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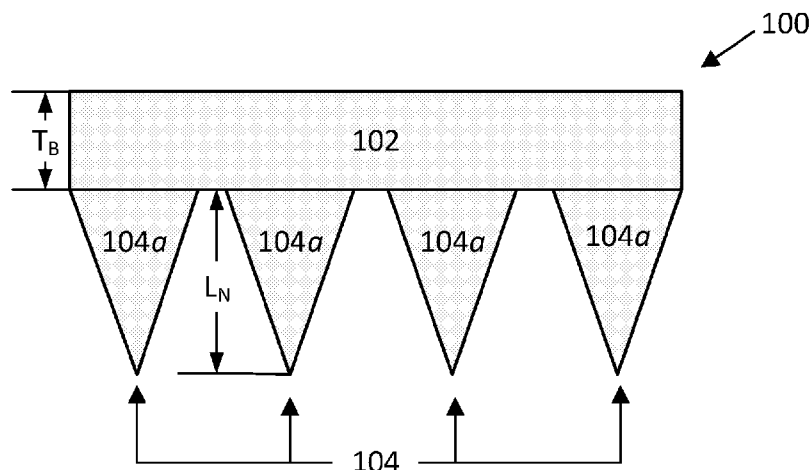


FIG. 1

(57) Abstract: Described herein are devices comprising a detachable microneedle array and materials, methods, and techniques for preparing the same. Further described herein are detachable microneedle arrays comprising a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel, the multi-component hydrogel comprising a biopolymer and a supramolecular network.



DETACHABLE MICRONEEDLE ARRAYS

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/479,255, filed on January 10, 2023, and the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

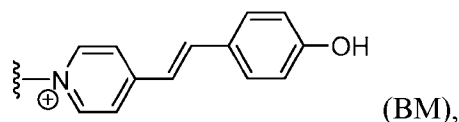
[0002] The present disclosure relates to devices comprising a detachable microneedle array and materials, methods, and techniques for preparing the same. Exemplary detachable microneedle arrays comprise a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel. Exemplary multi-component hydrogels may comprise a biopolymer and a supramolecular network.

INTRODUCTION

[0003] Typically, the administration of vaccines and pharmaceuticals require the use of hypodermic needles, with injections performed by trained medical professionals, caregivers, and patients themselves. What is needed are minimally invasive transdermal devices that can afford self-administration with minimal pain or discomfort.

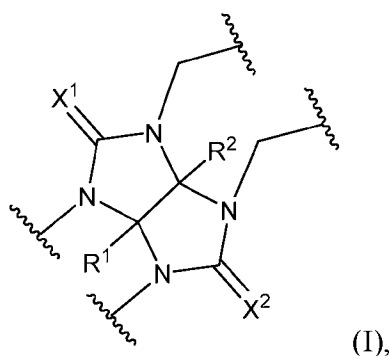
SUMMARY

[0004] In some aspects, the present disclosure provides a device comprising a detachable microneedle array, the detachable microneedle array comprising a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel, the multi-component hydrogel comprising: a biopolymer; and a supramolecular network, the supramolecular network comprising: an optionally substituted cucurbit[8]uril non-covalently crosslinked with two moieties of formula (BM):



wherein each moiety of formula (BM) is attached to a multi-armed polymer.

[0005] The biopolymer may comprise a polysaccharide, a polypeptide, or a combination thereof. The polysaccharide may be selected from the group consisting of carboxymethyl cellulose, hyaluronic acid, dextran, alginate, chitosan, chitin, cellulose, and combinations thereof. The optionally substituted cucurbit[8]uril may comprise 8 repeating units of formula (I) arranged in a barrel shape:



wherein:

X^1 and X^2 are each independently O or S;

R^1 and R^2 are each independently hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, G^x , $-C_{1-6}$ alkylene- G^x , $-C_{1-6}$ alkylene- OR^{1x} , $-C_{1-6}$ alkylene- SR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, $-C_{1-6}$ alkylene- SO_2R^x , $-C_{1-6}$ alkylene- $C(O)R^x$, $-C_{1-6}$ alkylene- $C(O)OR^x$, or $-C_{1-6}$ alkylene- $C(O)N(R^x)_2$; or R^1 and R^2 , together with the atoms to which they attach, form a 5- to 8-membered unsaturated or partially unsaturated carbocyclic or heterocyclic ring, the carbocyclic or heterocyclic ring being unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-2} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

G^x , at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl containing 1-3 heteroatoms, a 4- to 12-membered heterocyclyl containing 1-2

heteroatoms, or a 3- to 12-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^x, at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, -C₁₋₆alkylene-OH, oxo, OH, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, C₃₋₄cycloalkyl, and -C₁₋₃alkylene-C₃₋₄cycloalkyl.

[0006] X¹ and X² may each be O. R¹ and R² may each be hydrogen.

[0007] The multi-armed polymer may comprise polyethylene glycol. The multi-armed polymer may be a four-armed or an eight-armed polymer. The device may be air-bubble free. The biopolymer and the supramolecular network may be present in the multi-component hydrogel at a mass ratio of 0.1:1 to 10:1. The optionally substituted cucurbit[8]uril and the multi-armed polymer may be present in the supramolecular network at a molar ratio of 1:1 to 5:1. A therapeutic agent may be encapsulated within the multi-component hydrogel. The therapeutic agent may be a biomolecule. The biomolecule may be a protein, peptide, antibody, or nucleic acid. The biomolecule may be insulin.

[0008] In other aspects, the present disclosure provides methods of preparing devices, the methods comprising mixing an optionally substituted cucurbit[8]uril with a multi-armed polymer in water to provide a cucurbit[8]uril-polymer mixture; lyophilizing the cucurbit[8]uril-polymer mixture to provide a lyophilized cucurbituril-polymer mixture; adding the lyophilized cucurbit[8]uril-polymer mixture to water to form the supramolecular network; mixing the supramolecular network with the biopolymer to form the multi-component hydrogel; adding the multi-component hydrogel to a mold, the mold comprising a plurality of microneedle molds; applying a force to the multi-component hydrogel such that the multi-component hydrogel fills each microneedle mold; drying the multi-component hydrogel in the mold to provide the device comprising the detachable microneedle array; and removing the device comprising the detachable microneedle array from the mold.

[0009] In some instances, before adding the multi-component hydrogel to the mold, a therapeutic agent may be mixed with the multi-component hydrogel. In some instances, after adding the multi-component hydrogel to the mold, the method may not comprise a covalent crosslinking operation. In other instances, after adding the multi-component hydrogel to the mold, the method further comprises a covalent crosslinking operation. In some instances, after applying

the force to the multi-component hydrogel, no air-bubble may be present in the multi-component hydrogel in the mold.

[0010] In other aspects, the present disclosure provides methods of transdermally delivering a therapeutic agent to a subject in need thereof, the method comprising penetrating an area of the subject's skin with a device comprising a detachable microneedle array, so that each detachable microneedle is embedded within the subject's skin; allowing each detachable microneedle to swell within the subject's skin; and removing the backing from the subject's skin. After removing the backing from the subject's skin, the detachable microneedles may remain embedded within the subject's skin. After removing the backing from the subject's skin, the drug may be transdermally delivered for 1 hour to 200 hours. The subject in need thereof may have diabetes.

DESCRIPTION OF DRAWINGS

[0011] FIG. 1 schematically illustrates a side view of an exemplary detachable microneedle array described herein

[0012] FIG. 2 is a flowchart of an exemplary method for preparing exemplary detachable microneedle arrays described herein.

[0013] FIG. 3 schematically illustrates an exemplary detachable microneedle array comprising an exemplary supramolecular network ("PEG_{8a}-BM-CB[8]") and a biopolymer, and methods for making the same.

[0014] FIG. 4 shows the ¹H NMR spectrum of (*E*)-4-(4-hydroxystyryl)-1-(6-(prop-2-yn-1-yloxy)hexyl)pyridin-1-ium.

[0015] FIGS. 5A–5B show the scanning electron microscopy (SEM) images of exemplary detachable microneedle arrays prepared from PEG_{8a}-BM-CB[8] supramolecular networks and various mechanical biopolymers of carboxymethyl cellulose (CMC, *top row*), hyaluronic acid (HA, *middle row*) or dextran (*bottom row*). Porcine skin was used to assess the exemplary detachable microneedle arrays shown in FIGS. 5A–5B.

[0016] FIG. 5A shows SEM images of exemplary detachable microneedle arrays prepared from multi-component hydrogel formulations, without UV crosslinking. Without UV treatment, the supramolecular multi-component formulations produce well-formed microneedles from all

biopolymers, evident in scanning electron microscopy (SEM) images (*left side microscopy images*) that can penetrate and become embedded within porcine skin (*right side photographs*).

[0017] FIG. 5B shows SEM images of exemplary detachable microneedle arrays prepared with photodimer crosslinking. Upon UV treatment to convert PEG_{8a}-BM $\subset$ CB[8] complexes to a covalently crosslinked PEG network (*right column*) the needles retain their regular shape by SEM (*left side microscopy images*) but are not retained in pig skin following device application and removal (*right side photographs*).

[0018] FIG. 6 shows a comparison of the ¹H NMR spectra of (*E*)-4-(4-hydroxystyryl)-1-(6-(prop-2-yn-1-yloxy)hexyl)pyridin-1-ium (PEG_{8a}-BM) (top), ¹H NMR spectra of PEG_{8a}-BM non-covalently associated with CB[8] (middle), and the ¹H NMR spectra of UV-crosslinked PEG_{8a}-BM with CB[8] (bottom).

[0019] FIG. 7A shows the rheological frequency sweeps for PEG_{8a}-BM $\subset$ CB[8]/carboxymethylcellulose (CMC) multi-component hydrogels in both supramolecular and UV-crosslinked covalent states.

[0020] FIG. 7B graphically shows compression testing results exemplary dried microneedle arrays prepared from PEG_{8a}-BM $\subset$ CB[8]/CMC multi-component hydrogels in both their supramolecular and UV-crosslinked covalent state, with the slope of the linear regime of their deformation used to determine the stiffness.

[0021] FIG. 7C graphically shows the release of FITC-Insulin over time from exemplary microneedle arrays prepared from PEG_{8a}-BM $\subset$ CB[8]/CMC multi-component hydrogels in both their supramolecular and UV-crosslinked covalent state and fit to the Korsmeyer-Peppas equation.

[0022] FIG. 7D shows fluorescence images depicting the distribution of FITC insulin in the needles and backing layer.

[0023] FIG. 8A schematically illustrates the mouse model experiment, which includes applying an exemplary device for 5 minutes to the skin of a fasted diabetic rat with serial blood glucose monitoring for 12 h following peeling of the device.

[0024] FIG. 8B graphically compares the blood glucose levels (BGL) for PEG_{8a}-BM $\subset$ CB[8]/CMC multi-component hydrogels in supramolecular (black) and covalent (grey) states.

DETAILED DESCRIPTION

[0025] Before any embodiments of the disclosure are explained in detail, it is to be understood that the disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The disclosure is capable of other embodiments and of being practiced or of being carried out in various way.

I. Definitions

[0026] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0027] The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of” and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0028] The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9–1.1. Other meanings of “about” may be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0029] As used herein, the terms “control,” or “reference” are used herein interchangeably. A “reference” or “control” level may be a predetermined value or range, which is employed as a baseline or benchmark against which to assess a measured result. “Control” also refers to control experiments or control cells.

[0030] As used herein, the term “dose” denotes any form of an active ingredient formulation or composition, including cells, that contains an amount sufficient to initiate or produce a therapeutic effect with at least one or more administrations. “Formulation” and “composition” are used interchangeably herein.

[0031] As used herein, the term “prophylaxis” refers to preventing or reducing the progression of a disorder, either to a statistically significant degree or to a degree detectable by a person of ordinary skill in the art.

[0032] As used herein, the terms “effective amount” or “therapeutically effective amount,” refers to a substantially non-toxic, but sufficient amount of an action, agent, composition, or cell(s) being administered to a subject that will prevent, treat, or ameliorate to some extent one or more of the symptoms of the disease or condition being experienced or that the subject is susceptible to contracting. The result can be the reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An effective amount may be based on factors individual to each subject, including, but not limited to, the subject’s age, size, type or extent of disease, stage of the disease, route of administration, the type or extent of supplemental therapy used, ongoing disease process, and type of treatment desired.

[0033] As used herein, the term “subject” refers to an animal. Typically, the subject is a mammal. A subject also refers to primates (e.g., humans, male or female; infant, adolescent, or adult), non-human primates, rats, mice, rabbits, pigs, cows, sheep, goats, horses, dogs, cats, fish, birds, and the like. In one embodiment, the subject is a primate. In one embodiment, the subject is a human.

[0034] As used herein, a subject is “in need of treatment” if such subject would benefit biologically, medically, or in quality of life from such treatment. A subject in need of treatment does not necessarily present symptoms, particular in the case of preventative or prophylaxis treatments.

[0035] As used herein, “treatment” or “treating” refers to prophylaxis of, preventing, suppressing, repressing, reversing, alleviating, ameliorating, or inhibiting the progress of biological process including a disorder or disease, or eliminating a disease. A treatment may be

either performed in an acute or chronic way. The term “treatment” also refers to reducing the severity of a disease or symptoms associated with such disease prior to affliction with the disease. “Repressing” or “ameliorating” a disease, disorder, or the symptoms thereof involves administering a cell, composition, or compound described herein to a subject after clinical appearance of such disease, disorder, or its symptoms. “Prophylaxis of” or “preventing” a disease, disorder, or the symptoms thereof involves administering a cell, composition, or compound described herein to a subject prior to onset of the disease, disorder, or the symptoms thereof. “Suppressing” a disease or disorder involves administering a cell, composition, or compound described herein to a subject after induction of the disease or disorder thereof but before its clinical appearance or symptoms thereof have manifest.

[0036] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0037] The term “alkoxy,” as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0038] The term “alkyl,” as used herein, means a straight or branched, saturated hydrocarbon chain. The term “lower alkyl” or “C₁₋₆alkyl” means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term “C₁₋₄alkyl” means a straight or branched chain saturated hydrocarbon containing from 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

[0039] The term “alkenyl,” as used herein, means a straight or branched, hydrocarbon chain containing at least one carbon-carbon double bond.

[0040] The term “alkoxyalkyl,” as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

[0041] The term “alkylene,” as used herein, refers to a divalent group derived from a straight or branched saturated chain hydrocarbon, for example, of 1 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂CH₂-, and -CH₂CH₂CH₂CH₂CH₂-.

[0042] The term “deuterioalkylene,” as used herein, means an alkylene group, as defined herein, in which one or more hydrogen atoms in the alkylene are the isotope deuterium, i.e., ²H. Representative examples of deuterioalkylene include -CD₂-, -CH₂CD₂-, and -CD₂CD₂-.

[0043] The term “alkylamino,” as used herein, means at least one alkyl group, as defined herein, is appended to the parent molecular moiety through an amino group, as defined herein.

[0044] The term “amide,” as used herein, means -C(O)NR- or -NRC(O)-, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0045] The term “aminoalkyl,” as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0046] The term “amino,” as used herein, means -NR_xR_y, wherein R_x and R_y may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl. In the case of an aminoalkyl group or any other moiety where amino appends together two other moieties, amino may be -NR_x-, wherein R_x may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0047] The term “aryl,” as used herein, refers to a phenyl or a phenyl appended to the parent molecular moiety and fused to a cycloalkane group (e.g., the aryl may be indan-4-yl), fused to a 6-membered arene group (i.e., the aryl is naphthyl), or fused to a non-aromatic heterocycle (e.g., the aryl may be benzo[d][1,3]dioxol-5-yl). The term “phenyl” is used when referring to a substituent and the term 6-membered arene is used when referring to a fused ring. The 6-membered arene is monocyclic (e.g., benzene or benzo). The aryl may be monocyclic (phenyl) or bicyclic (e.g., a 9- to 12-membered fused bicyclic system).

[0048] The term “cyanoalkyl,” as used herein, means at least one -CN group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0049] The term “cycloalkoxy,” as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[0050] The term “cycloalkyl” or “cycloalkane,” as used herein, refers to a saturated ring system containing all carbon atoms as ring members and zero double bonds. The term “cycloalkyl” is used herein to refer to a cycloalkane when present as a substituent. A cycloalkyl may be a monocyclic cycloalkyl (e.g., cyclopropyl), a fused bicyclic cycloalkyl (e.g., decahydronaphthalenyl), or a bridged cycloalkyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptanyl). Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, and bicyclo[1.1.1]pentanyl.

