greater risk of adverse immune response. Formulations that can be applied in a variety of physical states to quickly and reliably establish hemostasis without the risk of secondary immunologic responses would be highly desirable and of great commercial interest.

Summary of the Invention

In a first embodiment of the invention there is provided a therapeutic formulation adapted for positive-pressure application and effective for controlling biological fluid at a desired site in a subject, the formulation comprising about 25% to about 99% by weight liquid-crystal forming compound and 0% to about 75% by weight solvent, wherein the formulation effectively controls biological fluid at the desired site in the subject. In related embodiments, the solvent may be a polar solvent, a non-polar solvent, a semi-polar solvent or a combination thereof, and particular formulations may comprise about 97% liquid-crystal forming compound and about 3% normal saline solution; about 65% liquid-crystal forming compound and about 15% normal saline solution; about 35% liquid-crystal forming compound and about 65% normal saline solution; about 92.5%
hyaluronate; about 95% liquid-crystal forming compound and about 5% isopropyl myristate; about 95% liquid-crystal forming compound and about 5% 190 proof ethanol; or about 80% liquid-crystal forming compound and about 20% cottonseed oil.

Other particular embodiments may comprise platelets, platelet-rich plasma, plasma or whole blood, in addition to, or in place of, the above-mentioned solvents. Some particular embodiments may thus comprise about 97% liquid-crystal forming compound and about 3% whole blood; about 80% liquid-crystal forming compound and about 9% whole blood; about 65% liquid-crystal forming compound and about 15% whole blood; about 35% liquid-crystal forming compound and about 25% blood plasma, about 97% liquid-crystal forming compound and about 3% blood plasma; about 65% liquid-crystal forming compound and about 15% blood plasma; or about 35% liquid-crystal forming compound and about 25% blood plasma.

In another embodiment, there is provided an absorbent article comprising an absorbent layer and a formulation effective for controlling biological fluid of a human or veterinary subject, wherein the formulation comprises from about 25% to 99% by weight liquid-crystal forming compound and about 0% to 75% by weight solvent and is present within or on at least a portion of the article. Related embodiments may comprise an absorbent layer that further includes an absorbent additive; a liquid-permeable and moisture vapor-permeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer; a liquid-impermeable and moisture vapor-permeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer; an absorbent article further comprising a liquid-impermeable and moisture vapor impermeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer; a liquid-permeable liner, adapted to be non-adherent to a wound, having a surface that is substantially coextensive with an inner surface of the absorbent layer such that the absorbent layer is located between the liquid-permeable liner and the outer layer; or any combination thereof.

In other embodiments, the composition effective for controlling biological fluids in the article provides utility as an anti-adherent between the article and bodily tissue to assist in placement or removal of the article from a site of use thereby reducing trauma
from application or removal of said article, and the biological fluid controlling
formulation may be applied to the article by spray coating, hot-melt coating, dip coating,
direct transfer, manual application or a combination thereof. Specific embodiments
provide an article that may be any of a wound dressing, a medical sponge, a hemostatic
article, a hemostatic article for the nose, an adhesive bandage, a wound packing, an
internal vascular closure packing, an external vascular closure dressing, a swellable
absorbent article, a fibrotic wound packing article, or a feminine hygiene product, and the
liquid-crystal forming compound may be any of a fatty acid ester, a polyethylene oxide, a
glycolipid, a polyester, a polyethylene glycol, or a combination thereof. In related
embodiments, the fatty acid ester may be a monoester, diester, triester or mixture thereof,
and the monoester may be glyceryl monoarachidonate, glyceryl monolaurate, glyceryl
monolinoleate, glyceryl monolinoenate, glyceryl monomyristate, glyceryl
monopalmitoleate, glyceryl monooleate, and glyceryl monostearate; isopropyl
monoarachidonate, isopropyl monolaurate, isopropyl monolinoleate, isopropyl
monolinolenate, isopropyl monomyristate, isopropyl monopalmitoleate, isopropyl
monooleate, and isopropyl monostearate; methyl monoarachidonate, methyl monolaurate,
methyl monolinoleate, methyl monolinoenate, methyl monomyristate, methyl
monopalmitoleate, methyl monooleate, and methyl monostearate; and propylene glycol
monoarachidonate, propylene glycol monolaurate, propylene glycol monolinoleate,
propylene glycol monolinolenate, propylene glycol monomyristate, propylene glycol
monopalmitoleate, monoooleate, and propylene glycol monostearate, or a combination
thereof.

Another particular embodiment provides an infection resistant device, the device
treated with an anti-infective formulation comprising about 25% to 99% by weight fatty
acid or fatty acid ester, wherein said anti-infective formulation inhibits the formation of
pathogen growth on the device, or in adjacent tissues, thereby imparting infection
resistance to the device. In related embodiments, the anti-infective formulation may
further comprise about 0% to 75% solvent and the fatty acid or fatty acid ester may be a
liquid-crystal forming compound, and in some embodiments, upon formation of a liquid
crystal, the anti-infective formulation thereby lessons migration within or upon bodily
tissues and attenuates clearance of the formulation from the site of device placement, or a
site adjacent to or near to where the device is placed within a subject. In still other
embodiments, the liquid crystal formulation may act as a controlled-release delivery
system of degradation products from the formulation, wherein said degradation products provide an additional anti-infective effect.

Related embodiments provide a device that is effective for treatment of an acute or chronic wound, and the acute wound may be an abrasion, burn, laceration, puncture or incision, and the chronic wound may be an ulceration including an ulcer of a leg, decubitus, fungal, diabetic, gastric, foot, sacral or indolent ulcer. In other embodiments, the device may be effective as a filler of a tissue void created by trauma, disease or a surgical procedure, and in still other embodiments, the device may be treated with an anti-infective formulation by spray coating, hot-melt coating, dip coating or a combination thereof prior to use. In some embodiments, the device may be composed of organic material, inorganic material, or a combination thereof, and in still other embodiments, the device may be a catamenial absorption device, condom, prophylactic, medical sponge, surgical dressing, wound dressing, adhesive bandage or a combination thereof. Alternatively, the device may be a prosthetic, an implant or a combination thereof. In related embodiments, the prosthetic or implant type may be a spinal, orthopedic, dental, cardiac, neural, or cosmetic prosthetic or implant type, or a combination thereof. In particular embodiments, the orthopedic prosthetic or implant may be an artificial joint, fracture repair hardware, artificial cartilage, a plate, a screw, a nail, a wire or a combination thereof; the dental prosthetic or implant may be a root form, a Ramus frame, a transosseous implant, a blade form, fracture repair hardware, a prosthetic device, general hardware, a plate, a screw, a nail, a wire or a combination thereof; the cardiac prosthetic or implant may be a pacemaker, a defibrillator, a heart valve, a vascular graft or a combination thereof; and the cosmetic prosthetic or implant may be a breast implant, a dermal filler, a tissue void filler, a buttocks implant, a facial implant or a combination thereof.

Still other embodiments provide an infection resistant device, the device treated with an anti-infective formulation wherein the anti-infective formulation comprises about 25% to 99% liquid-crystal forming compound, about 0% to 50% fatty acid and about 0% to 50% solvent, by weight; about 90% liquid-crystal forming compound, about 5% lauric acid and about 5% solvent by weight; about 65% liquid-crystal forming compound, about 10% myristic acid and about 25% solvent, by weight; or about 35% liquid-crystal forming compound, about 15% palmitic and about 40% solvent, by weight.

Another embodiment provides a hemostatic formulation effective for controlling bleeding at a desired site in a human or veterinary subject, the composition comprising
25% to about 99% by weight liquid-crystal forming compound and 0% to about 75% by weight solvent, wherein the hemostatic formulation is adapted for positive pressure application upon or within tissue, effects hemostasis and induces local effects at the desired site within about 15 minutes or less, thereby controlling bleeding. More particularly, hemostasis may be effected and local effects induced at the site within about 10 minutes or less of application, still more particularly within about 5 minutes or less of application, still more particularly within about 2 minutes or less of application, and still more particularly within about 30 seconds or less of application.

In related embodiments of a hemostatic formulation, the solvent may be any of an alcohol, polyethylene glycol, propylene glycol, polypropylene glycol, water, isotonic aqueous solution, biological fluid, a physiologic buffered system, urine, saliva, serous fluid, synovial fluid, gastric secretions, cerebrospinal fluid, vitreous humor, lymph, wound exudate, cholesterol, a physiologic buffered system or combination thereof; the liquid-crystal forming compound may be any of a fatty acid, fatty acid monoester, fatty acid diester, fatty acid triester or combination thereof further comprising at least one unsaturated carbon-carbon bond. More particularly, the liquid crystal forming-agent may be a glyceryl monoester, diester, triester, or combination thereof, and still more particularly, the liquid-crystal forming compound may be glyceryl monooleate.

Still yet another embodiment provides a formulation for a thrombin inhibitor comprised of about 25 to 99% by weight liquid-crystal forming compound and about 0% to 75% by weight solvent, wherein the formulation is adapted for positive pressure application to desired site in a subject. In related embodiments, the liquid-crystal forming compound may be a fatty acid ester. More particularly, the thrombin inhibitor formulation may be effective as a filler of a tissue void, such as those created by trauma, disease or a surgical procedure, and more particularly, the thrombin inhibitor formulation may also be a neuroprotective agent.

Another embodiment provides a cosmetic formulation effective for mimicking soft tissue at a desired site in a subject, the formulation comprising about 25% to 99% by weight liquid-crystal forming compound, about 0% to about 75% by weight solvent, and other compounds, as required, to provide viscosities and textures effective for mimicking soft tissue. In related embodiments, the cosmetic formulation may further comprise an antioxidant, and the antioxidant may be a water soluble or oil soluble antioxidant, including any of vitamin C, sodium bisulfate, sodium sulfate, sodium metabisulfite, cysteine hydrochloride, thioglycolic acid, sulfur dioxide, ascorbyl palmitate, butylated
hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, vitamin D or any combination thereof.

Embodiments of the invention also provide that any of the disclosed formulations may further comprise an augmentative or therapeutic agent, including a hemostat; an coagulation augmentative agent; a vasoactive agent; a tissue growth stimulant; a healing promoter; an anti-infective agent, an adhesion enhancer; a swelling agent; a thickening agent; an anesthetic; a solvent; a co-solvent; a thinning agent; a filler; an anti-scarring agent, an anti-inflammatory agent; a physiologically compatible monovalent ion, divalent ion, trivalent ion and salt thereof; a bleaching agent including a teeth whitening agent, a peroxide; a miscellaneous medicament; a controlled-release augmentative material; an embolic augmentative material; or any combination thereof. Moreover, in any disclosed formulation, the augmentative agent or medicament may be suspended or dissolved in the formulation, the controlled-release delivery component may be a biodegradable polymer, the swelling enhancer may be a starch, a natural gum, a cellulosic polymer, a pyrrolidone polymer, a polyacrylic acid or a combination thereof. In addition, any disclosed formulation may be a liquid, gel or semisolid, it may form a cubic phase prior to or after application, and the liquid-crystal forming compound may be hydrophobic and/or amphiphilic, and any disclosed formulation is preferably biocompatible and/or biodegradable.

