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(54) Title: ARTICLES AND METHODS RELATED TO TRANSDERMAL DELIVERY OF A THERAPEUTIC AGENT

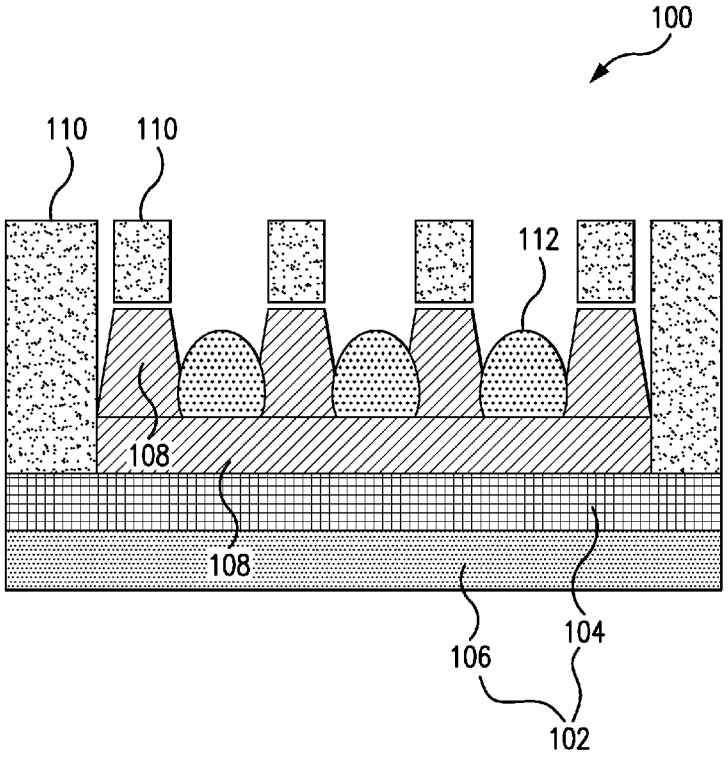

FIG. 1

(57) Abstract: Disclosed herein are articles and methods related to an article comprising a) a first stimuli-responsive porous material, wherein the first stimuli-responsive porous material has a first and second side opposite from each other; b) a therapeutic agent; and c) support material. The articles and methods are useful for transdermal delivery of therapeutic agents.

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ARTICLES AND METHODS RELATED TO TRANSDERMAL DELIVERY OF A THERAPEUTIC AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 61/807,803, filed on April 3, 2013, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTIONS

[0002] The articles and methods disclosed herein relates to transdermal delivery of a therapeutic agent.

BACKGROUND

[0003] Systemic delivery of therapeutic agents can in some cases be disadvantageous because of side effects in, for example, the GI tract after oral dosing. Therefore, in some cases, local administration of therapeutic agents can be beneficial, for example, as for the treatment of a wound, a burn, or osteoarthritis, etc. Local administration of therapeutic agents can be achieved by transdermal drug delivery devices. Transdermal drug delivery devices are well known in the pharmaceutical arts as a method for delivering a wide variety of drugs, such as nitroglycerin, estradiol, testosterone, fentanyl, and clonidine. Transdermal drug delivery devices typically involve a carrier (such as a liquid, gel, or solid matrix, or a mechanically sensitive adhesive) into which the drug to be delivered is incorporated. Because the skin presents a substantial barrier to ingress of foreign substances into the body, it is often desirable to incorporate excipients, such as penetration enhancers, into the carrier that enhance the rate at which the drug passes through the skin.

[0004] There is a need for articles and methods related thereto that can achieve advantageous transdermal delivery of therapeutic agents. Such articles and methods are described herein.

SUMMARY OF THE INVENTION

[0005] Disclosed herein is an article comprising: a) a first stimuli-responsive porous material, wherein the first stimuli-responsive porous material has a first and second side opposite from each other; b) a therapeutic agent; and c) a support material.

[0006] Also disclosed herein is a method of treating a disorder comprising application of an article disclosed herein to a subject in need of treatment of the disorder.

[0007] Also disclosed herein is a method of application of the disclosed articles.

[0008] Additional advantages will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the aspects described below. The advantages described below will be realized and attained by means of the chemical compositions, methods, and combinations thereof particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

DESCRIPTION OF THE FIGURES

[0009] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0010] FIG. 1 shows a non-limiting configuration of the articles described herein.

[0011] FIG. 2 shows a non-limiting configuration of the articles described herein.

[0012] FIG. 3 shows a non-limiting configuration of the articles described herein.

[0013] FIG. 4 shows a non-limiting configuration of the articles described herein.

[0014] FIG. 5 shows a non-limiting configuration of the articles described herein.

[0015] FIG. 6 shows a non-limiting configuration of the articles described herein. The article of figure 1 is incorporated in figure 6.

[0016] FIG. 7 shows a non-limiting configuration of the articles described herein. The article of figure 1 is incorporated in figure 7.

[0017] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

[0018] The disclosed methods and articles can be understood more readily by reference to the following detailed description.

[0019] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific articles or

methods unless otherwise specified. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0020] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

1. Definitions

[0021] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for stereochemistry can be employed to designate stereochemical priority, *E*/*Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAW™ (Cambridgesoft Corporation, U.S.A.).

[0022] In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

[0023] It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to ["a therapeutic agent" includes mixtures of therapeutic agents, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like].

[0024] "Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not. For example, the phrase "optionally comprising an

adhesive material" means that the adhesive material can or cannot be present and that the description includes both situations.

[0025] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0026] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition or material, in which the component is included.

[0027] References in the specification and concluding claims to parts by weight, of a particular element or component in a composition or article, denote the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a composition containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the composition.

[0028] As used herein, the term "subject" refers to the target of administration, e.g. an animal. Thus the subject of the herein disclosed methods can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Alternatively, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig, fish, bird, or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more muscle

disorders prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for treatment of osteoarthritis prior to the administering step.

[0029] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes the use of disclosed articles as means for delivering therapeutic agents. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; (iii) relieving the disease, i.e., causing regression of the disease; or (iv) relieving symptoms of the disease, i.e., relieving pain caused by the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human.

[0030] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0031] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with osteoarthritis" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can treat or prevent osteoarthritis.

[0032] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to a microbial infection) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0033] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In one aspect, administering is transdermal administration. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0034] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the

effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0035] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0036] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile

solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0037] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[0038] As used herein, a "porous material," for example a stimuli-responsive porous material, or the like terms refer to a material that has a large enough free volume space to accommodate a second composition, such as a composition comprising a therapeutic agent. For example, a material can have a free volume range from 40% to 99%.

[0039] As used herein, the term "stimuli-responsive porous material" or the like terms refer to a material that changes one or more properties according to the environment they are in. A stimuli-responsive porous material can change the one or more properties due to changes in one or more factors including, but not limited to temperature, mechanical load of the material, humidity, pH, light intensity, electrical field, or magnetic field. The change of the one or more

properties is drastic and discontinuous at a particular point of the one or more factors and results in release of cargo upon response. For example, for a "thermo-responsive porous material" is a material that exhibits a drastic and discontinuous change of its physical property at a particular temperature or temperature range. The change in physical property can be the solubility of the material in a given solvent which results in reversible change in material free volume due to material shrinkage or swelling. As such, thermo-responsive porous materials have a lower critical solution temperature (LCST) at which thethermo-responsive porous materials change from being soluble in a given solvent to being insoluble in a given solvent. In one aspect, the solvent can be water. For example, poly(N-vinylcaprolactam) has a LCST of 36 °C when the solvent is water. In one aspect, the thermo-responsive material can have a LCST from 27 °C to 40 °C. In yet another aspect, the thermo-responsive material can have a LCST from 32 °C to 40 °C. In yet another aspect, the thermo-responsive material can have a LCST from 32 °C to 38 °C. In yet another aspect, the thermo-responsive material can have a LCST from 32 °C to 46 °C. In another example, a "mechanically-responsive porous material" is a material that exhibits a drastic and discontinuous change of its physical property with the force applied to the material. The change of property can be the ability of material to retain a substance, such as a composition comprising a therapeutic agent, inside the material. Accordingly, then a lower critical force is applied to the material a substance located within the mechanically-responsive porous material is released. For example, gellan gum and alginate are examples of mechanically-responsive porous materials.

[0040] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

2. Articles

[0041] The articles disclosed herein are useful for transdermal delivery of therapeutic agents. Thus, in one aspect, the article can be a transdermal delivery article. The article can be configured to achieve local delivery of the therapeutic agent. The article can be configured in various sizes to fit a desired area of a body, such as, for example, a finger joint, a toe joint, a shoulder, a knee, an elbow, or an ankle joint.

[0042] Disclosed herein is an article comprising: a) a first stimuli-responsive porous material, wherein the first stimuli-responsive porous material has a first and second side opposite from each other; b) a therapeutic agent; and c) a support material.

[0043] In one aspect, the article further comprises a second stimuli-responsive porous material.

[0044] In one aspect, the article further comprises one or more penetration enhancers.

[0045] In one aspect, the article further comprises an adhesive material. In another aspect, the adhesive material is present on the support material. In another aspect, the adhesive material is present on the second side of the first stimuli-responsive porous material.

[0046] In one aspect, the article further comprises a matrix material. In one aspect, the matrix material can be a stimuli-responsive porous material, for example a stimuli-responsive porous matrix material.

[0047] In one aspect, the matrix material can be loaded with a therapeutic agent. In another aspect, the matrix material can be loaded with a penetration enhancer. In yet another aspect, the matrix can be loaded with a penetration enhancer and a therapeutic agent. The penetration enhancer can comprise one or more substances.

[0048] In one aspect, the article comprises one or more formulations comprising a therapeutic agent and one or more penetration enhancers. The formulation can be fast acting and/or provide sustained release of the therapeutic agent. An article with a fast acting formulation can deliver a therapeutically effective amount of a therapeutic agent within 10, 15, 20, 25, 30, 45, or 60 minutes after application of the article. An article with a sustained release formulation can deliver a therapeutically effective amount of a therapeutic agent for at least 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12, hrs, 18 hrs, or 24 hrs.