[0051] The term “cycloalkenyl” or “cycloalkene,” as used herein, means a non-aromatic monocyclic or multicyclic ring system containing all carbon atoms as ring members and at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. The term “cycloalkenyl” is used herein to refer to a cycloalkene when present as a substituent. A cycloalkenyl may be a monocyclic cycloalkenyl (e.g., cyclopentenyl), a fused bicyclic cycloalkenyl (e.g., octahydronaphthalenyl), or a bridged cycloalkenyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptenyl). Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

[0052] The term “carbocyclyl” means a “cycloalkyl” or a “cycloalkenyl.” The term “carbocycle” means a “cycloalkane” or a “cycloalkene.” The term “carbocyclyl” refers to a “carbocycle” when present as a substituent.

[0053] The term “halogen” or “halo,” as used herein, means Cl, Br, I, or F.

[0054] The term “haloalkyl,” as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by a halogen.

[0055] The term “haloalkoxy,” as used herein, means at least one haloalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom.

[0056] The term “halocycloalkyl,” as used herein, means a cycloalkyl group, as defined herein, in which one or more hydrogen atoms are replaced by a halogen.

[0057] The term “heteroalkyl,” as used herein, means an alkyl group, as defined herein, in which one or more of the carbon atoms has been replaced by a heteroatom selected from S, O, P and N. Representative examples of heteroalkyls include, but are not limited to, alkyl ethers, secondary and tertiary alkyl amines, amides, and alkyl sulfides.

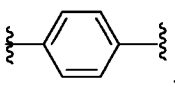
[0058] The term “heteroaryl,” as used herein, refers to an aromatic monocyclic heteroatom-containing ring (monocyclic heteroaryl) or a bicyclic ring system containing at least one monocyclic heteroaromatic ring (bicyclic heteroaryl). The term “heteroaryl” is used herein to refer to a heteroarene when present as a substituent. The monocyclic heteroaryl are five or six membered rings containing at least one heteroatom independently selected from the group consisting of N, O and S (e.g. 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N). The five membered aromatic monocyclic rings have two double bonds and the six membered aromatic monocyclic rings have three double bonds. The bicyclic heteroaryl is an 8- to 12-membered ring system and includes a fused bicyclic heteroaromatic ring system (i.e., 10π electron system) such as a monocyclic heteroaryl ring fused to a 6-membered arene (e.g., quinolin-4-yl, indol-1-yl), a monocyclic heteroaryl ring fused to a monocyclic heteroarene (e.g., naphthyridinyl), and a phenyl fused to a monocyclic heteroarene (e.g., quinolin-5-yl, indol-4-yl). A bicyclic heteroaryl/heteroarene group includes a 9-membered fused bicyclic heteroaromatic ring system having four double bonds and at least one heteroatom contributing a lone electron pair to a fully aromatic 10π electron system, such as ring systems with a nitrogen atom at the ring junction (e.g., imidazopyridine) or a benzoxadiazolyl. A bicyclic heteroaryl also includes a fused bicyclic ring system composed of one heteroaromatic ring and one non-aromatic ring such as a monocyclic heteroaryl ring fused to a monocyclic carbocyclic ring (e.g., 6,7-dihydro-5H-cyclopenta[b]pyridinyl), or a monocyclic heteroaryl ring fused to a monocyclic heterocycle (e.g., 2,3-dihydrofuro[3,2-b]pyridinyl). The bicyclic heteroaryl is attached to the parent molecular moiety at an aromatic ring atom. Other representative examples of heteroaryl include, but are not limited to, indolyl (e.g., indol-1-yl, indol-2-yl, indol-4-yl), pyridinyl (including pyridin-2-yl, pyridin-3-yl, pyridin-4-yl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl (e.g., pyrazol-4-yl), pyrrolyl, benzopyrazolyl, 1,2,3-triazolyl (e.g., triazol-4-yl), 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, imidazolyl, thiazolyl (e.g., thiazol-4-yl), isothiazolyl, thienyl, benzimidazolyl (e.g., benzimidazol-5-yl), benzothiazolyl, benzoxazolyl, benzoxadiazolyl,

benzothienyl, benzofuranyl, isobenzofuranyl, furanyl, oxazolyl, isoxazolyl, purinyl, isoindolyl, quinoxaliny, indazolyl (e.g., indazol-4-yl, indazol-5-yl), quinazoliny, 1,2,4-triazinyl, 1,3,5-triazinyl, isoquinoliny, quinoliny, imidazo[1,2-*a*]pyridinyl (e.g., imidazo[1,2-*a*]pyridin-6-yl), naphthyridinyl, pyridoimidazolyl, thiazolo[5,4-*b*]pyridin-2-yl, and thiazolo[5,4-*d*]pyrimidin-2-yl.

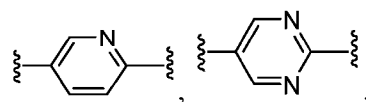
[0059] The term “heterocycle” or “heterocyclic,” as used herein, means a monocyclic heterocycle, a bicyclic heterocycle, or a tricyclic heterocycle. The term “heterocyclyl” is used herein to refer to a heterocycle when present as a substituent. The monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocyclyls include, but are not limited to, azetidiny, azepany, aziridinyl, diazepany, 1,3-dioxany, 1,3-dioxolany, 1,3-dithiolany, 1,3-dithianyl, imidazoliny, imidazolidinyl, isothiazoliny, isothiazolidinyl, isoxazoliny, isoxazolidinyl, morpholiny, 2-oxo-3-piperidinyl, 2-oxoazepan-3-yl, oxadiazoliny, oxadiazolidinyl, oxazoliny, oxazolidinyl, oxetany, oxepany, oxocany, piperazinyl, piperidinyl, pyranyl, pyrazoliny, pyrazolidinyl, pyrroliny, pyrrolidinyl, tetrahydrofurany, tetrahydropyranyl, tetrahydropyridinyl, tetrahydrothienyl, thiadiazoliny, thiadiazolidinyl, 1,2-thiazinany, 1,3-thiazinany, thiazoliny, thiazolidinyl, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a 6-membered arene, or a monocyclic heterocycle fused to a monocyclic cycloalkane, or a monocyclic heterocycle fused to a monocyclic cycloalkene, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a monocyclic heterocycle fused to a monocyclic heteroarene, or a spiro heterocycle group, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. The bicyclic heterocyclyl is attached to the parent molecular moiety at a non-aromatic ring atom (e.g., indolin-1-yl). Representative examples of bicyclic heterocyclyls

include, but are not limited to, chroman-4-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzothien-2-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), azabicyclo[3.1.0]hexanyl (including 3-azabicyclo[3.1.0]hexan-3-yl), 2,3-dihydro-1*H*-indol-1-yl, isoindolin-2-yl, octahydrocyclopenta[*c*]pyrrolyl, octahydropyrrolopyridinyl, tetrahydroisoquinoliny, 7-oxabicyclo[2.2.1]heptanyl, hexahydro-2*H*-cyclopenta[*b*]furanyl, 2-oxaspiro[3.3]heptanyl, 3-oxaspiro[5.5]undecanyl, 6-oxaspiro[2.5]octan-1-yl, and 3-oxabicyclo[3.1.0]hexan-6-yl. Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a 6-membered arene, or a bicyclic heterocycle fused to a monocyclic cycloalkane, or a bicyclic heterocycle fused to a monocyclic cycloalkene, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Examples of tricyclic heterocycles include, but are not limited to, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[*b*]furan, hexahydro-1*H*-1,4-methanocyclopenta[*c*]furan, aza-adamantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). The monocyclic, bicyclic, and tricyclic heterocyclyls are connected to the parent molecular moiety at a non-aromatic ring atom.

[0060] The term “1,4-phenylene” refers to the following divalent group that links two portions

of a molecule in a 1,4 or para relationship: 

[0061] The term “6-membered 1,4-heteroarylene” refers to a divalent 6-membered heteroarene that links two portions of a molecule in a 1,4 or para relationship on the heteroarene, e.g.,



[0062] The term “hydroxyl” or “hydroxy,” as used herein, means an -OH group.

[0063] The term “hydroxyalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0064] Terms such as “alkyl,” “cycloalkyl,” “alkylene,” etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., “C₁₋₄alkyl,” “C₃₋₆cycloalkyl,” “C₁₋₄alkylene”). These designations are used as generally understood by those skilled

in the art. For example, the representation "C" followed by a subscripted number indicates the number of carbon atoms present in the group that follows. Thus, "C₃alkyl" is an alkyl group with three carbon atoms (i.e., n-propyl, isopropyl). Where a range is given, as in "C₁₋₄," the members of the group that follows may have any number of carbon atoms falling within the recited range. A "C₁₋₄alkyl," for example, is an alkyl group having from 1 to 4 carbon atoms, however arranged (i.e., straight chain or branched).

[0065] The terms "parent molecule" or "parent molecular moiety" refer to the entire portion of a molecule to which a substituent is attached, i.e., the remainder of the molecule.

[0066] The term "sulfonamide," as used herein, means -S(O)₂NR^z- or -NR^zS(O)-, wherein R^z may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0067] The term "substituents" refers to a group "substituted" on a group such as an alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heteroalkyl, or heterocycle group, at any atom of that group. Any atom can be substituted.

[0068] The term "substituted" refers to a group that may be further substituted with one or more non-hydrogen substituent groups. Substituent groups include, but are not limited to, halogen, =O (oxo), =S (thioxo), cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, amide, carbamate, and acyl. In some embodiments, a group is optionally substituted. In some embodiments, a group is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, an aryl, heteroaryl, cycloalkyl, or heterocycle is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, an aryl, heteroaryl, cycloalkyl, or heterocycle may be independently unsubstituted or substituted with 1, 2, or 3 substituents.

[0069] The term "optionally substituted" refers to being substituted or unsubstituted. In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when

more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound.

[0070] For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

II. Multi-Component Hydrogels

[0001] Various multi-component hydrogels are used to prepare exemplary devices comprising a detachable microneedle array described herein. Various aspects of exemplary multi-component hydrogels are discussed below.

[0002] As used herein, the term “hydrogel” is a three-dimensional network of polymers or related building blocks that is insoluble in water or other aqueous media, but which is capable of absorbing and retaining water to form a structured and hydrated network.

As used herein, the term “multi-component hydrogel” is a hydrogel comprising at least two different materials.

[0003] Exemplary multi-component hydrogels described herein comprise a biopolymer and a supramolecular network. The biopolymer and the supramolecular network may be present in the multi-component hydrogel at a mass ratio of 0.1:1 to 10:1. In some instances, the multi-component hydrogel may be present at a mass ratio of 0.5:1 to 9.5:1; 1:1 to 9:1; 1.5:1 to 8.5:1; 2:1 to 8:1; 2.5:1 to 7.5:1; 3:1 to 7:1; 3.5:1 to 6.5:1; 4:1 to 6:1; or 4.5:1 to 5.5:1. In some instances, the multi-component biopolymer and the supramolecular network may be present in the hydrogel at a mass ratio of no greater than 10:1; no greater than 9:1; no greater than 8:1; no greater than 7:1; no greater than 6:1; no greater than 5:1; no greater than 4:1; no greater than 3:1; no greater than 2:1; or no greater than 1:1. In some instances, the biopolymer and the supramolecular network may be present in the hydrogel at a mass ratio of no less than 0.1:1; no less than 0.5:1; no less than 1:1; no less than 2:1; no less than 3:1; no less than 4:1; no less than 5:1; no less than 6:1; no less than 7:1; no less than 8:1; or no less than 9:1.

[0004] Various biopolymers and supramolecular networks may be used for the multi-component hydrogels described herein. Various aspects of exemplary biopolymers and supramolecular networks are discussed below.

A. Exemplary Biopolymers

[0005] The term “biopolymer,” as used herein, means a naturally occurring polymer produced by a living organism, or a synthetic variation of the same.

[0006] The biopolymer may comprise, without limitation, a polysaccharide, a polypeptide, a nucleic acid, or a combination thereof.

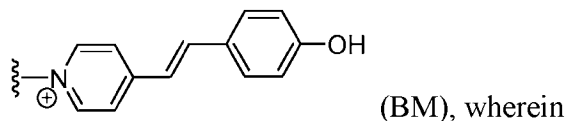
[0007] The polysaccharide may comprise, without limitation, carboxymethyl cellulose, hyaluronic acid, dextran, alginate, chitosan, chitin, cellulose, or a combination thereof.

[0008] The polypeptide may comprise, without limitation, silk fibroin, collagen, gelatin, synthetically polymerized amino acids, or a combination thereof.

B. Exemplary Supramolecular Networks

[0009] The term “supramolecular network,” as used herein, means a material wherein points of crosslinking are prepared from “supramolecular recognition motifs.” The term “supramolecular recognition motif,” as used herein, means a molecular self-assembly of two or more compounds interacting with each other via intermolecular interactions, such as, for example, hydrogen bonding, dipole-dipole interactions, van der Waals forces, cation- π interactions, π - π bonds, CH/ π interactions, host-guest inclusion, and/or hydrophobic effects, resulting in the formation of intermolecular complexes with enhanced or different functionality compared to each compound individually.

[0010] Exemplary supramolecular recognition motifs useful in preparing a model supramolecular network as described herein comprise an optionally substituted cucurbit[8]uril non-covalently crosslinked with two moieties of formula (BM):



each moiety of formula (BM) is attached to a multi-armed polymer.

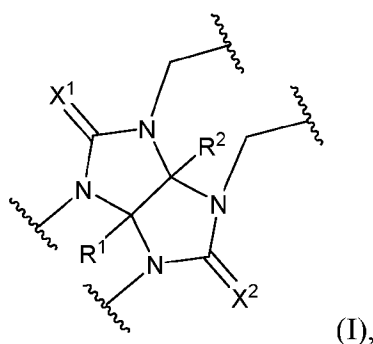
[0011] The cucurbit[8]uril non-covalently crosslinked with two moieties of formula (BM) may be referred to as a ternary complex. The term “ternary complex,” as used herein, means a complex

formed between a host (e.g., the optionally substituted cucurbit[8]uril) and two guests (e.g., the two moieties of formula (BM)).

1. Optionally Substituted Cucurbit[8]urils

[0012] Cucurbit[8]uril (CB[8]; CAS 259886-51-6) is a barrel-shaped container molecule which has eight repeat glycoluril units. CB[8] and its derivatives may readily be synthesized using standard techniques and is available commercially (e.g., Sigma-Aldrich, Mo. USA).

[0013] For exemplary supramolecular networks described herein, the optionally substituted cucurbit[8]uril may comprise 8 repeating units of formula (I) arranged in a barrel shape,



wherein:

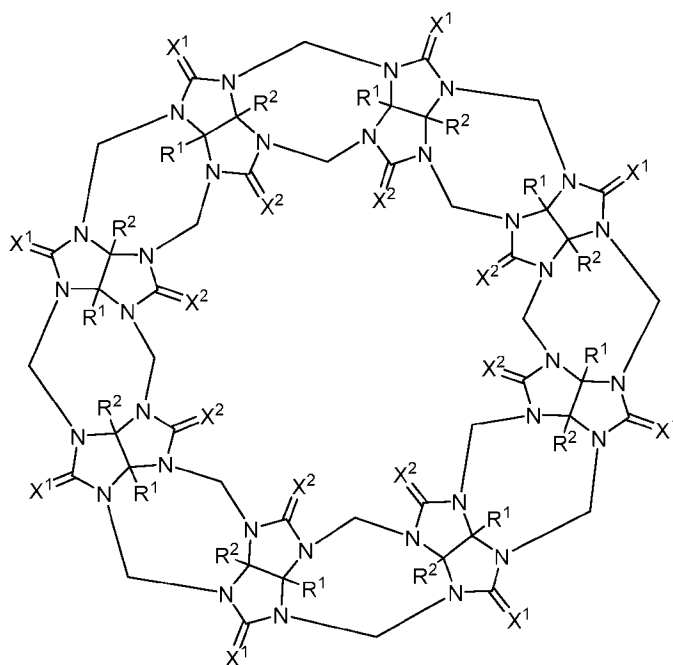
X^1 and X^2 are each independently O or S;

R^1 and R^2 are each independently hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, G^x , $-C_{1-6}$ alkylene- G^x , $-C_{1-6}$ alkylene- OR^{1x} , $-C_{1-6}$ alkylene- SR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, $-C_{1-6}$ alkylene- SO_2R^x , $-C_{1-6}$ alkylene- $C(O)R^x$, $-C_{1-6}$ alkylene- $C(O)OR^x$, or $-C_{1-6}$ alkylene- $C(O)N(R^x)_2$; or R^1 and R^2 , together with the atoms to which they attach, form a 5- to 8-membered unsaturated or partially unsaturated carbocyclic or heterocyclic ring, the carbocyclic or heterocyclic ring being unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-2} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4

substituents independently selected from the group consisting of halogen, C₁₋₄alkyl, and C₁₋₄haloalkyl; and

G^x, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl containing 1-3 heteroatoms, a 4- to 12-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 12-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^x, at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, -C₁₋₆alkylene-OH, oxo, OH, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, C₃₋₄cycloalkyl, and -C₁₋₃alkylene-C₃₋₄cycloalkyl, i.e., a cucurbit[8]uril of formula:

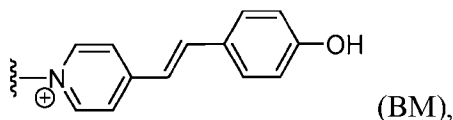


[0014] In some instances, X¹ and X² are each O. In some instances, R¹ and R² are each hydrogen.

