

(51) International Patent Classification:
A61K 9/70 (2006.01)(21) International Application Number:
PCT/US2014/026046(22) International Filing Date:
13 March 2014 (13.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

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(54) Title: AMPHIPHILIC RESIN LINEAR COPOLYMERS FOR PHARMACEUTICAL DRUG DELIVERY APPLICATIONS

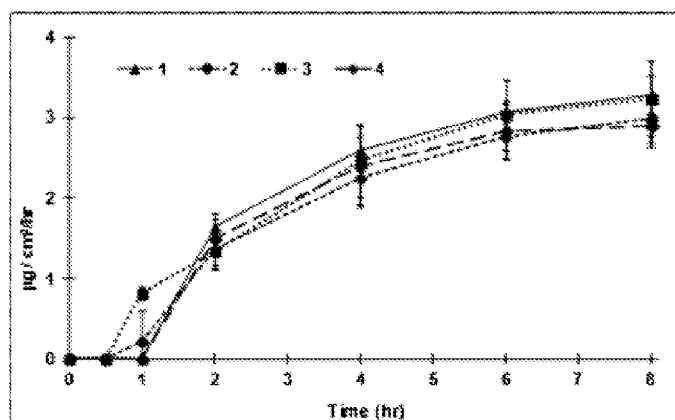


FIG. 1

(57) Abstract: The present disclosure relates to a drug delivery formulation. The drug delivery formulation includes an amphiphilic resin-linear copolymer, a resin-linear organosiloxane block copolymer, or a combination thereof in a first solvent, wherein the first solvent is configured to dissolve the amphiphilic resin-linear copolymer or the resin-linear organosiloxane block copolymer; at least one active ingredient configured to be topically delivered through skin for an intended therapeutic application; and at least one penetration enhancer or penetration excipient. The formulation may additionally include a solid silicone resin. The formulation may additionally include an occlusivity agent. The formulation is configured to form a temporary film on the substrate onto which the formulation is applied.





Published:

- *without international search report and to be republished
upon receipt of that report (Rule 48.2(g))*

**AMPHIPHILIC RESIN LINEAR COPOLYMERS FOR PHARMACEUTICAL DRUG
DELIVERY APPLICATIONS**

BRIEF DESCRIPTION OF THE INVENTION

[0001] The invention relates to a novel controlled release topical drug delivery formulation. The controlled-release formulation is for topical application of an active ingredient to a substrate, such as mammalian skin. The formulation is configured to form a temporary film on the substrate and to deliver a therapeutic amount of an active ingredient to the skin for an extended period of time. The formulation is configured to deliver a therapeutic amount of active to the substrate for an extended period of time.

[0002] One aspect of the invention relates to a drug delivery formulation. The drug delivery formulation includes an organosiloxane copolymer wherein the organosiloxane copolymer is (i) an amphiphilic resin-linear copolymer (component (a)(i)); a resin-linear organosiloxane block copolymer (component (a)(ii)); or (iii) a combination of (i) and (ii) (component (a)(iii)) in a first solvent (component (b)), wherein the first solvent is configured to dissolve the amphiphilic resin-linear copolymer or the resin-linear organosiloxane block copolymer; at least one active ingredient (component (c)) configured to be topically delivered through skin for an intended therapeutic application; and at least one penetration enhancer or penetration excipient (component (d)). The formulation may additionally include a solid silicone resin (optional component (e)) in a second solvent (optional component (f)). The formulation may additionally include an occlusivity agent (optional component (g)). The formulation may additionally include a pressure sensitive adhesive (optional component (h)). The formulation is configured to form a temporary film on the substrate onto which the formulation is applied.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] The foregoing and other advantages of the invention will become apparent upon reading the following detailed description and upon reference to the drawings.

[0004] FIGs. 1-5 illustrate flux profiles for formulation examples 1-16.

[0005] While the invention is susceptible to various modifications and alternative forms, specific embodiments have been shown by way of example in the drawings and will be described in detail herein. It should be understood that the invention is not intended to be limited to the particular forms disclosed. Rather, the invention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0006] The term “ambient conditions” as used throughout the specification refers to surrounding conditions under about one atmosphere of pressure, at about 50% relative

humidity, and at about 25°C, unless otherwise specified. All percentages, parts, and ratios are based upon the total weight of the topical formulation, unless otherwise specified.

[0007] The topical formulation may be prepared by mixing an amphiphilic resin-linear organosiloxane block copolymer ("ARL copolymer") (component (a)(i)) or a resin-linear organosiloxane block copolymer ("RL copolymer") (component (a)(ii)) or a combination of the ARL copolymer and the RL copolymer (component (a)(iii)) in a suitable solvent (component (b)) configured to dissolve the ARL copolymer or the RL copolymer with at least one active ingredient (component (c)) configured to be topically delivered through skin for an intended therapeutic application; and at least one penetration enhancer or penetration excipient (component (d)). According to another aspect of the invention, the formulation includes a solid silicone resin (optional component (e)) in a second solvent (optional component (f)) that is configured to dissolve the solid silicone resin. The topical formulation may also include at least one occlusivity agent (optional component (g)) configured to provide occlusivity when the formulation is applied to the skin. The formulation may also include additional ingredients depending on the application.

[0008] The formulation may include between about 5-85%w/w of the ARL copolymer, RL copolymer, or combination thereof. Alternatively, the formulation may include between about 38-77%w/w of the ARL copolymer, the RL copolymer, or combination thereof. The amount of the ARL copolymer and/or the RL copolymer is determined based on the desired application. When the application includes more of the ARL copolymer or the RL copolymer, the formulation becomes higher in viscosity.

[0009] The formulation may include no solid silicone resin. The formulation may include between about 5-60%w/w or, alternatively, about 30%w/w of the solid silicone resin. The amount of the solid silicone resin in the formulation may be adjusted depending on the desired formulation properties. A larger amount of the solid silicone resin tends to make the formulation stick to the skin for a longer period of time.

[0010] The amount of healthcare or pharmaceutical active ingredient present in the topical formulation may vary. The formulation may include between about 0.001-50%w/w, or, alternatively, between 0.05-25%w/w, or, alternatively, between 0.05-10%w/w of the active.

[0011] The formulation according to the invention may include between about 0-80%w/w, or, alternatively between 0.5-50%w/w, or alternatively between 0.5-15%w/w of at least one penetration enhancer or penetration excipient.

[0012] The formulation according to the invention may additionally include between about 0-50%w/w, or, alternatively, between about 0.5-25%w/w of the at least one agent configured to provide occlusivity.

[0013] The formulation may additionally include between about 0-25%w/w of the pressure sensitive adhesive.

[0014] The substrate to which the formulation is applied typically is a biological surface, human body tissue, and/or animal body tissue. More specific substrates include, but are not limited to, skin, hair, mucous membrane, teeth, nails, and eyes.

[0015] The formulation is typically applied for topical therapy, such as to treat damaged or diseased skin, and wound care, such as to treat cuts, burns, scars, and the like, with a dressing formed from, or including, the controlled-release topical formulation where the ARL or the RL copolymer functions as a substantive cream or a liquid bandage that continuously delivers the active agent to the substrate. The disclosure, including films formed by the controlled-release formulations of the disclosure, may also be applied in various transdermal, pharmaceutical, veterinary, and oral health care applications. It may be used as an in situ formed patch standing by itself, or it can be protected with a secondary film, dressing, or patch, or it can be part of a more complex construction such as a transdermal patch or wound dressing. As indicated above, the controlled-release formulation, hereafter referred to as the composition or the formulation, includes an ARL copolymer or a RL copolymer and an active agent uniformly incorporated into or dispersed in the formulation.

[0016] According to one aspect, the formulation is configured to deliver a therapeutic active to the skin throughout the treatment or after a certain initial period, e.g., ½ hour, 1 hour, 2 hours, etc. depending on the composition and application.

[0017] According to one aspect, the topical formulation is sprayed onto a substrate. A few seconds after being sprayed onto a substrate (e.g., 0-10 seconds), the formulation becomes dry. According to one aspect of the invention, the person on whose skin the formulation is being applied does not need to touch the formulation; in other words, the patient may simply spray the formulation onto his or her skin and wait a few seconds until the formulation becomes dry, which eases the application procedure and improves patient compliance. According to other aspects, the formulation may be manually spread on the substrate or applied to the substrate in any suitable manner. The container including the formulation may include a brush, sponge, or other device configured to assist in spreading the formulation on the substrate without requiring physical contact with (i.e., without requiring manually touching) the formulation, which improves patient compliance with treatment. The topical formulation may be in the form of an emulsion, gel, liquid, aerosol, or any other suitable form, depending on the intended therapeutic application.

[0018] After the formulation becomes dry, the patient may put clothing on top of the formulation and may sleep on areas where the formulation was applied. The formulation is configured to remain intact and on top of the substrate for an extended period of time.

According to one aspect of the invention, a patient may apply the formulation on bare skin in the morning, wait several seconds for the volatile solvents in the formulation to evaporate, then place clothes on top of the formulation, and the formulation will stay intact on the skin throughout the day (or for a period of time that the therapeutic treatment is needed or desired). When desired to be removed, the patient may simply gently rub the formulation and it will dust off the skin. Alternatively, the formulation may be gently peeled off the skin after the end of the desired therapeutic treatment. The formulation may be adjusted in such a way that the formulation becomes dry and easy to take off the skin after a desired length of the therapeutic treatment. For example, if the desired length of treatment is 12 hours, after 12 hours the formulation will become very easy to take off; washing may assist in removal of the formulation from the skin. Similarly, a patient may apply the formulation on the skin at night, and the formulation will remain intact throughout the night despite any friction caused by clothing or by movement during sleep. Thus, the length of time that the formulation will stay on the skin may be tailored depending on the desired length of treatment. Similarly, the strength of adherence of the formulation to the skin may also be formulated depending on the application and the location on a patient's body where the formulation is applied.