In particular embodiments of a formulation, the augmentative or therapeutic agent may be any of a hemostat and coagulation augmentative agent including catecholamines such as epinephrine, a phospholipid, gelatin, collagen, chitosan, glucosamines such as n-acetylglucosamine, an enzyme, an enzyme inhibitor, a fatty acid, a hormone, a silicone compound, bentonite, fumed silica, colloidal silica, micronized silica, diatomaceous earth, talc, titanium dioxide, potassium sulfate, aluminum sulfate, aluminum chloride, ammonium chloride, ferric sulfate, ferric sub sulfate, copper sulfate, an astringent, whole blood, blood plasma, a blood product such as (a) platelets (b) prothrombin (c) thrombin (d) fibrinogen (e) fibrinogen (f) thromboplastin (g) a clotting factor, an exothermic compound such as (a) calcium bromide (b) calcium oxide (c) calcium chloride; or a vasoactive agent including a vasoconstrictor, a cholinomimetic agent, an anticholinergic agent, a cholinergic blocker, a sympathomimetic, an antiadrenergic agent, an adrenergic blocker, an immunogenic agent, a hormone such as vasopressin, an astringent, blood plasma, a blood product such as (a) platelets (b) prothrombin (c) thrombin (d) fibrinogen (e) fibrinogen (f) thromboplastin (g) a clotting
factor, an enzyme, an enzyme inhibitor; or a tissue growth and healing stimulant
including gelatin, collagen, whole blood, blood plasma, a blood product such as (a)
platelets (b) prothrombin (c) thrombin (d) fibrin (e) fibrinogen (f) thromboplastin (g)
a clotting factor, insulin-like growth factor, vascular endothelial growth factor, a
hormone, hydroxyapatite, platelet growth factor, an enzyme, an enzyme inhibitor, stem
cells, hormones, thrombin inhibitors, pepsin; or an anti-infective including tea tree oil,
peroxide, an antibiotics such as ampicillin, a fatty acid, an antifungal, an antiviral, an
immunogenic agent; or an adhesion enhancer including a natural polymer, a synthetic
polymer, a cellulose polymer, a carboxymethylcellulose, a polyethylene glycol or a PEG
derivative, a polybutylene terephthalate or PBT derivative, a polyethylene oxide or PEO
derivative, a polyacrylic acid, a poly methyl vinyl ether/maleic anhydride copolymer, a
poly methyl vinyl ether/maleic acid copolymer, a poly vinyl methyl-ether maleate, a poly
ethylene oxide, a cationic polyacrylamide polymer, an alginate acid derivative, chitosan, a
glucosamine such as n-acetylglucosamine, a natural or synthetic protein, gluten, gelatin,
collagen, ampicillin, a gum, karaya gum, a cellulosic gum, a phospholipids, a fatty acid,
bentonite, fumed silica, colloidal silica, micronized silica, diatomaceous earth, talc,
titanium dioxide; or a swelling agent including a natural or synthetic swellable polymer,
karaya gum, a cellulosic gum, an alginate acid derivative, gelatin, chitosan, a glucosamine
such as n-acetylglucosamine; or a thickening agent including a natural polymer, a
synthetic polymer, a cellulose polymer, carboxymethylcellulose, a polyethylene glycol or
PEG derivative, a polybutylene terephthalate or PBT derivative, a polyethylene oxide or
PEO derivative, a poly methyl vinyl ether/maleic anhydride copolymer, a poly methyl
vinyl ether/maleic acid copolymer, a poly vinyl methyl-ether maleate, a poly ethylene
oxide, a cationic polyacrylamide polymer, an alginate acid derivative, chitosan, a
glucosamine such as n-acetylglucosamine, a natural or synthetic protein, gluten, gelatin,
collagen, ampicillin, a gum, karaya gum, a cellulosic gum, a phospholipid, a fatty acids, a
multiparticulate, a poly(lactic-co-glycolide) PLGA multiparticulate, bentonite, fumed
silica, colloidal silica, micronized silica, diatomaceous earth, talc, titanium dioxide, an
oleaginous ointment base, an absorbent ointment base, an emulsion ointment base; or an
anesthetic including clove oil-eugenol, tea tree oil, benzocaine, lidocaine, dibucaine,
pramoxine, dyclonine; or a solvent and/or co-solvent including dodecane, peroxide,
phospholipids, a fatty acid, a polyethylene glycol or PEG derivative, a polyethylene oxide
or PEO derivative, a polybutylene terephthalate or PBT derivative, whole blood, blood
plasma; or a thinning agent including a natural or synthetic polymer, a polar or nonpolar
solvent, ethanol, dodecane, a phospholipid, a fatty acid, a polyethylene glycol or PEG derivative, an exothermic compound such as (a) calcium bromide (b) calcium oxide (c) calcium chloride; or a filler including a hyaluronic acid, a fatty acid, a polyethylene glycol or PEG derivative, a polyethylene oxide or PEO derivative, collagen, whole blood, blood plasma, a blood product; or an antiscarring/anti-inflammatory/healing promoter including an onion extract, a UV radiation blocker, a steroid, a non-steroidal anti-inflammatory drug, an oleaginous ointment base, an absorbent ointment base, an emulsion ointment base, an enzyme, an enzyme inhibitor, a tissue growth inhibitor; or a physiologically compatible monovalent, divalent or trivalent ion and salt thereof including a calcium derivative, a potassium derivative, a sulfate derivative, a chloride derivative, a fluoride derivative, potassium aluminum sulfate, aluminum chloride, ammonium chloride, ferric sulfate, ferric sub-sulfate, copper sulfate; or a bleaching agent including a teeth whitening agent, a peroxide; or a miscellaneous medicament including botulinum toxin; or a controlled-release augmentative material including a multiparticulate, a multiparticulate containing a medicament, a poly(lactic-co-glycolide) (PLGA) multiparticulate; or an embolic augmentative material including a multiparticulate, a multiparticulate containing a medicament, a poly(lactic-co-glycolide) (PLGA) multiparticulate; or any combination thereof.

Other embodiments provide a method for effectively controlling biological fluid at a desired site in a subject, the method comprising administering an effective amount of a therapeutic formulation at the site comprising about 25% to 100% by weight liquid-crystal forming compound and about 0% to about 75% by weight solvent for a period of time effective to control biological fluid at the desired site. In a related embodiment, there is provided a method for effectively controlling biological fluid at a desired site in a subject, the method comprising administering an effective amount of any formulation as disclosed above, for a period of time effective to control biological fluid at the desired site. In such embodiments, the methods may further effectively control biological fluid by promoting hemostasis at the desired site; promoting coagulation at the desired site; facilitating healing by inducing local effects at the desired site; and/or maintaining moisture at the desired site, particularly when desired site is a burn.

Still another embodiment provides a method for effectively controlling biological fluid at a desired site in a subject by providing any formulation as disclosed above, the formulation comprising tissue filler and having increased residence time at or near the desired site, such that the formulation resists bodily clearance. In related embodiments,
providing increased residence time further comprises administering a liquid-crystal formulation, thereby lessening migration within and surrounding the desired site so as to increase residence time at the site. In such methods, the tissue filler may be a dermal filler, bone filler, brain filler, synovial filler or muscle filler; the dermal filler may be used for lip augmentation or to adjust the apparent tonicity of skin or attenuate the appearance of wrinkles; the synovial filler may be used as a synovial fluid replacement media; and the tissue filler may be injected via needle access to site.

Yet another embodiment provides a method for effectively controlling biological fluid at a desired site in a subject by providing any formulation as disclosed above wherein effectively controlling biological fluid further comprises forming a protective sealant at the desired site, so as to control flow and exchange of biological fluid and promote sealing of tissue via formation of the protective sealant at the site. In related embodiments, the formulation may provide a healing matrix for tissue re-growth; the tissue may be an epithelial, connective, skeletal, glandular, muscular or nervous tissue site of the subject; and the desired site may be bone tissue, dural tissue, vascular tissue, spinal tissue, or hepatic tissue.

Another particular embodiment provides a method for effectively controlling biological fluid at a desired site in a subject by providing any formulation as disclosed above, wherein effectively controlling biological fluid further comprises retarding the formation of a surgical adhesion, so as to inhibit the formation of undesired scar tissue that may result in the post operative period at or adjacent to a site of surgical intervention. In related embodiments, retarding the formation of a surgical adhesion further comprises administering the formulation such that it coats internal tissue and impedes intimate contact and exchange of bodily fluid containing physiological stimulants for scarring at the site, thereby retarding development of any surgical tissue adhesion. In more particular embodiments, the formulation forms a liquid crystal system, thereby lessening migration within or upon bodily tissues and attenuating clearance of the formulation from the site of application via adhesion, viscosity and cohesion of the formed liquid crystal system; administering may further comprise administering a formulation containing a scar tissue growth inhibitor to further retard the formation of an internal surgical scar tissue adhesion; and the scar tissue growth inhibitor may be an antineoplastic agent, an anti-inflammatory agent, an antibiotic agent or a combination thereof.

In still other related embodiments, the surgical field or site may be treated with the formulation by spray coating, hot-melt coating, direct transfer, manual application or
a combination thereof; the bodily fluid may be any of blood, urine, saliva, serous fluid, synovial fluid, gastric secretions, cerebrospinal fluid, sweat, tears, bile, vitreous humor, chyme, mucous, lymph or wound exudates; and the desired site may be part of the female gynecological region, including the vagina, uterus or cervix.

In any of the disclosed methods for effectively controlling biological fluid at a desired site in a subject, effectively controlling biological fluid may further comprise inducing local effects at the desired site so as to facilitate healing; administering a formulation containing an augmentative agent or medicament, or a combination thereof; the site may be an acute trauma wound or a chronic wound wherein the acute trauma wound may be an abrasion, a burn, a laceration, a puncture or an incision and wherein the chronic wound may be a leg, decubitus, fungal, diabetic, gastric, foot, sacral or indolent ulcer.

In related embodiments, effectively controlling may further comprise delivering the formulation to the large intestinal, rectal or anal cavity by application of an ointment, gel, enema or suppository; filling a tissue void created by trauma, disease or a surgical procedure; administering the formulation in a molten state; administering the formulation by continuous or intermittent positive-pressure administration; and/or administering the formulation to the site by laparoscopy, irrigation, continuous spray, intermittent spray, continuous stream, intermittent stream, lavage, douche, enema, implant, deposition, direct manual administration or by incorporation into a medical article. In embodiments administering the formulation by incorporation into a medical article, the medical article may be a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing or a feminine hygiene article. In related embodiments, administering may further comprise administering by douche, suppository, enema, irrigation, spray, stream, manual application, lavage, or impregnation of a medical article, wherein direct manual administration may be by direct transfer by hand or by an instrument controlled by the hand and wherein indirect manual application may be by utilizing a carrier for or a device impregnated with the formulation, to aid transfer of the formulation to the site, wherein transfer comprises manually wiping, smearing or holding the formulation onto and/or into a tissue site.

In another particular embodiment, there is provided a method for controlling blood loss at a site in a subject, the method comprising administering a thrombin inhibitor formulation as disclosed above at a site of blood loss in a subject, wherein the
formulation facilitates blood coagulation, thereby controlling blood loss at the site. In related embodiments, the blood loss is any of menstrual discharge, post-partum bleeding, reproductive tract bleeding or is any bodily blood or exudate discharge containing water and the blood loss may be internal or external. In such embodiments, administering may further comprise filling a tissue void created by trauma, disease or a surgical procedure; administering by continuous or intermittent positive-pressure administration; administering the formulation in a molten state; or administering to the site by laparoscopy, irrigation, continuous spray, intermittent spray, continuous stream, intermittent stream, lavage, douche, enema, implant, deposition, direct manual application or by incorporation into a medical article. In particular related embodiments, the medical article may be any of a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing or a feminine hygiene article.

Still other particular embodiments provide a method for administering any therapeutic formulation as described above, the method comprising administering the formulation directly to a venous or arterial tissue at a vascular access site in a subject; administering the formulation so as to contact tissue adjacent to a vascular access site in a subject; administering by back-filling an access tract with the formulation from the vascular access site to the epidermis; delivering the formulation to superficial tissue of a venous or arterial access site; and/or utilizing an implant article for administering which has been impregnated with the formulation. In such embodiments, the article may comprise collagen, gelatin, chitosan, chitin, poly(lactic-co-glycolide) (PLGA), poly n-acetylglucosamine or a combination thereof; and administering may further comprise application of the therapeutic formulation during or immediately upon withdrawal of a needle, sheath or access catheter from the access site.

Another particular embodiment provides a method for administering any therapeutic formulation as described above to a desired tissue site in a subject, the method comprising administering the formulation to the desired tissue site to effect tissue sealing, wherein the tissue is selected from the group consisting of epithelial, connective, skeletal, glandular, muscular and neural tissue. In related embodiments, administering may further comprise administering to neural tissue to inhibit progression of paralysis, wherein the formulation comprises cerebrospinal fluid as a solvent, and wherein the cerebrospinal fluid is obtained from the subject. Other related embodiments may further comprise
administering the formulation to a bone tissue site to seal an opening, thereby inhibiting loss of bodily fluid and providing a protective barrier at the opening, wherein the formulation comprises whole blood, platelets, platelet-rich plasma, or plasma as a solvent, wherein the whole blood or platelets, platelet-rich plasma, or plasma is obtained from the subject, and wherein administering further comprises promoting bone re-growth.

In more particular related embodiments, there is provided a method for administering any therapeutic formulation as described above to a desired tissue site in a subject to effect tissue sealing, wherein effecting tissue sealing may further comprise filling a tissue void created by trauma, disease or a surgical procedure; administering may further comprise continuous or intermittent positive-pressure administration; administering the formulation in a molten state; and/or administering to the site by laparoscopy, irrigation, continuous spray, intermittent spray, continuous stream, intermittent stream, lavage, douche, enema, implant, deposition, direct manual applications or by incorporation into a medical article. In such embodiments, the medical article may be any of a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing or a feminine hygiene article.

Still another particular embodiment provides a method for facilitating effective closure of a vascular wound or incision site at a desired site in a subject, the method comprising administering, optionally by positive pressure, an effective amount of a biocompatible biodegradable therapeutic formulation at the vascular wound site or incision site, the formulation comprising about 25% to 100% by weight liquid-crystal forming compound and about 0% to about 75% by weight solvent, wherein the formulation effects hemostasis by physically staunching blood flow, absorbs fluid, and induces local effects at the site within about 10 minutes or less of administration at the site, thereby facilitating effective closure of the vascular wound or incision. In related particular embodiments, the formulation physically staunches blood flow, absorbs fluids, and induces local effects within about 5 minutes or less, more particularly within about 1 minute or less, and still more particularly within about 30 seconds or less.

Yet another particular embodiment provides a method for delivering any formulation as described above to a desired site in a subject, the method comprising delivering the formulation to the desired site by injection, more particularly,
administering the formulation by injection directly within the circulatory system of the
subject, still more particularly injecting via an access device such as a wire guided
catheter, and still more particularly injecting and thereby delivering the formulation for
embolization therapy. In such embodiments, the embolization therapy is treatment of
tumors, or treatment of bleeding.

Another particular embodiment provides a method for inhibiting tissue adhesion
to a medical article, the method comprising coating said medical article with any
formation as described above, thereby inhibiting tissue adhesion to said article and
reducing pain and trauma upon application and subsequent removal of the medical article.

In particular related embodiments, the medical article is a wound dressing, a burn
dressing, fibrotic packing, an adhesive bandage, a hemostatic article for nose-bleeds, an
implantable medical article or medical hardware intended for a human or veterinary
subject.

Still another particular embodiment provides a method for sterilizing any
formulation described above or device containing such formulation, the method
comprising sterile filtering, distillation, thermally exposing, exposing to ionizing
radiation, aseptically processing, heating with steam under pressure, heating with
pressure, or exposing to a gas the formulation or device containing the formulation prior
to use.

Another particular embodiment provides a hemostatic emergency kit for effecting
hemostasis at a site of bleeding in a subject within about 15 minutes or less, the kit
comprising any sterile formulation as described above, and means for applying the
formulation to the site of bleeding. In a more particular related embodiment, the means
for applying the formulation is any of a positive pressure irrigation device, a swab, a
spray applicator, a syringe, an eye dropper, a wound dressing, an adhesive bandage, a
squeeze bulb, a pipette, an enema, a suppository, a sealed container for direct application
to the site of bleeding after unsealing, or any other suitable means for applying said
formulation.