2. Multi-Armed Polymers

[0015] The term “multi-armed polymer,” as used herein means a branched or star-like macromolecule having at least 3 arms emanating from a central core or branch point.

[0016] Suitable multi-armed polymers for the detachable microneedle arrays described herein include any multi-armed polymer comprising a moiety of formula (BM):



In various instances, each arm of the multi-armed polymer is terminated with a moiety of formula (BM).

[0017] The multi-armed polymer may vary depending on the specific implementation. In various instances, the multi-armed polymer may comprise polyethylene glycol. In some instances, the multi-armed polymer is a four-armed polymer. In other instances, the multi-armed polymer is an eight-armed polymer.

[0018] The optionally substituted cucurbit[8]uril and the multi-armed polymer may be present at various molar ratios. The particular molar ratio may depend on the specific cucurbit[8]uril and multi-armed polymer. In various instances, the optionally substituted cucurbit[8]uril and the multi-armed polymer may be present in the supramolecular network at a molar ratio of 1:1 to 5:1. In some instances, the optionally substituted cucurbit[8]uril and the multi-armed polymer may be present in the supramolecular network at a molar ratio of 1.5:1 to 4.5:1; 2:1 to 4:1; 2.5:1 to 3.5:1; or 3:1 to 4:1. In some instances, the optionally substituted cucurbit[8]uril and the multi-armed polymer may be present in the supramolecular network at a molar ratio of no greater than 5:1; no greater than 4.5:1; no greater than 4:1; no greater than 3.5:1; no greater than 3:1; no greater than 2.5:1; no greater than 2:1; or no greater than 1.5:1. In some instances, the optionally substituted cucurbit[8]uril and the multi-armed polymer may be present in the supramolecular network at a molar ratio of no less than 1:1; no less than 1.5:1; no less than 2:1; no less than 2.5:1; no less than 3:1; no less than 3.5:1; no less than 4:1; or no less than 4.5:1.

C. Exemplary Therapeutic Agents

[0019] Exemplary multi-component hydrogels may further comprise a therapeutic agent. The term “therapeutic agent,” as used herein includes substance that may be used for the treatment or mitigation of a disease condition or ailment. The specific therapeutic agent may vary, for example, on the condition being treated. In various instances, the therapeutic agent is encapsulated within the multi-component hydrogel.

[0020] In some instances, the therapeutic agent may be a biomolecule. As generally defined herein, “biomolecule” refers to any compound or biological material which may be found in a

living organism. Examples of classes of biomolecules include, but are not limited to, proteins, peptides, nucleic acids, lipids, polysaccharides, small molecules, primary metabolites, secondary metabolites, and natural products.

[0021] The biomolecule may be a protein, peptide, antibody, nucleic acid, or a combination thereof. In various instances, the biomolecule may be insulin or an insulin variant or analogue. Exemplary insulin variants or analogues include, without limitation, Humalog® (insulin lispro); Novolog® (insulin aspart); Lantus®, Toujeo®, Basaglar®, Semglee®, (insulin glargine); Levemir® (insulin detemir); Apidra® (insulin glulisine), and combinations thereof.

III. Devices

[0022] Further disclosed herein are devices comprising a detachable microneedle array. The detachable microneedle array may be prepared in any suitable shape. Example shapes include a square shape, a rectangular shape, a circular shape, an oval shape, and a letter shape. In addition, the shape of the detachable microneedle is not limited. Examples of detachable microneedle shapes include a conical shape, a circular truncated cone shape, a quadrangular pyramid shape, a triangular pyramid shape, and a konide-like shape. Additionally, exemplary detachable microneedle arrays 100 may include different populations of microneedles where the different populations have different shapes. The number of detachable microneedles in the array 100 is also generally not limited and may vary depending on the specific implementation. Example arrays include 2×2 , 4×4 , 5×5 , 10×10 , 10×20 , 20×20 , 50×10 , 50×50 , 100×100 detachable microneedles, and the like.

[0023] FIG. 1 schematically illustrates an exemplary detachable microneedle array 100. As shown in FIG. 1, the detachable microneedle array 100 comprises a plurality of detachable microneedles 104 attached to a backing 102. The detachable microneedles 104 and the backing 102 may comprise the multi-component hydrogel described above. Accordingly, the description above for the hydrogel can be applied to the discussion below.

[0024] In various instances, the backing layer 102 comprises the same multi-component hydrogel as each detachable microneedle 104a. In other words, the backing layer 102 may be made from the same materials as the plurality of detachable microneedles 104.

[0025] In some instances, each detachable microneedle 104a is solid, i.e., does not comprise any air-bubble or channel. In various instances, the entire detachable microneedle array 100 may be air-bubble free.

[0026] In various instances, each detachable microneedle 104a may comprise a therapeutic agent. For example, in some instances, each microneedle 104a may comprise insulin. In some instances, at least a portion of the plurality of microneedles 104 can comprise the therapeutic agent. In some instances, at least a portion of the plurality of microneedles 104 may comprise the therapeutic agent.

[0027] In various instances, the detachable microneedle array 100 may have a surface area of 1 mm² to 40,000 mm². In some instances, the detachable microneedle array 100 may have a surface area of 5 mm² to 30,000 mm²; 10 mm² to 20,000 mm²; 15 mm² to 10,000 mm²; 20 mm² to 9,000 mm²; 25 mm² to 8,000 mm²; 30 mm² to 7,000 mm²; 40 mm² to 6,000 mm²; 50 mm² to 5,000 mm²; 60 mm² to 4,000 mm²; 70 mm² to 3,000 mm²; 80 mm² to 2,000 mm²; 90 mm² to 1,000 mm²; 100 mm² to 900 mm²; 200 mm² to 800 mm²; 300 mm² to 700 mm²; or 400 mm² to 600 mm². In some instances, the detachable microneedle array 100 may have a surface area of no greater than 40,000 mm²; no greater than 30,000 mm²; no greater than 20,000 mm²; no greater than 10,000 mm²; no greater than 9,000 mm²; no greater than 8,000 mm²; no greater than 7,000 mm²; no greater than 6,000 mm²; no greater than 5,000 mm²; no greater than 4,000 mm²; no greater than 3,000 mm²; no greater than 2,000 mm²; no greater than 1,000 mm²; no greater than 900 mm²; no greater than 800 mm²; no greater than 700 mm²; no greater than 600 mm²; no greater than 500 mm²; no greater than 400 mm²; no greater than 300 mm²; no greater than 200 mm²; no greater than 100 mm²; no greater than 90 mm²; no greater than 80 mm²; no greater than 70 mm²; no greater than 60 mm²; no greater than 50 mm²; no greater than 40 mm²; no greater than 30 mm²; no greater than 20 mm²; no greater than 15 mm²; or no greater than 10 mm². In some instances, the detachable microneedle array 100 may have a surface area of no less than 1 mm²; no less than 5 mm²; no less than 10 mm²; no less than 15 mm²; no less than 20 mm²; no less than 30 mm²; no less than 40 mm²; no less than 50 mm²; no less than 60 mm²; no less than 70 mm²; no less than 80 mm²; no less than 90 mm²; no less than 100 mm²; no less than 200 mm²; no less than 300 mm²; no less than 400 mm²; no less than 500 mm²; no less than 600 mm²; no less than 700 mm²; no less than 800 mm²; no less than 900 mm²; no less than 1,000 mm²; no less than 2,000 mm²; no less than 3,000 mm²; no less than 4,000 mm²; no less than 5,000 mm²; no less than 6,000 mm²; no less than 7,000 mm²; no less than

8,000 mm²; no less than 9,000 mm²; no less than 10,000 mm²; no less than 20,000 mm²; or no less than 30,000 mm².

[0028] In various instances, the backing layer 102 may have a thickness T_B of 50 μm to 5,000 μm . In some instances, the backing layer 102 may have a thickness T_B of 60 μm to 4,000 μm ; 70 μm to 3,000 μm ; 80 μm to 2,000 μm ; 90 μm to 1,000 μm ; 100 μm to 900 μm ; 200 μm to 800 μm ; 300 μm to 700 μm ; or 400 μm to 600 μm . In some instances, the backing layer 102 may have a thickness T_B of no greater than 5,000 μm ; no greater than 4,000 μm ; no greater than 3,000 μm ; no greater than 2,000 μm ; no greater than 1,000 μm ; no greater 900 μm ; no greater than 800 μm ; no greater than 700 μm ; no greater than 600 μm ; no greater than 500 μm ; no greater than 400 μm ; no greater than 300 μm ; no greater than 200 μm ; no greater than 100 μm ; no greater than 90 μm ; no greater than 80 μm ; no greater than 70 μm ; or no greater than 60 μm . In some instances, the backing layer 102 may have a thickness T_B of no less than 50 μm ; no less than 60 μm ; no less than 70 μm ; no less than 80 μm ; no less than 90 μm ; no less 100 μm ; no less than 200 μm ; no less than 300 μm ; no less than 400 μm ; no less than 500 μm ; no less than 600 μm ; no less than 700 μm ; no less than 800 μm ; no less than 900 μm ; no less than 1,000 μm ; no less than 2,000 μm ; no less than 3,000 μm ; or no less than 4,000 μm .

[0029] In various instances, each detachable microneedle 104a may have a length L_n of about 100 μm to about 1,000 μm . In some instances, each detachable microneedle 104a may have a length L_n of about 150 μm to about 950 μm ; about 200 μm to about 900 μm ; about 250 μm to about 850 μm ; about 300 μm to about 800 μm ; about 350 μm to about 750 μm ; about 400 μm to about 700 μm ; about 450 μm to about 650 μm ; or about 500 μm to about 600 μm . In various instances, each detachable microneedle 104a may have a length L_n of no greater than about 1,000 μm ; no greater than about 900 μm ; no greater than about 800 μm ; no greater than about 700 μm ; no greater than about 600 μm ; no greater than about 500 μm ; no greater than about 400 μm ; no greater than about 300 μm ; or no greater than about 200 μm . In various instances, each detachable microneedle 104a may have a length L_n of no less than about 100 μm ; no less than about 200 μm ; no less than about 300 μm ; no less than about 400 μm ; no less than 500 μm ; no less than 600 μm ; no less than 700 μm ; no less than 800 μm ; or no less than 900 μm .

[0030] In various instances, each detachable microneedle 104a may have a failure point of 0.01 N/needle to 10 N/needle. In some instances, each detachable microneedle 104a may have a failure point of 0.05 N/needle to 9.5 N/needle; 1 N/needle to 9 N/needle; 1.5 N/needle to 8.5 N/needle; 2

N/needle to 8 N/needle; 2.5 N/needle to 7.5 N/needle; 3 N/needle to 7 N/needle; 3.5 N/needle to 6.5 N/needle; 4 N/needle to 6 N/needle; or 4.5 N/needle to 5.5 N/needle. In some instances, each detachable microneedle 104a may have a failure point of no greater than 10 N/needle; no greater than 9 N/needle; no greater than 8 N/needle; no greater than 7 N/needle; no greater than 6 N/needle; no greater than 5 N/needle; no greater than 4 N/needle; no greater than 3 N/needle; no greater than 2 N/needle; no greater than 1 N/needle; or no greater than 0.05 N/needle. In some instances, each detachable microneedle 104a may have a failure point of no less than 0.01 N/needle; no less than 0.05 N/needle; no less than 1 N/needle; no less than 2 N/needle; no less than 3 N/needle; no less than 4 N/needle; no less than 5 N/needle; no less than 6 N/needle; no less than 7 N/needle; no less than 8 N/needle; or no less than 9 N/needle.

[0031] In various instances, each detachable microneedle may have a stiffness of 1 N/m to 10,000 N/m. In some instances, each detachable microneedle may have a stiffness of 5 N/m to 9,500 N/m; 10 N/m to 9,000 N/m; 15 N/m to 8,500 N/m; 20 N/m to 8,000 N/m; 25 N/m to 7,500 N/m; 30 N/m to 7,000 N/m; 35 N/m to 6,500 N/m; 40 N/m to 6,000 N/m; 45 N/m to 5,500 N/m; 50 N/m to 5,000 N/m; 55 N/m to 4,500 N/m; 60 N/m to 4,000 N/m; 65 N/m to 3,500 N/m; 70 N/m to 3,000 N/m; 75 N/m to 2,500 N/m; 80 N/m to 2,000 N/m; 85 N/m to 1,500 N/m; 90 N/m to 1,000 N/m; 150 N/m to 950 N/m; 100 N/m to 900 N/m; 250 N/m to 850 N/m; 200 N/m to 800 N/m; 350 N/m to 750 N/m; 300 N/m to 700 N/m; 450 N/m to 650 N/m; or 400 N/m to 600 N/m. In some instances, each detachable microneedle may have a stiffness of no greater than 10,000 N/m; no greater than 9,000 N/m; no greater than 8,000 N/m; no greater than 7,000 N/m; no greater than 6,000 N/m; no greater than 5,000 N/m; no greater than 4,000 N/m; no greater than 3,000 N/m; no greater than 2,000 N/m; no greater than 1,000 N/m; no greater than 900 N/m; no greater than 800 N/m; no greater than 700 N/m; no greater than 600 N/m; no greater than 500 N/m; no greater than 400 N/m; no greater than 300 N/m; no greater than 200 N/m; no greater than 100 N/m; no greater than 90 N/m; no greater than 80 N/m; no greater than 70 N/m; no greater than 60 N/m; no greater than 50 N/m; no greater than 40 N/m; no greater than 30 N/m; no greater than 20 N/m; or no greater than 10 N/m. In some instances, each detachable microneedle may have a stiffness of no less than 1 N/m; no less than 5 N/m; no less than 10 N/m; no less than 20 N/m; no less than 30 N/m; no less than 40 N/m; no less than 50 N/m; no less than 60 N/m; no less than 70 N/m; no less than 80 N/m; no less than 90 N/m; no less than 100 N/m; no less than 200 N/m; no less than 300 N/m; no less than 400 N/m; no less than 500 N/m; no less than 600 N/m; no less than 700 N/m; no

less than 800 N/m; no less than 900 N/m; no less than 1,000 N/m; no less than 2,000 N/m; no less than 3,000 N/m; no less than 4,000 N/m; no less than 5,000 N/m; no less than 6,000 N/m; no less than 7,000 N/m; no less than 8,000 N/m; or no less than 9,000 N/m.

IV. Methods of Preparation

[0032] Exemplary methods for preparing the devices comprising detachable microneedle arrays may include one or more exemplary operations.

[0033] FIG. 2 shows an exemplary method 200 for preparing exemplary detachable microneedle arrays disclosed and contemplated herein.

[0034] Broadly, method 200 includes supramolecular network preparation operations (200a), multi-component hydrogel preparation operations (200b), and multi-component hydrogel processing operations (200c). Various optional operations are shown in dotted outline in FIG. 2. Other embodiments may include more or fewer operations. Because the disclosed methods of making the detachable microneedle arrays include the multi-component hydrogel as disclosed above, the description above for the multi-component hydrogels, cucurbit[8]urils, multi-armed polymers, and therapeutic agents can be applied to the methods of making the detachable microneedle arrays.

[0035] As shown in FIG. 2, preparing the supramolecular network involves mixing an optionally substituted cucurbit[8]uril with a multi-armed polymer bearing a guest (e.g., the moiety of formula (BM)) in water to provide a cucurbit[8]uril-polymer mixture (operation 202), lyophilizing the cucurbit[8]uril-polymer mixture to provide a lyophilized cucurbituril-polymer mixture (operation 204), and adding the lyophilized cucurbituril-polymer mixture to water (operation 206).

[0036] Exemplary method 200 further includes preparing a multi-component hydrogel by mixing the supramolecular network with a biopolymer (operation 208). In some instances, method 200 may further comprise adding a therapeutic agent to the multi-component hydrogel (operation 209). In some instances, mixing the supramolecular network with the biopolymer (operation 208) and adding the therapeutic agent (operation 209) may occur concurrently. In other instances, mixing the supramolecular network with the biopolymer (operation 208) and adding the therapeutic agent (operation 209) may occur sequentially (i.e., operation 208 then operation 209).