[0019] The formulation is configured to not form cracks on the surface of the formulation for the duration of the desired treatment, which may be a few hours (e.g., about 2, 4, 8, 12, or longer than 12 hours). The formulation remains intact on the skin for a time period ranging from 1 hour to 24 hours and resists the formation of cracks on the surface of the film. Formation of cracks would result in the treatment being delivered only to areas of the skin in between the cracks, which is undesirable. The formulation is configured to leave a flexible film, so that it will not form cracks after the application, which allows the patient to move freely. The formulation is configured to deliver a therapeutic amount of the active ingredient evenly throughout the application area throughout the entire duration of the treatment.

[0020] Upon application to a substrate, the formulation forms a temporary thin film on top of the substrate. According to certain aspects of the invention, a few seconds (e.g., about 0-30, 0-60, 0-120 seconds) after application to the substrate, the formulation becomes dry to the touch. The film may form a barrier that is configured to prevent contamination to the application site. According to one aspect of the invention, the film that forms on the substrate may be translucent or have a slight tint of color to make it easier to locate the area where the formulation was applied. Alternatively, the film may be entirely transparent.

Component (a)(i) – ARL Copolymer

[0021] ARL Copolymers and their formation are described in U.S. Provisional Patent Application Serial No. 61/616,689, filed March 28, 2012, titled "Amphiphilic Resin-Linear Organosiloxane Block Copolymers," which is incorporated herein by reference in its entirety.

[0022] ARL copolymers are generally solid materials, soluble in organic solvents such as ethyl acetate. ARL copolymer synthesis includes a reaction between a Si-H terminated polydimethylsiloxane (PDMS) and a polyglycol to form a Si-H intermediate. The intermediate is then further reacted with a vinyl functionalized silsesquioxane resin to form the ARL copolymer.

[0023] ARL copolymers relate to resin-linear organosiloxane block copolymers comprising:

i) a linear block of repeating units having the formula $B-[AB]_n$

where B is a diorganopolysiloxane having an average of from 10 to 400

disiloxy units of the formula $[R^1_2SiO_{2/2}]$

A is a divalent organic group comprising at least one polyether group, and

n is ≥ 1

ii) a resinous block of repeating units of the formula $[R^2SiO_{3/2}]$ arranged in non-linear blocks having a molecular weight of at least 500 g/mol, wherein

each R^1 is independently a C_1 to C_{30} hydrocarbyl,

each R^2 is independently a C_1 to C_{20} hydrocarbyl,

each linear block is linked to at least one non-linear block

by a divalent C_2 to C_{12} hydrocarbon group, and

the organosiloxane block copolymer has a molecular weight of at least 20,000 g/mole.

[0024] The compositions incorporate an amphiphilic “linear” segment with an aryl containing “resinous” segment. For example, a polyether (A) modified PDMS (B) with $(AB)_n$ architecture and polydiorganosiloxane with SiH end-groups can be reacted with a phenyl silsesquioxane resin bearing vinyl functionality to form an amphiphilic resin-linear copolymer. Using such methods, ARL copolymers that are soluble in organic solvents and can be processed by heat were discovered. The amphiphilic nature can be used to improve solubility of hydrophilic actives into the siloxane matrix.

[0025] The presence of the phenyl resin imparts physical cross-link points, which result in the ability to form elastomers, gels, or films at room temperature without the need for any additional chemical cross-linking. Additional benefits include the introduction of additives that would otherwise inhibit chemical cure, for example nitrogen and sulfur moieties that inhibit platinum catalyzed hydrosilylation. Additional benefits are introduced through the control of the glass transition of the resin phase which can be tuned to reside below, at or above room temperature. For example, a glass transition above room temperature can be used to form a tack-free film, while a glass transition below or close to room temperature could be used to tune tack for certain applications. The present process also provides

compositions that form optically clear materials due to the chemical grafting of the amphiphilic flexible blocks with the aryl-containing resinous hard blocks.

[0026] In one embodiment, the solid compositions containing the present ARL copolymers have improved water vapor permeation rates (WVPR), as compared to similar copolymers that do not contain polyether units in its structure. In this embodiment, the solid films of ARL copolymer compositions having a thickness of 0.3-0.4 mm have WVPR of at least 30 g/m²·day, at least 40 g/m²·day, at least 50 g/m²·day, or at least 60 g/m²·day.

[0027] Organopolysiloxanes are polymers including siloxy units independently selected from (R₃SiO_{1/2}), (R₂SiO_{2/2}), (RSiO_{3/2}), or (SiO_{4/2}) siloxy units, where R may be any organic group. These siloxy units are commonly referred to as M, D, T, and Q units respectively. These siloxy units can be combined in various manners to form cyclic, linear, or branched structures. The chemical and physical properties of the resulting polymeric structures vary depending on the number and type of siloxy units in the organopolysiloxane. “Linear” organopolysiloxanes typically include mostly D or (R₂SiO_{2/2}) siloxy units, which results in polydiorganosiloxanes that are fluids of varying viscosity, depending on the “degree of polymerization” or DP as indicated by the number of D units in the polydiorganosiloxane. “Linear” organopolysiloxanes typically have glass transition temperatures (T_g) that are lower than 25°C. “Resin” organopolysiloxanes result when a majority of the siloxy units are selected from T or Q siloxy units. When T siloxy units are predominately used to prepare an organopolysiloxane, the resulting organosiloxane is often referred to as a “silsesquioxane resin”. Increasing the amount of T or Q siloxy units in an organopolysiloxane typically results in polymers having increasing hardness and/or glass like properties. “Resin” organopolysiloxanes thus have higher T_g values, for example siloxane resins often have T_g values greater than 50°C

[0028] As used herein ARL copolymers refer to organopolysiloxanes including “linear” blocks of repeating D siloxy units and polyether units in combination with “resin” T siloxy units. The present organosiloxane copolymers are “block” copolymers, as opposed to “random” copolymers. The “linear blocks” of the present ARL copolymers may be considered as -[AB]_n- silicone polyether copolymers having repeating units of A, a divalent organic group including at least one polyether group, and B, a diorganopolysiloxane. The subscript *n* represents on average the number repeating units of [AB] in the copolymer, and *n* is ≥ 1, alternatively *n* ranges from 1 to 50.

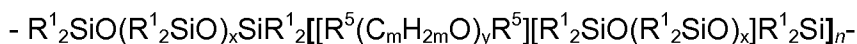
[0029] The divalent organic group including at least one polyether group, designated as A, comprises at least one polyether group. As used herein, “polyether” designates a polyoxyalkylene group. The polyoxyalkylene group may be represented by the formula (C_mH_{2m}O)_y wherein *m* is from 2 to 4 inclusive, and *y* is greater than 3, alternatively *y* may range from 4 to 60, or alternatively from 5 to 30. The polyoxyalkylene group may comprise

oxyethylene units (C_2H_4O), oxypropylene units (C_3H_6O), oxybutylene units (C_4H_8O), or mixtures thereof. Typically, the polyoxyalkylene group comprises oxyethylene units (C_2H_4O) or mixtures of oxyethylene units and oxypropylene units.

[0030] The linear block of repeating units having the formula $B-[AB]_n$ also includes a diorganopolysiloxane, designated as B. The diorganopolysiloxane has an average of from 10 to 400 disiloxy units of the formula $[R^1_2SiO_{2/2}]$.

[0031] R^1 in the above disiloxy unit formula is independently a C_1 to C_{30} hydrocarbyl. The hydrocarbon group may independently be an alkyl, aryl, or alkylaryl group. As used herein, hydrocarbyl also includes halogen substituted hydrocarbyls. R^1 may be a C_1 to C_{30} alkyl group, alternatively R^1 may be a C_1 to C_{18} alkyl group. Alternatively, R^1 may be a C_1 to C_6 alkyl group such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. Alternatively R^1 may be methyl. R^1 may be an aryl group, such as phenyl, naphthyl, or an anthryl group. Alternatively, R^1 may be any combination of the aforementioned alkyl or aryl groups.

[0032] In one embodiment, the linear block comprises a silicone polyether copolymer which may be represented by the average formula;



where x is ≥ 0 , m is from 2 to 4 inclusive, y is ≥ 4 , n is ≥ 1 , R^1 is independently a monovalent hydrocarbon group including 1 to 30 carbons, R^5 is a divalent hydrocarbon including 2 to 30 carbons.

[0033] At least one end of each polyether block A is linked to a silicone block B by a divalent hydrocarbon group, designated R^5 . This linkage is determined by the reaction employed to prepare the $(AB)_n$ block silicone polyether copolymer. The divalent hydrocarbon group R^5 may be independently selected from divalent hydrocarbon groups containing 2 to 12 carbons. Representative, non-limiting examples of such divalent hydrocarbon groups include; ethylene, propylene, butylene, isobutylene, and the like. Representative, non-limiting examples of such divalent organofunctional hydrocarbons groups include acrylate and methacrylate. Typically, R^5 is ethylene, propylene, $(-CH_2CH_2CH_2-)$, or isobutylene $(-CH_2CH(CH_3)CH_2-)$.

[0034] ARL copolymers include a resinous block of repeating units of the formula $[R^2SiO_{3/2}]$ arranged in non-linear blocks having a molecular weight (MW) of at least 500g/mol.

[0035] Each R^2 in the above trisiloxy unit formula is independently a C_1 to C_{20} hydrocarbyl. As used herein, hydrocarbyl also includes halogen substituted hydrocarbyls. R^2 may be an aryl group, such as phenyl, naphthyl, anthryl group. Alternatively, R^2 may be an alkyl group, such as methyl, ethyl, propyl, or butyl. Alternatively, R^2 may be any combination of the aforementioned alkyl or aryl groups. Alternatively, R^2 is phenyl or methyl.