In other related embodiments, kits may be prepared for other methods of
treatment, such as methods for controlling bodily fluid, promoting healing, treating a
burn, dressing a wound, sealing tissue, as disclosed above, said kits providing appropriate
sterile formulations and means for applying such formulations. Related embodiments
may further comprise wound dressing articles, such as bandages, gauze, plugs, sutures,
cleaning materials, all treated with or containing sterile formulations for the required
treatment, the kits being assembled in easy to use containers.

Another particular embodiment provides a method for effectively mimicking soft bodily tissues at a desired site in a subject, the method comprising administering an effective amount of a cosmetic formulation as disclosed above internally at the desired site. In related embodiments, the formulation is any of a liquid, a gel or a semi-solid; the formulation may be adapted for use as a fill media for a cosmetic and reconstructive implant device; the formulation may form a cubic phase after filling the device; the formulation may form a cubic phase prior to filling the device. In other related embodiments, the implant device is a breast implant, a tissue void implant, a buttocks implant, a facial implant or a pectoris implant; the formulation fill media may be increased, decreased or exchanged via an access site to the implant when the implant is positioned just under the skin of a subject; the implant device may be constructed of a plurality of compartments to hold media wherein the compartments allow media movement between compartments and wherein compartments are connected by an opening, the size of which affects rate of media movement between compartments; the implant device is constructed of a plurality of compartments to hold media wherein the compartments do not allow media movement between compartments; or the plurality of compartments have a wedge shape, each compartment expanding from a center point where the compartments meet centrally, as in a pie-graph.

Brief Description of the Drawings

The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

Fig. 1A is a photograph of showing three physical states of a hemostatic composition in accordance with the present invention, wherein the physical state is a liquid, a more viscous liquid or a firm semi-solid, respectively, from left to right.

Figs. 2A, 2B and 2C show a series of photographs representing a hemostatic composition in accordance with the present invention as a low-viscosity liquid that can be sprayed, a viscous gel that can be extruded from a syringe, or a firm semi-solid, respectively, from left to right.

Figs 3A and 3B show a prior art hemostatic agent being applied to a rat tail amputation site (A) and failure to control bleeding (B).
Figs. 4A and 4B show a hemostatic agent according to the present invention being applied to a rat tail amputation site resulting in immediate post-irrigation hemostasis (A) and total control of bleeding (B).

Figs. 5A and 5B show application of a hemostatic agent according to the present invention to a rat saphenous vein laceration (A) followed by post-irrigation hemostasis and control of bleeding (B).

Figs. 6A and 6B show application by pulse pressure stream of a hemostatic agent according to the present invention seconds after an exsanguinating injury (on 50% and 25% excision of rat liver lobes) to a swine liver lobe (A) followed by immediate post-irrigation hemostasis and total control of bleeding.

Figs. 7A and 7B show application of a hemostatic agent using a non-optimal pouring technique according to the present invention seconds after a 10-minute exsanguinating injury (2 cm incision) to a swine liver (A) followed by immediate post-irrigation hemostasis and control of bleeding, despite the poor technique application (B).

Figs. 8A and 8B show pulse pressure stream application of a hemostatic agent according to the present invention seconds after an exsanguinating injury to a swine liver lobe (A), compared to application of a hemostatic agent according to the present invention seconds after an exsanguinating injury to a swine liver lobe using non-optimal pouring (B).

Figs. 9A and 9B show application of a hemostatic agent using a positive pulse-pressure stream technique according to the present invention at a 5-minute exsanguinating injury (3 cm incision) to a swine liver lobe (A) followed by post-irrigation hemostasis, hemorrhage control using gauze treated with a hemostatic formulation according to the present invention, and clean immediate control of bleeding (B).

Figs. 10A through E show application of a hemostatic agent according to the present invention applied to a dog bite on a human thumb (A) followed by post-irrigation hemostasis and control of bleeding (B), continued hemostasis after 12 hrs (C) and minimal tissue disfigurement and scarring at site of injury (D and E).

Figs. 11A through D show Scanning Electron Microscope (SEM) images at 2 seconds (A), 1 minute (B), 5 minutes (C) and 10 minutes (D) after application of a hemostatic agent according to the present invention to a site of bleeding in a subject. As can be seen in (A), platelets have already lined up non-randomly at the site at two seconds, large numbers of platelets have congregated at the site by one minute (B), evidence of tertiary clotting/healing is evident after 5 minutes (C), and continued clotting/healing is evident at 10 minutes after application (D).
Figs. 12A and 12B show a hemostatic formulation according to the present invention comprising glyceryl monooleate and whole blood in the cubic liquid crystalline phase, wherein distorted whole red blood cells can be seen binding to the liquid crystal GMO formulation, as well as an activated platelet and a thin mesh of fibrin at 20 seconds (A) and a close-up of an activated platelet binding to the formulation (B).

**Detailed Description of Specific Embodiments**

*Definitions.* As used in this description and the accompanying claims, the following terms shall have the meanings indicated, unless the context otherwise requires:

"Liquid crystal" as used herein, means any substance that has as one of its physical states a liquid crystalline state. Liquid crystals are typically moderate size organic molecules, but they can also be large (i.e. polymers) which tend to be elongated and oblong-shaped, although a variety of other shapes are possible as well. Because of their elongated shape, under appropriate conditions the molecules can exhibit orientational order, such that all the axes line up in a particular direction. In consequence, the bulk order has profound influences on the physicochemical properties of the material, and the way the material acts. For example, if the direction of the orientation varies in space, the orientation of light (i.e., the polarization) can follow this variation. A well-known application of this phenomenon is the ubiquitous liquid crystal display. Under other conditions the molecules may form a stack of layers along one direction, but remain liquid like (in terms of the absence of translational order) within the layers. As the system changes from one of these phases to another, a variety of physical parameters such as susceptibility and heat capacity, will exhibit "pre-transitional behavior." Based solely on symmetry, this behavior may be related to other physical systems, such as superconductivity, magnetism, or superfluidity; this is the so-called "universality" of these phase transitions. As used herein, "Liquid crystal" also encompasses a large class of highly anisometric molecules (as opposed to ordinary fluids that are isotropic in nature and appear optically, magnetically, electrically, etc. to be the same from any perspective) which result in anisotropic macroscopic behavior, giving rise to unusual, fascinating, and potentially technologically and biologically relevant behavior. Examples of such molecules include polymers, micelles, microemulsions, and materials of biological significance, such as fatty acids, DNA and membranes. As used herein, a disclosed formulation comprising a liquid crystal-forming compound may be a liquid, gel or semisolid, it may form a cubic phase prior to or after application, and the liquid crystal-
forming compound may be hydrophobic and/or amphiphilic. Moreover, the disclosed formulations comprising a liquid crystal-forming compound are preferably biocompatible and/or biodegradable.

"Glycerol monooleate" as used herein, encompasses glycerol monooleate, the two being used interchangeably to represent the same monoester formed between reaction of oleic acid with glycerol. Accordingly, as used herein, "GMO" stands for glycerol monooleate or glycerol monooleate, the two being understood to be one and the same compound. For all formulations, the exact percentage of the liquid crystal-forming compound, particularly glycerol monooleate may vary, depending on the source or supplier of the compound, because all commercially available reagents are not identical, and exact purity levels may vary. For example, one commercial source for GMO lists the purity as not less than 80% glycerol monooleate.

"Positive Pressure" as used herein, means use of force to create pressure greater than would exist by existing atmospheric, gravitational or a biological systemic force alone, whether through a spray or pump device, physical pressure applied manually, directly or indirectly, application of force through manual or automated use of a device. The phrase, used in conjunction with application, as in "Positive Pressure Application" includes application of a formulation as disclosed herein, or device comprising a formulation as disclosed herein, by using a positive pressure irrigation device such as a swab, a spray applicator, a syringe, an eye dropper, a wound dressing, an adhesive bandage, a squeeze bulb, a pipette, an enema, a suppository, a sealed container for direct application to the site of bleeding after unsealing, or any other suitable means for applying the formulation in conjunction with the use of indirect or direct force. For example, in a wound to a vein or artery, where blood loss is exacerbated by pumping from the heart, positive pressure means use of force at the site to apply a disclosed formulation, or device comprised such formulation, to an extent greater than the force from the heart contributing to the blood loss. Other examples of positive pressure include using force generated by spray or pulsed stream application of a disclosed formulation to a desired site, such as a burn, such that the formulation is directed, using a force greater than gravity, to the desired site.

One particular embodiment of the invention provides a method of producing a liquid crystalline formulation capable of being formulated in fluid or non-fluid forms of
varying viscosity wherein the forms may be applied to the site of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids. The method may comprise producing the liquid crystalline formulation by hydrating or solvating a liquid crystalline precursor material, for example, glyceryl monooleate (GMO). The liquid crystalline formulation of glyceryl monooleate is produced by heating the material to melting with the addition of an aqueous solvent system. A particular example of an aqueous solvent system appropriate for addition to the crystalline precursor material is sodium chloride solution (saline solution). An example of a liquid crystalline formulation formulated as a fluid or in a liquid state is a GMO-based formulation comprising about 5% normal saline w/w (final NaCl concentration about 0.045%, by weight), therein producing a formulation with a viscosity in the range of about 80-300 centipoise. An example of a liquid crystalline formulation being formulated as a fluid semisolid would be a GMO-based formulation comprising about 10% saline, therein producing a formulation with a viscosity in the range of about 1000-5000 centipoise. 

Another embodiment of the invention is a method of producing a liquid crystalline formulation capable of being formulated in fluid or non-fluid forms of varying viscosity that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the method comprising: producing the liquid crystalline formulation by hydrating or solvating the liquid crystalline precursor material. An example of a liquid crystalline precursor material is glyceryl monooleate (GMO). The liquid crystalline formulation of glyceryl monooleate is produced by heating the material to melting with the addition of a non-aqueous solvent formulation. An example of a non-aqueous solvent system is isopropyl myristate. An example of a liquid crystalline formulation being formulated as a fluid or liquid state would be a GMO-based formulation containing about 10% isopropyl myristate producing a formulation with a viscosity in about the range of 80-500 centipoise. 

Another embodiment of the invention is a method of producing a liquid crystalline formulation capable of being formulated in fluid or non-fluid forms of varying viscosity that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the method comprising: producing the liquid crystalline formulation by hydrating or solvating the liquid crystalline precursor material. An example of a liquid crystalline precursor material is glyceryl monooleate (GMO). The liquid crystalline formulation of glyceryl monooleate is produced by heating the material to melting with the addition of a non-aqueous solvent formulation. An example of a non-aqueous solvent system is isopropyl myristate. An example of a liquid crystalline formulation being formulated as a fluid or liquid state would be a GMO-based formulation containing about 10% isopropyl myristate producing a formulation with a viscosity in about the range of 80-500 centipoise.
slow or stop the loss of blood or bodily fluids, the method comprising: producing the liquid crystalline formulation by hydrating or solvating the liquid crystalline precursor material. An example of a liquid crystalline precursor material is glyceryl monooleate (GMO). The liquid crystalline formulation of glyceryl monooleate is produced by heating the material to melting with the addition of a non-aqueous, semi-polar solvent system. An example of a non-aqueous, semipolar solvent system is Polyethylene Glycol 200. An example of a liquid crystalline formulation being formulated as a fluid or liquid state would be a GMO-based formulation containing about 10% Propylene Glycol producing a formulation with a viscosity in about the range of 80-500 centipoise.

Another embodiment of the invention is a method of producing a liquid crystalline formulation capable of being formulated in fluid or non-fluid forms of varying viscosity that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the method comprising: producing the liquid crystalline formulation by hydrating or solvating the liquid crystalline precursor material. An example of a liquid crystalline precursor material is glyceryl monooleate (GMO). The liquid crystalline formulation of glyceryl monooleate is produced by heating the material to melting with the addition of a mixture of aqueous and non-aqueous solvent system. An example of a liquid crystalline formulation being formulated as a fluid or liquid state would be a GMO-based formulation containing about 5% normal saline and about 5% ethanol producing a formulation with a viscosity in about the range of 80-500 centipoise.

(Method of producing LCS containing augmentative/therapeutic agent)

Another embodiment provides a pharmaceutical formulation comprising a liquid-crystal forming compound and an augmentative or therapeutic agent that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids. More particularly, the formulation comprises a solvated or hydrated liquid crystalline formulation with a therapeutic agent or augmentative agent dissolved, suspended or dispersed in an aqueous solvent system prior to production of the liquid crystalline formulation. An example of an aqueous solvent system is purified water. An example of an augmentative or therapeutic agent is a soluble calcium salt such as calcium gluconate or calcium chloride.

Another embodiment provides a method of producing a liquid crystalline formulation containing augmentative/therapeutic agents that may be applied to the sight
of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the formulation comprising a solvated or hydrated liquid crystalline formulation with a therapeutic agent or agents suspended or dispersed in an aqueous solvent system prior to production of the liquid crystalline formulation. An example of an aqueous solvent system is purified water. An example of a therapeutic agent is colloidal silicon dioxide.

Another embodiment provides a method of producing a liquid crystalline formulation containing therapeutic agents that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the formulation comprising a solvated or hydrated liquid crystalline formulation with a therapeutic agent or agents dissolved or dispersed in a non-aqueous solvent system prior to production of the liquid crystalline formulation. An example of a non-aqueous solvent system is ethanol. An example of a therapeutic agent is benzocaine.