[0049] In one aspect, the article can comprise two or more formulations. For example, the article can comprise two or more formulations comprising the same therapeutic agent but with different penetration enhancers. Such article can, thus, can comprise a fast acting formulation and a sustained release formulation. The different formulations can be present at different location or in different materials in the article. For example, a fast acting formulation can be present in a first stimuli-responsive porous material and the sustained release formulation can be present in a second stimuli-responsive porous material and/or in the matrix material. In one aspect, the fast acting formulation and the sustained release formulation are physically and chemically separated from each other. In another example, the fast acting formulation and the sustained release formulation can be physically separated by a barrier, such as a matrix

material. An article comprising both a fast acting formulation and a sustained release formulation can provide both fast and sustained of the therapeutic agent, thereby, providing immediate and long-term relief for a subject using the article.

[0050] In another aspect, the article can comprise two or more formulations comprising different therapeutic agents. The different therapeutic agents can be in the same class of therapeutic agents, such as, for example, in the class of non-steroidal anti-inflammatory drugs (NSAID). The different therapeutic agents can also be in different classes of therapeutic agents, such as for example, an NSAID and an anesthetic agent. The article would then provide two different benefits to a subject, such as a human, upon application of the article. For example, upon application of such article comprising both an NSAID and an anesthetic agent to an inflamed area, the article would provide both pain relief and anti-inflammatory relief to the subject. The two or more formulations comprising different therapeutic agents can be present at different location or in different materials in the article. For example, one formulation can be present in a first stimuli-responsive porous material and the second formulation can be present in a second stimuli-responsive porous material and/or in the matrix material. In one aspect, the two or more formulations are physically and chemically separated from each other. In another example, the two or more formulations can be physically separated by a barrier, such as a matrix material.

[0051] In another aspect, the article can comprise three or more formulations comprising different therapeutic agents. The different therapeutic agents can be in the same class of therapeutic agents, such as, for example, in the class of non-steroidal anti-inflammatory drugs (NSAID). Two of the different therapeutic agents can be in the same class of therapeutic agents, such as, for example, in the class of non-steroidal anti-inflammatory drugs (NSAID), and one of the therapeutic agents could be in a different class of therapeutic agents, such as, for example, an anesthetic agent. The different therapeutic agents can also be in different classes of therapeutic agents, such as for example, an NSAID, an anesthetic agent, and an antibiotic agent. The article could then provide multiple, such as two or three, different benefits to a subject, such as a human, upon application of the article. The three or more formulations comprising different therapeutic agents can be present at different location or in different materials in the article. For example, one formulation can be present in a first stimuli-responsive porous material, the second formulation can be present in a second stimuli-responsive porous material, and the third formulation can be present in the matrix material. In one aspect, the three or more formulations are physically and chemically separated from each

other. In another example, the three or more formulations can be physically separated by a barrier, such as a matrix material.

[0052] In one aspect, the article is configured to conform to the shape of a body part. In another aspect, the article is configured to conform to the shape of a body where a joint is present. In one aspect, the joint is the distal interphalangeal joint (DIP). In another aspect, the joint is the basilar joint of the thumb (trapezium) and/or the first three bones of the thumb (metacarpal). In yet another aspect, the joint is the metatarsophalangeal joint. In yet another aspect, the joint is a finger joint, a toe joint, an ankle, an elbow, a wrist, a shoulder or a knee.

[0053] In one aspect, the article has the shape of a hollow tube. In one aspect, the hollow tube can be fitted to a body part, such as the DIP.

[0054] In one aspect, the support material extends beyond the first stimuli-responsive porous material. In another aspect, the support material extends beyond the first stimuli-responsive porous material and the second stimuli-responsive porous material.

[0055] In one aspect, the support material is flexible. In another aspect, the support material is elastic. In yet another aspect, the support material is attached to the first side of the first stimuli-responsive porous material.

[0056] In one aspect, the article comprises a matrix material. In another aspect, comprises a matrix material, wherein the matrix material is attached to the support material. In one aspect, the matrix material is configured on the support material to form one or more wells. In another aspect, the first thermo-responsive and/or mechanically-responsive material is present in the one or more wells. In yet another aspect, the matrix material is present between the first side of the stimuli-responsive porous material and the support material. In yet another aspect, the first stimuli-responsive porous material and the second stimuli-responsive porous material are present in different wells. In yet another aspect, the therapeutic agent is present in the one or more wells.

[0057] In one aspect, the therapeutic agent is present between the first side of the first stimuli-responsive porous material and the support material. In another aspect, the first side of the first stimuli-responsive porous material is attached to the support material. In yet another aspect, first side of the first stimuli-responsive porous material and the second stimuli-response material is attached to the support material. In yet another aspect, first side of the first stimuli-responsive porous material is attached to the second stimuli-response material.

[0058] In one aspect, the article is configured so that the first stimuli-responsive porous material will be in contact with skin upon use of the article.

[0059] In one aspect, the article is configured so that the therapeutic agent is present between the first stimuli-response porous material and the support material. In one aspect, the article is configured so that the therapeutic agent is in contact with and is present between the first stimuli-response porous material and the support material.

[0060] In one aspect, the article is configured so that the porous matrix material loaded with a therapeutic agent is present between the first stimuli-response porous material and the support material. In one aspect, the article is configured so that the porous matrix material loaded with a therapeutic agent is in contact with and is present between the first stimuli-response porous material and the support material.

[0061] In one aspect, the article is configured so that the porous matrix material loaded with a therapeutic agent and one or more penetration enhancers is present between the first stimuli-response porous material and the support material. In one aspect, the article is configured so that the porous matrix material loaded with a therapeutic agent and one or more penetration enhancers is in contact with and is present between the first stimuli-response porous material and the support material.

[0062] In one aspect, the article is configured so that the first stimuli-responsive porous material and the support material are in contact. In one aspect, the article is configured so that the first stimuli-responsive porous material loaded with the therapeutic agent and the support material are in contact. In one aspect, the article is configured so that the first stimuli-responsive porous material loaded with the therapeutic agent and one or more penetration enhancers and the support material are in contact.

[0063] In one aspect, the article is configured so that one or more discrete areas of the article comprise the first stimuli-responsive porous material, and wherein the article comprises an adhesive material. In another aspect, the article comprises at least 2, 5, 10, 15, 20, 25, 30, 35, 50, 100, 200, 500, 1,000, 5,000, 10,000, or 20,000 discrete areas. FIG 6 shows an article with 24 discrete areas.

[0064] Now referring to FIG. 1, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 1 shows article (**100**) with a support material (**102**), the support material (**102**) comprises a flexible fabric (**104**), such as a flexible hydrophobic fabric, and a backing membrane (**106**). The flexible fabric (**104**), such as a flexible hydrophobic fabric, and the

backing membrane (**106**) are attached to each other. In one aspect, a matrix material (**108**) is attached to the support material (**102**), for example, the matrix material (**108**) is attached to the flexible fabric (**104**). The matrix material (**108**) can be configured on the support material (**102**) to provide wells in the article (**100**). In one aspect, an adhesive material (**110**) is present and attached to the support material (**102**), for example, the adhesive material (**110**) is attached to the flexible fabric (**104**). In another aspect, the adhesive material (**110**) is present and attached to the matrix material (**108**). A first stimuli-responsive porous material (**112**) is in contact with the matrix material (**108**), which can be configured to provide wells. Thus, the first stimuli-responsive porous material (**112**), in one aspect, is present in the wells of the matrix material (**108**).

[0065] Now referring to FIG. 2, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 2 shows article (**200**) with a support material (**202**), the support material (**202**) comprises a flexible fabric (**204**), such as a flexible hydrophobic fabric, and a backing membrane (**206**). The flexible fabric (**204**), such as a flexible hydrophobic fabric, and the backing membrane (**206**) are attached to each other. In one aspect, a therapeutic agent (**208**) is in contact with the support material (**102**), for example, therapeutic agent (**208**) is in contact with the flexible fabric (**204**). In one aspect, an adhesive material (**210**) is present and attached to the support material (**202**), for example, the adhesive material (**210**) is attached to the flexible fabric (**204**). A first stimuli-responsive porous material (**212**) is in contact with the therapeutic agent (**208**).

[0066] Now referring to FIG. 3, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 3 shows article (**300**) with a support material (**302**), the support material (**302**) comprises a flexible fabric (**304**), such as a flexible hydrophobic fabric, and a backing membrane (**306**). The flexible fabric (**304**), such as a flexible hydrophobic fabric, and the backing membrane (**306**) are attached to each other. In one aspect, matrix material loaded with a therapeutic agent (**308**) is in contact with the support material (**302**), for example, matrix material loaded with a therapeutic agent and/or a penetration enhancer (**308**) is in contact with the flexible fabric (**304**). In one aspect, an adhesive material (**310**) is present and attached to the support material (**302**), for example, the adhesive material (**310**) is attached to the flexible fabric (**304**). A first stimuli-responsive porous material (**312**) is in contact with the matrix material loaded with a therapeutic agent and/or a penetration enhancer (**308**).

[0067] Now referring to FIG. 4, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 4 shows article (**400**) with a support material (**402**), the support material (**402**) comprises a flexible fabric (**404**), such as a flexible hydrophobic fabric, and a backing membrane (**406**). The flexible fabric (**404**), such as a flexible hydrophobic fabric, and the backing membrane (**406**) are attached to each other. In one aspect, matrix material loaded with a therapeutic agent (**408**) is in contact with the support material (**402**), for example, matrix material loaded with a therapeutic agent (**408**) is in contact with the flexible fabric (**404**). In one aspect, an adhesive material (**410**) is present and attached to the support material (**402**), for example, the adhesive material (**410**) is attached to the flexible fabric (**404**). A first stimuli-responsive porous material loaded with a therapeutic agent and/or a penetration enhancer (**412**) is in contact with the matrix material loaded with a therapeutic agent and/or a penetration enhancer (**408**).