[0036] The amount of linear and resinous blocks in the ARL copolymer may vary, but typically the ARL copolymer includes sufficient amounts of the resinous block to provide 10 – 70 mole percent trisiloxy units, or alternatively 20 – 60 mole percent trisiloxy units, of the total siloxy units present in the RL organosiloxane block copolymer.

[0037] Alternatively the amounts of the linear and resinous blocks in the ARL copolymer may be reported in weight percent of the resin component. Typically the ARL copolymer includes sufficient amounts of the resinous block to provide 10-90wt%, alternatively 20-70, or alternatively 20-60wt% of the resinous block in the ARL copolymer.

[0038] The present ARL organosiloxane block copolymers have an average MW of at least 20,000, at least 40,000, or at least 50,000 g/mole determined using Gel Permeation Chromatography (GPC) techniques.

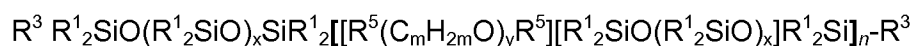
[0039] The structural ordering of the disiloxy and trisiloxy units may be further described as follows; the disiloxy units $[R^1_2SiO_{2/2}]$ and polyether units are arranged in linear blocks having an average of from 10 to 400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block, and the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a MW of at least 500 g/mol. Each linear block is linked to at least one non-linear block in the block copolymer. Furthermore, at least at 30% of the non-linear blocks are crosslinked with each other, alternatively at least at 40% of the non-linear blocks are crosslinked with each other, alternatively at least at 50% of the non-linear blocks are crosslinked with each other.

[0040] The crosslinking of the non-linear blocks may be accomplished via a variety of chemical mechanisms and/or moieties. For example, crosslinking of non-linear blocks within the block copolymer may result from the condensation of residual silanol groups present in the non-linear blocks of the copolymer. Crosslinking of the non-linear blocks within the block copolymer may also occur between “free resin” components and the non-linear blocks. “Free resin” components may be present in the block copolymer compositions as a result of using an excess amount of an organosiloxane resin during the preparation of the block copolymer. The free resin component may crosslink with the non-linear blocks by condensation of the residual silanol groups present on the non-linear blocks and on the free resin. The free resin may provide crosslinking by reacting with lower MW compounds added as crosslinkers. Alternatively, certain compounds may have been added during the preparation of the block copolymer to specifically crosslink the non-resin blocks (as discussed below).

[0041] The ARL organosiloxane block copolymers may be prepared by

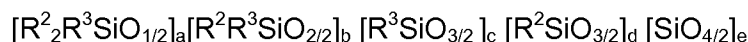
l) reacting

a) a linear organosiloxane of the formula



where x is ≥ 0 , m is from 2 to 4 inclusive, y is ≥ 3 , n is ≥ 1 ,
 R^1 is independently a C_1 to C_{30} hydrocarbyl,
 R^5 is a divalent hydrocarbon containing 2 to 30 carbons,
 R^3 is independently H
 or R^4 where R^4 is a C_2 to C_{12} hydrocarbyl having at least one aliphatic unsaturated bond;

b) an organosiloxane resin having the average formula:



where the subscripts a , b , c , d , and e represent the mole fraction of each siloxy unit present in the organosiloxane resin and range as follows; a may vary from 0-0.7, b may vary from 0-0.3, c may vary from 0-0.8, d may vary from 0-0.9, e may vary from 0-0.7, with the provisos that $a+b+c > 0$, $c+d+e \geq 0.6$, and $a+b+c+d+e \approx 1$, with the proviso at least one R^3 substituent is H on either of the linear organosiloxane or organosiloxane resin, and one R^3 substituent is R^4 on the other organosiloxane, and

c) a hydrosilylation catalyst,

in an organic solvent, to form a resin-linear organosiloxane block copolymer;

wherein the amounts of a) and b) used in step I are selected to provide the resin-linear organosiloxane block copolymer with 10-90mol% of disiloxo units $[R^1_2SiO_{2/2}]$ and 10-70mol% of $[R^2SiO_{3/2}]$ or $[SiO_{4/2}]$ siloxy units, and at least 95wt% of linear organosiloxane added in step I is incorporated into the resin-linear organosiloxane block copolymer,

II) optionally, reacting the resin-linear organosiloxane block copolymer from step I) to crosslink the $[R^2SiO_{3/2}]$ or $[SiO_{4/2}]$ siloxy units of the resin-linear organosiloxane block copolymer sufficiently to increase the average MW of the resin-linear organosiloxane block copolymer by at least 50%.

[0042] The linear organosiloxane (a) used in step I may be prepared according the methods described in WO2008/127519, which is hereby incorporated by reference in its entirety. For example, the linear organosiloxane may be prepared by reacting: A) a polyoxyalkylene having an unsaturated hydrocarbon group at each molecular terminal B) a SiH terminated organopolysiloxane, C) a hydrosilylation catalyst, D) an optional solvent.

Component (a)(ii) – RL Copolymer

[0043] RL copolymers and their formation are described in PCT Application No. PCT/US2011/52518, filed September 21, 2011, titled “Resin-Linear Organosiloxane Block Copolymers,” which is incorporated herein by reference in its entirety.

[0044] The RL copolymers include

40 to 90 mole percent disiloxo units of the formula $[R^1_2SiO_{2/2}]$;

10 to 60 mole percent trisiloxy units of the formula $[R^2SiO_{3/2}]$;

0.5 to 35 mole percent silanol groups $[≡SiOH]$;

where each R^1 is independently a C_1 to C_{30} hydrocarbyl;

each R^2 is independently a C_1 to C_{20} hydrocarbyl;

wherein

the disiloxy units $[R^1_2SiO_{2/2}]$ are arranged in linear blocks having an average of from 10 to 400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block;

the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a molecular weight of at least 500 g/mol, and at least 30% of the non-linear blocks are crosslinked with each other;

each linear block is linked to at least one non-linear block; and

the organosiloxane block copolymer has a molecular weight of at least 20,000 g/mole.

[0045] As used herein RL copolymers refer to organopolysiloxanes including “linear” D siloxy units in combination with “resin” T siloxy units. The present RL copolymers refer to organopolysiloxanes including D and T siloxy units, where the D units are primarily bonded together to form polymeric chains having 10 to 400 D units, which are referred herein as “linear blocks”. The T units are primarily bonded to each other to form branched polymeric chains, which are referred to as “non-linear blocks”. A significant number of these non-linear blocks may further aggregate to form “nano-domains” when solid forms of the block copolymer are provided. More specifically, the disiloxy units $[R^1_2SiO_{2/2}]$ are arranged in linear blocks having an average of from 10-400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block, and the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a MW of at least 500g/mol and at least 30% of the non-linear blocks are crosslinked with each other.

[0046] RL copolymers comprising 40-90 mole% disiloxy units of the formula $[R^1_2SiO_{2/2}]$ and 10-60 mole% trisiloxy units of the formula $[R^2SiO_{3/2}]$ may be represented by the formula $[R^1_2SiO_{2/2}]_a[R^2SiO_{3/2}]_b$ where the subscripts a and b represent the mole fractions of the siloxy units in the copolymer, “a” may vary from 0.4 to 0.9, alternatively from 0.5 to 0.9, alternatively from 0.6 to 0.9. “b” may vary from 0.1 to 0.6, alternatively from 0.1 to 0.5, alternatively from 0.1 to 0.4. R^1 is independently a C_1 to C_{30} hydrocarbyl. R^2 is independently a C_1 to C_{10} hydrocarbyl.

[0047] It should be understood that the present RL copolymers may include additional siloxy units, such as M siloxy units, Q siloxy units, other unique D or T siloxy units (for example having a organic groups other than R^1 or R^2), provided the RL copolymer includes the mole fractions of the disiloxy and trisiloxy units as described above. In other words, the sum of the mole fractions as designated by subscripts a and b, do not necessarily have to sum to

one. The sum of $a + b$ may be less than one to account for minor amounts of other siloxy units that may be present in the RL copolymer. Alternatively, the sum of $a + b$ is greater than 0.6, greater than 0.7, greater than 0.8, or alternatively greater than 0.9.

[0048] In one embodiment, the RL copolymer consists essentially of the disiloxy units of the formula $[R^1_2SiO_{2/2}]$ and trisiloxy units of the formula $[R^2SiO_{3/2}]$, while also including 0.5 to 25 mole percent silanol groups $[≡SiOH]$, where R^1 and R^2 are as defined above. Thus, in this embodiment, the sum of $a + b$ (when using mole fractions to represent the amount of disiloxy and trisiloxy units) is greater than 0.95, alternatively greater than 0.98.

[0049] The RL copolymers also include silanol groups $(≡SiOH)$. The amount of silanol groups present on the RL copolymer may vary from about 0.5-35 mole% silanol groups $[≡SiOH]$, alternatively from 2-32 mole% silanol groups $[≡SiOH]$, alternatively from 8-22 mole% silanol groups $[≡SiOH]$. The silanol groups may be present on any siloxy units within RL copolymer. The amount described above represents the total amount of silanol groups found in RL copolymer.

[0050] R^1 in the above disiloxy unit formula is independently a C_1 to C_{30} hydrocarbyl. The hydrocarbon group may independently be an alkyl, aryl, or alkylaryl group. As used herein, hydrocarbyl also includes halogen substituted hydrocarbyls. R^1 may be an aryl group, such as phenyl, naphthyl, or an anthryl group. Alternatively, R^1 may be any combination of the aforementioned alkyl or aryl groups.

[0051] Each R^2 in the above trisiloxy unit formula is independently a C_1 to C_{20} hydrocarbyl. R^2 may be an aryl group, such as phenyl, naphthyl, anthryl group. Alternatively, R^2 may be an alkyl group, such as methyl, ethyl, propyl, or butyl. Alternatively, R^2 may be any combination of the aforementioned alkyl or aryl groups.