[0037] As further illustrated in FIG. 2, method 200 may further comprise adding the multi-component hydrogel to a mold comprising a plurality of microneedle molds (operation 210). The number, shape, and dimensions of the molds is generally not limited and can correspond to the description of the microneedles and array thereof described above. Additionally, the mold can include populations of different shapes and populations of different dimensions (e.g., lengths).

[0038] Exemplary methods may further comprise applying a force to the multi-component hydrogel such that the multi-component hydrogel fills each microneedle mold (operation 212). Exemplary methods of applying force to the multi-component hydrogel include vacuum and centrifugation. In some instances, the mold is centrifuged, thereby applying a force to the multi-component hydrogel such that the multi-component hydrogel fills each microneedle mold. Application of the force to the multi-component hydrogel can aid in drying the multi-component hydrogel.

[0039] In some instances, after adding the multi-component hydrogel to the mold, the method does not comprise a covalent crosslinking operation. In other instances, after adding the multi-component hydrogel to the mold, the method further comprises a covalent crosslinking operation (operation 213). Exemplary crosslinking methods include exposing the multi-component hydrogel to ultra-violet (UV)-crosslinking conditions.

[0040] Method 200 may further include drying the multi-component hydrogel to provide a device comprising a microneedle array, the microneedle array comprising a plurality of microneedles that align in number and arrangement with the plurality of microneedle molds (operation 214). In some instances, drying the multi-component hydrogel is achieved by placing in a desiccator. Drying the hydrogel provides a plurality of microneedles, wherein each microneedle comprises the dehydrated multi-component hydrogel.

V. Methods of Treatment

[0041] Further disclosed herein are methods of transdermally delivering a therapeutic agent to a subject in need thereof. Exemplary methods of transdermally delivering the therapeutic agent to the subject in need thereof may comprise penetrating an area of the subject's skin with a device described herein.

[0042] Upon contacting the area of the subject's skin, each detachable microneedle may be embedded within the subject's skin. Exemplary methods may further comprise allowing each detachable microneedle to swell within the subject's skin and removing the backing from the subject's skin.

[0043] In various instances, upon penetrating an area of the subject's skin with the detachable microneedle array, the backing may be removed after a period of 0.1 minutes to 10 minutes. In some instances, upon penetrating an area of the subject's skin with the detachable microneedle array, the backing may be removed after a period of 0.5 minutes to 9.5 minutes; 1 minute to 9 minutes; 1.5 minutes to 8.5 minutes; 2 minutes to 8 minutes; 2.5 minutes to 7.5 minutes; 3 minutes to 7 minutes; 3.5 minutes to 6.5 minutes; 4 minutes to 6 minutes; or 4.5 minutes to 5.5 minutes. In some instances, upon penetrating an area of the subject's skin with the detachable microneedle array, the backing may be removed after a period of no greater than 10 minutes; no greater than 9 minutes; no greater than 8 minutes; no greater than 7 minutes; no greater than 6 minutes; no greater than 6 minutes; no greater than 5 minutes; no greater than 4 minutes; no greater than 3 minutes; no greater than 2 minutes; or no greater than 1 minute. In some instances, upon penetrating an area of the subject's skin with the detachable microneedle array, the backing may be removed after a period of no less than 0.1 minutes; no less than 0.5 minutes; no less than 1 minute; no less than 2 minutes; no less than 3 minutes; no less than 4 minutes; no less than 5 minutes; no less than 6 minutes; no less than 7 minutes; no less than 8 minutes; or no less than 9 minutes.

[0044] In some instances, after removing the backing from the subject's skin, the detachable microneedles may remain embedded within the subject's skin. In other instances, the microneedles may be removed with the backing.

[0045] Additionally, after removing the backing from the subject's skin, the drug may be transdermally delivered for 1 hour to 200 hours. In various instances, the drug may be delivered for 5 hours to 195 hours; 10 hours to 190 hours; 15 hours to 185 hours; 20 hours to 180 hours; 25 hours to 175 hours; 30 hours to 170 hours; 35 hours to 165 hours; 40 hours to 160 hours; 45 hours to 155 hours; 50 hours to 150 hours; 55 hours to 145 hours; 60 hours to 140 hours; 65 hours to 135 hours; 70 hours to 130 hours; 75 hours to 125 hours; 80 hours to 120 hours; 85 hours to 115 hours; or 90 hours to 110 hours. In various instances, the drug may be delivered for no greater than 200 hours; no greater than 175 hours; no greater than 150 hours; no greater than 125 hours; no greater than 100 hours; no greater than 75 hours; no greater than 50 hours; no greater than 25 hours; or no

greater than 5 hours. In various instances, the drug may be delivered for no less than 1 hour; no less than 5 hours; no less than 25 hours; no less than 50 hours; no less than 75 hours; no less than 100 hours; no less than 125 hours; no less than 150 hours; or no less than 175 hours.

[0046] The subject in need thereof may have a metabolic disease or disorder. The term “metabolic disorder” refers to any disorder that involves an alteration in the normal metabolism of carbohydrates, lipids, proteins, nucleic acids, or a combination thereof. A metabolic disorder is associated with either a deficiency or excess in a metabolic pathway resulting in an imbalance in metabolism of nucleic acids, proteins, lipids, and/or carbohydrates. Factors affecting metabolism include, and are not limited to, the endocrine (hormonal) control system (e.g., the insulin pathway, the enteroendocrine hormones including GLP-1, PYY or the like), the neural control system (e.g., GLP-1 in the brain), or the like. Examples of metabolic disorders include, but are not limited to, diabetes (e.g., Type I diabetes, Type II diabetes, gestational diabetes), hyperglycemia, hyperinsulinemia, insulin resistance, and obesity. In various instances, the subject in need thereof may have diabetes.

EXAMPLES

I. Example 1: Synthesis of Compounds

Abbreviations

PEG is polyethylene glycol;

DCM is dichloromethane;

TEA is triethylamine;

CDCl₃ is chloroform;

THF is tetrahydrofuran;

TS is toluene sulfonate, i.e., tosylate;

IPA is isopropyl alcohol;

PMDETA is N, N, N',N'',N'''-pentamethyl diethylenetriamine

NMR is nuclear magnetic resonance;

LRMS is low resolution mass spectrometry;

ESI is electron spray ionization;

TLC is thin-layer chromatography;

eq. or equiv. is equivalents;

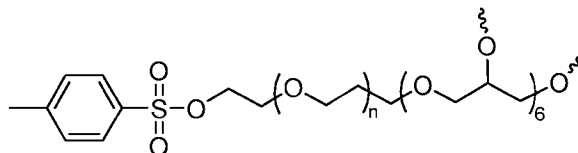
min or min. is minute(s);

h or hr. is hour(s);

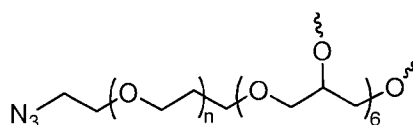
rt, RT, or r.t. is room temperature; and

sat'd or sat. is saturated.

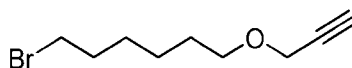
A. Synthesis of Example PEG Intermediates



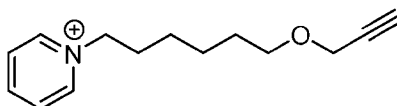
[0047] PEG_{8a}-Tosylate (PEG_{8a}-TS): In a dry round bottom flask, PEG_{8a}-OH (Mn = 20,852, 5 g, 0.24 mmol) was dissolved in 30 mL dichloromethane (DCM) followed by the addition of trimethylamine (TEA, 0.668 mL, 4.8 mmol). The solution was cooled to 0 °C in an ice bath and stirred for 15 min, following which 4-toluenesulfonyl chloride (Ts-Cl, 0.914 g, 4.8 mmol) was added dropwise. The reaction mixture was stirred for 16 h at room temperature (RT). The mixture was then diluted into 60 mL of DCM and washed with brine three times. The organic layer was collected and dried over sodium sulfate and concentrated by a rotary evaporator. The crude product was then precipitated into cold ether twice. The white powder product was recovered by filtration (4.59 g, 87% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, J = 8.3 Hz, 2H), 7.34 (dd, J = 8.5, 0.6 Hz, 2H), 4.24 – 4.04 (m, 2H), 2.45 (s, 3H).



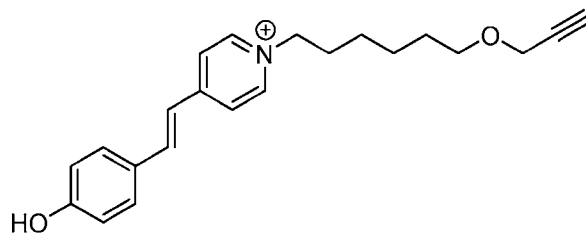
[0048] PEG_{8a}-Azide (PEG_{8a}-N₃): Sodium azide (0.54 g, 8.4 mmol) and PEG_{8a}-TS (4.59 g, 0.21 mmol) were dissolved in 100 mL dimethylformamide (DMF) and stirred at 60 °C for 48 h. The reaction mixture was then concentrated under vacuum and diluted into 100 mL of DCM. The crude solution was washed with brine three times. The organic layer was recovered and dried over sodium sulfate and concentrated by a rotary evaporator. The concentrated crude solution was precipitated into cold ether twice. The white powder product was collected by filtration and dried in an oven (4.38 g, 63% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.68 (t, J = 0.8 Hz, 2H), 3.65 - 3.60 (m, 313H).

B. Synthesis of Example Biological Molecule Intermediates

[0049] 1-Bromo-6-(prop-2-yn-1-yloxy)hexane: In a dry round bottom flask, propargyl alcohol (1.09 mL, 19 mmol) was dissolved in 80 mL dry tetrahydrofuran (THF) followed by adding sodium hydride (0.94 g, 23.3 mmol). The mixture was stirred at RT for 20 min prior adding 1,6-dibromohexane (8.64 mL, 56 mmol). The reaction mixture was then stirred at RT for 24 h. The mixture was quenched with a small amount of water and the precipitate was separated by centrifugation. The supernatant was concentrated by a rotary evaporator and the crude product was purified by flash chromatography with hexane/ethyl acetate (20:1 v/v) as an eluent. The product was collected as brownish oil (2.19 g, 53% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.13 (d, J = 2.4 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 2.4 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.60 (dd, J = 14.3, 6.9 Hz, 2H), 1.43 (dtd, J = 15.6, 8.7, 4.1 Hz, 4H).

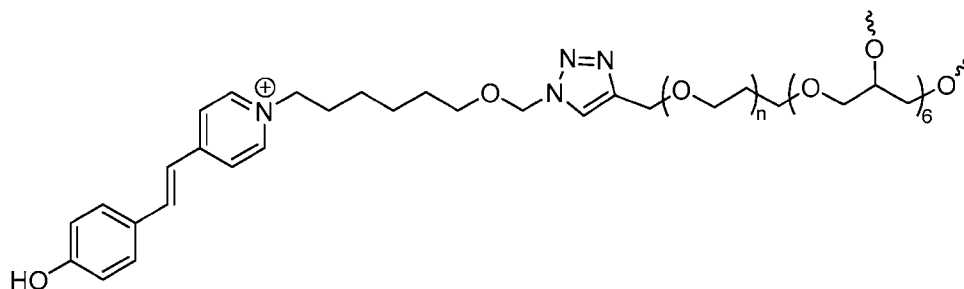


[0050] 1-(6-(Prop-2-yn-1-yloxy)hexyl)pyridin-1-ium: 1-Bromo-6-(prop-2-yn-1-yloxy)hexane 3 (2.19 g, 10 mmol) was dissolved in 10 mL of isopropyl alcohol (IPA) followed by the addition of 4-methylpyridine (1.6 mL, 16 mmol). The reaction mixture was stirred at 80 °C for 12 h. The product was concentrated and precipitated into cold ether, collected by filtration, and washed twice with cold ether. The product was collected as light brown powder (2.97 g, 95% yield). ¹H NMR (500 MHz, CDCl₃) δ 9.31 (d, J = 6.8 Hz, 2H), 7.86 (d, J = 6.2 Hz, 2H), 4.91 (t, J = 7.4 Hz, 2H), 4.08 (d, J = 2.4 Hz, 2H), 3.46 (q, J = 5.9 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 1H), 2.04 – 1.97 (m, 2H), 1.54 (dd, J = 8.0, 5.2 Hz, 2H), 1.39 (dd, J = 6.9, 3.3 Hz, 4H).



[0051] **(*E*)-4-(4-Hydroxystyryl)-1-(6-(prop-2-yn-1-yloxy)hexyl)pyridin-1-ium.** In a round bottom flask, 1-(6-(prop-2-yn-1-yloxy)hexyl)pyridin-1-ium (2.97 g, 9.5 mmol), 4-hydroxybenzaldehyde (1.19 mL, 12 mmol), and piperidine (0.15 mL, 1.56 mmol) were dissolved in 12 mL IPA and stirred at 70 °C for 18 h. The crude mixture was cooled to RT. The red precipitate was collected by centrifugation and washed three times with IPA. The product was recovered by centrifugation as red powder (2.65 g, 70% yield). ¹H NMR (400 MHz, D₂O) δ 8.50 (d, *J* = 6.8 Hz, 2H), 7.92 (d, *J* = 6.6 Hz, 2H), 7.71 (d, *J* = 16.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 16.2 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.45 – 4.38 (m, 2H), 4.14 (d, *J* = 2.3 Hz, 2H), 3.59 – 3.50 (m, 2H), 2.84 – 2.79 (m, 1H), 2.01 – 1.89 (m, 2H), 1.60 – 1.50 (m, 2H), 1.41 – 1.25 (m, 4H).

C. Synthesis of Example PEGylated Biological Molecules



[0052] **PEG_{8a}-BM:** In a Schlenk flask, PEG_{8a}-Azide (2.5 g, 0.12 mmol) and (*E*)-4-(4-hydroxystyryl)-1-(6-(prop-2-yn-1-yloxy)hexyl)pyridin-1-ium (0.59 g, 1.44 mmol) were dissolved in 25 mL DMF. Copper (II) sulfate pentahydrate (25 mg, 0.1 mmol) and N,N,N',N'',N'''-pentamethyldiethylenetriamine (PMDETA, 21 μL, 0.1 mmol) were added into the Schlenk flask followed by three cycles of freeze-pump-thaw degassing process. On the last cycle, the flask was opened, and sodium ascorbate (0.2 g, 1 mmol) was added quickly followed by recapping the flask. The flask was vacuumed and refilled with N₂ over five cycles. The click reaction was stirred at 50 °C in an oil bath for 72 h. The crude product was diluted with 50 mL DCM and passed through a short alumina plug to remove the catalyst. The filtrate was concentrated and precipitated into cold ether. The product was collected as red powder (2.45 g, 85% yield). ¹H NMR (500 MHz, D₂O, FIG. 2) δ 8.37 (s, 2H), 7.91 (s, 1H), 7.79 (s, 2H), 7.57 (d, *J* = 12.3 Hz, 1H), 7.46 (s, 2H), 6.96 (d, *J* = 12.0 Hz, 1H), 6.75 (s, 1H), 4.51 – 4.39 (m, 4H), 4.27 (s, 2H), 3.78 (dd, *J* = 23.3, 18.3 Hz, 2H), 3.64 – 3.28 (m, 310H), 1.81 (s, 2H), 1.42 (dd, *J* = 13.3, 6.5 Hz, 2H), 1.26 – 1.07 (m, 4H).

II. Example 2: Preparation and Application of Microneedles

A. General Experimental Material and Methods

[0053] **Preparation of Microneedles.** Cucurbit[8]uril (CB[8]) was synthesized and purified following known methods (Zou, L., et al., *Chem. Commun.* 2019, 55 (67), 9931–9934). The crude CB were precipitated in a large amount of water to obtain the mixtures of cucurbit[6]uril (CB[6]) and CB[8]. CB[8] was further purified by several times of extractions with formic acid/water (1:1 v/v) and recrystallization with hot 37% HCl. PEG_{8a}-BM and CB[8] were mixed in water at a molar ratio of 1:3 at 1 wt %. After the CB[8] was fully dissolved, the PEG_{8a}-BM⊂CB[8] mixture was lyophilized. The lyophilized solid was redissolved in water at 10 wt % to form PEG_{8a}-BM⊂CB[8] supramolecular networks. Carboxymethyl cellulose (CMC, ~90,000 g/mol, Acros Organics), hyaluronic acid (HA, ~60,000 g/mol, Lifecore Biomedical), and dextran (~70,000 g/mol, TCI America) were dissolved in water at 10 wt % to prepare biopolymer solutions. The 10 wt % PEG_{8a}-BM⊂CB[8] supramolecular network and each 10 wt % biopolymer solution were mixed at a weight ratio of 1:1 and stirred by a spatula to form homogeneous hydrogel mixtures at 5 wt % of each of the respective networks. Premixed PEG_{8a}-BM⊂CB[8]/CMC, PEG_{8a}-BM⊂CB[8]/HA, and PEG_{8a}-BM⊂CB[8]/dextran supramolecular networks were loaded onto a polydimethylsiloxane (PDMS) microneedle mold fabricated by Blueacre Technology Ltd. and restrained from flowing off the mold using a custom-cut PDMS holder. The PDMS mold contained a 20 × 20 array of conical shaped needles (300-μm base diameter, 600-μm height, and 600-μm tip-to-tip spacing). The loaded hydrogels were centrifuged at 4255 × g and 37 °C to fill the mold cavities and remove air bubbles. After 2 h of centrifugation, the hydrogels were either directly dried in a desiccator overnight to prepare the Supramolecular Microneedle or dried similarly under UV irradiation at 365 nm wavelength in a UV reactor (RPR-100, Southern New England Ultraviolet Co.) overnight to prepare the Covalent Microneedle. The microneedle patches were detached from the PDMS mold after drying.