[0068] Now referring to FIG. 5, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 5 shows article (**500**) with a support material (**502**), the support material (**502**) comprises a flexible fabric (**504**), such as a flexible hydrophobic fabric, and a backing membrane (**506**). The flexible fabric (**504**), such as a flexible hydrophobic fabric, and the backing membrane (**506**) are attached to each other. In one aspect, an adhesive material (**508**) is present and attached to the support material (**502**), for example, the adhesive material (**508**) is attached to the flexible fabric (**504**). A first stimuli-responsive porous material loaded with a therapeutic agent and/or a penetration enhancer (**510**) is in contact with the support material (**502**), for example, the adhesive material (**508**) is attached to the flexible fabric (**504**).

[0069] Now referring to FIG. 6, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 6 shows a bandage (**600**), which comprises one or more articles disclosed herein, for example, article (**602**), which is inclusive of articles (**100**), (**200**), (**300**), (**400**), and (**500**) described above. The one or more articles (**602**) can be arranges in a matrix (**608**). The bandage (**600**) comprises an adhesive (**606**) on one side of the bandage. The adhesive (**606**) and the article (**602**) are present on the same side of bandage (**600**). The bandage is configured to covers a body part, such as, for example, finger (**604**).

[0070] Now referring to FIG. 7, which shows a non-limiting exemplary aspect of the articles disclosed herein. FIG. 7 shows a joint sleeve (**700**), which comprises one or more articles disclosed herein, for example, article (**702**), which is inclusive of articles (**100**), (**200**), (**300**), (**400**), and (**500**) described above. The one or more articles (**702**) are present on the inner

surface of the joint sleeve (**700**). The joint sleeve (**700**) comprises an elastomeric polymer (**704**), which can be made of a natural or synthetic polymer.

a. First stimuli-responsive porous material

[0071] In one aspect, the first stimuli-responsive porous material can be a gel. In another aspect, the first stimuli-responsive porous material can be a hydrogel. In yet another aspect, the first stimuli-responsive porous material can be a polymer, such as a cross-linked polymer.

[0072] In one aspect, the first stimuli-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In another aspect, the first stimuli-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[0073] In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, first stimuli-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet

another aspect, the first stimuli-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[0074] In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, first stimuli-responsive porous material can be loaded with at least 0.5% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another

aspect, the first stimuli-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[0075] In one aspect, the first stimuli-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In another aspect, the first stimuli-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[0076] In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, first stimuli-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than

3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[0077] In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, first stimuli-responsive porous material can be loaded with less than 0.5% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 2% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the first stimuli-

responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the first stimuli-responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[0078] In one aspect, the first stimuli-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

[0079] In one aspect, the first stimuli-responsive porous material can be a first thermo-responsive and/or mechanically-responsive porous material. In another aspect, the first stimuli-responsive porous material can be a first thermo-responsive porous material. In yet another aspect, the first stimuli-responsive porous material can be a first mechanically-responsive porous material.

b. Second stimuli-responsive porous material

[0080] In one aspect, the second stimuli-responsive porous material can be a gel. In another aspect, the second stimuli-responsive porous material can be a hydrogel. In yet another aspect, the second stimuli-responsive porous material can be a polymer, such as a cross-linked polymer.

[0081] In one aspect, the second stimuli-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In another aspect, the second stimuli-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can

be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[0082] In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, second stimuli-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[0083] In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, second stimuli-responsive porous material can be loaded with at least 0.5% by weight of a penetration

enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[0084] In one aspect, the second stimuli-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In another aspect, the second stimuli-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 9% by

weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[0085] In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, second stimuli-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[0086] In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, second stimuli-responsive porous material can be loaded with less than 0.5% by weight of a penetration

enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 2% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the second stimuli-responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[0087] In one aspect, the second stimuli-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

[0088] In one aspect, the second stimuli-responsive porous material can be a second thermo-responsive and/or mechanically-responsive porous material. In another aspect, the second stimuli-responsive porous material can be a second thermo-responsive porous material. In yet another aspect, the second stimuli-responsive porous material can be a second mechanically-responsive porous material. In yet another aspect, the second stimuli-responsive porous material can be a first mechanically-responsive porous material. In yet another aspect, the second stimuli-responsive porous material can be a first mechanically-responsive porous material.

[0089] In one aspect, the first stimuli-responsive porous material and the second stimuli-responsive porous material are loaded with different substances. In another aspect, the first stimuli-responsive material is loaded with a therapeutic agent and the second stimuli-responsive material is loaded with a penetration enhancer. In another aspect, the first stimuli-responsive

material is not loaded and the second stimuli-responsive material is loaded with a penetration enhancer. In another aspect, the first stimuli-responsive material is not loaded and the second stimuli-responsive material is loaded with a therapeutic agent.

I. First thermo-responsive porous material

[0090] In one aspect, the first thermo-responsive porous material can be a gel. In another aspect, the first thermo-responsive porous material can be a hydrogel. In yet another aspect, the first thermo-responsive porous material can be a polymer, such as a cross-linked polymer. In one aspect, the first thermo-responsive porous material can have a LCST close to the body temperature of a human, for example, the first thermo-responsive porous material can have a LCST from 27 °C to 40 °C, from 32 °C to 40 °C, from 32 °C to 38 °C, or from 32 °C to 46 °C. In one aspect, the first thermo-responsive porous material can comprise poly(N-isopropylacrylamide), poly(N-vinylcaprolactam), or poly(vinyl methyl ether), co-polymers thereof, or a mixture thereof. In another aspect, the first thermo-responsive porous material can comprise poly(N-isopropylacrylamide). In yet another aspect, the first thermo-responsive porous material can comprise poly(N-vinylcaprolactam). In yet another aspect, the first thermo-responsive porous material can comprise poly(vinyl methyl ether). In another aspect, the first thermo-responsive porous material is poly(N-isopropylacrylamide). In yet another aspect, the first thermo-responsive porous material is poly(N-vinylcaprolactam). In yet another aspect, the first thermo-responsive porous material is poly(vinyl methyl ether). In yet another aspect, the first thermo-responsive porous material can comprise a copolymer comprising poly(N-isopropylacrylamide). In yet another aspect, the first thermo-responsive porous material can comprise a copolymer comprising poly(N-vinylcaprolactam). In yet another aspect, the first thermo-responsive porous material can comprise a copolymer comprising poly(vinyl methyl ether). In yet another aspect, the first thermo-responsive porous material is a copolymer comprising poly(N-isopropylacrylamide). In yet another aspect, the first thermo-responsive porous material is a copolymer comprising poly(N-vinylcaprolactam). In yet another aspect, the first thermo-responsive porous material is a copolymer comprising poly(vinyl methyl ether).

[0091] In one aspect, the first thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 20 kDa to 50 kDa. In another aspect, the first thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 50 kDa to 100 kDa. In yet another aspect, the first thermo-responsive porous material comprises a thermo-responsive polymer

with a number average molecular weight from 100 kDa to 200 kDa. In yet another aspect, the first thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 200 kDa to 500 kDa.

[0092] In one aspect, the first thermo-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In yet another aspect, first thermo-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[0093] In yet another aspect, the first thermo-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, first thermo-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 4% by weight of a therapeutic

agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[0094] In yet another aspect, the first thermo-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, first thermo-responsive porous material can be loaded with at least 0.5% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another

aspect, the first thermo-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[0095] In one aspect, the first thermo-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In yet another aspect, first thermo-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[0096] In yet another aspect, the first thermo-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, first thermo-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous

material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[0097] In yet another aspect, the first thermo-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, first thermo-responsive porous material can be loaded with less than 0.5% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 2% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the first thermo-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the first thermo-

responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[0098] In one aspect, the first thermo-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

[0099] Poly(N-isopropylacrylamide) is known in the art as is described by Vihola, H., et al (J. Biomaterials 2005, 26, 3055); Li, J., et al., (Int. J. Pharmacol. 2006, 2, 513); Zhu, Z., et al. A. (ACS Nano 2009, 3, 3595); Nash, M. A., et al. (Nano Lett. 2009, 10, 85); Zhang, X, et al., (Nano Lett. 2011, 11, 3239); and Wu, T., et al. (S. Chem. Mater. 2011, 23, 2370).

[00100] Poly(N-vinylcaprolactam) is known in the art as is described by Medeiros, S. F. et al., (J. Polym. Sci. A: Polym. Chem. 2010, 48, 3932); Imaz, A., et al. (Polym. Sci. A: Polym. Chem. 2010, 48, 1173); Cakal, E. I., et al. (Ind. Eng. Chem. Res. 2010, 49, 11741); Srivastava, A., et al. (J. Mater. Sci.: Materials in Medicine 2010, 21, 2937); and Balaceanu, A., et al. (Macromolecules 2011, 44, 2161).

[00101] Poly(vinyl methyl ether) is known in the art and is described by Kabra, B.G., et al.. (Polymer, 1992, 33, 990); Pich, A., et al. (Polymer 2002, 43, 5723); and Kharlampieva, E., et al. (Macromolecules 2005, 38, 10523).