Another embodiment provides a method of producing a liquid crystalline formulation containing therapeutic agents that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the formulation comprising a solvated or hydrated liquid crystalline formulation with a therapeutic agent or agents suspended, dissolved or dispersed in a non-aqueous solvent system prior to production of the liquid crystalline formulation. An example of a non-aqueous solvent system is cottonseed oil. An example of a therapeutic agent is aluminum potassium sulfate.

Another embodiment provides a method of producing a liquid crystalline formulation containing augmentative/therapeutic agents that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the formulation comprising a solvated or hydrated liquid crystalline formulation with a augmentative/therapeutic agent or agents dissolved or dispersed in a liquid crystalline precursor material prior to production of the liquid crystalline formulation. An example of a augmentative/therapeutic agent is phosphatidylycerine.

Another embodiment provides a method of producing a liquid crystalline formulation containing augmentative/therapeutic agents that may be applied to the sight of injury or tissue disruption in humans or animals to slow or stop the loss of blood or bodily fluids, the formulation comprising a solvated or hydrated liquid crystalline formulation with a augmentative/therapeutic agent or agents suspended or dispersed in a liquid crystalline
precursor material prior to production of the liquid crystalline formulation. An example of a augmentative/therapeutic agent is collagen.

*Method of application/delivery of LCS*

Another embodiment of the invention provides an improved method of delivery to a sight of injury or tissue disruption reducing the possibility of secondary contamination. The improved method of delivery comprising: gravity directed stream or flow of the formulation by means of the primary packaging container. (Terminally sterile)

Another embodiment of the invention provides an improved method of delivery to a sight of injury or tissue disruption reducing the possibility of secondary contamination. The improved method of delivery comprising: directed pressurized spray or stream of the formulation by means of mechanical pressurization as in a plunger or piston type system.

Another embodiment of the invention provides an improved method of delivery to a sight of injury or tissue disruption reducing the possibility of secondary contamination. The improved method of delivery comprising: directed pressurized spray or stream of the formulation by means of gaseous propellants as in an aerosol type system.

*Method of application/delivery of LCS within or upon secondary medical structures*

Another embodiment of the invention provides a method of delivery to a sight of injury or tissue disruption. The method of delivery comprising: delivery of the formulation through conveyance within or upon a medical structure such as a surgical gauze.

Another embodiment of the invention provides a method of delivery to a sight of injury or tissue disruption. The method of delivery comprising: delivery of the formulation through conveyance within or upon a medical structure such as a cotton swab device.

Another embodiment of the invention provides a method of delivery to a sight of injury or tissue disruption. The method of delivery comprising: delivery of the
formulation through conveyance within or upon a medical structure such as a primary occlusive or non-occlusive bandage.

Another embodiment of the invention provides a method of delivery to the tissues surrounding the site of venous or arterial access. The method of delivery comprising: delivery of the formulation by direct injection or instillation into the access tract upon withdrawal of a needle or access catheter.

Another embodiment of the invention provides a method of delivery to the tissues surrounding the site of venous or arterial access. The method of delivery comprising: delivery of the formulation by injection or instillation through a multiple lumen, balloon catheter system used to back-fill the access tract. The catheter system is withdrawn following placement of the invention.

Another embodiment of the invention provides a method of delivery to the superficial tissues of a venous or arterial access site. The method of delivery comprising: delivery of the formulation by direct application to the superficial access tract during or immediately upon withdrawal of a needle or access catheter. The invention may be placed on the sight alone or in combination with an occlusive or non-occlusive dressing or pressure dressing.

Another embodiment of the invention provides a method of delivery to the circulatory system for embolization therapy. The method of delivery comprising: delivery of the formulation by injection through an intravenous or intra-arterial access method such as a wire-guided catheter.

Another embodiment of the invention provides a method of delivery to the feminine reproductive tract. The method of delivery comprising: delivery of the formulation through conveyance within or upon catamenial products within or upon the feminine reproductive tract such as a tampon or feminine napkin or pad.

Another embodiment of the invention provides a method of delivery to the feminine reproductive tract. The method of delivery comprising: delivery of the formulation through conveyance in the form of a douche.
Another embodiment of the invention provides a method of delivery to the feminine reproductive tract. The method of delivery comprising: delivery of the formulation through conveyance in the form of a suppository or ovule.

(METHOD OF APPLICATION/Delivery of LCS - Lower GI - Rectal)

Another embodiment of the invention provides a method of delivery to the large intestine, rectal and anal structures. The method of delivery comprising: delivery of the formulation through conveyance in the form of an enema.

Another embodiment of the invention provides a method of delivery to the large intestine, rectal and anal structures. The method of delivery comprising: delivery of the formulation through conveyance in the form of a suppository.

(LUBRICANT)

Another embodiment of the invention provides a method of persistent lubrication to assist in the placement or removal a device or structure within the body. The method comprising: application of the formulation within or upon a device or structure such as a surgical epistaxis gauze or nasal packing. The liquid crystalline formulation provides a physical, insoluble barrier between the tissue and the device or structure that will easily shear and lubricate the surfaces for insertion or removal from the site of application.

(COSMETIC SURGERY)

Another embodiment of the invention provides a method of utility for direct cosmetic augmentation of tissues. The method comprising: injection of the formulation into tissues of the body to augment the volume of the tissues to increase the aesthetic features.

Another embodiment of the invention provides a method of utility in implantable cosmetic augmentation devices such as breast and gluteal implants. The method comprising: producing the formulation having the consistency of the desired adipose or muscle tissue and subsequent incorporation into a polymeric or elastomeric envelope for implantation.
(Biohardware)

Another embodiment of the invention provides a method of application to implantable prosthetic hardware to reduce or eliminate the formation of bacterial biofilm infections. The method comprising: application of the formulation within or upon a hardware device or structure by a method of spray coating, hot-melt coating or dip coating prior to or at the time of implantation. The liquid crystalline formulation provides a physical, insoluble barrier that resists the adhesion or deposition of bacteria capable of producing biofilm infections.

(Wound Healing)

Another embodiment of the invention provides a method of application to chronic wounds of soft tissues such as decubitus ulcers. The method comprising: application of the formulation to the wound bed following cleaning or debridement. The liquid crystalline formulation provides a physical, insoluble barrier that resists contamination as well as maintains an advantageous moisture balance beneath the barrier.

(Adhesions)

Another embodiment of the invention provides a method to reduce or eliminate the formation of surgical adhesions. The method comprises applying the formulation near or upon the site of a surgical manipulation. The liquid crystalline formulation provides a physical, insoluble barrier between the manipulated tissues reducing the propensity for hypertrophic scarring leading to tissue adhesion.

Example 1

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified Water, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>

Purified water, USP was heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The purified water was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-500 centipoise.
The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>

Normal Saline for Injection, USP, was heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The Normal Saline was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-500 centipoise.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 3

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol, 190 proof</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>
Ethanol 95%, was heated to approximately 40°C in a closed container. Glyceryl Monooleate (GMO) was heated to melting. The ethanol was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-500 centipoise.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 4

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol, 190 proof</td>
<td>5%</td>
</tr>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>90%</td>
</tr>
</tbody>
</table>

Ethanol and normal saline was mixed thoroughly and heated to approximately 40°C in a closed container. Glyceryl Monooleate (GMO) was heated to melting. The ethanol/normal saline mixture was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-500 centipoise.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.
Example 5

Propylene Glycol, USP 5%
Glyceryl monooleate 95%

Propylene Glycol, USP, was heated to approximately 40 ºC. Glyceryl Monooleate (GMO) was heated to melting. The propylene glycol was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a clear liquid formulation with a viscosity in the approximate range of 80-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 6

Cottonseed Oil, NF 20%
Glyceryl monooleate 80%

Cottonseed Oil, NF, was heated to approximately 40 ºC. Glyceryl Monooleate (GMO) was heated to melting. The cottonseed oil was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a clear liquid formulation with a viscosity in the approximate range of 80-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or
internal wounds, and affected tissue. The formulation may also be used in wound
dressing articles for treating burns of varying degree, to protect the burn surface from
exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and
protect the burn surface from abrasion and new injury/loss of tissue upon change of
dressing. The use of the nonpolar solvent in the present example offered the ability to
alter the rate of conversion to the final liquid crystalline state as well as the character of
the system. In this instance the rate of conversion was slowed to a process that required
2-5 minutes for completion with a reduction in the viscosity of the terminal state.

Example 7

Phosphatidylserine 20% powder  10%
Normal Saline for Injection, USP  5%
Glyceryl monooleate  85%

Phosphatidylserine 20% (PS) powder was dispersed in and hydrated with Normal Saline
for Injection, USP. Glyceryl Monooleate (GMO) was heated to melting. The PS mixture
was combined with GMO and mixed well. The resulting mixture produced a brownish-
yellow gel formulation with a viscosity in the approximate range of 800-2000 centipoise.

The present example possessed characteristics making it operable as a hemostatic
agent in formulations for delivery by means of lavage or irrigation, as well as by
pressurized methods of delivery, to superficial or internal wounds and affected tissue in
instances where precision of application and reduction in potential migration of the
system in the field or to surrounding tissues is desired. The addition of
phosphatidylserine serves an adjunctive role as a potential mediator in the normal
coagulation cascade.

Example 8

Phosphatidylserine 20% powder  10%
Normal Saline for Injection, USP  5%
Glyceryl monooleate  85%

Glyceryl Monooleate (GMO) was heated to melting. Phosphatidylserine 20% (PS)
powder was dispersed in the molten GMO. The molten mixture was then hydrated with
Normal Saline for Injection, USP, with mixing. The PS mixture was combined with
GMO and mixed well. The resulting mixture produced a brownish-yellow liquid formulation with a viscosity in the approximate range of 60-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue. The addition of phosphatidylserine serves an adjunctive role as a potential mediator in the normal coagulation cascade.

Example 9

Ampicillin 250 mg Powder for Injection
Glyceryl monooleate qs 1ml

Glyceryl Monooleate (GMO) was heated to melting. Ampicillin 250 mg powder for reconstitution was dispersed in the molten GMO. The resulting mixture produced a high viscosity adhesive, elastic mass.

The present example produced an adhesive elastic formulation operable as a therapeutic dressing system for insertion into and adherence upon wound beds as produced by venous stasis and diabetic foot ulcers. The formulation facilitates healing and may be used to prevent or treat secondary bacterial infections that often accompany these conditions. The formulation may also be used in wound dressing articles for treating burns of varying degree, to control infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 10

Potassium Chloride Solution 1 meq/mL 10%
Glyceryl monooleate 90%

Concentrated potassium chloride (KCl) 2 meq/ml was diluted to a concentration of 1 meq/ml using Water for Injection, USP. This dilution was heated to approximately 40º C. Glyceryl Monooleate (GMO) was heated to melting. The KCl solution was combined with GMO and mixed well. The resulting mixture produced a clear solid formulation with a viscosity in the approximate range in excess of 1.2 million centipoise.
Example 11

Potassium Chloride Solution 1 meq/mL 5%
Glyceryl monooleate 95%

Potassium Chloride (KCl) 2 meq/ml was diluted to a concentration of 1 meq/ml using Water for Injection, USP. This dilution was heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The KCl solution was combined with GMO and mixed well. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue.

Example 12

Cholesterol, USP 10%
Normal Saline for Injection, USP 5%
Glyceryl monooleate 85%

Glyceryl Monooleate (GMO) was heated to melting. Cholesterol, USP powder was dispersed in the molten GMO. The molten mixture was then hydrated with Normal Saline for Injection, USP with mixing. The resulting mixture produced a white liquid formulation with a viscosity in the approximate range of 60-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent or as a wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue. The addition of cholesterol serves to slow the rate of conversion to as well as the consistency of the terminal phase.

Example 13

Crosopovidone, NF 10%
Normal Saline for Injection, USP 5%
Glyceryl monooleate 85%
Glyceryl Monooleate (GMO) was heated to melting. Crospovidone, NF powder was dispersed in the molten GMO. The molten mixture was then hydrated with Normal Saline for Injection, USP with mixing. The resulting mixture produced a firm, white gel formulation with a viscosity in the approximate range of 10,000-30,000 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue, in instances where precision of application and reduction in potential migration of the system in the field or to surrounding tissues is desired. The addition of crospovidone serves an adjunctive role as a swelling agent that is able to absorb blood or bodily fluids and subsequently swell in a controllable fashion to further apply secondary physical pressure to the treated area.

Example 14

Crospovidone, NF 10%
Normal Saline for Injection, USP 5%
Glyceryl monooleate 85%

Glyceryl Monooleate (GMO) was heated to melting. Povidine K29/32, NF powder was dispersed in the molten GMO. The molten mixture was then hydrated with Normal Saline for Injection, USP with mixing. The resulting mixture produced a thick, opaque, silky gel formulation with a viscosity in the approximate range of 2000-5000 centipoise.

The present example possessed characteristics making it operable as a hemostatic or therapeutic wound care agent in formulations for delivery to superficial or internal wounds and affected tissue by means of lavage or irrigation, as well as by pressurized methods of delivery, in instances where precision of application and reduction in potential migration of the agent in the field or to surrounding tissues is desired. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing. The addition of crospovidone serves an adjunctive role as an agent to increase the tissue adhesion.
Example 15

Pemulen® TR2 1%
Normal Saline for Injection, USP 5%
Glyceryl monooleate 85%

Glyceryl Monooleate (GMO) was heated to melting. Pemulen® TR2, NF powder was dispersed in the molten GMO. The molten mixture was then hydrated with Normal Saline for Injection, USP with mixing. The resulting mixture produced an adhesive, elastic gel formulation with a viscosity in the approximate range of 100,000-300,000 centipoise. It is understood that other methacrylic acid copolymers and derivatives thereof may be interchanged for Pemulen® TR2 in the present example. The present example possessed characteristics making it operable as a hemostatic or therapeutic wound care agent in formulations for delivery to superficial or internal wounds and affected tissue by means of lavage or irrigation, as well as by pressurized methods of delivery, in instances where precision of application and reduction in potential migration of the agent in the field or to surrounding tissues is desired.