[0052] The formula $[R^1_2SiO_{2/2}]_a[R^2SiO_{3/2}]_b$, and related formulae using mole fractions, as used herein to describe the present RL copolymers, does not indicate structural ordering of the disiloxy $[R^1_2SiO_{2/2}]$ and trisiloxy $[R^2SiO_{3/2}]$ units in the copolymer. Rather, this formula is meant to provide a convenient notation to describe the relative amounts of the two units in the copolymer, as per the mole fractions described above via the subscripts a and b .

[0053] The present organosiloxane block copolymers have an average MW of at least 20,000, at least 40,000, at least 50,000, at least 60,000, at least 70,000, or alternatively at least 80,000 g/mole.

[0054] The structural ordering of the disiloxy and trisiloxy units may be further described as follows; the disiloxy units $[R^1_2SiO_{2/2}]$ are arranged in linear blocks having an average of from 10 to 400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block, and the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a MW of at least 500 g/mol. Each linear block is linked to at least one non-linear block in the block copolymer. Furthermore, at least about 30%, at

least about 40%, or alternatively at least about 50% of the non-linear blocks are crosslinked with each other.

[0055] The crosslinking of the non-linear blocks may be accomplished via a variety of chemical mechanisms and/or moieties. For example, crosslinking of non-linear blocks within the block copolymer may result from the condensation of residual silanol groups present in the non-linear blocks of the copolymer. Crosslinking of the non-linear blocks within the block copolymer may also occur between “free resin” components and the non-linear blocks. “Free resin” components may be present in the block copolymer compositions as a result of using an excess amount of an organosiloxane resin during the preparation of the block copolymer. The free resin component may crosslink with the non-linear blocks by condensation of the residual silanol groups present on the non-blocks and on the free resin. The free resin may provide crosslinking by reacting with lower MW compounds added as crosslinkers, as described below.

[0056] Alternatively, certain compounds may have been added during the preparation of the block copolymer to specifically crosslink the non-resin blocks. These crosslinking compounds may include an organosilane having the formula $R^5_qSiX_{4-q}$ is added during the formation of the block copolymer (step II as discussed below), where R^5 is a C_1 to C_8 hydrocarbyl or a C_1 to C_8 halogen-substituted hydrocarbyl, X is a hydrolysable group, and q is 0, 1, or 2. R^5 is a C_1 to C_8 hydrocarbyl or a C_1 to C_8 halogen-substituted hydrocarbyl, or alternatively R^5 is a C_1 to C_8 alkyl group, or alternatively a phenyl group, or alternatively R^5 is methyl, ethyl, or a combination of methyl and ethyl. X is any hydrolyzable group, alternatively X may be a, an oximo, acetoxo, halogen atom, hydroxyl (OH), or an alkoxy group. In one embodiment, the organosilane is an alkyltriacetoxysilane, such as methyltriacetoxysilane, ethyltriacetoxysilane, or a combination of both. Commercially available representative alkyltriacetoxysilanes include ETS-900 (Dow Corning Corp., Midland, MI). Other suitable, non-limiting organosilanes useful as crosslinkers include; methyl- tris(methylethylketoxime)silane (MTO), methyl triacetoxysilane, ethyl triacetoxysilane, tetraacetoxysilane, tetraoximesilane, dimethyl diacetoxysilane, dimethyl dioximesilane, methyl tris(methylmethylketoxime)silane.

[0057] The crosslinks within the block copolymer will primarily be siloxane bonds $\equiv Si-O-Si \equiv$, resulting from the condensation of silanol groups, as discussed above.

[0058] Typically, crosslinking the block copolymer increases its average MW. Thus, an estimation of the extent of crosslinking may be made, given the average MW of the block copolymer, the selection of the linear siloxy component (that is the chain length as indicated by its degree of polymerization), and the molecular weight of the non-linear block (which is

primarily controlled by the selection of the selection of the organosiloxane resin used to prepare the block copolymer).

[0059] Solid compositions including the RL copolymers may be prepared by removing the solvent from the curable RL copolymer compositions. Curable RL copolymer compositions may include the RL copolymer and a solvent, which may be an aromatic solvent such as benzene, toluene, or xylene. Curable compositions may also include an organosiloxane resin. Curable compositions may also include a catalyst, including catalysts known in the art to affect condensation cure of organosiloxanes, such as various tin or titanium catalysts. The solvent may be removed by any known processing techniques. In one embodiment, a film of the curable compositions containing the ARL copolymers is formed, and the solvent is allowed to evaporate from the film. Subjecting the films to elevated temperatures, and/or reduced pressures, will accelerate solvent removal and subsequent formation of the solid curable composition. Alternatively, the curable compositions may be passed through an extruder to remove solvent and provide the solid composition in the form of a ribbon or pellets. Coating operations against a release film could also be used as in slot die coating, knife over roll, rod, or gravure coating. Also, roll-to-roll coating operations could be used to prepare a solid film. In coating operations, a conveyer oven or other means of heating and evacuating the solution can be used to drive off the solvent and obtain the final solid film.

[0060] The structural ordering of the disiloxy and trisiloxy units in the RL copolymer as described above may provide it with certain unique physical property characteristics when solid compositions of the RL copolymer are formed. For example, the structural ordering of the disiloxy and trisiloxy units in the copolymer may provide solid coatings that allow for a high optical transmittance of visible light. The structural ordering may also allow the RL copolymer to flow and cure upon heating, yet remain stable at room temperature. They may also be processed using lamination techniques. These properties are useful in coatings to improve weather resistance and durability, while providing low cost and easy procedures that are energy efficient.

[0061] Solid forms of the aforementioned RL copolymers and solid compositions derived from the curable compositions described above comprising the RL copolymers may comprise:

40 to 90 mole percent disiloxy units of the formula $[R^1_2SiO_{2/2}]$;

10 to 60 mole percent trisiloxy units of the formula $[R^2SiO_{3/2}]$;

0.5 to 25 mole percent silanol groups $[≡SiOH]$,

where R^1 is independently a C_1 to C_{30} hydrocarbyl; and

R^2 is independently a C_1 to C_{20} hydrocarbyl, wherein;

the disiloxy units $[R^1_2SiO_{2/2}]$ are arranged in linear blocks having an average of from 10 to 400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block;

the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a MW of at least 500 g/mol, at least 30% of the non-linear blocks are crosslinked with each other and are predominately aggregated together in nano-domains, each linear block is linked to at least one non-linear block, the organosiloxane block copolymer has a molecular weight of at least 20,000 g/mole, and is a solid at 25°C.

[0062] In this embodiment, the aforementioned organosiloxane block copolymers are isolated in a solid form, for example by casting films of a solution of the RL copolymer in an organic solvent and allowing the solvent to evaporate. Upon drying or forming a solid, the non-linear blocks of the block copolymer further aggregate together to form “nano-domains”. As used herein, “predominately aggregated” means the majority of the non-linear blocks of the RL copolymer are found in certain regions of the solid composition, described herein as “nano-domains”. As used herein, “nano-domains” refers to those phase regions within the solid block copolymer compositions that are phase separated within the solid block copolymer compositions and possess at least one dimension sized from 1 to 100 nanometers. The nano-domains may vary in shape, providing at least one dimension of the nano-domain is sized from 1 to 100 nanometers. Thus, the nano-domains may be regular or irregularly shaped. The nano-domains may be spherically shaped, tubular shaped, and in some instances lamellar shaped.

[0063] In a further embodiment, the RL copolymers as described above contain a first phase and an incompatible second phase, the first phase containing predominately the disiloxy units $[R^1_2SiO_{2/2}]$ as defined above, the second phase containing predominately the trisiloxy units $[R^2SiO_{3/2}]$ as defined above, the non-linear blocks being sufficiently aggregated into nano-domains which are incompatible with the first phase.

[0064] The present RL copolymers may provide coatings that have an optical transmittance of visible light greater than 95%. One skilled in the art recognizes that such optical clarity is possible (other than refractive index matching of the two phases) only when visible light is able to pass through such a medium and not be diffracted by particles (or domains as used herein) having a size greater than 150 nanometers. As the particle size or domains further decreases, the optical clarity may be further improved.

[0065] The advantage of the present RL copolymers is that they can be processed several times providing the processing temperature ($T_{\text{processing}}$) is less than the temperature required to finally cure (T_{cure}) the organosiloxane block copolymer, i.e. if $T_{\text{processing}} < T_{\text{cure}}$. However the organosiloxane copolymer will cure and achieve high temperature stability when $T_{\text{processing}} > T_{\text{cure}}$. Thus, the present RL copolymers offer the significant advantage of being “re-

processable" in conjunction with the benefits typically associated with silicones, such as; hydrophobicity, high temperature stability, moisture/UV resistance.

[0066] In one embodiment, the solid compositions of the RL copolymers may be considered as "melt processable". In this embodiment, the solid compositions, such as a coating formed from a film of a solution containing the RL copolymers, exhibit fluid behavior at elevated temperatures, that is upon "melting". The "melt processable" features of the solid compositions of the RL copolymers may be monitored by measuring the "melt flow temperature" of the solid compositions - when the solid composition demonstrates liquid behavior.