II. Second thermo-responsive porous material

[00102] In one aspect, the second thermo-responsive porous material can be a gel. In another aspect, the second thermo-responsive porous material can be a hydrogel. In yet another aspect, the second thermo-responsive porous material can be a polymer, such as a cross-linked polymer. In one aspect, the second thermo-responsive porous material can comprise poly(N-isopropylacrylamide), poly(N-vinylcaprolactam), or poly(vinyl methyl ether), a co-polymer thereof, or a mixture thereof. In another aspect, the second thermo-responsive porous material can comprise poly(N-isopropylacrylamide). In yet another aspect, the second thermo-responsive porous material can comprise poly(N-vinylcaprolactam). In yet another aspect, the second thermo-responsive porous material can comprise poly(vinyl methyl ether). In another aspect, the second thermo-responsive porous material is poly(N-isopropylacrylamide). In yet another aspect, the second thermo-responsive porous material is poly(N-vinylcaprolactam). In yet another aspect, the second thermo-responsive porous material is poly(vinyl methyl ether). In yet another aspect, the second thermo-responsive porous material can comprise a copolymer comprising poly(N-isopropylacrylamide). In yet another aspect, the second thermo-responsive porous material can comprise a copolymer comprising poly(N-vinylcaprolactam). In yet

another aspect, the second thermo-responsive porous material can comprise a copolymer comprising poly(vinyl methyl ether). In yet another aspect, the second thermo-responsive porous material is a copolymer comprising poly(N-isopropylacrylamide). In yet another aspect, the second thermo-responsive porous material is a copolymer comprising poly(N-vinylcaprolactam). In yet another aspect, the second thermo-responsive porous material is a copolymer comprising poly(vinyl methyl ether).

[00103] In one aspect, the second thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 20 kDa to 50 kDa. In another aspect, the second thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 50 kDa to 100 kDa. In yet another aspect, the second thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 100 kDa to 200 kDa. In yet another aspect, the second thermo-responsive porous material comprises a thermo-responsive polymer with a number average molecular weight from 200 kDa to 500 kDa.

[00104] In one aspect, the second thermo-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In yet another aspect, second thermo-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another

aspect, the second thermo-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[00105] In yet another aspect, the second thermo-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, second thermo-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[00106] In yet another aspect, the second thermo-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, second thermo-responsive porous material can be loaded with at least 0.5% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer.

In yet another aspect, the second thermo-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[00107] In one aspect, the second thermo-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In yet another aspect, second thermo-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 15% by

weight of a therapeutic agent. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[00108] In yet another aspect, the second thermo-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, second thermo-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[00109] In yet another aspect, the second thermo-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, second thermo-responsive porous material can be loaded with less than 0.5% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 2% by weight of a

penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the second thermo-responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[00110] In one aspect, the second thermo-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

[00111] In one aspect, the first thermo-responsive porous material and the second thermo-responsive porous material are loaded with different substances. In another aspect, the first thermo-responsive material is loaded with a therapeutic agent and the second thermo-responsive material is loaded with a penetration enhancer. In another aspect, the first thermo-responsive material is not loaded and the second thermo-responsive material is loaded with a penetration enhancer. In another aspect, the first thermo-responsive material is not loaded and the second thermo-responsive material is loaded with a therapeutic agent.

III. First mechanically-responsive porous material

[00112] In one aspect, the first mechanically-responsive porous material can be a gel. In another aspect, the first mechanically-responsive porous material can be a hydrogel. In yet another aspect, the first mechanically-responsive porous material can be a polymer, such as a cross-linked polymer.

[00113] In one aspect, the first mechanically-responsive porous material can comprise gellan gum. In another aspect, the first mechanically-responsive porous material can comprise

gellan gum and a cross-linked polymer selected from polylactic acid, poly(lactic-co-glycolic acid), polyethylene glycol, polycaprolactam, polyesters, polyesteramides, polyanhydrides, polycarbonates, poly(amino acids), polyacetyls, polycyanoacrylates, blends and copolymers thereof. In one aspect, the cross-linked polymer is selected from polylactic acid, poly(lactic-co-glycolic acid), blends and copolymers thereof.

[00114] In one aspect, the polymer can have a number average molecular weight from 20 kDa to 50 kDa. In another aspect, the polymer can have a number average molecular weight from 50 kDa to 100 kDa. In yet another aspect, the polymer can have a number average molecular weight from 100 kDa to 200 kDa. In yet another aspect, the polymer can have a number average molecular weight from 200 kDa to 500 kDa.

[00115] In one aspect, the first mechanically-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In yet another aspect, first mechanically-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[00116] In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet

another aspect, first mechanically-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[00117] In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, first mechanically-responsive porous material can be loaded with at least 0.5% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the

first mechanically-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[00118] In one aspect, the first mechanically-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In yet another aspect, first mechanically-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[00119] In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, first mechanically-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[00120] In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, first mechanically-responsive porous material can be loaded with less than 0.5% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 2% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the

first mechanically-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the first mechanically-responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[00121] In one aspect, the first mechanically-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

[00122] In one aspect, the first mechanically-responsive porous material and the second mechanically-responsive porous material are loaded with different substances. In another aspect, the first mechanically-responsive material is loaded with a therapeutic agent and the second mechanically-responsive material is loaded with a penetration enhancer. In another aspect, the first mechanically-responsive material is not loaded and the second mechanically-responsive material is loaded with a penetration enhancer. In another aspect, the first mechanically-responsive material is not loaded and the second mechanically-responsive material is loaded with a therapeutic agent.

IV. Second mechanically-responsive material

[00123] In one aspect, the second mechanically-responsive porous material can be a gel. In another aspect, the second mechanically-responsive porous material can be a hydrogel. In yet another aspect, the second mechanically-responsive porous material can be a polymer, such as a cross-linked polymer.

[00124] In one aspect, the second mechanically-responsive porous material can comprise gellan gum. In another aspect, the second mechanically-responsive porous material can comprise gellan gum and a cross-linked polymer selected from polylactic acid, poly(lactic-

co-glycolic acid), polyethylene glycol, polycaprolactam, polyesters, polyesteramides, polyanhydrides, polycarbonates, poly(amino acids), polyacetyls, polycyanoacrylates, blends and copolymers thereof. In one aspect, the cross-linked polymer is selected from polylactic acid, poly(lactic-co-glycolic acid), blends and copolymers thereof.

[00125] In one aspect, the polymer can have a number average molecular weight from 20 kDa to 50 kDa. In another aspect, the polymer can have a number average molecular weight from 50 kDa to 100 kDa. In yet another aspect, the polymer can have a number average molecular weight from 100 kDa to 200 kDa. In yet another aspect, the polymer can have a number average molecular weight from 200 kDa to 500 kDa.

[00126] In one aspect, the second mechanically-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent. In yet another aspect, second mechanically-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent.

[00127] In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet

another aspect, second mechanically-responsive porous material can be loaded with at least 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 20% by weight of a therapeutic agent and a penetration enhancer.

[00128] In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 0.1% by weight of a penetration enhancer. In yet another aspect, second mechanically-responsive porous material can be loaded with at least 0.5% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 1% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 2% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 3% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 4% by weight of a penetration enhancer. In yet another aspect, the second mechanically-

responsive porous material can be loaded with at least 5% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 6% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 7% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 8% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 9% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 10% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 15% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with at least 20% by weight of a penetration enhancer.

[00129] In one aspect, the second mechanically-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent. In yet another aspect, second mechanically-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent. In yet another aspect, the

second mechanically-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent.

[00130] In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 0.1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, second mechanically-responsive porous material can be loaded with less than 0.5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 1% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 2% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 3% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 4% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 5% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 6% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 7% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 8% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 9% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 10% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 15% by weight of a therapeutic agent and a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 20% by weight of a therapeutic agent and a penetration enhancer.

[00131] In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 0.1% by weight of a penetration enhancer. In yet another aspect, second mechanically-responsive porous material can be loaded with less than 0.5% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 1% by weight of a penetration enhancer. In yet another

aspect, the second mechanically-responsive porous material can be loaded with less than 2% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 3% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 4% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 5% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 6% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 7% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 8% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 9% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 10% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 15% by weight of a penetration enhancer. In yet another aspect, the second mechanically-responsive porous material can be loaded with less than 20% by weight of a penetration enhancer.

[00132] In one aspect, the second mechanically-responsive porous material is not loaded with therapeutic agent or a penetration enhancer.

c. Therapeutic agent

[00133] In one aspect, the therapeutic agent is a pharmaceutical agent. In one aspect, the therapeutic agent can be in the form of a gel, a paste, a foam, a powder, agglomerated particles, a microencapsulated liquid, a suspension, a liquid, and combinations thereof. In another aspect, the therapeutic agent can be in the form of a microencapsulated liquid, a suspension or a liquid, or a mixture thereof.

[00134] In another aspect, the therapeutic agent comprises a non-steroidal anti-inflammatory drug (NSAID), a steroid drug, an antibiotic, an anesthetic agent, nicotine, fentanyl, estrogen, testosterone, estradiol, clonidine, nitroglycerine, an antimicrobial agent, an antifungal agent, a cosmetic agent, a motion sickness agent, or an anti-hypertensive agent, or a mixture thereof, and pharmaceutically acceptable salts and esters thereof. In another aspect, the therapeutic agent comprises anti-inflammatory drugs, both steroidal (e.g., hydrocortisone, prednisolone, triamcinolone) and nonsteroidal (e.g., naproxen, piroxicam); antibacterials (e.g.,

penicillins such as penicillin V, cephalosporins such as cephalexin, erythromycin, tetracycline, gentamycin, sulfathiazole, nitrofurantoin, and quinolones such as norfloxacin, flumequine, and ibafloxacin); antiprotozoals (e.g., metronidazole); antifungals (e.g., nystatin); coronary vasodilators (e.g., nitroglycerin); calcium channel blockers (e.g., nifedipine, diltiazem); bronchodilators (e.g., theophylline, pirbuterol, salmeterol, isoproterenol); enzyme inhibitors such as collagenase inhibitors, protease inhibitors, elastase inhibitors, lipoxygenase inhibitors (e.g., zileuton), and angiotensin converting enzyme inhibitors (e.g., captopril, lisinopril); other antihypertensives (e.g., propranolol); leukotriene antagonists; anti-ulceratives such as H2 antagonists; steroidal hormones (e.g., progesterone, testosterone, estradiol); antivirals and/or immunomodulators (e.g., 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine, and other compounds disclosed in U.S. Pat. No. 4,689,338, acyclovir); local anesthetics (e.g., benzocaine, propofol); cardiotonics (e.g., digitalis, digoxin); antitussives (e.g., codeine, dextromethorphan); antihistamines (e.g., diphenhydramine, chlorpheniramine, terfenadine); narcotic analgesics (e.g., morphine, fentanyl); peptide hormones (e.g., human or animal growth hormones, LHRH); sex hormones (e.g., estrogens, testosterone, progestins such as levonorgestrel, norethindrone, gestodene); cardioactive products such as atriopeptides; proteinaceous products (e.g., insulin); enzymes (e.g., anti-plaque enzymes, lysozyme, dextranase); antinauseants (e.g., scopolomine); anticonvulsants (e.g., carbamazine); immunosuppressives (e.g., cyclosporine); psychotherapeutics (e.g., diazepam); sedatives (e.g., phenobarbital); anticoagulants (e.g., heparin); analgesics (e.g., acetaminophen); antimigraine agents (e.g., ergotamine, melatonin, sumatriptan); antiarrhythmic agents (e.g., flecainide); antiemetics (e.g., metaclopromide, ondansetron); anticancer agents (e.g., methotrexate, 5-fluouracil); neurologic agents such as anxiolytic drugs; hemostatics; anti-obesity agents; and the like, and a mixture thereof, and pharmaceutically acceptable salts and esters thereof.