[0054] **Microneedle Insertion into Tissue Mimics.** Gelatin hydrogels were prepared according to previous work to mimic the skin dermis tissue for visualization of the microneedle swelling and separation in the skin (Tsioris, K. et al., *Advanced Functional Materials*. 2012, pp 330–335). Briefly, gelatin powder (Knox Original Unflavored Gelatin) was dissolved in water at a concentration of 0.112 g/mL by heating. The gelatin solution was poured into a Petri dish (100

mm $\times$ 15 mm) and cooled to RT to form a hydrogel layer of $\sim$ 5 mm in thickness. The gelatin hydrogel was then evaporated in air to $\sim$ 1 mm thickness. This experimental set-up was adapted from a previous report (Yang, S. et al., Nature Communication. 2013, 4, 1702). A glass slide was fixed on the lid of a 6-well plate by double-sided tape and used to support a piece of gelatin hydrogel on its edge. A single row of microneedles was affixed to the edge of a different movable glass slide. The setup was then mounted on the motorized stage of an EVOS FL Auto fluorescence microscope (Life Technologies). The microneedles were inserted into the gelatin layer by moving the glass slides together using tweezers. Bright-field images were taken at 10x with 3 s intervals and processed as a video using ImageJ.

[0055] Scanning Electron Microscopy. Microneedle patches were sputter-coated with a 5 nm Pd/Au layer using a Leica EM ACE600 sputter coater and imaged by a Prisma environmental scanning electron microscope (ESEM, Thermo Scientific) at an accelerating voltage of 5 kV.

[0056] Porcine Skin Insertion. Porcine skin was obtained from Martin's Custom Butchering (Wakarusa, IN, USA). The microneedle patches were cut to 10 $\times$ 10 arrays and pressed onto porcine skin. After being applied on the skin for 5 min, the microneedle patches were peeled, and photographs of the porcine skin surfaces were immediately collected.

[0057] Rheology. The supramolecular hydrogel was prepared by mixing PEG_{8a}-BM $\subset$ CB[8] and CMC at 5 wt%, following material preparation methods described in the microneedle fabrication procedures herein. A covalent hydrogel was further prepared on a portion of this material via UV- crosslinking in a closed glass vial placed in a UV reactor overnight. Dynamic oscillatory rheology was performed using a rheometer (Discovery HR-2, TA Instruments) with a 25 mm parallel plate and 200 μ m gap. Amplitude sweeps (10 rad/s, 0.1-200% strain) and frequency sweeps (1% strain, 0.1-200 rad/s) were then conducted.

[0058] Compression Testing. The mechanical properties of the supramolecular and covalent microneedles were assessed on 10 $\times$ 10 arrays using the dynamic mechanical analysis (DMA) of the Discovery HR-2 rheometer. The patches were attached on the bottom plate and the top plate was compressed at a constant speed of 0.01 mm/s until the maximum axial force of 50 N was reached.

[0059] In Vitro Release of FITC-Insulin. Fluorescein isothiocyanate (FITC)-insulin was dissolved in water at 2 mg/mL. After mixing the PEG_{8a}-BM $\subset$ CB[8] and CMC to prepare the hydrogel, FITC-insulin was added in an amount totaling 1.5% of the total dry mass of the materials.

The supramolecular and covalent microneedles encapsulated with FITC-insulin were then fabricated by the same method as described above. The obtained patches were cut into 10×10 arrays and affixed within the wells of a 12-well plate ($n=4/\text{group}$). To each well, 2 mL of phosphate buffered saline (PBS) was added. At each timepoint, 200 μL of PBS was transferred into a black 96-well plate and replaced with 200 μL fresh PBS. Fluorescence was measured using a microplate reader (Tecan Infinite M200 PRO) at excitation wavelength of 485 nm and emission wavelength of 520 nm. The cumulative release of FITC-insulin was calculated using a standard curve in the range of 10 ng/mL to 10 $\mu\text{g/mL}$.

[0060] Fluorescence Microscopy. A row of FITC-insulin encapsulated microneedles, either supramolecular or covalent, was attached to the edge of a glass slide and imaged using the EVOS FL Auto fluorescence microscope at 10x with irradiation from a GFP light cube.

[0061] Diabetic Rat Model. The diabetic rat model was induced by streptozotocin (STZ) following a previously reported protocol (Ye, Z. *Biomacromolecules* 2022, 23 (10), 4401–4411). The studies were approved by the University of Notre Dame Animal Care and Use Committee. Briefly, male Sprague Dawley rats (200-230 g) were fasted for 8 h, injected intraperitoneally with 10 mg/mL STZ at a dose of 65 mg/kg, and provided with water containing 10% sucrose and food immediately after injection. After 24 h, the rats were provided regular water and food for 7 d and monitored for blood glucose level (BGL) using a hand-held glucose meter and tail-vein blood collection. Diabetic rats were measured when the 12-h fasted BGL measured >250 mg/dL. Similar to the process of encapsulating FITC-insulin, the microneedles were fabricated with 5 IU insulin (calculated by the needle volume of a 10×10 array) by mixing 10 wt % PEG8a-BM $\subset$ CB[8] hydrogels, 10 wt % CMC solutions, and 10 mg/mL insulin solutions in the fabrication process. The total loaded insulin was estimated to be 25 IU/kg for one device based on an average rat weight of 225 g. Three groups were assessed: supramolecular or covalent microneedle patches encapsulating insulin, as well as supramolecular microneedles without insulin ($n=4/\text{group}$). The rats were shaved and fasted for 12 h before experiments. Initial BGLs before applying microneedle patches were measured and the rats were randomly grouped to an average initial BGL of ~ 350 mg/dL. The patches were pressed onto the shaved rat skin and kept in place for 5 min. Afterwards, the patches were removed, and the skin was covered by a 3M Tegaderm Transparent Film Dressing. Rats were then maintained in a fasted state for an additional 12 h of serial BGL monitoring.

B. Microneedle Design

[0062] A schematic overview of the design and function of the microneedles is shown in FIG. 3. Initial work explored the exclusive use of a PEG-based supramolecular network for the creation of microneedles. These efforts were motivated by inherent advantages to the filling of a microneedle master mold with a dynamic supramolecular hydrogel, subsequently leveraging previously reported chemistry to switch the material to a covalent hydrogel by UV-induced [2+2] photodimerization of the BM guests forming the ternary complex once in the mold. However, the PEG8a-BM $\subset$ CB[8] hydrogel either with or without UV crosslinking proved too brittle to be removed from the mold following drying. This was attributed to the low tensile strength of PEG of only ~23 kPa. To address this challenge, a second mechanical biopolymer network was introduced to lend high strength and provide mechanical support to the microneedles (FIG. 3). Carboxymethyl cellulose (CMC) was initially selected as the mechanical biopolymer, given it is a soluble and biocompatible polymer and offers a tensile strength of 28 MPa. CMC has been previously used to fabricate dissolving microneedles, both alone and in combination with other polymers. The PEG8a-BM $\subset$ CB[8] network was thus blended with a solution of the CMC polymer to facilitate mixing of the two disparate polymer networks and form a homogenous supramolecular hydrogel.

[0063] When PEG8a-BM $\subset$ CB[8] and CMC were mixed at a mass ratio of 1:1, the resulting hydrogel could be loaded to the microneedle mold and dried to form uniform and defect-free microneedle arrays, as visualized by SEM (FIGS. 5A–5B). Yet, when the mass ratio of these same components was increased to 2:1, the microneedle patch did not retain its integrity once peeled from the mold. Since CMC dissolves more rapidly, to ensure controlled release of eventual cargo proteins the ratio of PEG8a-BM $\subset$ CB[8] to CMC was not increased beyond 1:1. To further explore the universality of this general microneedle design, CMC was replaced with other mechanical biopolymers, including hyaluronic acid (HA) and dextran. HA has been reported for use in fabricating dissolvable microneedles with good mechanical strength to penetrate skin and used in the context of therapeutic delivery for insulin and other agents. Similarly, dextran has been employed in the fabrication of dissolving microneedles due to its excellent solubility, biocompatibility, and mechanical properties. The mixture of both PEG8a-BM $\subset$ CB[8]/HA and PEG8a-BM $\subset$ CB[8]/dextran was also able to form homogeneous hydrogels, with the fabricated

microneedles prepared from these hydrogel having intact morphology without defects (FIGS. 5A–5B).

[0064] One key feature of the $\text{BM}_2\text{C}\text{CB}[8]$ supramolecular motif is the ability for the ternary complex to template [2+2] photodimerization of two BM guests by UV irradiation (FIG. 6), resulting in a supramolecular-to-covalent crosslink transition. Well-formed microneedle arrays could thus be prepared from all three polymers by the same methods as in the supramolecular case, exposing the samples to UV light during the drying process to form microneedles with a now covalent PEG network replacing the supramolecular PEG network (FIG. 5B).

C. Skin Insertion

[0065] To recreate the act of skin insertion, porcine skin was sourced for evaluation of the different microneedle arrays, comparing the ease of insertion for microneedles prepared from the three different mechanical polymers with both the supramolecular and UV-induced covalent PEG network (FIG. 5A–5B). For all cases, the microneedles demonstrated an ability to penetrate the skin under a reasonable applied pressure. Interestingly, when the microneedle arrays prepared from the supramolecular $\text{PEG8a-BM}_2\text{C}\text{CB}[8]/\text{CMC}$ network were removed from the skin after 5 min, the distinct yellow color of the material was visibly embedded in the skin, while the device backing was clearly lacking any remaining needles. This observation existed for $\text{PEG8a-BM}_2\text{C}\text{CB}[8]$ in combination with all three mechanical biopolymers (CMC, HA, and dextran). The microneedle arrays that were instead prepared from the UV-induced covalent PEG network were readily removed and no visible material remained in the sites where the needles had punctured the skin.

[0066] Transparent gelatin hydrogels were prepared as skin mimics to enable visualization of the insertion and separation process for the $\text{PEG8a-BM}_2\text{C}\text{CB}[8]/\text{CMC}$ microneedles using microscopy. From the video, after insertion into the gelatin hydrogel, the dried supramolecular microneedles swelled by absorbing water from the surrounding gelatin hydrogels, transitioning from conical shapes to bulkier truncated cones. Upon separation of the two layers, the microneedles detached from the backing and remained embedded in the gelatin. By comparison, the covalent microneedles also swelled upon insertion to the gelatin hydrogel but remained attached to their backing layer on removal. Taken together, these observations support a mechanism whereby microneedle swelling may cause mechanical interlocking within the tissue mimic, introducing strain during the process of device removal that was sufficient to separate the

mechanically weaker supramolecular microneedles but not the stronger covalent microneedles (FIG. 5). Mechanical interlocking has been previously postulated to underlie the anchoring function of other classes of microneedles, further supporting the feasibility of this mechanism.

D. Mechanical Testing

[0067] The mechanical properties of the bulk PEG8a-BM $\subset$ CB[8]/CMC hydrogels were first assessed in both their supramolecular and covalent form using dynamic oscillatory rheology (FIG. 7A). These studies were performed on hydrogels prepared from 5 wt % PEG8a-BM $\subset$ CB[8] and 5 wt % CMC, both without and with UV irradiation. Both hydrogels demonstrated frequency-dependent change in their moduli characteristic of a dynamic network. Supramolecular PEG8a-BM $\subset$ CB[8]/CMC hydrogels behaved in line with typical expectations for a dynamic supramolecular hydrogel, with a G'/G'' crossover point occurring at ~ 31 rad/s. This crossover point offers insight into the kinetics of supramolecular bond exchange in the network, and in this case translated to an estimate of the network relaxation time (τ_R) on the order of ~ 0.2 s. Meanwhile, no G'/G'' crossover point was evident in the UV-induced covalent networks and dynamic behavior was significantly reduced, yet a steady increase in G' as frequency was increased was still suggestive of some underlying dynamic interactions in the covalent hydrogel network. This contrasts with previous work on the [2+2] crosslinking of a PEG-only network, wherein the materials displayed frequency-independent behavior following UV irradiation. This residual dynamic character may arise from incomplete photocrosslinking and/or non-idealities in the PEG network arising from inclusion of the CMC polymer. The storage modulus of both networks converged at higher oscillatory frequencies, expected given that at higher frequency the oscillation rate exceeds the dynamic bond exchange rate.

[0068] The mechanical strength of the dry microneedle arrays was next assessed by compressing a 10×10 array against a flat stainless-steel plate. The force/displacement curves were overlaid for both the supramolecular and covalent PEG8a-BM $\subset$ CB[8]/CMC microneedles (FIG. 7B). In addition, no fracture or buckling points were observed up to a maximum force of 0.5 N/needle. This value is far in excess of the force of 0.01 N/needle suggested to be necessary in order to penetrate human skin. The stiffness was calculated by the slope of the linear region of the displacement curve, yielding an estimated stiffness of ~ 2100 N/m. Interestingly, the mechanical

properties of both dried microneedle arrays were nearly identical, indicating no crosslinking-dependent differences in performance of the devices as-applied.

D. Controlled Release of Insulin

[0069] Diabetes is a chronic disease of increasing global prevalence, necessitating rigorous treatments consisting of frequent insulin self-administration that is often plagued by poor compliance. Strategies for controlled and sustained release of insulin have been explored, including injectable hydrogels, nanoparticles, liposomes, and even microneedles. Ongoing efforts have further sought glucose-responsive insulin delivery by these and related delivery technologies. These technologies, and especially microneedle delivery approaches, have worked to advance development of new materials and devices that would offer more controlled and need-directed insulin delivery, yet at present still struggle with achieving the appropriate dose and kinetics of delivery.

[0070] As a model therapeutic, insulin was therefore encapsulated within these PEG_{8a}-BM $\subset$ CB[8]/CMC microneedles. To assess the ability to achieve prolonged controlled release, FITC-labeled insulin was loaded in the supramolecular microneedles and demonstrated distribution throughout the needle and backing layer (FIGS. 7C-7D). Both supramolecular and covalent PEG_{8a}-BM $\subset$ CB[8]/CMC microneedle arrays were then placed into PBS to assess the time-dependent release of insulin from these materials. A pronounced burst release of ~48% of encapsulated FITC-insulin was evident in the supramolecular microneedles, with release reduced to ~17% over this same timeframe for the covalent arrays. When fitting the release data to the Korsmeyer-Peppas equation, the rates of release were estimated at 0.36 h⁻¹ for the supramolecular arrays and 0.14 h⁻¹ for the covalent arrays. The release was effectively completed within ~52 h for the supramolecular microneedle arrays, whereas the covalent microneedle arrays release for upwards of ~96 h.

E. Functional Insulin Delivery

[0071] A previously reported STZ-induced diabetic rat model was selected to explore the ability of the microneedle arrays here to functionally deliver insulin through the skin, manifest in changes to blood glucose level. Rats were fasted for 12 h to exclude variables of the time since last meal and improve insulin sensitivity. Both supramolecular and covalent PEG_{8a}-BM $\subset$ CB[8]/CMC microneedle arrays were applied to the shaved skin of the rat under manual restraint, pressing

patches by hand for 5 min before peeling the device for removal (FIG. 8A). In addition, a control patch prepared from the supramolecular material without insulin incorporated was assessed to account for changes in blood glucose related to device application or restraint. As was observed in the preliminary pig skin studies, both supramolecular microneedles with or without insulin left an arrayed orange pattern on the skin on removal; the covalent microneedles did not show the same obvious pattern. Accordingly, it was anticipated that insulin release from the covalent microneedle arrays would be limited to only the 5 min time-course of device application.