[0067] The RL block copolymers may be prepared by a process comprising:

I) reacting a) a linear organosiloxane having the formula



where each R^1 is independently a C_1 to C_{30} hydrocarbyl,

n is 10 to 400, q is 0, 1, or 2,

E is a hydrolyzable group containing at least one carbon atom, and

b) an organosiloxane resin comprising at least 60 mol % of $[R^2SiO_{3/2}]$ siloxy units in its formula, where each R^2 is independently a C_1 to C_{20} hydrocarbyl,

in c) an organic solvent

to form a resin-linear organosiloxane block copolymer;

wherein the amounts of a) and b) used in step I are selected to provide the resin-linear organosiloxane block copolymer with 40 to 90 mol% of disiloxy units $[R^1_2SiO_{2/2}]$ and 10 to 60 mol% of trisiloxy units $[R^2SiO_{3/2}]$, and

wherein at least 95 weight percent of the linear organosiloxane added in step I is incorporated into the resin-linear organosiloxane block copolymer,

II) reacting the resin-linear organosiloxane block copolymer from step I) to

crosslink the trisiloxy units of the resin-linear organosiloxane block copolymer sufficiently to increase the average molecular weight (M_w) of the resin-linear organosiloxane block copolymer by at least 50%,

III) optionally, further processing the resin-linear organosiloxane block copolymer to enhance storage stability and/or optical clarity,

IV) optionally, removing the organic solvent.

[0068] The first step in the present process involves reacting;

a) a linear organosiloxane having the formula



where each R^1 is independently a C_1 to C_{30} hydrocarbyl,

n is 10 to 400, q is 0, 1, or 2,

E is a hydrolyzable group containing at least one carbon atom, and

b) an organosiloxane resin comprising at least 60 mol % of $[R^2SiO_{3/2}]$ siloxy units in its formula, where each R^2 is independently an aryl or C_1 to C_{10} hydrocarbyl,

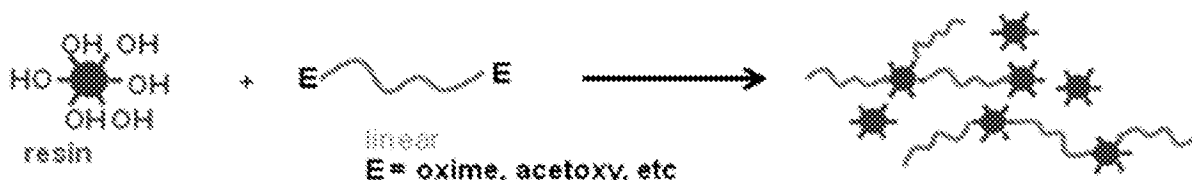
in c) an organic solvent

to form a resin-linear organosiloxane block copolymer;

wherein the amounts of a) and b) used in step I are selected to provide the resin-linear organosiloxane block copolymer with 40 to 90 mol% of disiloxo units $[R^1_2SiO_{2/2}]$ and 10 to 60 mol% of trisiloxo units $[R^2SiO_{3/2}]$, and

wherein at least 95 weight percent of the linear organosiloxane added in step I is incorporated into the resin-linear organosiloxane block copolymer.

[0069] The reaction of the first step of the process may be represented generally according to the following schematic;



[0070] The various OH groups on the organosiloxane resin are reacted with the hydrolyzable groups (E) on the linear organosiloxane, to form a resin-linear organosiloxane block copolymer and a H-(E) compound. The reaction in step I may be considered as a condensation reaction between the organosiloxane resin and the linear organosiloxane.

[0071] The Linear Organosiloxane

[0072] Component a) in step I of the present process is a linear organosiloxane having the formula $R^1_q(E)_{(3-q)}SiO(R^1_2SiO_{2/2})_nSi(E)_{(3-q)}R^1_q$, where each R^1 is independently a C_1 to C_{30} hydrocarbyl, the subscript "n" may be considered as the degree of polymerization (dp) of the linear organosiloxane and may vary from 10 to 400, the subscript "q" may be 0, 1, or 2, and E is a hydrolyzable group containing at least one carbon atom. While component a) is described as a linear organosiloxane having the formula $R^1_q(E)_{(3-q)}SiO(R^1_2SiO_{2/2})_nSi(E)_{(3-q)}R^1_q$, one skilled in the art recognizes small amount of alternative siloxy units, such as a T ($R^1SiO_{3/2}$) siloxy units, may be incorporated into the linear organosiloxane and still be used as component a). As such the organosiloxane may be considered as being "predominately" linear by having a majority of D ($R^1_2SiO_{2/2}$) siloxy units. Furthermore, the linear organosiloxane used as component a) may be a combination of several linear organosiloxanes.

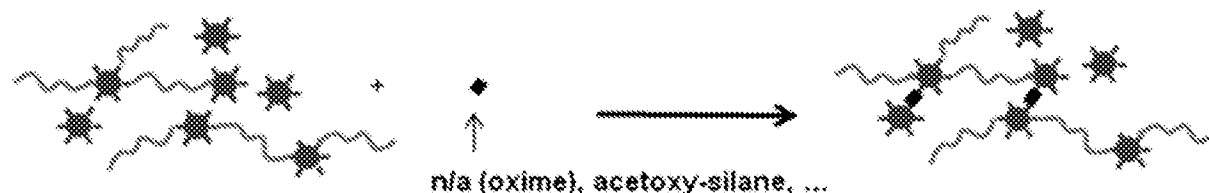
[0073] The Organosiloxane Resin

[0074] Component b) in the present process is an organosiloxane resin comprising at least 60 mol % of $[R^2SiO_{3/2}]$ siloxy units in its formula, where each R^2 is independently a C_1 to C_{20} hydrocarbyl. The organosiloxane resin may contain any amount and combination of other M, D, and Q siloxy units, provided the organosiloxane resin contains at least 70mol% or more of $[R^2SiO_{3/2}]$ siloxy units. Organosiloxane resins useful as component b) include those known as “silsesquioxane” resins.

[0075] The amounts of a) and b) used in the reaction of step I are selected to provide the resin-linear organosiloxane block copolymer with 40 to 90 mol% of disiloxo units $[R^1_2SiO_{2/2}]$ and 10 to 60 mol% of trisiloxo units $[R^2SiO_{3/2}]$. The mol% of disiloxo and trisiloxo units present in components a) and b) may be readily determined using ^{29}Si NMR techniques. The starting mol % then determines the mass amounts of components a) and b) used in step I.

[0076] The second step of the present process involves further reacting the resin-linear organosiloxane block copolymer from step I) to crosslink the trisiloxo units of the resin-linear organosiloxane block copolymer to increase the MW of the resin-linear organosiloxane block copolymer by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or alternatively by at least 100%.

[0077] The reaction of the second step of the process may be represented generally according to the following schematic;



[0078] The step II reaction conditions may depend on the selection of the hydrolyzable group (E) used in the starting linear organosiloxane. When (E) in the linear organosiloxane is an oxime group, it is possible for the step II reaction to occur under the same reaction conditions as step I. That is, as the linear-resin organosiloxane copolymer is formed in step I, it will continue to react via condensation of the silanol groups present on the resin component to further increase the MW of the resin-linear organosiloxane copolymer. When (E) is an oxime group, the hydrolyzed oxime group (for example methyl ethylketoxime) resulting from the reaction in step I may act as a condensation catalyst for the step II reaction. As such, the step II reaction may proceed simultaneously under the same conditions for step I. In other words, as the resin-linear organosiloxane copolymer is formed in step I, it may further react under the same reaction conditions to further increase its MW via a condensation reaction of the silanol groups present on the resin component of the

copolymer. However, when (E) on the linear organosiloxane is an acetoxy group, the resulting hydrolyzed group (acetic acid), does not sufficiently catalyze the step II) reaction. Thus, in this situation the step II reaction may be enhanced with a further component to affect condensation of the resin components of the resin-linear organosiloxane copolymer, as described in the embodiment below.

[0079] In one embodiment of the present process, an organosilane having the formula $R^5_qSiX_{4-q}$ is added during step II), where R^5 is a C_1 to C_8 hydrocarbyl or a C_1 to C_8 halogen-substituted hydrocarbyl, X is a hydrolysable group, and q is 0, 1, or 2. R^5 is a C_1 to C_8 hydrocarbyl or a C_1 to C_8 halogen-substituted hydrocarbyl, or alternatively R^5 is a C_1 to C_8 alkyl group, or alternatively a phenyl group, or alternatively R^5 is methyl, ethyl, or a combination of methyl and ethyl. X is any hydrolyzable group, alternatively X may be E, as defined above, a halogen atom, hydroxyl (OH), or an alkoxy group. In one embodiment, the organosilane is an alkyltriacetoxysilane, such as methyltriacetoxysilane, ethyltriacetoxysilane, or a combination of both. Commercially available representative alkyltriacetoxysilanes include ETS-900 (Dow Corning Corp., Midland, MI). Other suitable, non-limiting organosilanes useful in this embodiment include; methyltris(methylethylketoxime)silane (MTO), methyl triacetoxysilane, ethyl triacetoxysilane, tetraacetoxysilane, tetraoximesilane, dimethyl diacetoxysilane, dimethyl dioximesilane, methyl tris(methylmethylethylketoxime)silane.

[0080] The amount of organosilane having the formula $R^5_qSiX_{4-q}$ when added during step II) varies, but should be based on the amount of organosiloxane resin used in the process. The amount of silane used should provide a molar stoichiometry of 2 to 15 mol% of organosilane / mols of Si on the organosiloxane resin. Furthermore, the amount of the organosilane having the formula $R^5_qSiX_{4-q}$ added during step II) is controlled to ensure a stoichiometry that does not consume all the silanol groups on the organosiloxane block copolymer. In one embodiment, the amount of the organosilane added in step II is selected to provide an organosiloxane block copolymer containing 0.5 to 35 mole percent of silanol groups $[≡SiOH]$.