[00135] In one aspect, the therapeutic agent comprises an NSAID. Suitable NSAIDs include, but are not limited to, acetylsalicylic acid, celecoxib, dexdetoprofen, diclofenac, diflunisal, etodolac, etoricoxib, fenoprofen, firocoxib, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, licofelone, licofelone, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, oxaporozin, parecoxib, piroxicam, rofecoxib, salsalate, sulindac, tenoxicam, tolfenamic acid, and valdecoxib.

[00136] In yet another aspect, the therapeutic agent comprises a protein, peptide, antibody, or oligo nucleic acid. For example, the therapeutic agent can comprise reicade, humirainsulin, growth hormone, or epoetinalfa, or a combination thereof. The transdermal delivery of such therapeutic agents is described in Chen Y, et al. *Nat Biotechnol.* 2006;24(4):455–60; and Jain S, et al., Drug Dev. Ind. Pharm. 2003;29(9):1013–26.

d. Penetration enhancer and other useful excipients

[00137] In one aspect, the article comprises one or more penetration enhancers. Penetration enhancers are well known in the art. The article can also further comprise other useful pharmaceutical excipients such as a softening agent (softeners), a solubilizer. Suitable materials include, but are not limited to, C_8 -C_{36} fatty acids such as isostearic acid, octanoic acid, and oleic acid; C_8-C_{36} fatty alcohols such as oleyl alcohol and lauryl alcohol; lower alkyl esters of C_8-C_{36} fatty acids such as ethyl oleate, isopropyl myristate, butyl stearate, and methyl laurate; di(lower) alkyl esters of C_6 -C_8 diacids such as diisopropyladipate; monoglycerides of C_8-C_{36} fatty acids such as glycerylmonolaurate; tetraglycol (tetrahydrofurfuryl alcohol polyethylene glycol ether); tetraethylene glycol (ethanol,2,2'-(oxybis(ethylenoxy))diglycol); C_6-C_{36} alkyl pyrrolidone carboxylates; polyethylene glycol; propylene glycol; 2-(2-ethoxyethoxy)ethanol; diethylene glycol monomethyl ether; N,N-dimethyldodecylamine-N-oxide and combinations of the foregoing. Alkylaryl ethers of polyethylene oxide, polyethylene oxide monomethyl ethers, and polyethylene oxide dimethyl ethers are also suitable, as are solubilizers such as glycerol and N-methyl pyrrolidone. Terpenes are another useful class of additives, including pinene, d-limonene, carene, terpineol, terpinen-4-ol, carveol, carvone, pulegone, piperitone, menthone, menthol, neomenthol, thymol, camphor, bomeol, citral, ionone, and cineole, alone or in any combination. In another aspect, the article comprises glycerylmonolaurate, terpineol, lauryl alcohol, tetraglycol, tetraethylene glycol, propylene glycol, isopropyl myristate, dimethyl sulfoxide (DMSO), isopropyl alcohol, polysorbate, ethyl oleate, methyl laurate, or 2-(2-ethoxyethoxy)ethanol, or a mixture thereof.

[00138] In one aspect, the article can comprise two or more formulations comprising the same therapeutic agent but with different penetration enhancers. Such article can, thus, comprise a fast acting formulation and a sustained release formulation. The different formulations can be present at different location or in different materials in the article. For example, a fast acting formulation can be present in a first stimuli-responsive porous material and sustained release formulation can be present in a second stimuli-responsive porous material and/or in the matrix material. An article comprising both a fast acting formulation and a

sustained release formulation can provide both fast and sustained of the therapeutic agent, thereby, providing immediate and long-term relief for a subject using the article.

e. Adhesive

[00139] Any adhesive, including those described in Satas, et al., Handbook of Mechanically Sensitive Adhesives, 2nd ed. 1989, is suitable as the adhesive of the disclosed articles

[00140] Suitable adhesives include, but are not limited to, acrylics, natural and synthetic rubbers, ethylene vinyl acetate, poly(alpha-olefins), vinyl ethers, and silicones. The adhesive can be in the form of copolymers, bicontinuous adhesives, hydrogels, latex emulsions, macromers, and block copolymers. Suitable block copolymers are commercially available from Shell Oil Company (Houston, Tex.) under the trade designation KRATON.

[00141] In one aspect, the adhesive include, but are not limited to, acrylics, poly(olefins), KRATON, and silicones, and acrylics. Acrylic adhesives are disclosed, for example, in U.S. Pat. Nos. 3,239,478, 3,935,338, 5,169,727, RE 24,906, 4,952,650, 4,181,752, 5,986,011, 5,637,646 and 5,753,768. A suitable class of acrylate adhesives is the reaction product of at least one alkyl acrylate with at least one reinforcing co-monomer. Suitable alkyl acrylates are those having a homopolymer glass transition temperature below about -10 °C and include, for example, n-butyl acrylate, 2-ethylhexylacrylate, isoctylacrylate, isononyl acrylate, ethylene monoacrylate, octadecyl acrylate and the like. Suitable reinforcing monomers include, for example, acrylic acid, itaconic acid, isobornyl acrylate, N, N-dimethylacrylamide, N-vinyl caprolactam, N-vinyl pyrrolidone, and the like.

[00142] The adhesives can be prepared and coated using a variety of standard methods. For example, the adhesives can be polymers that are dispersed in solvent or water and coated onto the support material. If a solvent borne or water borne adhesive composition is employed, then the adhesive can undergo a drying step to remove all or a majority of the carrier liquid. The adhesive can be cured using an energy source (e.g., heat, UV radiation, e-beam, and the like). Alternatively, adhesives can be applied without dispersal in a solvent or water using a variety of methods, such as, for example, melting or extruding the adhesive onto a liner or molding tool. The adhesive can be cross-linked with an energy source such as heat, UV radiation, e-beam radiation, and the like. In yet another aspect, monomeric pre-adhesive compositions can be coated onto a liner or molding tool and polymerized and cross-linked with an energy source, as described above.

f. Support material

[00143] In one aspect, the support material is flexible. In another aspect, the support material is elastic. In yet another aspect, the support material is hydrophobic. In yet another aspect, the outer surface of the support material is hydrophobic. In yet another aspect, the inner surface of the support material is hydrophobic. In yet another aspect, the inner and outer surfaces of the support material are hydrophobic. In yet another aspect, the support material comprises kratonspunbondstyrenic block copolymers fabrics.

[00144] In one aspect, the support material comprises a backing layer. In another aspect, the support material comprises a fabric layer. The fabric layer can be a flexible fabric layer. The fabric layer can be an elastic fabric layer. In another aspect, the fabric layer can be a flexible hydrophobic fabric layer.

[00145] In one aspect, the support material is continuous, for example, in the shape of a tube.

[00146] In one aspect, the adhesive is present on a portion of the support material. In another aspect, the first stimuli-responsive material is present on a portion of the support material. In one aspect, the matrix material is present on a portion of the support material.

g. Matrix material

[00147] In one aspect, the matrix material is a porous matrix material. In one aspect, the matrix material is a polymer, such as a cross-linked polymer. In another aspect, the polymer is selected from polylactic acid, poly(lactic-co-glycolic acid), polyethylene glycol, polycaprolactam, polyesters, polyesteramides, polyanhydrides, polycarbonates, poly(amino acids), polyacetyls, polycyanoacrylates, blends and copolymers thereof. In yet another aspect, the cross-linked polymer is selected from polylactic acid, poly(lactic-co-glycolic acid), blends and copolymers thereof. In yet another aspect, the cross-linked polymer is polylactic acid.

[00148] In one aspect, the polymer can have a number average molecular weight from 3 kDa to 1,000 kDa. In another aspect, the polymer can have a number average molecular weight from 3 kDa to 500 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 300 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 200 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 100 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 80 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 60 kDa. In yet

another aspect, the polymer can have a number average molecular weight from 3 kDa to 40 kDa. In yet another aspect, the polymer can have a number average molecular weight from 3 kDa to 20 kDa. In yet another aspect, the polymer can have a number average molecular weight from 20 kDa to 80 kDa. In yet another aspect, the polymer can have a number average molecular weight from 20 kDa to 60 kDa.

3. Methods of use and Methods of treatment

[00149] Also disclosed herein is a method of treating a disorder comprising application of an article disclosed herein to a subject in need of treatment of the disorder. In one aspect, the therapeutic agent is released from article upon the application of the article. In one aspect, the therapeutic agent and the penetration enhancer are released from article upon the application of the article. In another aspect, a therapeutically effective amount of the therapeutic agent is released upon the application of the article. In yet another aspect, a therapeutically effective amount of the therapeutic agent is transdermally administered to the subject upon the application of the article. In one aspect, the treatment of a disorder comprises reducing pain of the subject.