Example 16

Polyethylene Glycol (PEG) 400, NF 10%
Polyethylene Glycol (PEG 200, NF 5%
Glyceryl monooleate 85%

PEG 400, NF and PEG 200, NF were mixed and heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The PEG mixture was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a clear liquid formulation with a viscosity in the approximate range of 80-200 centipoise. In the present embodiment, other MW PEGs may be useful as well, and interchanged with those described above to produce alternative formulations having similar properties making such formulations operable as hemostatic agents.

The present example possessed characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or
internal wounds, and affected tissue. The formulation may also be used in wound
dressing articles for treating burns of varying degree, to protect the burn surface from
exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and
protect the burn surface from abrasion and new injury/loss of tissue upon change of
dressing.

Example 17

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropyl Myristate, NF</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>

Isopropyl Myristate, NF, (IPM) was heated to approximately 40°C. Glyceryl Monooleate
(GMO) was heated to melting. The IPM was combined with GMO. The resulting system
was well mixed and allowed to return to ambient temperature undisturbed. The resulting
mixture produced a hazy gel formulation with a viscosity in the approximate range of
800-3000 centipoise.

The present example possessed characteristics making it operable as a hemostatic
agent in formulations for delivery by means of lavage or irrigation, as well as by
pressurized methods of delivery, to superficial or internal wounds and affected tissue, in
instances where precision of application and reduction in potential migration of the
system in the field or to surrounding tissues is desired.

Example 18

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Gluconate 10% Solution</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>

Calcium Gluconate solution was heated to approximately 40°C. Glyceryl Monooleate
(GMO) was heated to melting. The Calcium Gluconate was combined with GMO. The
resulting system was well mixed and allowed to return to ambient temperature
undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in
the approximate range of 80-200 centipoise.

The present example possessed characteristics making it operable as a hemostatic
agent in formulations for delivery by means of lavage or irrigation, as well as by
pressurized methods of delivery, to superficial or internal wounds and affected tissue. The addition of calcium ions served an adjunctive role as a physiologic mediator to supplement the normal coagulation cascade.

Example 19

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hyaluronate</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>92.5%</td>
<td></td>
</tr>
</tbody>
</table>

The Sodium Hyaluronate was dissolved in the Normal Saline and heated to approximately 35°C. Glyceryl Monooleate (GMO) was heated to melting. The Sodium Hyaluronate solution was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 1000-3000 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue in instances where precision of application and reduction in potential migration of the system in the field or to surrounding tissues is desired. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing. The addition of hyaluronate serves as a adjuvant to assist in the physiologic process of healing.

Example 20

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hyaluronate</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>92.5%</td>
<td></td>
</tr>
</tbody>
</table>

Glyceryl Monooleate (GMO) was heated to melting. The Sodium Hyaluronate was dispersed with agitation in the GMO. The Normal Saline solution was combined with GMO mixture. The resulting system was well mixed and allowed to return to ambient
temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 1000-3000 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue, in instances where precision of application and reduction in potential migration of the system in the field or to surrounding tissues is desired. The formulation may also be used in wound dressing articles for treating burns of varying degree, to protect the burn surface from exposure to microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn surface from abrasion and new injury/loss of tissue upon change of dressing. The addition of hyaluronate serves as a adjuvant to assist in the physiologic process of healing.

Example 21

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenated Lecithin</td>
<td>5%</td>
</tr>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>90%</td>
</tr>
</tbody>
</table>

The Hydrogenated Lecithin was dispersed in the Normal Saline and heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The Hydrogenated Lecithin solution was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 50,000-100,000 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue, in instances where precision of application and reduction in potential migration of the system in the field or to surrounding tissues is desired. The addition of lecithin serves as a source of physiologic phospholipids intermediates to accentuate the normal host coagulation cascade.

Example 22

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenated Lecithin</td>
<td>5%</td>
</tr>
</tbody>
</table>
Glyceryl Monooleate (GMO) was heated to melting. The Hydrogenated Lecithin was dispersed with agitation in the GMO. The Normal Saline solution was combined with GMO mixture. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 1000-3000 centipoise.

The present example possessed characteristics making it operable as a hemostatic agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds and affected tissue, in instances where precision of application and reduction in potential migration of the system in the field or to surrounding tissues is desired. The addition of lecithin serves as a source of physiologic phospholipids intermediates to accentuate the normal host coagulation cascade.

Example 23

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene Glycol, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>2.5%</td>
</tr>
<tr>
<td>Ethanol, USP</td>
<td>2.5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>90%</td>
</tr>
</tbody>
</table>

Glyceryl Monooleate (GMO) was heated to melting. The Propylene Glycol, Water for Injection and Ethanol were combined and mixed well forming a homogeneous solution. The molten GMO and PG/Water/Ethanol solution were combined with vigorous mixing. The resulting system was allowed to return to ambient temperature undisturbed. The resulting mixture produced a clear to hazy liquid formulation with a viscosity in the approximate range of 80-200 centipoise.

The present formulation is well suited for hemostatic applications by low and high pressure delivery methods. Following manufacture, the formulation was placed into a compressed air aerosol system. The formulation is easily applied at rates ranging from a fine mist to a course spray. This method of delivery allows for convenient and uniform application over a large surface area. The present example possesses characteristics
making it particularly operable as a fluid-controlling, and/or wound healing agent in
formulations for use in direct spray-application to burns, or in wound dressing articles for
treating burns of varying degree, to protect the burn surface from exposure to
microorganisms thereby inhibiting infection, control fluid (oozing) and protect the burn
surface from abrasion and new injury/loss of tissue upon change of dressing.

Example 24

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene Glycol, USP</td>
<td>2.56%</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>5.1%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>92.3%</td>
</tr>
</tbody>
</table>

Glyceryl Monooleate (GMO) was heated to melting. The Propylene Glycol and Water
for Injection were combined and mixed well forming a homogeneous solution. The
molten GMO and PG/Water solution were combined with vigorous mixing. The
resulting system was allowed to return to ambient temperature undisturbed. The resulting
mixture produced a clear to hazy liquid formulation with a viscosity in the approximate
range of 3000-5000 centipoise.

The present formulation is well suited for hemostatic applications by low and high
pressure delivery methods. Following manufacture, the formulation was placed into a
pump-type spray bottle. The formulation is easily applied as a thin stream and a course
spray. This method of delivery allows for convenient and directed application to a
specific tissue surface area. The present example possesses characteristics making it
particularly operable as a fluid-controlling, and/or wound healing agent in formulations
for use in direct spray-application to burns, or in wound dressing articles for treating
burns of varying degree, to protect the burn surface from exposure to microorganisms
thereby inhibiting infection, control fluid (oozing) and protect the burn surface from
abrasion and new injury/loss of tissue upon change of dressing.

Example 25

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>1000 U/g</td>
</tr>
<tr>
<td>Normal Saline for Injection, USP</td>
<td>5%</td>
</tr>
<tr>
<td>Glyceryl monooleate</td>
<td>95%</td>
</tr>
</tbody>
</table>
Normal Saline for Injection, USP, was heated to approximately 40°C. Glyceryl Monooleate (GMO) was heated to melting. The Normal Saline was combined with GMO. The resulting system was well mixed and allowed to return to ambient temperature undisturbed. The thrombin was dispersed in the system with gentle mixing. The resulting mixture produced a hazy liquid formulation with a viscosity in the approximate range of 80-500 centipoise.

The present example possessed a lower viscosity making it operable as a hemostatic agent for delivery by means of lavage or irrigation as well as by pressurized methods of delivery to superficial or internal wounds and affected. The addition of thrombin served an adjunctive role as a physiologic mediator to supplement the normal coagulation cascade.

Example 26A
Plasma, platelets, platelet-rich plasma, or whole blood ~1 to ~ 45% by weight
Glyceryl monooleate ~ 35 to ~99% by weight

Example 26B
Plasma, platelets, platelet-rich plasma, or whole blood ~ 6% by weight
Glyceryl monooleate ~ 94% by weight

Disease-free, drug-free, platelets, platelet-rich plasma, plasma or whole blood, from a patient to be treated, or other acceptable blood donor source, is heated to approximately 40°C. Glyceryl Monooleate (GMO) is heated to melting. The platelets, platelet-rich plasma, plasma or whole blood is then combined with GMO. The resulting system is well mixed and allowed to return to ambient temperature undisturbed. The resulting mixture produces a liquid formulation with a relatively low viscosity. The present example possesses characteristics making it operable as a hemostatic, fluid-controlling, and/or wound healing agent in formulations for delivery by means of lavage or irrigation, as well as by pressurized methods of delivery, to superficial or internal wounds, and affected tissue.
It is envisioned that many if not most of the other formulations specified above in Examples 1-25 may be formulated with donor-grade platelets, platelet-rich plasma, plasma or whole blood, either in place of the described solvent, or in addition to, to create formulations suitable for a variety of hemostatic, fluid-controlling and/or wound-healing purposes.

Example 27 – An absorbent article

In an embodiment there is provided an absorbent layer comprising a liquid-impermeable and moisture vapor-permeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer. The liquid-permeable liner may have a surface that is substantially coextensive with an inner surface of the absorbent layer such that the absorbent layer is located between the liquid-permeable sheet and the outer layer. In addition, the article has a biocompatible biodegradable hydrophobic composition on at least a portion of a surface of the liquid-permeable liner opposite that which is coextensive with the inner surface of the outer layer, wherein the composition comprises from about 50% to 99% by weight liquid-crystal forming compound and about 0% to 50% by weight solvent. When the absorbent device is used as a wound dressing, it can be positioned over the wound with the absorbent layer positioned adjacent to the wound. The device may then be adhered to the skin around the wound, for example, by tape or an adhesive wrap.

In another embodiment, the absorbent layer and the outer layer are not substantially coextensive and the other layer extends beyond at least a portion of the outer perimeter of the absorbent layer to form an extended portion with an upper and lower surface. The lower surface of the extended portion is adjacent to the absorbent layer and at least a portion of the lower surface carries an adhesive layer which can be used to adhere the absorbent article to the skin around a wound. Optionally, this embodiment can further comprise a release liner that is substantially coextensive with the outer layer and adhered to the liquid-permeable liner by the adhesive layer. The release liner would then be removed from the absorbent article prior to application to the wound or site of application of the article. Aqueous media absorbent
dévices frequently will comprise a substantially aqueous media impervious and moisture vapor-permeable outer layer, which may comprise any suitable material, such as polyethylene, polypropylene and polyurethane, with a thickness of about 0.02 mm to help retain fluid within the absorbent material. The outer layer may also comprise a fabric treated with a water repellent material. The outer layer may also be a moisture vapor-permeable adhesive coated film such as is described in US Pat. No. 4,726,989.

The liquid-permeable layer may comprise any material, such as polyester, polyolefin, rayon, and the like, that is substantially porous and permits aqueous media to readily pass therethrough into the underlying absorbent core. Examples of suitable adhesives for the adhesive layer include any of the non-cytotoxic adhesives such as hot-melt spray adhesives including HL-1685-X or HL-1710-X, both of which are commercially available from H. B. Fuller Co., St. Paul, MN. The hot melt adhesive can be applied using spiral spray adhesive systems such as those commercially available from Nordson Corporation, Duluth, GA. Typical adhesive application rates using such systems are about 6 to 10 grams/m². The absorbent layer may comprise fibers combined with commonly used materials to prepare absorbent fabrics or batts, such as wood pulp, cellulose, cotton, rayon, recycled cellulose, shredded cellulose sponge and binders, or shredded keratin. Typically the thickness of the absorbent layer is from about 0.5 to 10 mm. Release liner may be of any polymeric film, paper or foil known in the art to be useful as a release liner. Examples of useful liners include 50 g/m² basis weight SC 501FM40 white Sopal Flexible Packaging available from Day Cedex, France.

Embodiments as described may be bandages, gauze dressings, sponge dressings, or any other absorbent article, with added adhesive or simply the article alone, prepared under sterile conditions and pre-packed in sterile packages for direct usage at a wound or other desired site.

Example 28- Utility as Hemostatic System- Liver Lacerations in a Murine Model

Animal #1- an adult rodent was anesthetized, and then the tail was completely lacerated to produce a robust arterial bleed into 37 °C saline. After two minutes without slowing or cessation, tail was removed from saline and one drop of Formulation #2 was applied. Bleeding stopped, the after ~ 1 min, slow oozing started. This secondary bleeding was completely stopped with the second application.
Animal #2- Tail bleed was induced as in animal #1. After 10 sec in 37 °C saline the robustly bleeding tail was removed from saline and coated with a drop of Formulation #2. This greatly slowed the bleed with some breakthrough from arterial pressure. A second and third drop of Formulation #2 largely, but did not completely control, the bleed. A transverse laparotomy was performed to expose abdominal cavity. In the process of exposing the liver, a bleed occurred from an unintended wound of a major vessel (unidentified). The bleeding from this wound was completely controlled with two drops of Formulation #2.

Animal #3- After establishing a plane of anesthesia and performing transverse laparotomy, the liver was lacerated and allowed to freely bleed onto gaze for 30 seconds, at which time the surface of the laceration and surrounding field was liberally filled with Formulation #2. Bleeding was promptly controlled. Gauze with excess Formulation #2 was removed after one minute, and then a second piece of gauze was placed under the lacerated organ. Minimal blood was deposited from the wound site on the second piece of gauze. A tail bleed was induced as with animal #1, and then completely controlled with two drops of Formulation #2.