[0081] Step III in the present process is optional, and involves further processing the resin-linear organosiloxane block copolymer to enhance storage stability and/or optical clarity. As used herein the phrase "further processing" refers to any further reaction or treatment of the formed resin-linear organosiloxane copolymer to enhance its storage stability, and/or optical clarity. The resin-linear organosiloxane copolymer as produced in step II may still contain a significant amount of reactive "OZ" groups (that is $≡SiOZ$ groups, where Z is as defined above), and/or X groups (where X is introduced into the block copolymer when the organosilane having the formula $R^5_qSiX_{4-q}$ is used in step II). The OZ groups present on the resin-linear organosiloxane copolymer at this stage may be silanol groups that were

originally present on the resin component, or alternatively may result from the reaction of the organosilane having the formula $R^5_qSiX_{4-q}$ with silanol groups, when the organosilane is used in step II. "OZ" or X groups may further react during storage, limiting shelf stability, or diminishing reactivity of the resin-linear organosiloxane copolymer during end-use applications. Alternatively, further reaction of residual silanol groups may further enhance the formation of the resin domains and improve the optical clarity of the resin-linear organosiloxane copolymer. Thus, optional step III may be performed to further react OZ or X present on the organosiloxane block copolymer produced in Step II to improve storage stability and/or optical clarity. The conditions for step III may vary, depending on the selection of the linear and resin components, their amounts, and the endcapping compounds used. Certain embodiments are described below.

[0082] In one embodiment of the process, step III is performed by reacting the resin-linear organosiloxane from step II with water and removing any small molecular compounds formed in the process such as acetic acid. In this embodiment, the RL copolymer is typically produced from a linear organosiloxane where E is an acetoxymethyl group, and/or an acetoxymethyl silane is used in step II. Although not wishing to be bound by any theory, the resin-linear organosiloxane formed in step II contains a significant quantity of hydrolyzable Si-O-C(O)CH₃ groups, which may limit the storage stability of the resin-linear organosiloxane copolymer. Thus, water may be added to the resin-linear organosiloxane copolymer formed from step II, which will hydrolyze most Si-O-C(O)CH₃ groups to further link the trisiloxane units, and eliminate acetic acid. The formed acetic acid, and any excess water, may be removed by known separation techniques. The amount of water added in this embodiment may vary, but typically 10 wt %, or 5 wt % is added per total solids (as based on RL copolymer in reaction medium).

[0083] In one embodiment of the process, step III is performed by reacting the resin-linear organosiloxane from step II with an endcapping compound selected from an alcohol, oxime, or trialkylsiloxy compound. In this embodiment, the resin-linear organosiloxane copolymer is typically produced from a linear organosiloxane where E is an oxime group. The endcapping compound may be a C₁-C₂₀ alcohol such as methanol, ethanol, propanol, butanol, or others in the series. The endcapping compound may also be a trialkylsiloxy compound, such as trimethylmethoxysilane or trimethylethoxysilane. The amount of endcapping compound may vary but typically is between 3 and 15wt % with respect to the resin-linear organosiloxane block copolymer solids in the reaction medium.

[0084] Step IV is optional, and involves removing the organic solvent used in reactions of steps I and II. The organic solvent may be removed by any known techniques, but typically

involves heating the resin-linear organosiloxane copolymer compositions at elevated temperatures, either at atmospheric conditions or under reduced pressures.

Silsesquioxane Resin For Preparation of ARL Copolymer or RL Copolymer

[0085] Examples of silsesquioxane resins that may be used for synthesis of ARL copolymers and resin-linear organosiloxane block copolymers include, but are not limited to, vinyl-functionalized silsesquioxane resin,

[0086] According to further aspects of the present invention, the silsesquioxane resin may be a MTTQ, MTT, or a T resin, wherein:

M is represented by building block $R^xSiO_{1/2}$;

T is represented by building block $R^xSiO_{3/2}$; and

Q is represented by building block: $SiO_{4/2}$,

Building block M represents a monofunctional unit. Building block T represents a trifunctional unit. Building block Q represents a tetrafunctional unit. The number of building blocks (M, T, Q) in the silsesquioxane resin typically may range from 1 to 10,000, for instance 4 to 1,000.

[0087] R^x designates hydrogen or any monovalent organic group exemplified by, but not limited to, monovalent hydrocarbon groups and monovalent halogenated hydrocarbon groups. Each R^x can be identical or different, as desired. Monovalent hydrocarbon groups are exemplified by, but not limited to, alkyl groups such as methyl, ethyl, propyl, pentyl, octyl, undecyl, and octadecyl; cycloalkyl groups such as cyclohexyl, and aryl groups such as phenyl, tolyl, xylyl, benzyl, and 2-phenylethyl.

[0088] According to certain aspects of the present invention, at least one R^x group is an aliphatically unsaturated group such as an alkenyl group. Suitable alkenyl groups include from 2-6 carbon atoms and may be exemplified by, but not limited to, vinyl, allyl, and hexenyl. The alkenyl groups in this component may be located at terminal, pendant (non-terminal), or both terminal and pendant positions.

Component (b) and Optional Component (f)

[0089] The ARL copolymer or the resin-linear organosiloxane block copolymer is dissolved in a suitable solvent configured to dissolve the ARL copolymer, the RL copolymer, or the solid silicone resin. Examples of suitable solvents include ethyl acetate, dimethylsulfoxide, silicone and siloxane fluids (e.g., hexamethyldisiloxane, decamethylcyclopentasiloxane, and other cyclosiloxanes, etc.), alcohols (e.g., isopropyl alcohol, ethyl alcohol), aliphatic hydrocarbons (e.g., hexane, heptane, isododecane), aromatic hydrocarbons (e.g., toluene, xylene), alkanes, and any combination thereof. The solvents that are used to dissolve the ARL copolymer, the RL copolymer, or the solid silicone may be the same or different in the formulation.

Component (c) – Active Ingredient

[0090] The formulation may include an active selected from any personal, healthcare, or pharmaceutical active. As used herein, a “personal care active” means any compound or mixtures of compounds that are known in the art as additives in the personal care formulations that are typically added for treating hair or skin to provide a cosmetic and/or aesthetic benefit. A “healthcare active” means any compound or mixtures of compounds that are known in the art to provide a pharmaceutical or medical benefit. Thus, “healthcare active” includes materials considered as an active ingredient or active drug ingredient as generally used and defined by the United States Department of Health & Human Services Food and Drug Administration, contained in Title 21, Chapter I, of the Code of Federal Regulations, Parts 200-299 and Parts 300-499.

[0091] Thus, active ingredient can include any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of a human or other animals. The phrase can include those components that may undergo chemical change in the manufacture of drug products and be present in drug products in a modified form intended to furnish the specified activity or effect.

[0092] Some representative examples of pharmaceutical or healthcare active ingredients include non-steroidal anti-inflammatory drug, a steroid, a retinoid, traditional Chinese medicines, anti-acne, anti-fungal, antibiotics, or any combination thereof.

[0093] The active ingredient can include a water-soluble or an oil-soluble active drug ingredient. Representative examples of some suitable water-soluble active drug ingredients which can be used are hydrocortisone, ketoprofen, morphine, penicillin G, niacinamide, salicylic acid, and ketoconazole.

[0094] Representative examples of some suitable oil-soluble active drug ingredients are clonidine, scopolamine, nitroglycerin, ibuprofen, naproxen.

[0095] Active ingredients for purposes of the present invention also include anti-acne agents such as benzoyl peroxide and tretinoin; anti-inflammatory agents; corticosteroidal drugs; non-steroidal anti-inflammatory agents such as diclofenac; anesthetic agents such as lidocaine; antipruritic agents; and antidermatitis agents.

[0096] Some additional representative examples of active ingredients include minerals; hormones; topical antimicrobial and antibacterial agents such as chlorohexadiene gluconate agents and antibiotic active ingredients, antifungal active ingredients, such as miconazole nitrate; astringent active ingredients; deodorant active ingredients; corn and callus remover active ingredients; pediculicide active ingredients for the treatment of head, pubic (crab), and

body lice; active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis, such as clobetasol propionate; and sunburn prevention and treatment agents.

[0097] The active agent may include antimicrobial agents, such as benzalkonium chloride, benzethonium chloride, silver ions, nanocrystalline silver, anticancer agents, smoking cessation compositions, vitamins, antiaging agents, anticellulites, cell growth nutrients, perfumes, drugs for the treatment of microbial diseases (such as ciprofloxacin, minocycline, clindamycin, acyclovir and), drugs for hormonal replacement therapy (such as estradiol, ethinyl estradiol and norethindrone and drugs used in dermatology for the treatment of dermatoses (such as betamethasone dipropionate, dexamethasone sodium phosphate, tretinoin, isotretinoin, dapson, calipotriene, and arotinoid).

[0098] Useful active ingredients for use in formulations according to the present disclosure include vitamins and its derivatives, including "pro-vitamins." Vitamins useful herein include, but are not limited to, Vitamin A₁, retinol, C₂-C₁₈ esters of retinol, vitamin E, tocopherol, esters of vitamin E, and mixtures thereof. Vitamin C and its derivatives, Vitamin B₁, Vitamin B₂, Pro Vitamin B₅, panthenol, Vitamin B₆, Vitamin B₁₂, folic acid, biotin, and pantothenic acid.

[0099] The active component of the present invention can be a protein, such as an enzyme. The internal inclusion of enzymes in these formulations has the advantages of preventing enzymes from deactivating and maintaining bioactive effects of enzymes for a longer time period. Enzymes include, but are not limited to, commercially available types, improved types, recombinant types, wild types, variants not found in nature, and mixtures thereof. For example, suitable enzymes include hydrolases, cutinases, oxidases, esterases, lactases, peroxidases, and mixtures thereof. Hydrolases include, but are not limited to, proteases (bacterial, fungal, acid, neutral or alkaline).

[00100] The pharmaceutical or healthcare active may also include one or more plant extracts. Examples of these components are as follows: Ginkgo Biloba extract, oolong tea extract, Echinacea extract, Scutellaria root extract, Chamomile extract, Horsetail extract, lemon extract, Chinese milk vetch extract, rose extract, rosemary extract, Roman Chamomile extract royal jelly extract or any other botanical extract that may be topically applied to achieve a pharmaceutical outcome.