[00150] In one aspect, the disorder is osteoarthritis, rheumatoid arthritis, post-surgical pain, trauma, a burn, a sting, a diabetic leg ulcer, scleroderma, or an infection. In another aspect, the application of the article treats a wound.

[00151] In one aspect, the article is applied over a desired part of the body. In another aspect, the first and/or second stimuli-responsive material is applied over a desired part of the body. In one aspect, the article is applied at the location of a joint of the subject. In one aspect, the joint is a DIP. In another aspect, the joint is the basilar joint of the thumb (trapezium) and/or the first three bones of the thumb (metacarpal). In another aspect, the joint is a finger joint, a toe joint, knee, elbow, shoulder, wrist, or ankle. In yet another aspect, the joint is the metatarsophalangeal joint. In another aspect, the article is applied over a wound. In yet another aspect, the article is applied over an inflamed portion of the body.

CLAIMS

What is claimed is:

1. An article comprising

a) a first stimuli-responsive porous material, wherein the first stimuli-responsive porous material has a first and second side opposite from each other;

b) a therapeutic agent; and

c) a support material.

2. The article of claim 1, wherein the first stimuli-responsive porous material is a first thermo-responsive and/or mechanically-responsive porous material.

3. The article of claims 1 or 2, wherein the first stimuli-responsive porous material comprises poly(N-isopropylacrylamide), poly(N-vinylcaprolactam), poly(vinyl methyl ether), or gellan gum, or a mixture thereof.

4. The article of any one of claims 1-3, wherein the first stimuli-responsive porous material is loaded with the therapeutic agent.

5. The article of any one of claims 1-4, wherein the therapeutic agent is present between the first side of the first stimuli-responsive porous material and the support material.

6. The article of any one of claims 1-5, wherein the therapeutic agent is present in a hydrogel.

7. The article of any one of claims 1-6, wherein the support material is attached to the first side of the first stimuli-responsive porous material.

8. The article of any one of claims 1-7, wherein the first stimuli-responsive porous material is loaded with one or more penetration enhancers.

9. The article of any one of claims 1-7, wherein the article further comprises one or more penetration enhancers.

10. The article of claim 9, wherein the one or more penetration enhancers is present in a hydrogel.

11. The article of any one of claims 1-10, wherein the article further comprises a second stimuli-responsive porous material, wherein the second stimuli-responsive porous material is loaded with one or more penetration enhancers.

12. The article of any one of claims 1-11, wherein the therapeutic agent comprises a non-steroidal anti-inflammatory drug (NSAID),steroid drug, an antibiotic, an anesthetic agent, nicotine, fentanyl, estrogen, testosterone, estradiol, clonidine, nitroglycerine, an antimicrobial agent, an antifungal agent, a cosmetic agent, a motion sickness agent, an anti-hypertensive agent, a peptide, a protein, an antibody, an oligonucleic acid, or a mixture thereof.

13. The article of any one of claims 1-12, wherein the article is configured to conform to the shape of a body where a joint is present.

14. The article of any one of claims 1-12, wherein the article is configured to conform to the shape of a body part.

15. The article of claim 13, wherein the joint is a distal interphalangeal joint.

16. The article of any one of claims 1-15, wherein the article has the shape of a hollow tube.

17. The article of any one of claims 1-16, wherein the support material is flexible.

18. The article of any one of claims 1-17, wherein the article comprises a matrix material, wherein the matrix material is attached to the support material.

19. The article of claim 18, wherein the matrix material is configured on the support material to form one or more wells.

20. The article of claim 19, wherein the first thermo-responsive and/or mechanically-responsive material is present in the one or more wells.

21. The article of claim 18, wherein the matrix material is present between the first side of the stimuli-responsive porous material and the support material.

22. The article of any one of claims 19-21, wherein the first stimuli-responsive porous material and the second stimuli-responsive porous material are present in different wells.

23. The article of any one of claims 19-21, wherein the therapeutic agent is present in the one or more wells.

24. The article of any one of claims 19-21, wherein the therapeutic agent and the one or more penetration enhancers are present in different wells.

25. The article of any one of claims 19-21, wherein the matrix material is loaded with a therapeutic agent, penetration enhancer, or a mixture thereof.

26. The article of any one of claims 1-25, wherein the article comprises an adhesive material.

27. The article of claim 26, wherein the adhesive material is present on the support material.

28. The article of claim 26, wherein the adhesive material is present on the second side of the first stimuli-responsive porous material.

29. The article of claim 28, wherein the adhesive material is present on the matrix material.

30. The article of any one of claims 1-29, wherein article comprises one or more discrete areas comprising the first stimuli-responsive porous material, wherein the article comprises an adhesive material.

31. The article of any one of claims 1-30, wherein the article is elastic.

32. The article of any one of claims 1-31, wherein the article comprises a formulation comprising a therapeutic agent and a penetration enhancer, wherein the penetration enhancer comprises dimethyl sulfoxide.

33. The article of any one of claims 1-32, wherein the article comprises two or more formulations, wherein the two or more formulations comprise the same therapeutic agent, and wherein the two or more formulations comprise different penetration enhancers.

34. The article of any one of claims 1-33, wherein the article comprises two or more formulations, wherein the two or more formulations comprise different therapeutic agents.

35. The article of claim 34, wherein the two or more formulations are physically and chemically separated from each other in the article.

36. The article of claims 34 or 35, wherein one of the two or more formulations is present in the first stimuli-responsive porous material and wherein the second of the two or more formulations is present in the second stimuli-responsive porous material or in the matrix material.

37. The article of any one of claims 1-36, wherein the article comprises three or more formulations, wherein the three or more formulations comprise different therapeutic agents.

38. The article of claim 37, wherein the three or more formulations are physically and chemically separated from each other in the article.

39. The article of claims 37 or 38, wherein one of the three or more formulations is present in the first stimuli-responsive porous material, wherein the second of the three or more formulations is present in the second stimuli-responsive porous material, and wherein the third of the three or more formulations is present in the matrix material.

40. A method of treating or preventing a disorder comprising applying the article of any one of claims 1-39 to a subject in need of treatment or prevention of the disorder.

41. The method of claim 40, wherein the therapeutic agent is released from article upon the application of the article.

42. The method of claims 40 or 41, wherein the article is applied at the location of a joint of the subject.

43. The method of anyone of claims 40-42, wherein the disorder is osteoarthritis, rheumatoid arthritis, post-surgical pain, trauma, a burn, a sting, wound healing, a diabetic leg ulcer, scleroderma, or an infection.

44. The method of anyone of claims 40-43, wherein the treating a disorder comprises reducing pain of the subject.

45. The method of anyone of claims 40-44, wherein the article is applied to adistal interphalangeal joint, a figner joint, a toe joint, knee, ankle, wrist, or shoulder.

46. An article comprising

a) a first stimuli-responsive porous material, wherein the first stimuli-responsive porous material has a first and second side opposite from each other;

b) a support material;

c) a matrix material, wherein the matrix material is attached to the support material and wherein the matrix material is configured on the support material to form two or more wells; and

d) two or more formulations, wherein the two or more formulations comprise different therapeutic agents, wherein one of the two or more formulations is fast acting formulation and is present in a first well, wherein the second of the two or more formulations is a sustained release formulation and is present in a second well.