Overall conclusions concerning in vivo bleeding experiments- Formulation #2 application successfully controls bleeding that were from capillaries and from small vessels. Major arterial bleeds might require a GMO-impregnated matrix for mechanical strength.

Example 29- Utility as Hemostatic System- Liver Lacerations in a Murine Model
Eight male Sprague-Dawley rats (400-450 g) were anesthetized using ketamine 90 mg/kg and xylazine 10 mg/kg i.p. Following induction of anesthesia, a laparotomy was performed exposing the liver. Dissections of the median lobe were preformed first removing approximately 25% of the lobe mass followed by treatment and a second injury representing a mid-lobe transaction removing approximately 50% of the lobe mass. Application of the formulation provided in Example 2 applied by irrigation and positive pressure spray techniques were able to control the hemorrhage in all animals (n = 8) within 20 seconds (range 10-45 sec) compared with control animals that exsanguinated from the model injuries within 5-10 minutes. The control of hemorrhage was confirmed for a period of 30 minutes and the animals were subsequently euthanized.
Example 30- Utility as Hemostatic System- Saphenous Vein Transection in a Murine Model

Eight male Sprague-Dawley rats (400-450 g) were anesthetized using ketamine 90 mg/kg and xylazine 10 mg/kg i.p. Following induction of anesthesia, the groin was dissected to expose the superficial saphenous vein. The vein was transected by a single perpendicular incision. Application of the formulation provided in Example 2 applied by irrigation and positive pressure spray techniques were able to control the hemorrhage in all animals (n = 8) within 10-45 seconds compared with control animals that exsanguinated from the model injuries within 6-10 minutes. The control of hemorrhage was confirmed for a period of 30 minutes and the animals were subsequently euthanized.

Example 31- Utility as Hemostatic System- Liver Lacerations in a Porcine Model

A single farm pig weighing approximately 30 kg was anesthetized and a transverse laparotomy was performed to expose the liver. The was transected approximately 2.5 cm from the lateral edge to produce a diffuse capillary bed injury which if left untreated represents an exsanguinating injury in approximately 10 minutes. The injury was treated with an irrigation consisting of Rylo MG 19 (Danisco Corp.) 94.5%, dodecane 5% and epinephrine 0.5%. Following a single application of approximately 10 ml, the bleeding was well controlled with minor oozing noted in the injury bed. A subsequent injury was inflicted by removing a portion of the liver lobe approximately 5 cm from the outer margin. This injury resulted in a widespread capillary bed injury with the transection of multiple arterioles that would result in death in 5 minutes or less without supportive treatment and control. An irrigation of the Rylo/dodecane/epinephrine formulation once again maintained adequate control of the capillary bleeding. It was not adequate for the arterial injuries. However a Rylo/dodecane/epinephrine impregnated gauze was applied to the injury. The application maintained adequate control of the capillary and arterial bleeding while in place. Once the gauze was removed, hemostasis was maintained within the capillary bed, however the arterial injuries were not well controlled.

Example 32- Utility as a Hemostatic System- Traumatic Buccal Laceration

A white 4 yr old female subject presented with a traumatic laceration adjacent to the lower right bicuspid secondary to a playground fall. The laceration bled liberally following attempts to apply pressure and cold compress for approximately 5 minutes.
Approximately 1 ml of a formulation disclosed in Example #2 was applied to the injury. Hemostasis was established within 30 seconds without further need for subsequent treatment.

A white 2 yr old female subject presented with a traumatic laceration adjacent to the lower incisors secondary to an inadvertent collision with another child. The laceration bled liberally following attempts to apply pressure and cold compress for approximately 3-5 minutes. Approximately 1 ml of a formulation disclosed in Example #2 was applied to the injury. Hemostasis was established within 30 seconds without further need for subsequent treatment.

Example 33- Utility as a Hemostatic System- Canine Bite

A 38 yr old white male presented with a single puncture wound and laceration approximately 1.5 cm in length on the anterior of the distal phalanx of the left thumb extending to the nail bed that bled freely despite application of direct pressure. Subsequently approximately 0.5 ml of a formulation disclosed in Example #2 was applied to the wound. The initial application formed a gel over the puncture site, however the bleeding was not completely controlled. A subsequent application of the preformed gel was directed into the puncture site with pressure. The second application established hemostasis within 30-45 seconds with only minor oozing of the wound over a period of 2-4 days post injury.

Example 34- Utility as a Hemostatic System- Epistaxis Treatment

A 37 yr old white male with an uneventful past medical history presented with acute, spontaneous epistaxis. Conventional treatment and pressure showed no benefit after 5-10 minutes. The application of approximately 0.25 ml of a formulation disclosed in Example #5 was achieved using a cotton swab. Following application, the nares were pinched for approximately 10 seconds to disperse the material in the nasal cavity. Immediate hemostasis was achieved following the single application without further bleeding.

Example 35- Utility as a Therapeutic/Protective Wound Care System- Canine Foot Pad Ulcerations

A 9 yr old Yorkshire Terrier with a past medical history of diabetes and seizure disorder presented with extensive foot pad ulcerations on all four feet making ambulation
increasingly difficult. The animal’s left front and right rear pad wounds were cleaned and dressed every other day with the formulations disclosed in Example #2 and 26B respectively; the right front and left rear pads were merely cleaned and dressed without treatment. Over a period of 30 days, the ulcerations of the treated pads improved and healed at a significantly more rapid rate than the untreated pads, which improved little if at all. The treated pads demonstrated resolution of the ulcerations within the 30 day period. Furthermore, one untreated ulcer became infected prior to the conclusion of the 30 day window. The other untreated ulcer became infected in the week following the 30 day period. Both treated ulcers healed with no sign of infection.

Example 36- Utility as a Protective Wound Care System- Strep Throat

A 36 yr old white male presented with profound pain in the oropharyngeal area secondary to acute tonsillitis and strep A infection. A formulation consisting of GMO 85% and PEG 400, 10% and PEG 200, 5% was applied using a cotton swab. The system formed a protective gel coating over the inflamed region allowing relief of pain and the consumption of liquids for approximately a 4 hr period.

The described embodiments of the invention are intended to be merely exemplary and numerous variations and modifications will be apparent to those skilled in the art. Different brands for particular ingredients may be used, and other compounds having similar physicochemical properties may be interchanged with those described to yield alternative formulations with desired hemostatic, wound healing, fluid-absorbing, antimicrobial and/or pain-relieving characteristics. All such variations and modifications are intended to be within the scope of the present invention as defined in the appended claims.

Example 37- Utility as a Therapeutic/Protective Wound Care System- Burn

A patient suffering from 2nd and 3rd degree burns is treated with an absorbent article as described in Example 27, wherein a wound dressing article, its surface infused or coated with a wound-healing, fluid-absorbing formulations described in Examples 1-6, 9, 11, 16, 19, 20, and 23 and 24, especially, is applied to the burn area after cleaning. The burn surface is cleaned and dressed every other day, every day, or more frequently, as needed, with a sterile absorbent article containing a formulation as described. As a control, comparable burn areas are treated with other conventional wound dressing articles and burn treatment formulations at the same time, with burn surface cleaning and
dressing procedures identical for both control areas and burn areas treated with formulations described herein. The burn areas treated with the absorbent articles infused or coated with formulations as disclosed herein improve and heal at a significantly more rapid rate than the areas being treated with conventional wound dressing articles and burn treatment formulations. Moreover, there is significantly less tissue removal upon dressing change when using absorbent articles and wound dressing articles as disclosed herein, having formulations described above present in or on the wound dressing article material or surface, and faster healing is seen, with less oozing and infection.

Alternatively, the burn area may be treated with formulations from Examples 1-6, 9, 11, 19, 20, 23 or 24 by spraying, coating, bathing, or otherwise applying the formulation directly on the burn area, with the wound dressing material, such as a conventional gauze or other bandage applied after application of the formulation disclosed herein.

Example 38- Utility as a Protective Wound Care System- Open Sore
A patient suffering from an open sore, such as a bed sore, abrasive burn, caustic burn, or similar wound creating an open, oozing sore, is treated with an absorbent article as described in Example 27, wherein a wound dressing article, its surface infused or coated with a wound-healing, fluid-absorbing formulations described in above Examples is applied to the open sore area after cleaning. The sore surface is cleaned and dressed every other day, every day, or more frequently, as needed, with a sterile absorbent article containing a formulation as described. As a control, comparable sore areas are treated with other conventional wound dressing articles and open sore treatment formulations at the same time, with sore cleaning and dressing procedures identical for both control areas and sore areas treated with formulations described herein. The open sore areas treated with the absorbent articles infused or coated with formulations as disclosed herein improve and heal at a significantly more rapid rate than the areas being treated with conventional wound dressing articles and open sore treatment formulations. Moreover, there is significantly less tissue removal upon dressing change when using absorbent articles and wound dressing articles as disclosed herein, having formulations described above present in or on the wound dressing article material or surface, and faster healing is seen, with less oozing and infection.

Alternatively, the open sore area may be treated with formulations from above-described Examples by spraying, coating, bathing, or otherwise applying the formulation
directly on the open sore area, with the wound dressing material, such as a conventional gauze or other bandage, applied after application of the formulation disclosed herein.

The described embodiments of the invention are intended to be merely exemplary and numerous variations and modifications will be apparent to those skilled in the art. Different brands for particular ingredients may be used, and other compounds having similar physicochemical properties may be interchanged with those described to yield alternative formulations with desired hemostatic, wound healing, fluid-absorbing, antimicrobial and/or pain-relieving characteristics. All such variations and modifications are intended to be within the scope of the present invention as defined in the appended claims.
What is claimed is:

1. A therapeutic formulation adapted for positive-pressure application and effective for controlling biological fluid at a desired site in a subject, the formulation comprising:
   about 25% to about 99% by weight liquid-crystal forming compound; and
   0% to about 75% by weight solvent
wherein the formulation effectively controls biological fluid at the desired site in the subject.

2. A therapeutic formulation according to claim 1, wherein the solvent is selected from the group consisting of a polar solvent, a non-polar solvent, a semi-polar solvent or a combination thereof.

3. A therapeutic formulation according to claim 2, wherein the formulation comprises about 97% liquid-crystal forming compound and about 3% normal saline solution.

4. A therapeutic formulation according to claim 2, wherein the formulation comprises about 65% liquid-crystal forming compound and about 15% normal saline solution.

5. A therapeutic formulation according to claim 2, wherein the formulation comprises about 35% liquid-crystal forming compound and about 65% normal saline solution.

6. A therapeutic formulation according to claim 2, wherein the formulation comprises about 92.5% liquid-crystal forming compound, about 5% normal saline, and about 2.5% sodium hyaluronate.

7. A therapeutic formulation according to claim 2, wherein the formulation comprises about 95% liquid-crystal forming compound and about 5% isopropyl myristate.

8. A therapeutic formulation according to claim 2, wherein the formulation comprises about 95% liquid-crystal forming compound and about 5% 190 proof ethanol.

9. A therapeutic formulation according to claim 2, wherein the formulation comprises about 80% liquid-crystal forming compound and about 20% cottonseed oil.
10. A therapeutic formulation according to claim 2, wherein the formulation comprises platelets, platelet-rich plasma, plasma or whole blood.

11. A therapeutic formulation according to claim 10, wherein the formulation comprises about 97% liquid-crystal forming compound and about 3% whole blood.

12. A therapeutic formulation according to claim 10, wherein the formulation comprises about 80% liquid-crystal forming compound and about 9% whole blood.

13. A therapeutic formulation according to claim 10, wherein the formulation comprises about 65% liquid-crystal forming compound and about 15% whole blood.

14. A therapeutic formulation according to claim 10, wherein the formulation comprises about 35% liquid-crystal forming compound and about 25% whole blood.

15. A therapeutic formulation according to claim 10, wherein the formulation comprises about 97% liquid-crystal forming compound and about 3% blood plasma.

16. A therapeutic formulation according to claim 10, wherein the formulation comprises about 65% liquid-crystal forming compound and about 15% blood plasma.

17. A therapeutic formulation according to claim 10, wherein the formulation comprises about 35% liquid-crystal forming compound and about 25% blood plasma.

18. An absorbent article comprising:

(a) an absorbent layer;

(b) a formulation effective for controlling biological fluid of a subject wherein the formulation comprises from about 25% to 99% by weight liquid-crystal forming compound and about 0% to 75% by weight solvent and is present within or on at least a portion of the article.
19. The absorbent article of claim 18 wherein the absorbent layer further includes an absorbent additive.

20. The absorbent article of claim 18 wherein the absorbent article further comprises a liquid-permeable and moisture vapor-permeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer.

21. The absorbent article of claim 18 wherein the absorbent article further comprises a liquid-impermeable and moisture vapor-impermeable outer layer having an inner surface and an outer surface, the inner surface essentially coextensive with an outer surface of the absorbent layer.

22. The absorbent article of any of claims 18-22 wherein the absorbent article further comprises a liquid-permeable liner, adapted to be non-adherent to a wound, having a surface that is substantially coextensive with an inner surface of the absorbent layer such that the absorbent layer is located between the liquid-permeable liner and the outer layer.

24. The absorbent article of claim 18 wherein the composition effective for controlling biological fluids provides utility as an anti-adherent between the article and bodily tissue to assist in placement or removal of the article from a site of use thereby reducing trauma from application or removal of said article.

25. The absorbent article of claim 18, wherein the biological fluid controlling formulation is applied to the article by spray coating, hot-melt coating, dip coating, direct transfer, manual application or a combination thereof.
26. The absorbent article of claim 18-23, wherein the article is any of a wound dressing, a medical sponge, a hemostatic article, a hemostatic article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing article, or a feminine hygiene product.