[00101] The active ingredient may be selected depending on the application for which the topical formulation is used. For example, if the desired effect is pain relief, ibuprofen may be used as the active. If the desired effect is acne prevention and control, benzoyl peroxide may be used.

Component (d) – Penetration Enhancer or Penetration Excipient

[00102] In addition to active agent, ARL copolymer and solid silicone resin, various excipients and/or enhancing agents may be incorporated into the topical formulation. As generally understood by those skilled in the art, excipients are additives that are used to convert the active agent into appropriate dosage forms that are suitable for application to the substrate. Excipients may also be added to stabilize the formulation and to optimize application characteristics, such as flowability. Nonlimiting examples of suitable penetration enhancers or penetration excipients include, but are not limited to, propylene glycol, butylene glycol, dipropylene glycol, polyethylene glycol-20, oleic acid, oleyl alcohol, isopropyl myristate, dimethylisosorbide, isopropyl alcohol, ethyl alcohol, dimethylsulfoxide, or any combination(s) thereof.

[00103] Further examples of potential excipients include, but are not limited to, excipients that are found in the Cosmetics, Toiletry, Fragrance Association (CTFA) ingredient Database and the handbook of pharmaceutical excipients such as absorbents, anticaking agents, antioxidants (such as, ascorbic acid, ascorbic acid polypeptide, ascorbyl dipalmitate, BHA, BHT, magnesium ascorbate, magnesium ascorbyl phosphate, propyl gallate sodium ascorbate, sodium ascorbyl/cholesteryl phosphate, sodium bisulfite, sodium erythorbate, sodium metabisulfide, tocopheryl acetate,), antistatic agents, astringents, binders, buffering agents, bulking agents, chelating agents, colorants, biocides (such as parabens, organic acids, organic bases, alcohols, isothiazolinones and others), emollients, film formers, fragrance ingredients, humectants, lytic agents, moisturizing agents, occlusivity enhancers, opacifying agents, oxidizing agents, reducing agents, penetration enhancers, pesticides, plasticizers, preservatives, skin bleaching agents such as hydroquinone, skin conditioning agents, skin protectants such as Dimethicone, Glycerin, Kaolin, Lanolin, Mineral Oil, Petrolatum, solubilizing agents, solvents, sunscreen agents (surfactants and emulsifying agents, suspending agents, viscosity controlling agents including increasing or decreasing agents, or UV light absorbing agents. Other possible excipients include, but are not limited to, sugars and derivatives cellulosic materials (such as methyl cellulose, Ethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, and Hydroxypropylmethylcellulose,), polysaccharides.

[00104] Enhancers may also be exemplified by monohydric alcohols such as ethanol, isopropyl, and benzyl alcohols, or dihydric alcohols such as propylene glycol, dipropylene glycol and trimethylene glycol, or polyhydric alcohols such as butylene glycol, polypropylene glycol, and polyethylene glycol, which enhance drug solubility; polyethylene glycol ethers of aliphatic alcohols (such as cetyl, lauryl, oleyl and stearyl) including and polyoxyethylene oleyl ether commercially available under the trademark BRIJ® 30, 93 and 97, respectively, from Uniqema Americas LLC (Wilmington, DE), vegetable, animal and fish fats and oils such as

olive, and castor oils, squalene, lanolin; fatty acids such as oleic, linoleic, and capric acid, and the like; fatty acid esters such as propyl oleate, decyl oleate, isopropyl palmitate, glycol palmitate, glycol laurate, dodecyl myristate, isopropyl myristate and glycol stearate fatty acid amides such as oleamide and its derivatives polar solvents such as dimethyldecylphosphoxide, isosorbitol, dimethylacetone, dimethylsulfoxide, decylmethylsulfoxide and dimethylformamide which affect keratin permeability; amino acids; benzyl nicotinate; and higher MW aliphatic surfactants such as lauryl sulfate salts; and esters of sorbitol and sorbitol anhydride such as polysorbate 20 commercially available under the trademark Tween® 20 from Uniqema Americas LLC (Wilmington, DE). Other enhancers include enzymes, panthenol, and other non-toxic enhancers commonly used in transdermal or transmucosal compositions.

Optional Component (e) - Solid Silicone Resin

[00105] The formulation may include a silicone resin that may include a MQ resin, where the M and Q units are as discussed above. MQ is used when the solid silicone resin includes all monofunctional M and tetrafunctional Q units, or at least a high percentage of M and Q units such as to render the silicone resinous.

[00106] Solid silicone resins include but are not limited to, silsesquioxane resins, including vinyl-functionalized silsesquioxane resins. The silsesquioxane resin may be a MTTQ, MTT, or a T resin, wherein:

M is represented by building block $R^x_3SiO_{1/2}$;

T is represented by building block $R^xSiO_{3/2}$; and

Q is represented by building block: $SiO_{4/2}$,

Building block M represents a monofunctional unit. Building block T represents a trifunctional unit. Building block Q represents a tetrafunctional unit. The number of building blocks (M, T, Q) in the silsesquioxane resin typically may range from 1-10,000. In one embodiment, the silsesquioxane resin includes trimethylsiloxysilicate resin and resins including disiloxy units of the formula $R^x_3SiO_{1/2}$, wherein R^x is independently selected from monovalent hydrocarbon groups; and tetrafunctional units of the formula $SiO_{4/2}$.

[00107] The solid silicone resin may be dissolved in a suitable solvent. The solvent may be the same as or different from the solvent used for the ARL copolymer or the resin-linear organosiloxane block copolymer above. The wt % of the solid silicone resin in the solution may be about 50% w/w. According to further aspects of the present invention, the wt % of the solid silicone resin in the solution may be between about 10 and 60 %w/w. According to another aspect of the present invention, the formulation includes no solid silicone resin.

Optional Ingredient (g) - Occlusivity Agent

[00108] The formulation may include an occlusivity agent configured to provide occlusivity when the formulation is applied on top of the skin. The occlusivity agent may include petrolatum, organic wax, silicone wax, polyacrylates and methacrylates (exemplified by, but not limited to Eudragit® E100, S100, L100, and L100-55), polyvinyl pyrrolidone, polyvinyl alcohol, vinylacetate-vinylpyrrolidone copolymer, or any combination thereof. A majority of film-forming polymers can be considered to provide occlusive properties to the formulation and thus any suitable film-forming polymer may be used in the present formulation.

[00109] The occlusivity agent may be a wax or a wax-like material. The waxes or wax-like materials useful in the formulation according to the present disclosure generally have a melting point range of about 35-120°C at atmospheric pressure. Waxes in this category include synthetic wax, ceresin, paraffin, ozokerite, beeswax, carnauba, microcrystalline, lanolin, lanolin derivatives, candelilla, cocoa butter, shellac wax, spermaceti, bran wax, capok wax, sugar cane wax, montan wax, whale wax, bayberry wax, or mixtures thereof. Additionally, the occlusivity agent may include waxes capable of being used as non-silicone fatty substances, animal waxes, such as beeswax; vegetable waxes, such as carnauba, candelilla wax; mineral waxes, such as paraffin or lignite wax; microcrystalline waxes; ozokerites; synthetic waxes, including polyethylene waxes, and waxes obtained by the Fischer-Tropsch synthesis. Additionally, the occlusivity agent may include silicone waxes, polymethylsiloxane alkyls, alkoxys and/or esters.

Optional Component (h) – Pressure Sensitive Adhesive

[00110] Optional components included in the present formulation may also include pressure sensitive adhesives (PSAs). A PSA is a viscoelastic material which adheres to most substrates with application of slight pressure and essentially remains tacky through the useful life of the construction. Non limiting examples of PSAs include silicone, polyisobutylene and derivatives thereof, acrylics, natural rubbers, natural and synthetic polyisoprene, polybutylene and polyisobutylene, styrene/butadiene polymers, styrene-isoprene-styrene block polymers, hydrocarbon polymers such as butyl rubber, halogen polyvinylchloride, polyvinylidene chloride, polyvinylpyrrolidone, polychlorodiene, and any combination thereof.

Additional Optional Components

[00111] The formulation may also include a number of optional ingredients. In particular, these optional components are selected from those known in the art to be ingredients used in personal care or pharmaceutical formulations. Illustrative, non-limiting examples include surfactants, solvents, powders, coloring agents, thickeners, waxes, gelling agents or clays, stabilizing agents, pH regulators, silicones, or other suitable agents.

[00112] Thickening agent(s) may be added to provide a desired or convenient viscosity. Suitable thickening agents are exemplified by sodium alginate, gum arable, polyoxyethylene, guar gum, hydroxypropyl guar gum, ethoxylated alcohols, such as laureth-4 or polyethylene glycol 400, cellulose derivatives exemplified by methylcellulose, methylhydroxypropylcellulose, hydroxypropylcellulose, polypropylhydroxyethylcellulose, starch, and starch derivatives exemplified by hydroxyethylamylose and starch amylose, locust bean gum, electrolytes exemplified by sodium chloride and ammonium chloride, and saccharides such as fructose and glucose, and derivatives of saccharides such as PEG-120 methyl glucose diolate or mixtures of 2 or more of these. Alternatively the thickening agent is selected from cellulose derivatives, saccharide derivatives, and electrolytes, or from a combination of two or more of the above thickening agents exemplified by a combination of a cellulose derivative and any electrolyte, and a starch derivative and any electrolyte. The thickening agent may be present in an amount from about 0.05-10%w/w, or, alternatively about 0.05-5%w/w based on total formulation weight.