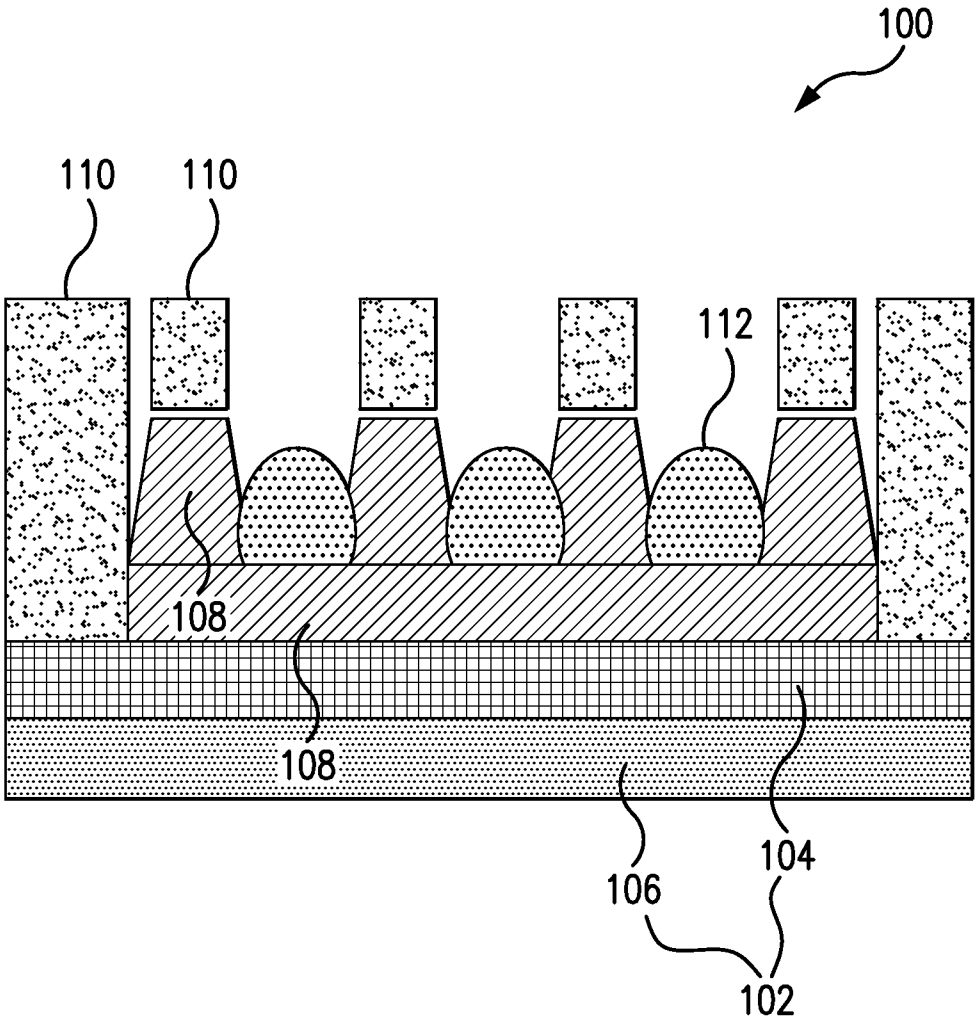

FIG. 1

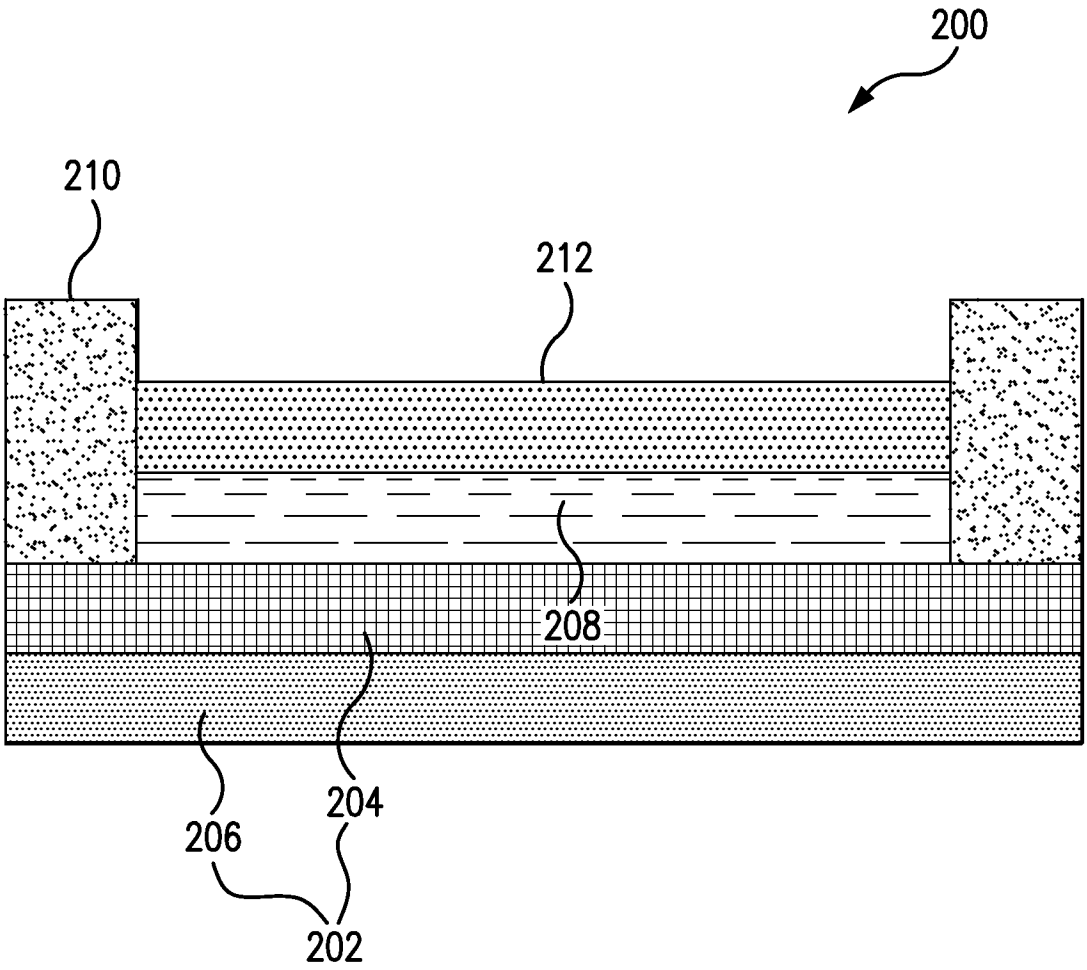

FIG. 2

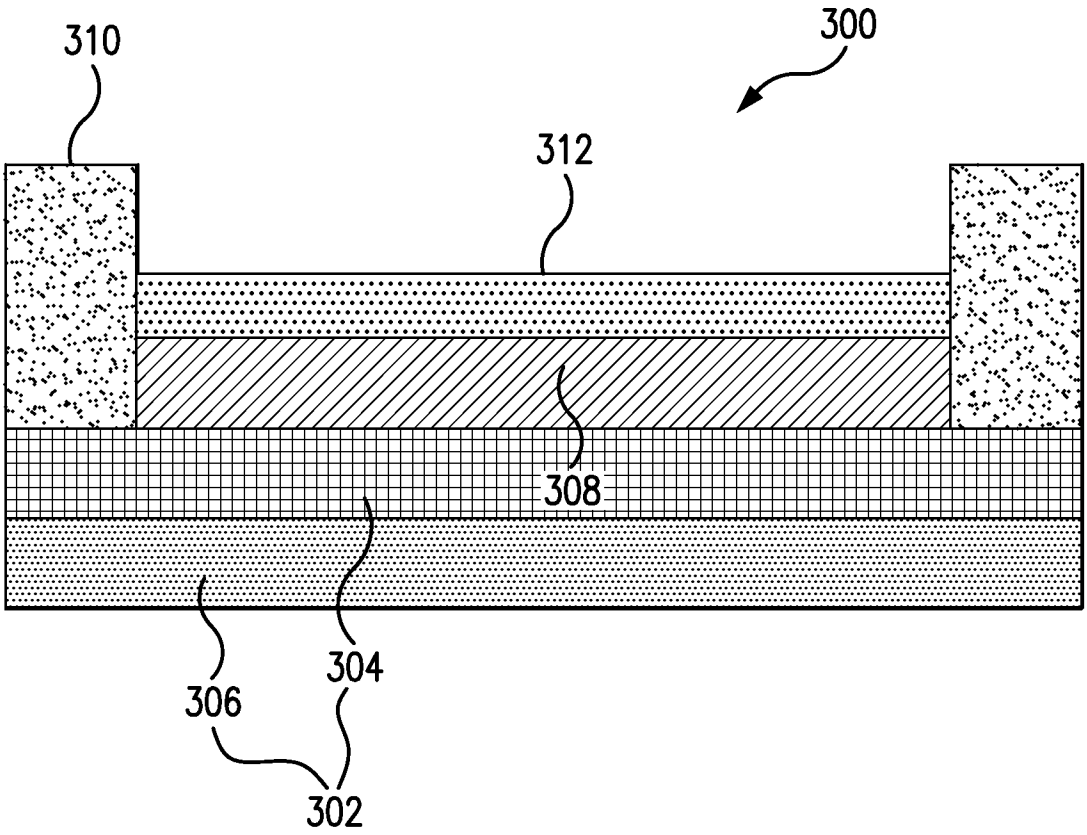

FIG. 3

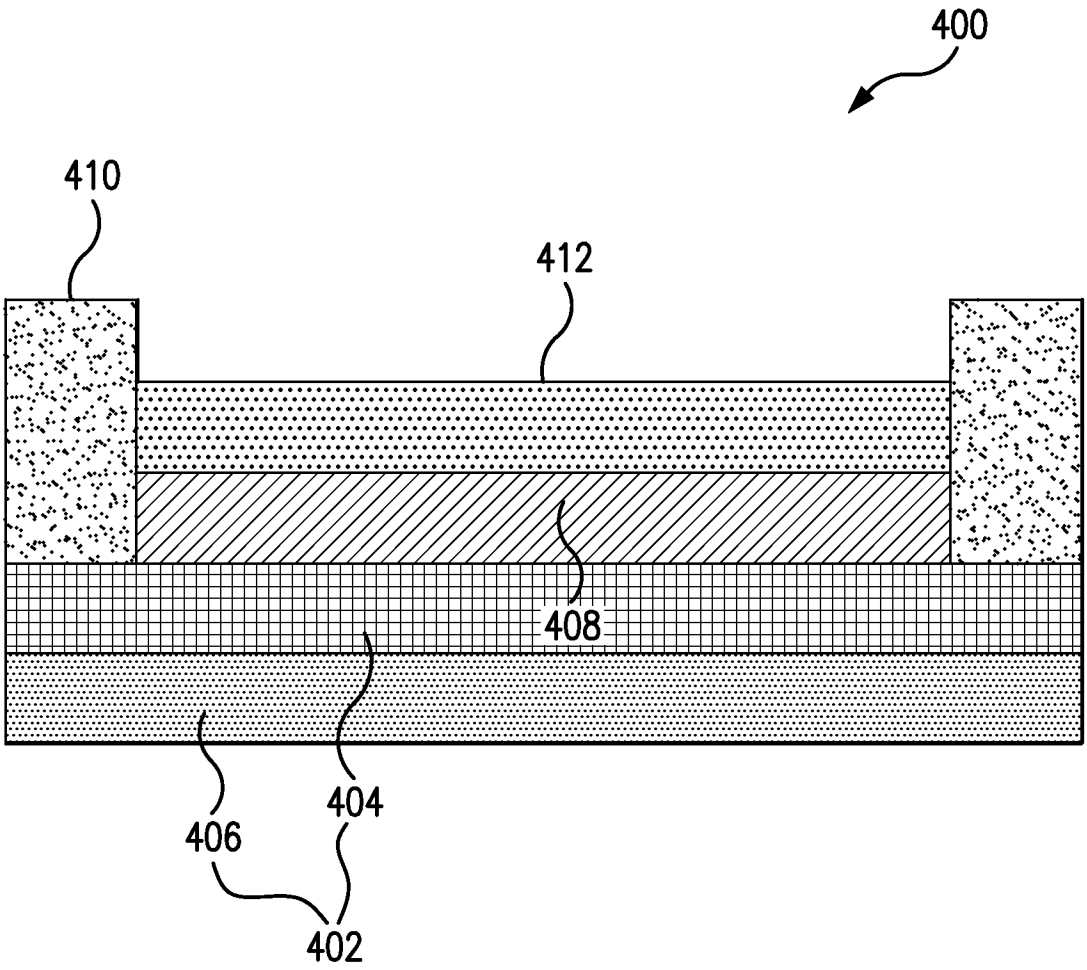

FIG. 4

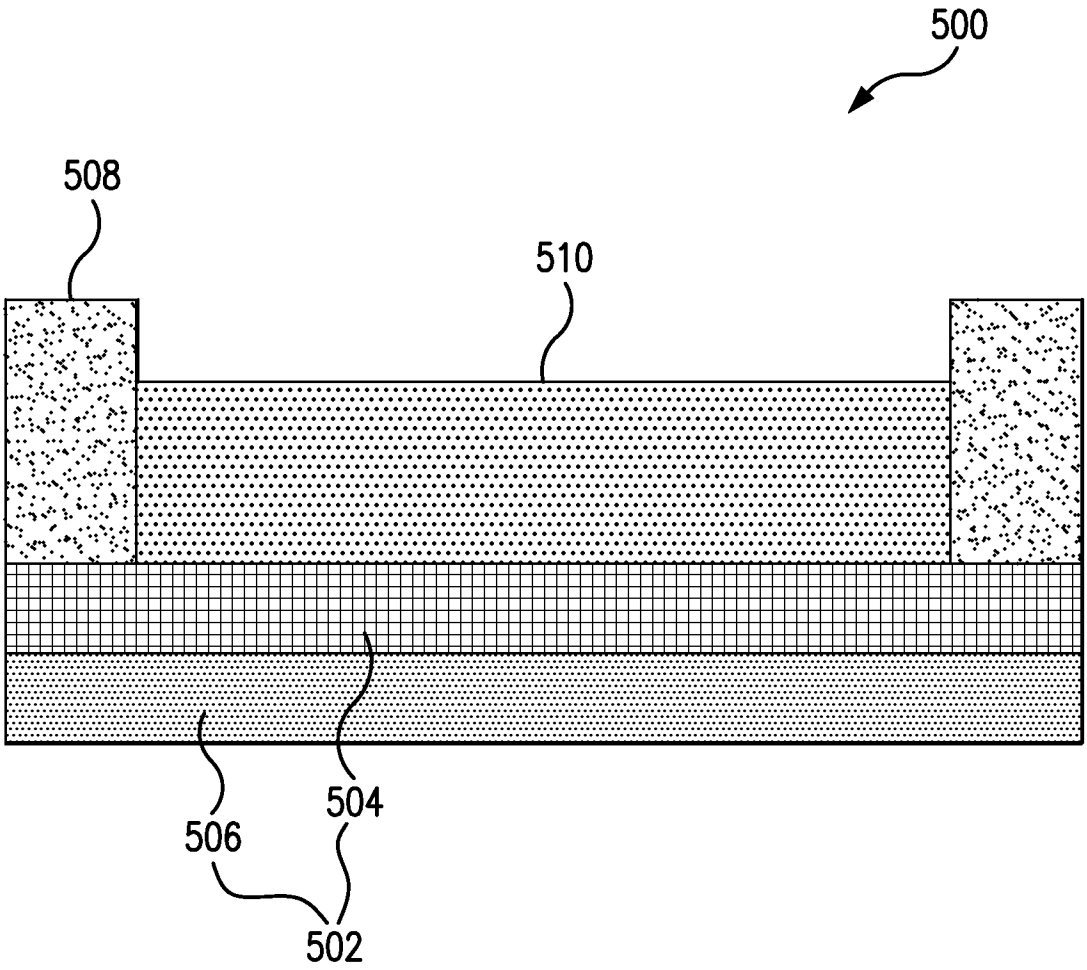

FIG. 5

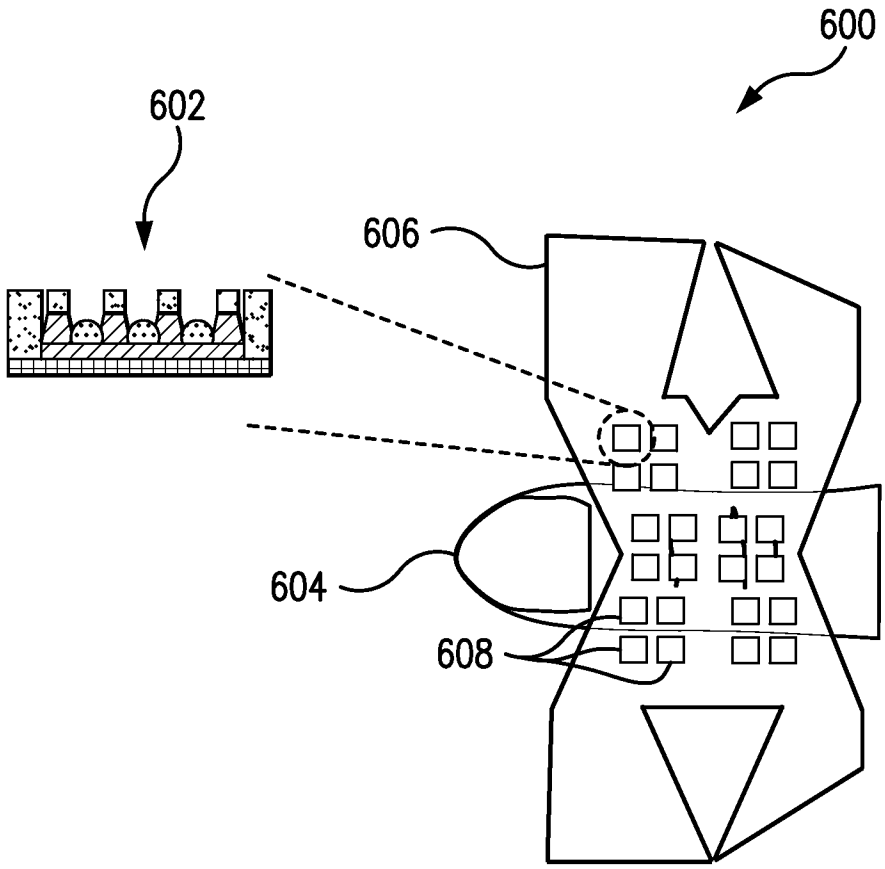

FIG. 6

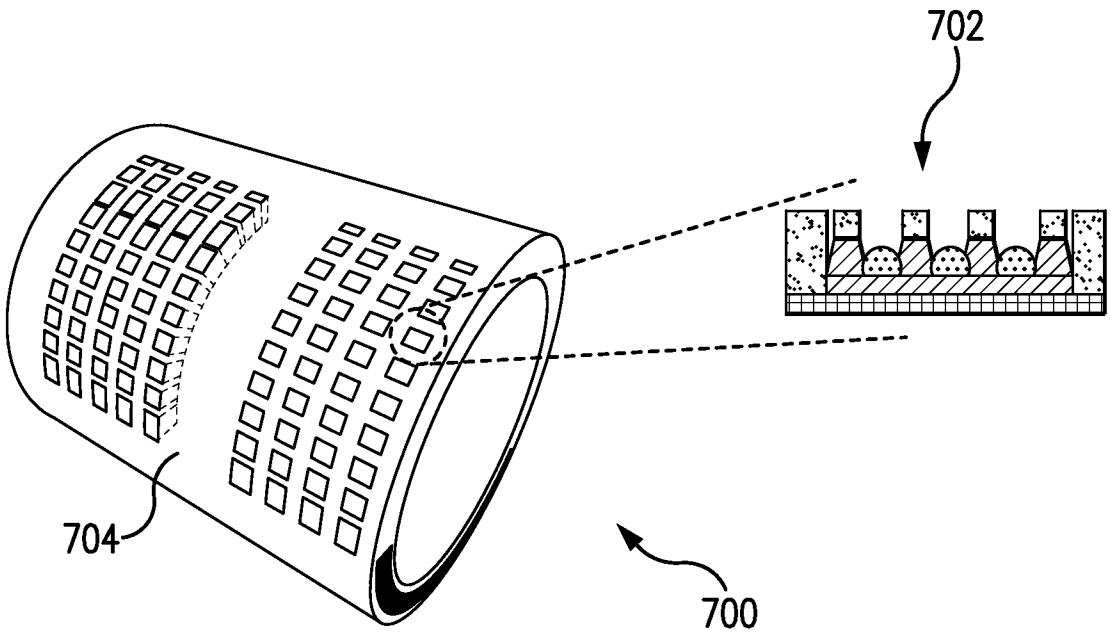

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/032662

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/32 (2014.01)
USPC - 424/457
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61F 2/00, 2/02; A61K 9/02, 9/22, 9/28, 9/32; B05D 5/00 (2014.01)
USPC - 424/422, 423, 457; 427/2.14, 2.16; 514/772.1, 964, 965; 523/113

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 9/0024, 9/1075, 9/1647, 9/2027, 9/2866, 9/2893; A61L 27/16, 31/16 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0263441 Al (MCKAY et al) 22 October 2009 (22.10.2009) entire document	1-3, 46
A	US 2011/0027340 A1 (KING) 03 February 2011 (03.02.2011) entire document	1-3, 46
A	US 2008/0220149 A1 (KETELSON) 11 September 2008 (11.09.2008) entire document	1-3, 46
A	US 2004/0258727 A1 (LIU et al) 23 December 2004 (23.12.2004) entire document	1-3, 46
A	POPESCU et al. "pH-Responsive Hydrogel/Liposome Soft Nanocomposites For Tuning Drug Release" Biomacromolecules, 05 July 2011 (05.07.2011), Vol. 12, Pgs. 3023–3030. entire document	1-3, 46

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 August 2014	22 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/032662

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 4-45
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.