[0072] Owing to their limited time-course of access to the body, insulin-loaded covalent microneedles had no impact on blood glucose level and blood glucose levels were effectively identical to the unloaded supramolecular microneedle control (FIG. 8B). For the detachable supramolecular microneedle arrays, however, blood glucose levels dropped steadily over the first ~1 h following application and maintained a range of 150-200 mg/dL for the ensuing 11 h of the study. This range aligns with normoglycemia for healthy rodents. After 12 h, protocol constraints limited continued fasting and these studies were ended. As the duration of action for insulin in a diabetic rodent typically only extends for 2–3 h following administration, these results support continued delivery of bioactive insulin from the detachable microneedles far beyond their initial device application. Moreover, it is anticipated that this device fabrication method enables the development of a generalized platform of detachable microneedles for prolonged delivery of biologic molecules in the skin without the need for long-term affixing of the device.

F. Conclusion

[0073] Combining supramolecular polymer networks and mechanical biopolymers yields devices that can penetrate the skin. Swelling following insertion into the skin promotes mechanical interlocking in the tissue, leading to detachment of the supramolecular microneedles upon peeling of the device from the skin. When this same microneedle formulation was converted from supramolecular to covalent crosslinking using UV irradiation, the resulting devices became swollen within the skin but did not detach upon peeling. The generalizability of the detachment for supramolecular microneedles was validated using three different mechanical biopolymers. Microneedles prepared from both supramolecular and covalent modes of crosslinking demonstrated controlled release of insulin, with the release rate accelerated for the supramolecular devices. Finally, in an *in vivo* study, the detachable supramolecular microneedle arrays demonstrated the ability to functionally deliver insulin to afford prolonged blood glucose control

in a diabetic rat model. Accordingly, this approach using supramolecular polymers to fabricate detachable microneedles points to a new route for transdermal delivery of active therapeutic agents through a simple fabrication process that leverages supramolecular crosslinking for device formation and function and improves on the complex engineering required by other detachable microneedle devices.

[0074] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents.

[0075] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of use of the invention, may be made without departing from the spirit and scope thereof.

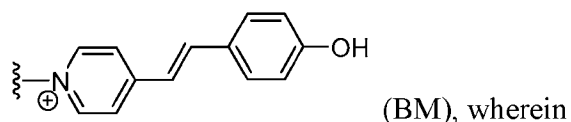
[0076] For reasons of completeness, various aspects of the invention are set out in the following numbered clauses:

Clause 1. A device comprising a detachable microneedle array, the detachable microneedle array comprising a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel, the multi-component hydrogel comprising:

a biopolymer; and

a supramolecular network, the supramolecular network comprising:

an optionally substituted cucurbit[8]uril non-covalently crosslinked with two moieties of formula (BM):

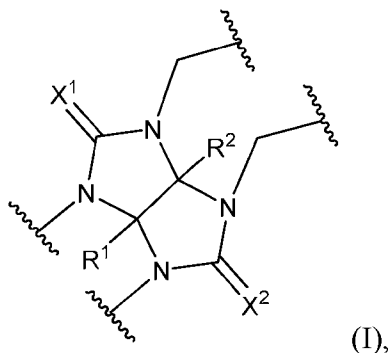


each moiety of formula (BM) is attached to a multi-armed polymer.

Clause 2. The device of clause 1, wherein the biopolymer comprises a polysaccharide, a polypeptide, or a combination thereof.

Clause 3. The device of clause 2, wherein the polysaccharide is selected from the group consisting of carboxymethyl cellulose, hyaluronic acid, dextran, alginate, chitosan, chitin, cellulose, and combinations thereof.

Clause 4. The device of any one of clauses 1-3, the optionally substituted cucurbit[8]uril comprising 8 repeating units of formula (I) arranged in a barrel shape:



wherein:

X^1 and X^2 are each independently O or S;

R^1 and R^2 are each independently hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, G^x , $-C_{1-6}$ alkylene- G^x , $-C_{1-6}$ alkylene- OR^{1x} , $-C_{1-6}$ alkylene- SR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, $-C_{1-6}$ alkylene- SO_2R^x , $-C_{1-6}$ alkylene- $C(O)R^x$, $-C_{1-6}$ alkylene- $C(O)OR^x$, or $-C_{1-6}$ alkylene- $C(O)N(R^x)_2$; or R^1 and R^2 , together with the atoms to which they attach, form a 5- to 8-membered unsaturated or partially unsaturated carbocyclic or heterocyclic ring, the carbocyclic or heterocyclic ring being unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-2} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

G^x, at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl containing 1-3 heteroatoms, a 4- to 12-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 12-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^x, at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, -C₁₋₆alkylene-OH, oxo, OH, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, C₃₋₄cycloalkyl, and -C₁₋₃alkylene-C₃₋₄cycloalkyl.

Clause 5. The device of clause 4, wherein X¹ and X² are each O.

Clause 6. The device of clause 4 or 5, wherein R¹ and R² are each hydrogen.

Clause 7. The device of any one of clauses 1-6, wherein the multi-armed polymer comprises polyethylene glycol.

Clause 8. The device of any one of clauses 1-7, wherein the multi-armed polymer is a four-armed or an eight-armed polymer.

Clause 9. The device of any one of clauses 1-8, wherein the device is air-bubble free.

Clause 10. The device of any one of clauses 1-9, wherein the biopolymer and the supramolecular network are present in the multi-component hydrogel at a mass ratio of 0.1:1 to 10:1.

Clause 11. The device of any one of clauses 1-10, wherein the optionally substituted cucurbit[8]uril and the multi-armed polymer are present in the supramolecular network at a molar ratio of 1:1 to 5:1.

Clause 12. The device of any one of clauses 1-11, wherein a therapeutic agent is encapsulated within the multi-component hydrogel.

- Clause 13. The device of clause 12, wherein the therapeutic agent is a biomolecule.
- Clause 14. The device of clause 13, wherein the biomolecule is a protein, peptide, antibody, or nucleic acid.
- Clause 15. The device of clause 14, wherein the biomolecule is insulin.
- Clause 16. A method of preparing the device of clause 1, the method comprising:
mixing the optionally substituted cucurbit[8]uril with the multi-armed polymer in water to provide a cucurbit[8]uril-polymer mixture;
lyophilizing the cucurbit[8]uril-polymer mixture to provide a lyophilized cucurbituril-polymer mixture;
adding the lyophilized cucurbit[8]uril-polymer mixture to water to form the supramolecular network;
mixing the supramolecular network with the biopolymer to form the multi-component hydrogel;
adding the multi-component hydrogel to a mold, the mold comprising a plurality of microneedle molds;
applying a force to the multi-component hydrogel such that the multi-component hydrogel fills each microneedle mold;
drying the multi-component hydrogel in the mold to provide the device comprising the detachable microneedle array; and
removing the device comprising the detachable microneedle array from the mold.
- Clause 17. The method of clause 16, wherein, before adding the multi-component hydrogel to the mold, a therapeutic agent is mixed with the multi-component hydrogel.
- Clause 18. The method of clause 16 or 17, wherein, after adding the multi-component hydrogel to the mold, the method does not comprise a covalent crosslinking operation.

- Clause 19. The method of clause 16 or 17, wherein, after adding the multi-component hydrogel to the mold, the method further comprises a covalent crosslinking operation.
- Clause 20. The method of any one of clauses 16-19, wherein, after applying the force to the multi-component hydrogel, no air-bubble is present in the multi-component hydrogel in the mold.
- Clause 21. A method of transdermally delivering a therapeutic agent to a subject in need thereof, the method comprising:
penetrating an area of the subject's skin with the device of clause 1 so that each detachable microneedle is embedded within the subject's skin;
allowing each detachable microneedle to swell within the subject's skin; and
removing the backing from the subject's skin.
- Clause 22. The method of clause 21, wherein, after removing the backing from the subject's skin, the detachable microneedles remain embedded within the subject's skin.
- Clause 23. The method of clause 21 or 22, wherein, after removing the backing from the subject's skin, the drug is transdermally delivered for 1 hour to 200 hours.
- Clause 24. The method of any one of clauses 21-23, wherein the subject in need thereof has diabetes.
- Clause 25. Use of the device of any one of clauses 1-15, for transdermally delivering a drug to a subject in need thereof.

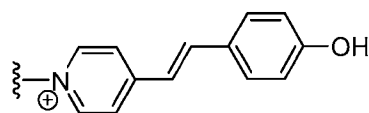
CLAIMS

1. A device comprising a detachable microneedle array, the detachable microneedle array comprising a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel, the multi-component hydrogel comprising:

a biopolymer; and

a supramolecular network, the supramolecular network comprising:

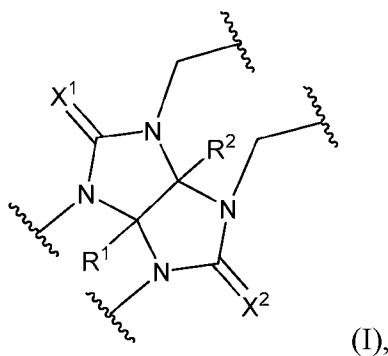
an optionally substituted cucurbit[8]uril non-covalently crosslinked with two moieties of formula (BM):



(BM), wherein

each moiety of formula (BM) is attached to a multi-armed polymer.

2. The device of claim 1, wherein the biopolymer comprises a polysaccharide, a polypeptide, or a combination thereof.
3. The device of claim 2, wherein the polysaccharide is selected from the group consisting of carboxymethyl cellulose, hyaluronic acid, dextran, alginate, chitosan, chitin, cellulose, and combinations thereof.
4. The device of claim 1, the optionally substituted cucurbit[8]uril comprising 8 repeating units of formula (I) arranged in a barrel shape:



(I),

wherein:

X^1 and X^2 are each independently O or S;

R^1 and R^2 are each independently hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, G^x , $-C_{1-6}$ alkylene- G^x , $-C_{1-6}$ alkylene- OR^{1x} , $-C_{1-6}$ alkylene- SR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, $-C_{1-6}$ alkylene- SO_2R^x , $-C_{1-6}$ alkylene- $C(O)R^x$, $-C_{1-6}$ alkylene- $C(O)OR^x$, or $-C_{1-6}$ alkylene- $C(O)N(R^x)_2$; or R^1 and R^2 , together with the atoms to which they attach, form a 5- to 8-membered unsaturated or partially unsaturated carbocyclic or heterocyclic ring, the carbocyclic or heterocyclic ring being unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-2} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

G^x , at each occurrence, is a 6- to 12-membered aryl, a 5- to 12-membered heteroaryl containing 1-3 heteroatoms, a 4- to 12-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 12-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^x , at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, $-C_{1-6}$ alkylene-OH, oxo, OH, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, C_{3-4} cycloalkyl, and $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl.

5. The device of claim 4, wherein X^1 and X^2 are each O.
6. The device of claim 4 or 5, wherein R^1 and R^2 are each hydrogen.
7. The device of claim 1, wherein the multi-armed polymer comprises polyethylene glycol.

8. The device of claim 1, wherein the multi-armed polymer is a four-armed or an eight-armed polymer.
9. The device of claim 1, wherein the device is air-bubble free.
10. The device of claim 1, wherein the biopolymer and the supramolecular network are present in the multi-component hydrogel at a mass ratio of 0.1:1 to 10:1.
11. The device of claim 1, wherein the optionally substituted cucurbit[8]uril and the multi-armed polymer are present in the supramolecular network at a molar ratio of 1:1 to 5:1.
12. The device of claim 1, wherein a therapeutic agent is encapsulated within the multi-component hydrogel.
13. The device of claim 12, wherein the therapeutic agent is a biomolecule.
14. The device of claim 13, wherein the biomolecule is a protein, peptide, antibody, or nucleic acid.
15. The device of claim 14, wherein the biomolecule is insulin.
16. A method of preparing the device of claim 1, the method comprising:
 - mixing the optionally substituted cucurbit[8]uril with the multi-armed polymer in water to provide a cucurbit[8]uril-polymer mixture;
 - lyophilizing the cucurbit[8]uril-polymer mixture to provide a lyophilized cucurbituril-polymer mixture;
 - adding the lyophilized cucurbit[8]uril-polymer mixture to water to form the supramolecular network;
 - mixing the supramolecular network with the biopolymer to form the multi-component hydrogel;

adding the multi-component hydrogel to a mold, the mold comprising a plurality of microneedle molds;

applying a force to the multi-component hydrogel such that the multi-component hydrogel fills each microneedle mold;

drying the multi-component hydrogel in the mold to provide the device comprising the detachable microneedle array; and

removing the device comprising the detachable microneedle array from the mold.

17. The method of claim 16, wherein, before adding the multi-component hydrogel to the mold, a therapeutic agent is mixed with the multi-component hydrogel.
18. The method of claim 16 or 17, wherein, after adding the multi-component hydrogel to the mold, the method does not comprise a covalent crosslinking operation.
19. The method of claim 16 or 17, wherein, after adding the multi-component hydrogel to the mold, the method further comprises a covalent crosslinking operation.
20. The method of claim 16, wherein, after applying the force to the multi-component hydrogel, no air-bubble is present in the multi-component hydrogel in the mold.
21. A method of transdermally delivering a therapeutic agent to a subject in need thereof, the method comprising:
 - penetrating an area of the subject's skin with the device of claim 1 so that each detachable microneedle is embedded within the subject's skin;
 - allowing each detachable microneedle to swell within the subject's skin; and
 - removing the backing from the subject's skin.
22. The method of claim 21, wherein, after removing the backing from the subject's skin, the detachable microneedles remain embedded within the subject's skin.

23. The method of claim 21, wherein, after removing the backing from the subject's skin, the drug is transdermally delivered for 1 hour to 200 hours.
24. The method of claim 21, wherein the subject in need thereof has diabetes.
25. Use of the device of any one of claims 1-15, for transdermally delivering a drug to a subject in need thereof.