27. The absorbent article of claim 18-23 wherein the liquid-crystal forming compound is any of a fatty acid, fatty acid ester, a polyethylene oxide, a glycolipid, a polyester, a polyethylene glycol, or a combination thereof.

28. The absorbent article of claim 27 wherein the fatty acid ester is a monoester, diester, triester or mixture thereof.

29. The absorbent article of claim 28 wherein the monoester is selected from the group consisting of glyceryl monoarachidonate, glycercyl monolaurate, glycercyl monolinoleate, glycercyl monolinolenate, glycercyl monomyristate, glycercyl monopalmitoleate, glycercyl monooleate, and glycercyl monostearate; isopropyl monoarachidonate, isopropyl monolaurate, isopropyl monolinoleate, isopropyl monolinolenate, isopropyl monomyristate, isopropyl monopalmitoleate, isopropyl monooleate, and isopropyl monostearate; methyl monoarachidonate, methyl monolaurate, methyl monolinoleate, methyl monolinolenate, methyl monomyristate, methyl monopalmitoleate, methyl monooleate, and methyl monostearate; and propylene glyceryl monoarachidonate, propylene glyceryl monolaurate, propylene glyceryl monolinoleate, propylene glyceryl monolinolenate, propylene glyceryl monomyristate, propylene glyceryl monopalmitoleate, propylene glyceryl monooleate, and propylene glyceryl monostearate.

30. An infection resistant device, the device treated with an anti-infective formulation comprising about 25% to 99% by weight fatty acid or fatty acid ester, wherein said anti-infective formulation inhibits the formation of pathogen growth on the device, or in adjacent tissues, thereby imparting infection resistance to the device.
31. An infection resistant device according to claim 30, wherein the anti-infective formulation further comprises about 0% to 75% solvent and the fatty acid or fatty acid ester is a liquid-crystal forming compound.

32. An infection resistant device according to claim 31, wherein upon formation of a liquid crystal, the anti-infective formulation thereby lessons migration within or upon bodily tissues and attenuates clearance of the formulation from the site of device placement, or a site adjacent to or near to where the device is placed within a subject.

33. An infection resistant device according to claim 32, wherein the liquid crystal formulation acts as a controlled-release delivery system of degradation products from the formulation, wherein said degradation products provide an additional anti-infective effect.

34. An infection resistant device according to any of claims 33, wherein the device is effective for treatment of an acute or chronic wound.

35. An infection resistant device according to claim 34, wherein the acute wound is selected from the group consisting of:

   an abrasion, burn, laceration, puncture and incision.

36. An infection resistant device according to claim 34, wherein the acute wound is an ulceration selected from the group consisting of a leg, decubitus, fungal, diabetic, gastric, foot, sacral and indolent ulcer.

37. An infection resistant device according to any of claims 32, wherein the device is effective as a filler of a tissue void created by trauma, disease or a surgical procedure.

38. An infection resistant device according to claim 30, wherein the device is treated with the anti-infective formulation by spray coating, hot-melt coating, dip coating or a combination thereof prior to use.
39. An infection resistant device according to any of claims 30 - 38, wherein the device is composed of organic material, inorganic material, or a combination thereof.

40. A device according to claim 39 wherein the device is selected from the group consisting of a catamenial absorption device, a condom, a prophylactic, a medical sponge, a surgical dressing, a wound dressing, an adhesive bandage or a combination thereof.

41. A device according to claim 39 wherein the device is selected from the group consisting of a prosthetic, an implant or a combination thereof.

42. A device according to claim 41 wherein the prosthetic or implant type is selected from the group consisting of a spinal, orthopedic, dental, cardiac, neural, and cosmetic prosthetic or implant type, or a combination thereof.

43. A device according to claim 42 wherein the orthopedic prosthetic or implant is further selected from the group consisting of an artificial joint, fracture repair hardware, artificial cartilage, a plate, a screw, a nail, and a wire, or a combination thereof.

44. A device according to claim 42 wherein the dental prosthetic or implant is further selected from the group consisting of a pacemaker, a defibrillator, a heart valve, and a vascular graft, or a combination thereof.

45. A device according to claim 42 wherein the cardiac prosthetic or implant is further selected from the group consisting of a breast implant, a dermal filler, a tissue void filler, a buttocks implant, and a facial implant, or a combination thereof.

46. A device according to claim 39, wherein the anti-infective formulation comprises about 25% to 99% liquid-crystal forming compound, about 0% to 50% fatty acid and about 0% to 50% solvent, by weight.
48. A device according to claim 47, wherein the anti-infective formulation comprises about 90% liquid-crystal forming compound, about 5% lauric acid and about 5% solvent by weight.

49. A device according to claim 47, wherein the anti-infective formulation comprises about 65% liquid-crystal forming compound, about 10% myristic acid and about 25% solvent, by weight.

50. A device according to claim 47, wherein the anti-infective formulation comprises about 35% liquid-crystal forming compound, about 15% palmitic and about 40% solvent, by weight.

51. A hemostatic formulation effective for controlling bleeding at a desired site in a subject, the composition comprising:
   25% to about 99% by weight liquid-crystal forming compound; and
   0% to about 75% by weight solvent,
wherein the hemostatic formulation is adapted for positive pressure application upon or within tissue, effects hemostasis and induces local effects at the desired site within about 15 minutes or less, thereby controlling bleeding.

52. A hemostatic formulation according to claim 51, wherein hemostasis is effected and local effects induced at the site within about 10 minutes or less of application.

53. A hemostatic formulation according to claim 51, wherein hemostasis is effected and local effects induced at the site within about 5 minutes or less of application.

54. A hemostatic formulation according to claim 51, wherein hemostasis is effected and local effects induced at the site within about 2 minutes or less of application.

55. A hemostatic formulation according to claim 51, wherein hemostasis is effected and local effects induced at the site within about 30 seconds or less of application.

56. A hemostatic formulation according to 51 wherein said solvent may be any of:
an alcohol, polyethylene glycol, propylene glycol, polypropylene glycol, water, isotonic aqueous solution, biological fluid, urine, saliva, serous fluid, synovial fluid, gastric secretions, cerebrospinal fluid, vitreous humor, lymph, wound exudate, cholesterol, a physiologic buffered system or combination thereof.

57. A hemostatic formulation according to 51 wherein said liquid-crystal forming compound may be any of:
   a fatty acid, fatty acid monoester, fatty acid diester, fatty acid triester or combination thereof further comprising at least one unsaturated carbon-carbon bond.

58. A hemostatic formulation according to 57, wherein said liquid crystal forming-agent is a glyceryl monoester, diester, triester, or combination thereof.

59. A hemostatic formulation according to 58, wherein said liquid crystal forming-agent is glyceryl monooleate.

60. A thrombin inhibitor formulation comprised of about 25 to 99% by weight liquid-crystal forming compound and about 0% to 75% by weight solvent, wherein the formulation is adapted for positive pressure application to desired site in a subject.

61. A thrombin inhibitor formulation according to claim 60, wherein the liquid-crystal forming compound is a fatty acid ester.

62. A thrombin inhibitor formulation according to claim 60, wherein the formulation is effective as a filler of a tissue void, such as those created by trauma, disease or a surgical procedure.

63. A thrombin inhibitor formulation according to claim 60, wherein the formulation is also a neuroprotective agent.

64. A cosmetic formulation effective for mimicking soft tissue at a desired site in a subject, the formulation comprising:
   about 25% to 99% by weight liquid-crystal forming compound;
about 0% to about 75% by weight solvent; and
other compounds, as required, to provide viscosities and textures effective for mimicking soft tissue.

65. A cosmetic formulation according to claim 64, wherein the cosmetic formulation further comprises an antioxidant.

66. A cosmetic formulation according to claim 65, wherein the antioxidant is a water soluble or oil soluble antioxidant.

67. A cosmetic formulation according to claim 66, wherein the antioxidant may be any of vitamin C, sodium bisulfate, sodium sulfite, sodium metabisulfite, cysteine hydrochloride, thioglycolic acid, sulfur dioxide, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, vitamin D or any combination thereof.

68. A formulation according to any of claims 1, 51, 60 or 64, further comprising an augmentative agent, medicament or combination thereof.

69. A formulation according to claim 68, wherein the augmentative agent or medicament is any of:
a hemostat; an coagulation augmentative agent; a vasoactive agent; a tissue growth stimulant; a healing promoter; an anti-infective agent, an adhesion enhancer; a swelling agent; a thickening agent; an anesthetic; a solvent; a co-solvent; a thinning agent; a filler; an anti-scarring agent, an anti-inflammatory agent; a physiologically compatible monovalent ion, divalent ion, trivalent ion and salt thereof; a bleaching agent including a teeth whitening agent, a peroxide; a miscellaneous medicament; a controlled-release augmentative material; an embolic augmentative material; or any combination thereof.

70. A formulation according to claim 69, wherein the augmentative agent or medicament is suspended or dissolved in the formulation.

71. A formulation according to claim 69, wherein the formulation further comprises a controlled-release delivery component.
72. A formulation according to claim 71, wherein the controlled-release delivery component is a biodegradable polymer.

73. A formulation according to claim 69, wherein the swelling enhancer is selected from the group consisting of a starch, natural gum, cellullosic polymer, pyrrolidone polymer, polyacrylic acid or combination thereof.

74. A formulation according to any of claims 1, 51, 60, 64 or 68, wherein the formulation is a liquid, gel or semisolid.

75. A formulation according to claim 74, wherein the formulation forms a cubic phase after application.

76. A formulation according to claim 74, wherein the formulation forms a cubic phase prior to application.

77. A formulation according to claim 74, wherein the liquid-crystal forming compound is hydrophobic and/or amphiphilic.

78. A formulation according to claim 74 wherein the formulation is biocompatible and/or biodegradable.

79. A method for effectively controlling biological fluid at a desired site in a subject, the method comprising:

    administering by positive pressure an effective amount of a therapeutic formulation comprising liquid-crystal forming compound at the site for a period of time effective to control biological fluid at the desired site.

80. A method for effectively controlling biological fluid at a desired site in a subject, the method comprising:

    administering an effective amount of a formulation according to any of claims 1 through 10 or 51 through 78 for a period of time effective to control biological fluid at the desired site.
81. A method according to claim 80, wherein the formulation is a liquid, a gel or a semi-solid.

82. The formulation according to claims 81, wherein formulation forms a cubic phase after application to the site.

83. The formulation according to claims 81, wherein formulation forms a cubic phase prior to application to the site.

84. A method according to claim 81, wherein effectively controlling biological fluid further comprises:
   promoting hemostasis at the desired site.

85. A method according to claim 81, wherein effectively controlling biological fluid further comprises:
   promoting coagulation at the desired site.

86. A method according to claim 79 or 80, wherein effectively controlling biological fluid further comprises:
   facilitating healing by inducing local effects at the desired site.
   wherein the desired site is a burn.

88. A method according to claim 81, wherein the formulation further comprises an augmentative agent or medicament or a combinations thereof.

89. A method according to claim 81 or 88, wherein effectively controlling biological fluid further comprises:
   providing a formulation as a tissue filler and having increased residence time at or near the desired site, such that the formulation resists bodily clearance.
90. A method according to claim 89, wherein providing increased residence time further comprises forming and administering a liquid-crystal formulation, thereby lessening migration within and surrounding the desired site so as to increase residence time at the site.

91. A method according to claim 89, wherein the tissue filler is a dermal filler, bone filler, brain filler, synovial filler or muscle filler.

92. A method according to claim 91, wherein the dermal filler is use for lip augmentation.

93. A method according to claim 91, wherein the dermal filler is used to adjust the apparent tonicity of skin or attenuate the appearance of wrinkles.

94. A method according to claim 91, wherein the synovial filler is used as a synovial fluid replacement media.

95. A method according to claim 91, wherein the tissue filler is injected via needle access to site.

96. A method according to claim 81, wherein effectively controlling biological fluid further comprises:

forming a protective sealant at the desired site, so as to control flow and exchange of biological fluids and promote sealing of tissue via formation of the protective sealant barrier at the site.

97. A method according to claim 81, wherein the formulation provides a healing matrix for tissue re-growth.

98. A method according to any of claims 96 or 97, wherein the tissue may be an epithelial, connective, skeletal, glandular, muscular or nervous tissue site of the subject.

100. A method according to claim 98, wherein the desired site may be bone tissue, dural tissue, vascular tissue, spinal tissue, gastric or hepatic tissue.
101. A method according to claim 79 or 80, wherein effectively controlling biological fluid further comprises:

        retarding the formation of a surgical adhesion, so as to inhibit the formation of undesired post operative scar tissue that may result at or adjacent to a site of surgical intervention.

102. A method according to claim 101, wherein retarding the formation of a surgical adhesion further comprises:

        administering the formulation such that it coats internal tissue and impedes intimate contact and exchange of bodily fluid containing physiological stimulants for scarring at the site, thereby retarding development of any surgical tissue adhesion.

103. A method according to claim 102, wherein upon administering, the formulation forms a liquid crystal system, thereby lessening migration within or upon bodily tissues and attenuating clearance of the formulation from the site of application via adhesion, viscosity and cohesion of the formed liquid crystal system.

104. A method according to claim 102 or 103, wherein administering further comprises administering a formulation containing a scar tissue growth inhibitor to further retard the formation of an internal surgical scar tissue adhesion.

105. A method according to claim 104, wherein the scar tissue growth inhibitor is selected from the group consisting of an antineoplastic agent, an anti-inflammatory agent, an antibiotic agent or a combination thereof.

106. A method according to claim 101, wherein the surgical field or site is treated with the formulation by spray coating, hot-melt coating, direct transfer, manual application or a combination thereof.