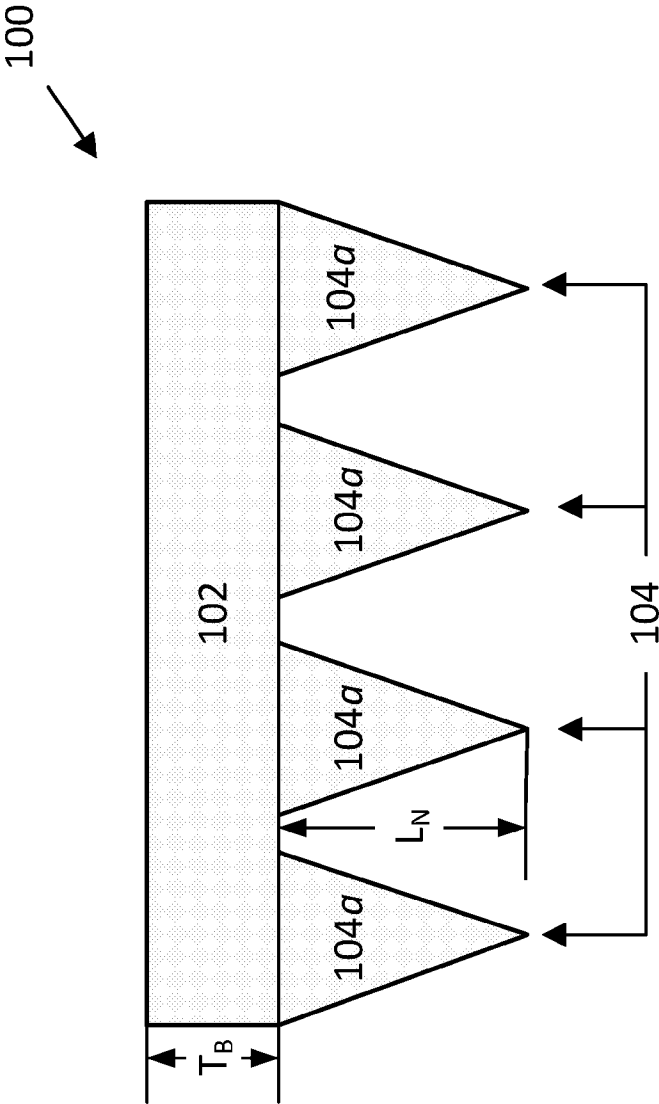


FIG. 1

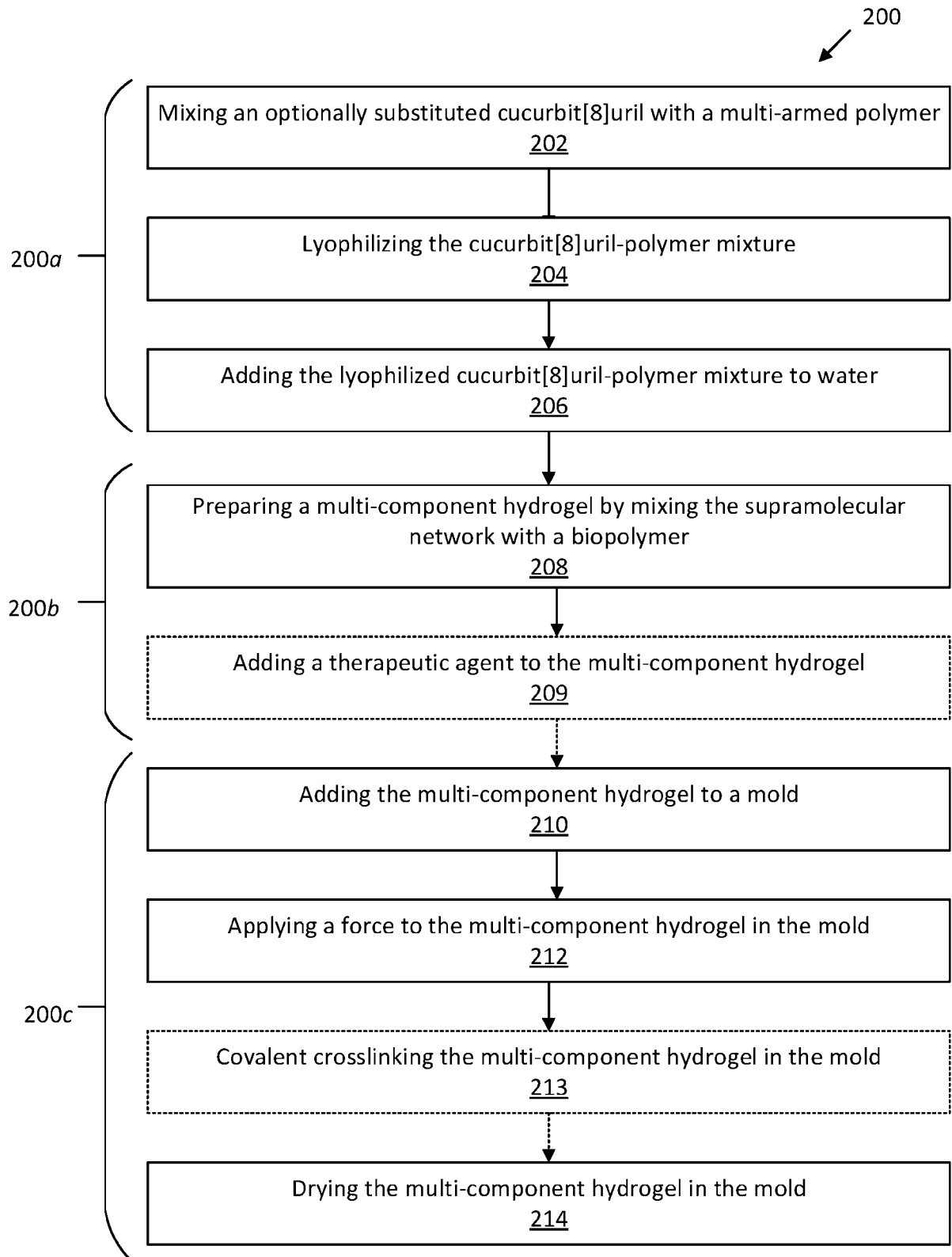


FIG. 2

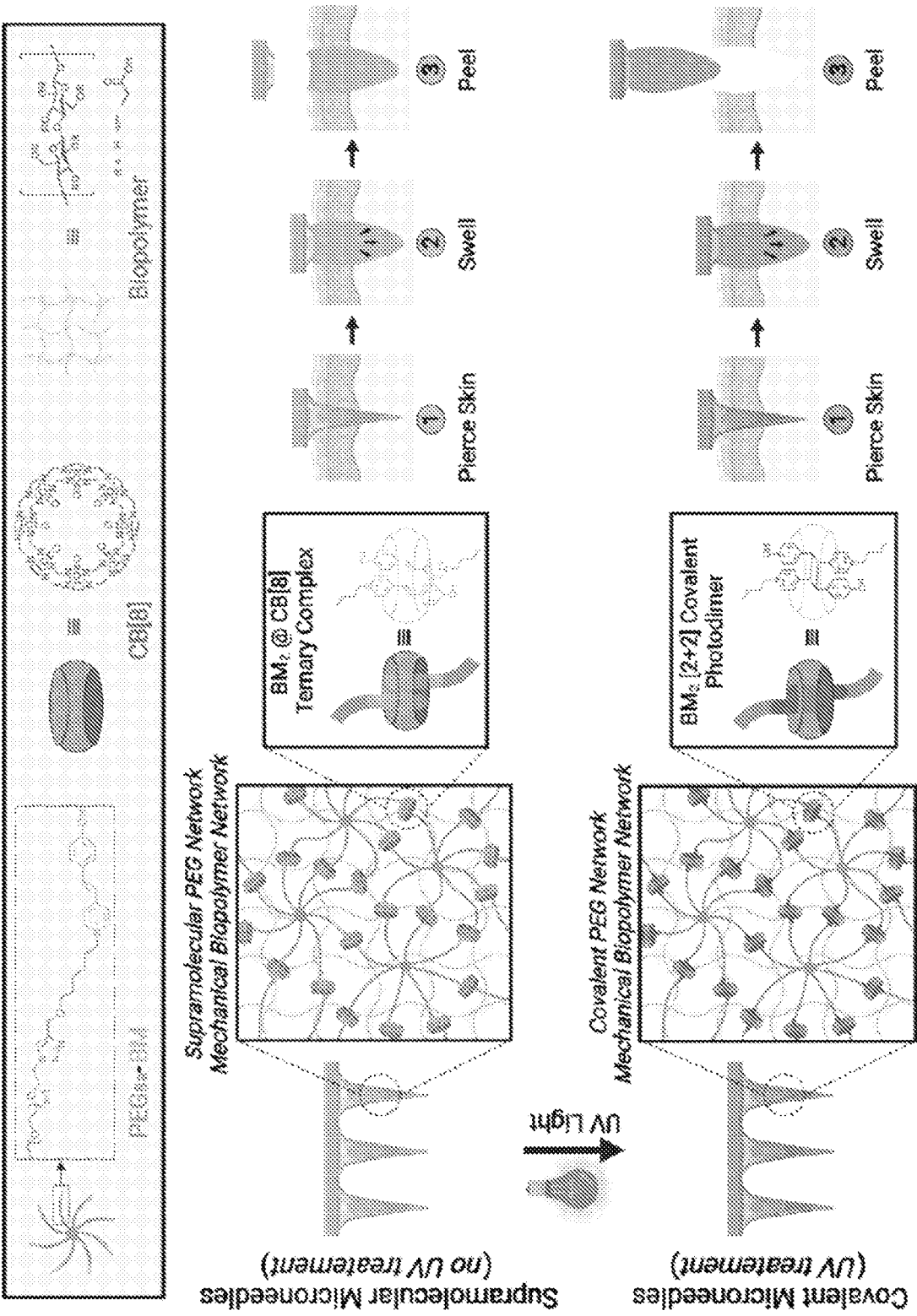


FIG. 3

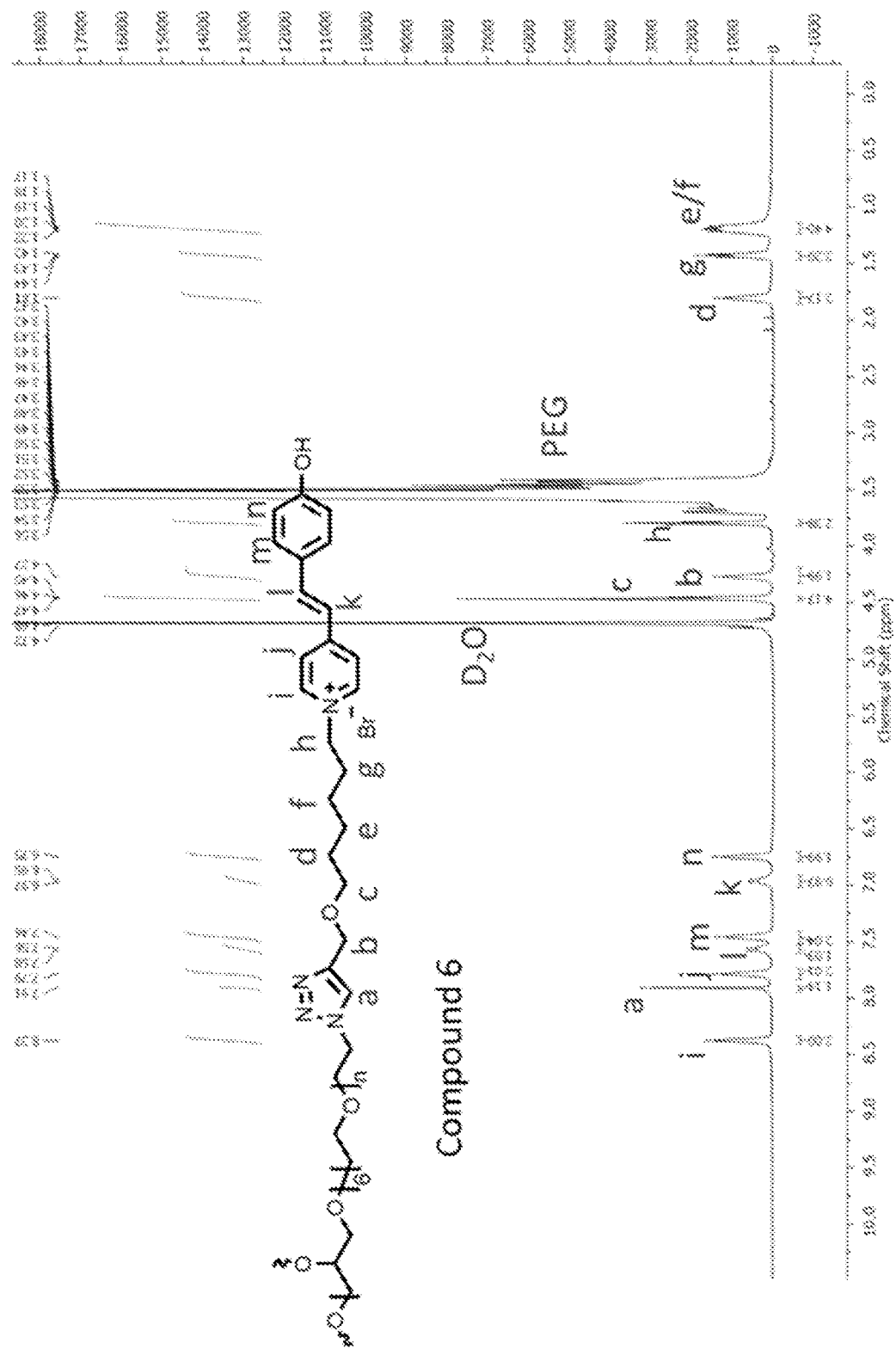
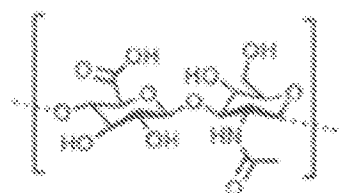
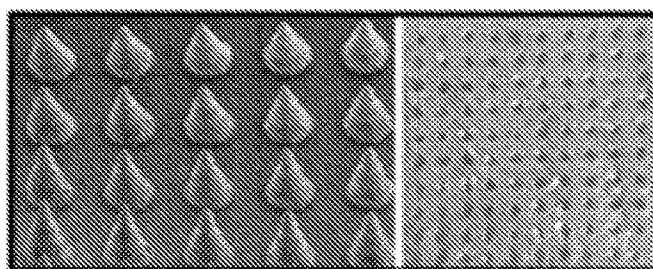
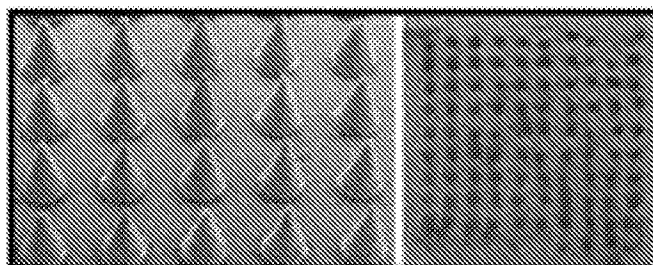
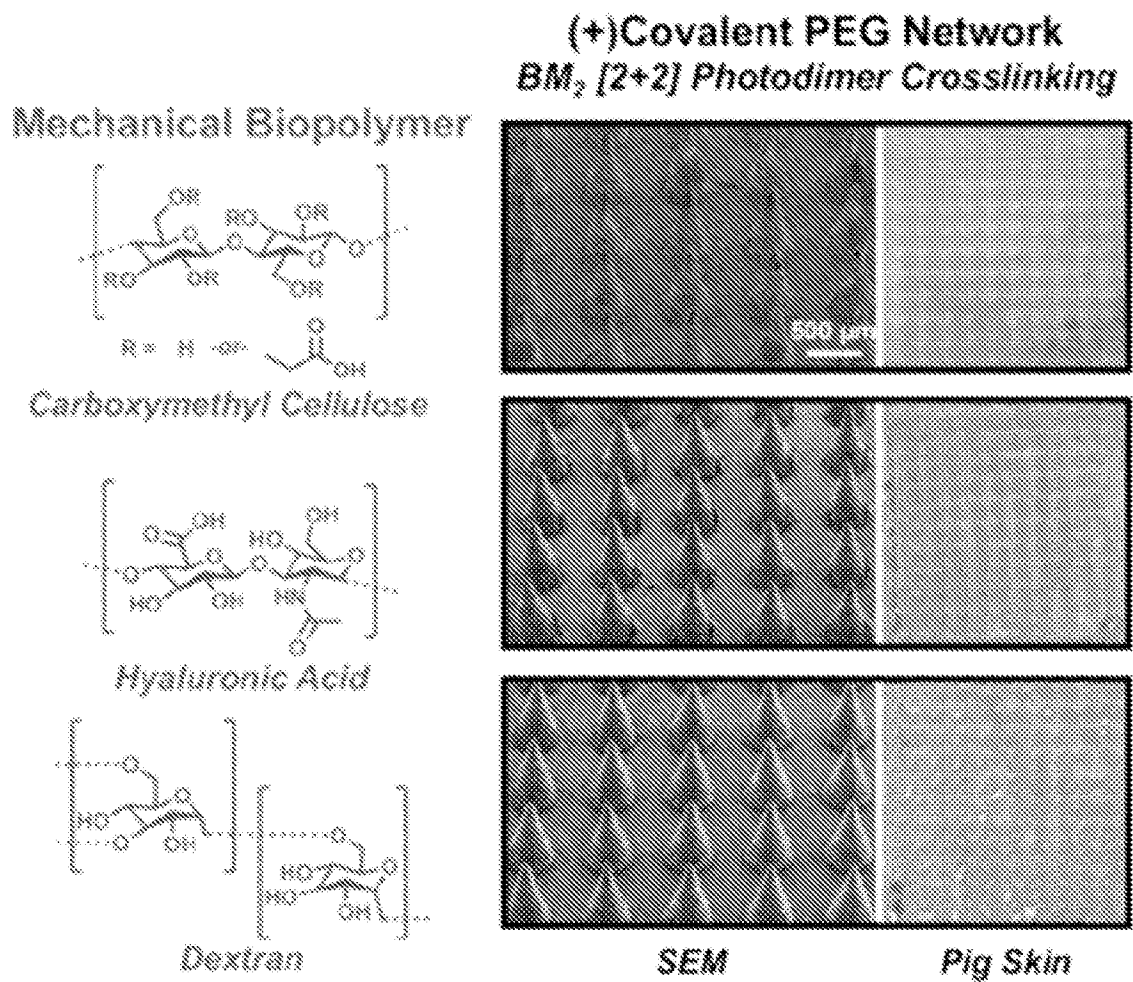


FIG. 4

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Mechanical Biopolymer**Carboxymethyl Cellulose****Hyaluronic Acid****Dextran****(+)Supramolecular PEG Network
BM₂ @ CB[8] Ternary Crosslinking****SEM****Pig Skin****FIG. 5A**

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**FIG. 5B**

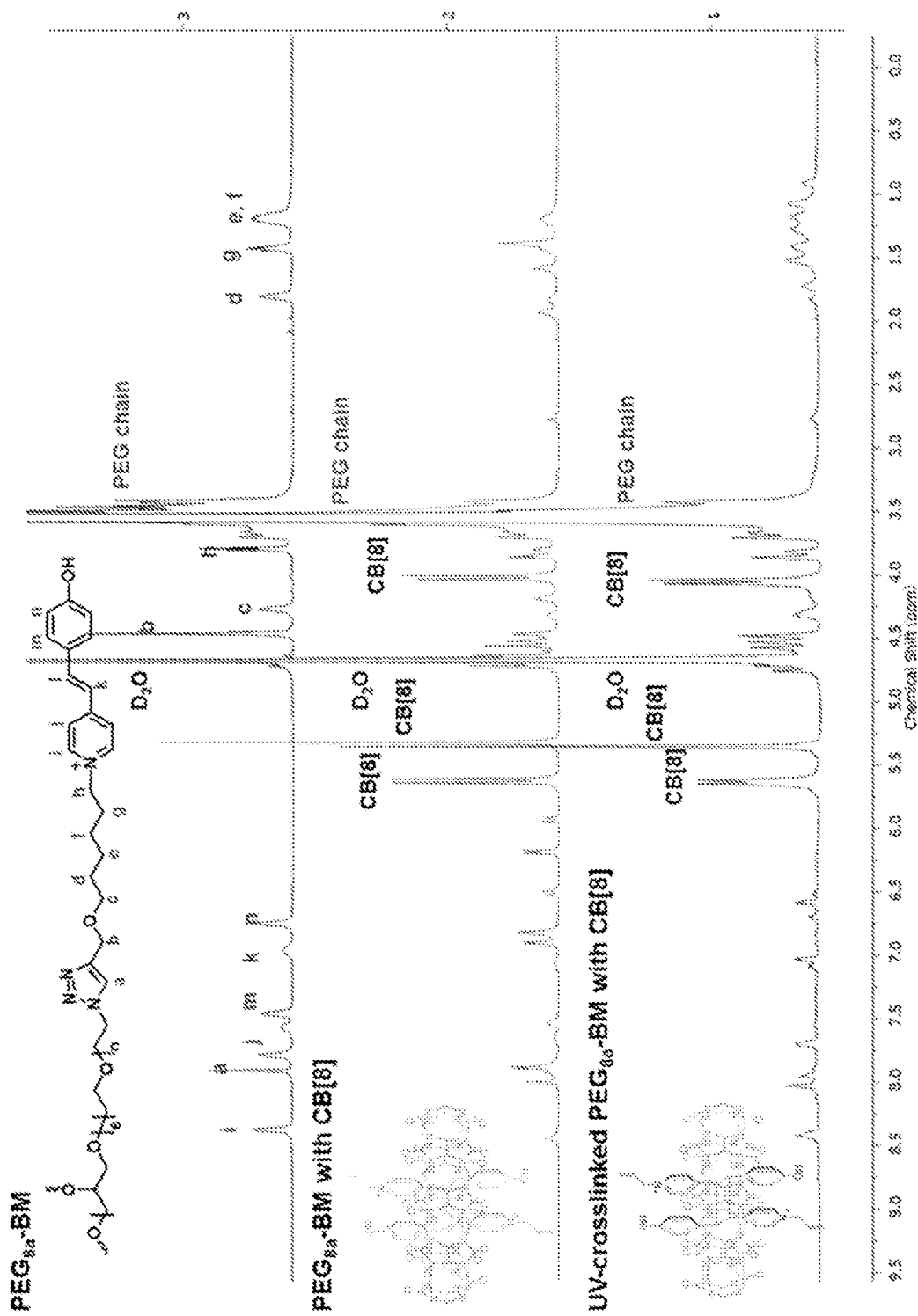


FIG. 6

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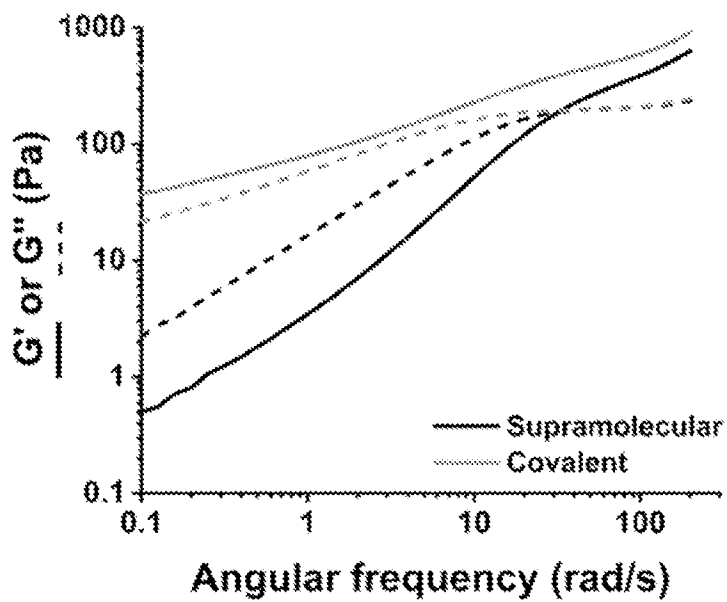


FIG. 7A

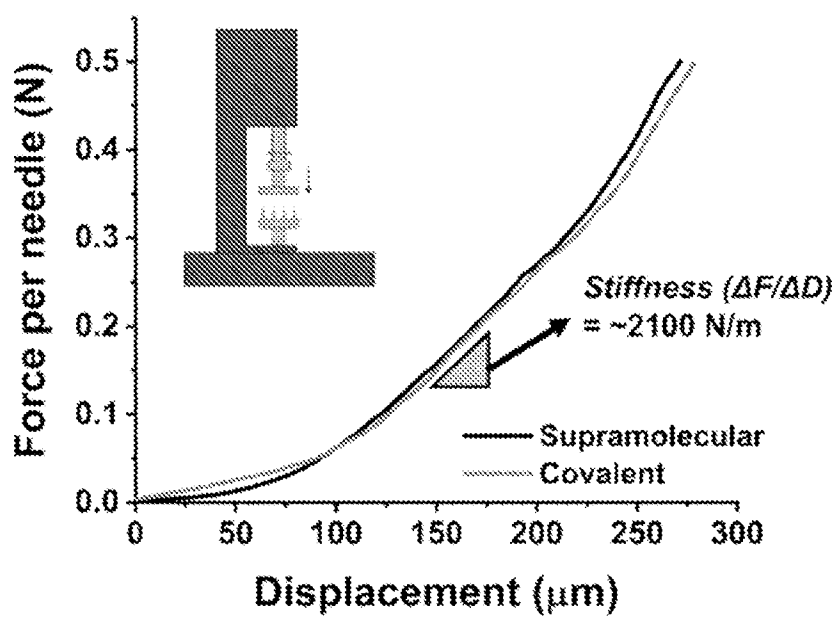


FIG. 7B

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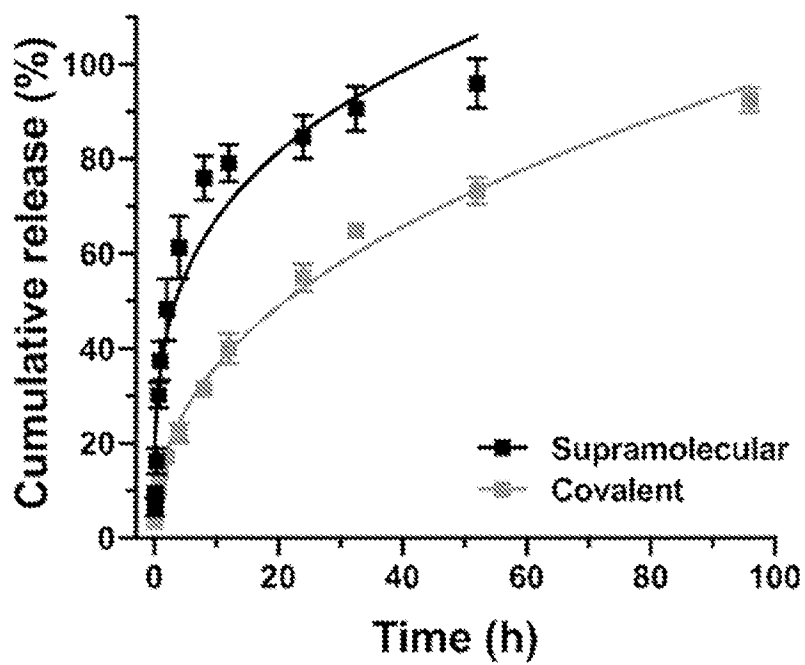


FIG. 7C

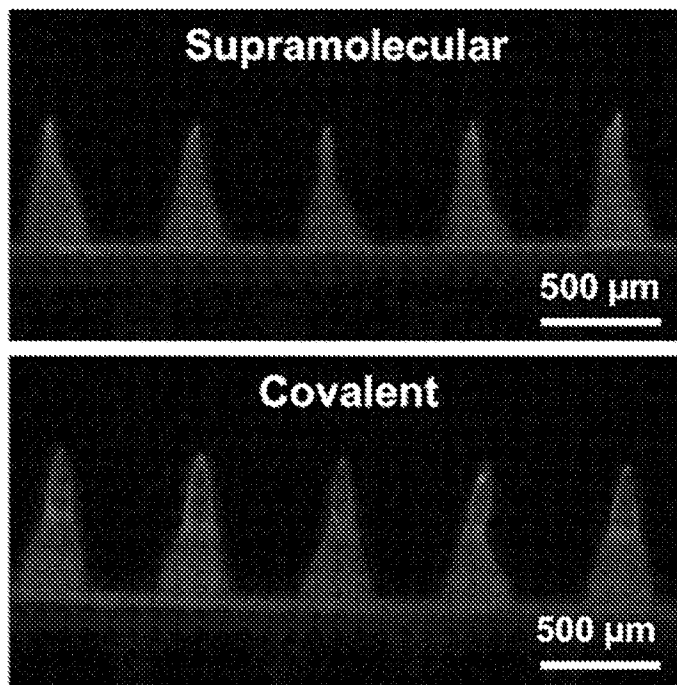


FIG. 7D

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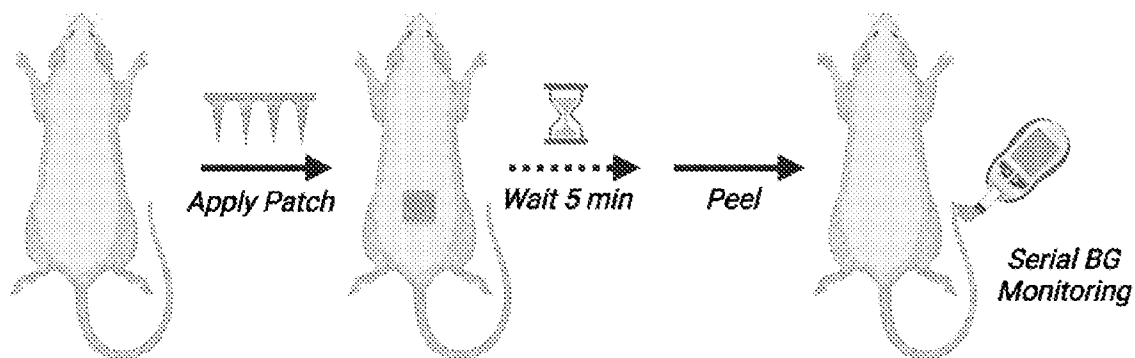


FIG. 8A

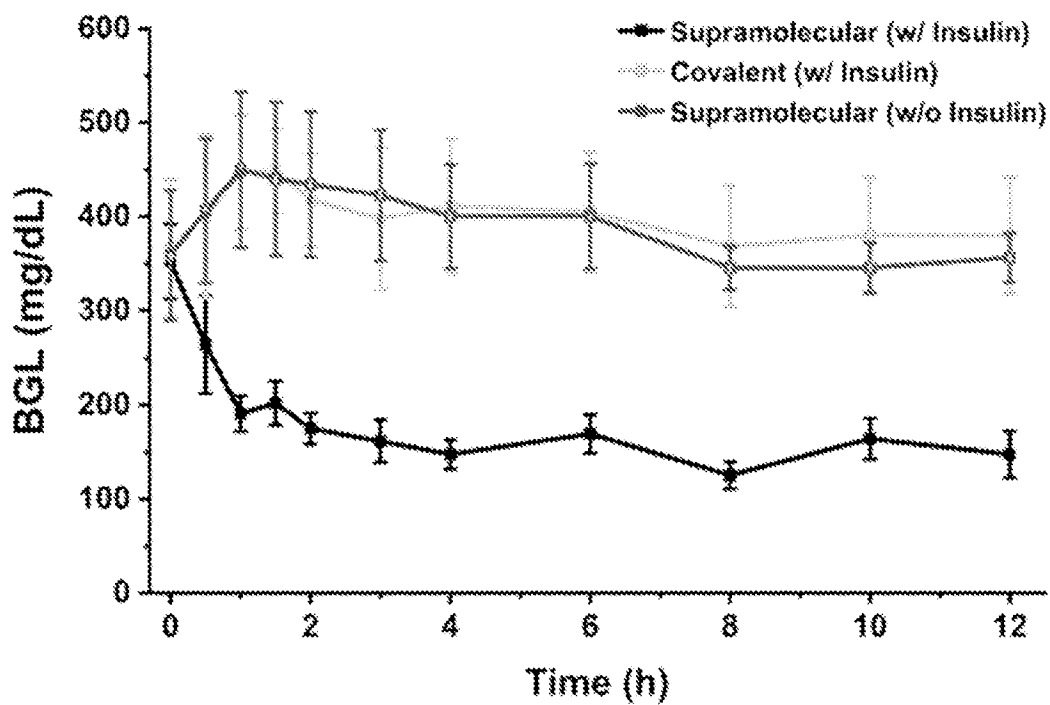


FIG. 8B

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.: **25**
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: Claims 1-15 are drawn to devices.

Group II: Claims 16-20 are drawn to methods of preparing.

Group III: Claims 21-24 are drawn to methods of transdermally delivering a therapeutic agent to a subject in need thereof.

The inventions listed in Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, devices, are not present in Groups II and III; the special technical features of Group II, methods of preparing, are not present in Groups I and III; and the special technical features of Group III, methods of transdermally delivering a therapeutic agent to a subject in need thereof, are not present in Groups I and II.

Additionally, even if Groups I-III were considered to share the technical features of a device comprising a detachable microneedle array, the detachable microneedle array comprising a plurality of detachable microneedles attached to a backing, the detachable microneedles and the backing comprising a multi-component hydrogel, the multicomponent hydrogel comprising: a biopolymer; and a supramolecular network; and a method thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 2006/0047242 A1 to Laurent et al. and "Reversible hydrogel dynamics by physical-chemical crosslink photoswitching using a supramolecular macrocycle template" to Zou et al.

US 2006/0047242 A1 to Laurent et al. teach a device comprising a detachable microneedle array, the detachable microneedle array comprising a plurality of detachable microneedles attached to a backing (Para. [0014], device is provided having a plurality of microneedles; Para. [0028], detachable part of the microabrader; Para. [0040], covering that is an integral part of, or is capable of being functionally attached to, the delivery device), the detachable microneedles and the backing comprising a hydrogel comprising a biopolymer (Para. [0044], the distal surface of the opening cover may be coated with hydrogel matrix or

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

other polymeric matrix; Para. [0011], bioactive substance, including but not limited to ... polypeptides); and a method thereof (Para. [0001], method and device for abrading the skin).

“Reversible hydrogel dynamics by physical–chemical crosslink photoswitching using a supramolecular macrocycle template” to Zou et al. teach the multicomponent hydrogel comprising: a biopolymer; and a supramolecular network (Pg. 1, Col. 2, Para. 1, Supramolecular polymers have been created from CB[8]-mediated photodimerization and chain extension of bi-functional BM building blocks; see also Scheme 1).

The inventions listed in Groups I-III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

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.: **1-15**

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/010837

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 38/28** (2024.01); **A61K 47/10** (2024.01); **A61K 47/22** (2024.01); **A61K 9/00** (2024.01)CPC: **A61K 9/0021**; **A61K 38/28**; **A61K 47/10**; **A61K 47/22**

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 108837299 B (WUHAN UNIVERSITY WHU) 07 August 2020 (07.08.2020) see machine translation and original	1-9, 12-15
Y	ZOU et al., Reversible hydrogel dynamics by physical–chemical crosslink photoswitching using a supramolecular macrocycle template, Chemical Communications, Vol. 55, 02 August 2019 [retrieved on 30 April 2024]. Retrieved from the Internet: <URL: https://pubs.rsc.org/en/content/articlelanding/2019/cc/c9cc04748d >. Abstract, S1-S16	1-9, 12-15
A	US 2006/0047242 A1 (LAURENT et al.) 02 March 2006 (02.03.2006) entire document	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

“D” document cited by the applicant in the international application

“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

30 April 2024 (30.04.2024)

Date of mailing of the international search report

08 May 2024 (08.05.2024)

Name and mailing address of the ISA/US

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