107. A method according to claim 79 or 80 wherein bodily fluid may be any of: blood, urine, saliva, serous fluid, synovial fluid, gastric secretions, cerebrospinal fluid, sweat, tears, bile, vitreous humor, chyme, mucous, lymph or wound exudates.

108. A method according to claim 79 or 80, wherein the desired site is part of the female
109. A method according to claim 79 or 80, wherein effectively controlling biological fluid further comprises:

inducing local effects at the desired site so as to facilitate healing.

110. A method according to claim 109, wherein effectively controlling biological fluid further comprises:

administering a formulation containing an augmentative agent or medicament, or a combination thereof.

111. A method according to claim 109, wherein the site is an acute trauma wound or a chronic wound.

112. A method according to claim 111, wherein the acute trauma wound is selected from the group consisting of an abrasion, a burn, a laceration, a puncture and an incision.

113. A method according to claim 111, wherein the chronic wound is selected from the group consisting of a leg, decubitus, fungal, diabetic, gastric, foot, sacral and indolent ulcer.

114. A method according to claim 81, wherein effectively controlling further comprises:

delivering the formulation to the large intestinal, rectal or anal cavity by application of an ointment, gel, enema or suppository.

115. A method according to claim 81, wherein effectively controlling biological fluid further comprises:

filling a tissue void created by trauma, disease or a surgical procedure.

116. A method according to any of claims 81, where administering further comprises administering the formulation in a molten state.

117. A method according to any of claims 81, wherein administering further comprises continuous or intermittent positive-pressure administration.
118. A method according to claim 81, wherein administering further comprises:
administering to the site by laparoscopy, irrigation, continuous spray, intermittent
spray, continuous stream, intermittent stream, lavage, douche, enema, suppository,
implant, deposition, direct or indirect manual administration or by incorporation into a
medical article.

119. A method according to claim 118, wherein the medical article may be:
a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound
packing, an internal vascular closure packing, an external vascular closure dressing, a
swellable absorbent article, a fibrotic wound packing or a feminine hygiene article.

120. A method according to claims 79-116, wherein administering further comprises
administering by douche, suppository, enema, irrigation, spray, stream, manual
application, lavage, or impregnation of a medical article.

121. A method according to claim 118, wherein direct manual administration may be by
direct transfer by hand or by an instrument controlled by the hand.

122. A method according to claim 118, wherein indirect manual application may be by
utilizing a carrier for or a device impregnated with the formulation, to aid transfer of the
formulation to the site.

123. A method according to claims 121 or 122, wherein transfer comprises manually
wiping, smearing or holding the formulation onto and/or into a tissue site.

124. A method for controlling blood loss at a site in a subject, the method comprising:
administering the thrombin inhibitor formulation of any of claims 60-63 at a site
of blood loss in a subject,
wherein the formulation facilitates blood coagulation, thereby controlling blood loss at
the site.

125. A method for controlling blood loss according to claim 124, wherein the
formulation further comprises an augmentative agent or medicament or a combinations thereof.

126. A method for controlling blood loss according to claim 124 or 125, wherein the blood loss is any of menstrual discharge, post-partum bleeding, reproductive tract bleeding or is any bodily blood or exudate discharge containing water.

127. A method for controlling blood loss according to claim 126, wherein the blood loss is internal or external.

128. A method according to any of claims 124-125, wherein administering further comprises:

filling a tissue void created by trauma, disease or a surgical procedure.

129. A method according to any of claims 124-128, wherein administering further comprises:

continuous or intermittent positive-pressure administration.

130. A method according to claims 124, where administering further comprises

administering the formulation in a molten state.

131. A method according to claim 124-130, wherein administering further comprises:

administering to the site by laparoscopy, irrigation, continuous spray, intermittent spray, continuous stream, intermittent stream, lavage, douche, enema, implant, deposition, direct or indirect manual application or by incorporation into a medical article.

132. A method according to claim 131, wherein a medical article may be any of:

a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing or a feminine hygiene article.

133. A method for administering the therapeutic formulation according to any of claims
1 through 10 or 51 through 78, the method comprising:
administering the formulation directly to a venous or arterial tissue at a vascular access site in a subject.

5 134. A method for administering a therapeutic formulation according to any of claims 1 through 10 or 51 through 78, the method comprising:
administering the formulation so as to contact tissue adjacent to a vascular access site in a subject.

10 135. A method according to claim 133 or 134, wherein the formulation further comprises an augmentative agent, medicament or a combination thereof.

15 136. A method according to claim 133, wherein administering further comprises back-filling an access tract with the formulation from the vascular access site to the epidermis.

137. A method according to claims 133-137, wherein administering further comprises utilizing an implant article for administering which has been impregnated with the formulation.

138. A method according to claim 137, wherein the article comprises collagen, gelatin, chitosan, chitin, poly(lactic-co-glycolide) (PLGA), poly n-acetylglucosamine or a combination thereof.

139. A method according to any of claims 133-138, wherein administering further comprises application of the therapeutic formulation during or immediately upon withdrawal of a needle, sheath or access catheter from the access site.

140. A method for administering a therapeutic formulation according to any of claims 1 through 10 or 51 through 78 to a desired tissue site in a subject, the method comprising administering the formulation to the desired tissue site to effect tissue sealing, wherein the tissue is selected from the group consisting of epithelial, connective, skeletal,
glandular, muscular and neural tissue.

141. A method according to claim 140, wherein the formulation further comprises an augmentative agent or medicament or a combination thereof.

142. A method according to claim 140 or 141, wherein administering further comprises administering to neural tissue to inhibit progression of paralysis.

143. A method according to claim 142, wherein the formulation comprises cerebrospinal fluid as a solvent.

144. A method according to claim 143, wherein the cerebrospinal fluid is obtained from the subject.

145. A method according to claim 140 or 141, wherein administering further comprises administering the formulation to a bone tissue site to seal a bone opening, thereby inhibiting loss of bodily fluid and providing a protective barrier at the opening.

146. A method according to claim 145, wherein the formulation comprises whole blood, plasma, platelet-rich plasma, or platelets as a solvent.

147. A method according to claim 146, wherein the whole blood or plasma is obtained from the subject.

148. A method according to claim 145 or 146, wherein administering further comprises promoting bone re-growth.

149. A method according to claim 140-141, wherein effecting tissue sealing further comprises:

filling a tissue void created by trauma, disease or a surgical procedure.

150. A method according to claim 140 - 141, wherein administering further comprises: continuous or intermittent positive-pressure administration.
151. A method according to claim 140 - 141, where administering further comprises administering the formulation in a molten state.

152. A method according to claims 140-141, wherein administering further comprises: administering to the site by laparoscopy, irrigation, continuous spray, intermittent spray, continuous stream, intermittent stream, lavage, douche, enema, implant, deposition, direct manual applications or by incorporation into a medical article.

153. A method according to claim 152, wherein the medical article may be any of: a wound dressing, a sponge, an article for the nose, an adhesive bandage, a wound packing, an internal vascular closure packing, an external vascular closure dressing, a swellable absorbent article, a fibrotic wound packing or a feminine hygiene article.

154. A method for facilitating effective closure of a vascular wound or incision site at a desired site in a subject, the method comprising: administering an effective amount of a biocompatible biodegradable therapeutic formulation at the vascular wound site or incision site, the formulation comprising about 25% to 100% by weight liquid-crystal forming compound and about 0% to about 75% by weight solvent, wherein the formulation effects hemostasis by physically staunching blood flow, absorbs fluid, and induces local effects at the site within about 10 minutes or less of administration at the site, thereby facilitating effective closure of the vascular wound or incision.

155. A method for facilitating effective closure according to claim 154, wherein the formulation physically staunches blood flow, absorbs fluids, and induces local effects within about 5 minutes or less.

156. A method for facilitating effective closure according to claim 154, wherein the formulation physically staunches blood flow, absorbs fluids, and induces local effects within about 1 minutes or less.
157. A method for facilitating effective closure according to claim 154, wherein the formulation physically staunches blood flow, absorbs fluids, and induces local effects within about 30 seconds or less.

158. A method for delivering a formulation as claimed in any of claims 1 through 10 or 51 through 78 to a desired site in a subject, the method comprising:

delivering the formulation to the desired site by injection.

159. A method according to claim 158, wherein the formulation further comprises an augmentative agent, a medicament or a combination thereof.

160. A method for administering the formulation according to claims 157-159, the method further comprising administering the formulation by injection directly within the circulatory system of the subject.

162. A method according to any of claims 157-161, wherein injecting further comprises delivering the formulation for embolization therapy.

163. A method according to claim 162, wherein the embolization therapy is treatment of tumors.

164. A method according to any of claims 162, wherein the therapy is treatment of bleeding.

165. A method for inhibiting tissue adhesion to a medical article, the method comprising coating said medical article with a formulation as claimed in any of claims 1 through 10 or 51 through 78, thereby inhibiting tissue adhesion to said article and reducing pain and trauma upon application and subsequent removal of the medical article.

166. A method for inhibiting tissue adhesion according to claim 165, wherein the medical article is a wound dressing, a burn dressing, fibrotic packing, an adhesive
bandage, a hemostatic article for nose-bleeds, an implantable medical article or medical hardware intended for a subject.

167. A method for sterilizing a formulation or device containing said formulation, the formulation as claimed in any of claims 1 through 10 or 51 through 78, the method comprising:
sterile filtering, distilling, thermally exposing, exposing to ionizing radiation, aseptically processing, heating steam under pressure, or exposing to a gas the formulation or device containing the formulation prior to use.

168. A hemostatic emergency kit for effecting hemostasis at a site of bleeding in a subject within about 15 minutes or less, the kit comprising:
a sterile formulation as claimed in any of claims 1 through 10 or 51 through 78;
means for applying the formulation to the site of bleeding.

169. A kit according to claim 168, wherein the means for applying is any of a positive pressure irrigation device, a swab, a spray applicator, a syringe, an eye dropper, a wound dressing, an adhesive bandage, a squeeze bulb, a pipette, an enema, a suppository, a sealed container for direct application to the site of bleeding after unsealing, or any other suitable means for applying said formulation.

170. A method for effectively mimicking soft bodily tissues at a desired site in a subject, the method comprising:
administering an effective amount of a formulation as claimed in any of claims 64-67 internally at the desired site.

171. A method according to claim 170, wherein the formulation is any of a liquid, a gel or a semi-solid.

172. A method according to claim 170, wherein the formulation is adapted for use as a fill media for a cosmetic and/or reconstructive implant device.

173. The formulation according to claims 172, wherein the formulation forms a cubic phase after filling the device.
174. The formulation according to claims 172, wherein the formulation forms a cubic phase prior to filling the device.

175. A method according to claim 172, wherein the implant device is any of a breast implant, a tissue void implant, a buttocks implant, a facial implant or a pectoris implant.

176. A method according to claim 172, wherein the formulation fill media may be increased, decreased or exchanged via an access site to the implant when the implant is positioned just under the skin of a subject.

177. A method according to claim 172, wherein the implant device is constructed of a plurality of compartments to hold media wherein the compartments allow media movement between compartments and wherein compartments are connected by an opening, the size of which affects rate of media movement between compartments.

178. A method according to claim 172, wherein the implant device is constructed of a plurality of compartments to hold media wherein the compartments do not allow media movement between compartments.

179. A method according to claim 177 or 178, wherein the plurality of compartments have a wedge shape, each compartment expanding from a center point where the compartments meet centrally, as in a pie-graph.

180. A method according to claim 154, wherein administering further comprises administering by positive pressure.
Glyceryl Monoooleate (GMO)

- A specific liquid crystalline system
- Water content drives crystallization
- Max water uptake of ~40%
- GMO is biodegradable
- Prior experience with insulin

Properties based on H₂O Content
- Lamellar Phase-viscous liquid
- "Vegetable oil"
- Some swelling
- Cubic (Q) - highly viscous gels
- "Sticky Gummy Bear"
- No swelling
Increasing water / blood / lymph content, increases solidity & tissue adhesion.

Low Viscosity Liquid → Viscous Gel → Firm Semisolid
Increasing water / blood / lymph content, increases solidity & tissue adhesion.

Low Viscosity Liquid → Viscous Gel → Firm Semisolid
Rat Tail Amputations

Also evaluated Sanguitec™ Vs:
- chitosan derivatives
- Biolife Ferrous Compound
- Quick Clot (US Military)

Oxidized Cellulose (Alltracel/Surgicel)
- No control of bleeding

- Clotisol (external veterinary)
- Potassium / Aluminum salts
- Calcium/Sodium Alginate
- Microcrystalline Cellulose

FIG 38
Rat Tail Amputations

Sanguitec™
Immediate post-irrigation hemostasis

FIG. 4A
Seconds after Saphenous vein lacerated - exsanguinating injury
Saphenous Vein Laceration

- Post-irrigation hemostasis & coagulate removal
- Instantaneous Control
- No pressure applied
Liver Laceration

25% excision

50% excision

Seconds after liver excisions - exsanguinating injury
Swine Liver Laceration

1st Liver Laceration:
- 2 cm excision
- 10 min exsanguinating injury
Swine Liver Laceration

GMO/epinephrine—literally poured onto wound
(a poor technique for application, but bleeding halted)

GMO converts to crystal instantaneously
wherever blood is present
(including pooled blood, lifted with finger)
Approximate 12 hours post injury does not re-bleed in shower!
Day 4 (Morning) 7:25 am
Rapid healing. Second intention confirmed.
"Moist Wound Healing lessens scarring."

Weeks Later, under nail trauma still visible
Primary, Secondary & Tertiary Evidence

SEM image of GMO-Cubic Phase and Whole Blood

RBC binding to the GMO phase with a distorted morphology (hemoglobin release)

Platelet in activated morphology

Deposition of a thin mesh of fibrin (20 seconds here)

FIG. 12A
Close up of activated platelet at 20 seconds