[00113] Also, various cosmetic, personal care, and cosmetic components may be included aside from the excipient or excipients. Examples of suitable cosmetic, and personal care components include, but are not limited to, alcohols, fatty alcohols and polyols, aldehydes, alkanolamines, alkoxyated alcohols butylene copolymers, carbohydrates (e.g. polysaccharides, chitosan and derivatives), carboxylic acids, carbomers, esters, ethers and polymeric ethers (e.g. PEG derivatives, PPG derivatives), glyceryl esters and derivatives, halogen compounds, heterocyclic compounds including salts, hydrophilic colloids and derivatives including salts and gums (e.g. cellulose derivatives, gelatin, xanthan gum, natural gums), imidazolines, inorganic materials (clay, TiO₂, ZnO), ketones (e.g. camphor), isethionates, lanolin and derivatives, organic salts, phenols including salts phosphorus compounds (e.g. phosphate derivatives), polyacrylates and acrylate copolymers, synthetic polymers including salts, siloxanes and silanes, sorbitan derivatives, sterols, sulfonic acids and derivatives and waxes.

[00114] Other additives can include powders and pigments. The powder component that may be included can be generally defined as dry, particulate matter having an average particle size of about 0.02-50 microns. The particulate matter may be colored or non-colored (for example, white). Suitable powders include, but are not limited to, bismuth oxychloride, titanated mica, fumed silica, spherical silica beads, polymethylmethacrylate beads. The above mentioned powders may be surface treated to render the particles hydrophobic in nature.

[00115] The powder component also may also include various organic and inorganic pigments. The organic pigments are generally various aromatic types including azo,

indigoid, triphenylmethane, anthraquinone, and xanthine dyes. Inorganic pigments generally consist of insoluble metallic salts of certified color additives, referred to as the Lakes or iron oxides. A pulverulent coloring agent, such as carbon black, and titanium dioxide, pearlescent agents, generally used as a mixture with colored pigments, or some organic dyes, generally used as a mixture with colored pigments and commonly used in the cosmetics industry, can be added to the formulation. In general, these coloring agents can be present in an amount by weight from about 0-20% with respect to the weight of the final formulation.

[00116] Pulverulent inorganic or organic fillers can also be added, generally in an amount by weight from about 0-40% with respect to the weight of the final formulation. These pulverulent fillers can be chosen from talc, micas, kaolin, zinc or titanium oxides, calcium or magnesium carbonates, silica, spherical titanium dioxide, glass or ceramic beads, metal soaps derived from carboxylic acids having 8-22 carbon atoms, non-expanded synthetic polymer powders, expanded powders and powders from natural organic compounds, such as cereal starches, which may or may not be crosslinked, copolymer microspheres, polytrap, and silicone resin microbeads.

[00117] Optional components included in the present formulation may also include other silicones (including any already described above), organofunctional siloxanes, alkylmethylsiloxanes, siloxane resins and silicone gums.

[00118] The topical formulations may be in the form of a cream, a gel, a powder, a paste, or a freely pourable liquid. Generally, such formulations can generally be prepared at room temperature if no solid materials at room temperature are present in the formulations, using simple propeller mixers, Brookfield counter-rotating mixers, or homogenizing mixers. No special equipment or processing conditions are typically required. Depending on the type of form made, the method of preparation will be different, but such methods are well known by those of ordinary skill in the art.

[00119] If the formulation is prepared without water, an anhydrous formulation results. Such formulations that do not include water may be prepared without the addition of any preservatives.

[00120] In embodiments where the substrate is skin, the formulation is applied to the skin to deliver the active agent to the skin. The skin may be healthy and intact, or it may be damaged or wounded. The formulation may be applied, i.e., rubbed or coated, directly onto the skin. Alternatively, the formulation may be included in a transdermal patch prior to application of the formulation to the substrate, i.e., to the skin.

[00121] The controlled-release formulation according to the present disclosure is capable of delivering performance properties such as controlled tack, controlled lubrication, water

resistance, and barrier properties. This controlled-release formulation has substantivity to the skin and other substrates, such as teeth. The significant substantivity of the formulation is particularly advantageous when a controlled rate of delivery of the active agent is required over an extended period of time. Simply stated, the controlled-release formulation is topically applied to the substrate where the film remains over the extended period of time, which may be longer than 4 or 8 hours. When the substrate is skin, the substantivity is important due to the presence of certain body oils and especially upon application to skin covered with hair. The formulation also has substantivity to wet substrates such as gums, teeth and mucosal membrane.

[00122] The formulations according can be used by standard and well-known methods, such as applying them to the human body, e.g. skin, hair, or teeth, using applicators, brushes, applying by hand, pouring them and/or possibly rubbing or massaging the formulation onto or into the body. Removal methods are also well known standard methods, including washing, wiping, peeling and the like. Application to the skin may include working the formulation into the skin. This method for applying to the skin comprises the steps of contacting the skin with the formulation in an effective amount and then rubbing the formulation onto the skin.

Examples

[00123] These examples are intended to illustrate the invention to one of ordinary skill in the art and should not be interpreted as limiting the scope of the invention set forth in the claims. All measurements and experiments were conducted at 25°C, unless indicated otherwise.

ARL Copolymer or RL Copolymer Formulation

[00124] The feed compositions of the ARL copolymers A-G are shown in Table 1 below. The feed compositions of the RL copolymers H-I are also shown in table 1 below.

[00125] Table 1. Feed Composition of ARL Copolymers A-G and RL Copolymers H-I

ARL/RL	Si-H terminated PDMS		DMAL 500	Silsesquioxane resin	
	Dp	wt. %		Type	wt. %
A	11.5	26.2	13.8	$M^{VI}_{0.10}T^{Pr}_{0.26}T^{Ph}_{0.54}Q_{0.11}$	60
B	18.5	54.2	17.8	$M^{VI}_{0.10}T^{Pr}_{0.26}T^{Ph}_{0.54}Q_{0.11}$	28
C	18.5	42.9	13.1	$M^{VI}_{0.10}T^{Pr}_{0.26}T^{Ph}_{0.54}Q_{0.10}$	44
D	18.5	54	18	$M^{VI}_{0.14}T^{Pr}_{0.26}T^{Ph}_{0.59}$	28
E	150	72	-	$M^{VI}_{0.14}T^{Pr}_{0.26}T^{Ph}_{0.59}$	28
F	11.5	37.3	18.7	$M^{VI}_{0.10}T^{Pr}_{0.26}T^{Ph}_{0.54}Q_{0.10}$	44
G	11.5	36.6	19.4	$M^{VI}_{0.10}T^{Pr}_{0.26}T^{Ph}_{0.54}Q_{0.11}$	44
	OH-terminated PDMS				
H	184	45	-	T^{Ph}_1	55
	OH-terminated PhMe				
I	130	55	-	T^{Ph}_1	45

[00126] The ARL synthesis includes a reaction between Si-H terminated polydimethylsiloxane (PDMS, Dow Corning, Midland, MI) and a polyglycol to form a Si-H terminated intermediate. This intermediate is further reacted with the vinyl functionalized silsesquioxane resin (Dow Corning, Midland, MI) to form the ARL. PDMS of various degree of polymerization (dp) was used. Dimethyl allyl polyethylene oxide (DMAL 500; Clariant, Mt. Holly West, NC) was used as a polyglycol. The feed composition of PDMS, DMAL 500 and silsesquioxane resin corresponding to each ARL is provided in Table 1. The RL-H and RL-I were made with no DMAL 500 and with either OH terminated PDMS or OH terminated poly phenylmethyl siloxane to know the properties of the final ARL without polyglycol.

[00127] The synthesis of the ARL copolymers A-G includes a reaction between Si-H terminated polydimethylsiloxane (PDMS, Dow Corning, Midland, MI) and a polyglycol to form a Si-H terminated intermediate.

Formation of ARL-A (26.2wt% PDMS, 13.8wt% DMAL, 60.0wt% Silsesquioxane-Tg 140°C)

[00128] A 500mL 4neck round bottom flask was loaded with Si-H terminated PDMS (DOW CORNING® 11.5dp PDMS, 23.77g, 0.0567mols Si-H), dimethallyl terminated polyethylene oxide (DMAL) (Clariant DMAL 500, 12.56g, 0.0505mols Vi), toluene (Fisher Scientific, 54.50g), and a 1wt% solution (0.73g) of tocopherols (Mixed tocopherols 95 - DSM Nutritional Products Inc.) dissolved in toluene. The flask was equipped with a stir paddle, thermometer, and a water-cooled condenser. A nitrogen blanket was applied. An 1850ppm solution (0.37g) of Pt (DOW CORNING® 2-0719) in toluene was added at room temperature. Reaction mixture was mixed at 30°C for 2.5hrs. A 7.56g sample was removed for analysis. A 63.8wt% solution of vinyl functional silsesquioxane resin (78.37g solution, 50.00g solids, 0.0429mols vinyl) in toluene was added at room temperature along with additional toluene (46.63g). The resin had a structure of $M_{0.10}^{Vi}T_{0.26}^{Pr}T_{0.54}^{Ph}Q_{0.11}$ and an Mw of 5060. The reaction mixture was heated at 110°C for 1hr. Next a solution (4.05g, 0.0151mols Si-H) of 25wt% tetramethyldisiloxane (DOW CORNING® 3-7010) in toluene was added. The reaction mixture was heated at 110°C for 2hrs.

Formation of ARL-D (54wt% PDMS, 18wt% DMAL, 28wt% Silsesquioxane-Tg 8°C)

[00129] A 1L 4neck round bottom flask was loaded with Si-H terminated PDMS (DOW CORNING® Q2-5057S, 86.88g, 0.128mols Si-H), dimethallyl terminated polyethylene oxide (Clariant DMAL 500, 28.32g, 0.114mols Vi), toluene (Fisher Scientific, 172.8g), and a 1wt% solution (2.32g) of tocopherols (Mixed tocopherols 95 - DSM Nutritional Products Inc.) dissolved in toluene. The flask was equipped with a stir paddle, thermometer, and a water-cooled condenser. A nitrogen blanket was applied. A 2350ppm solution (0.93g) of Pt (DOW CORNING® 2-0719) in toluene was added at room temperature. Reaction mixture was

mixed at room temperature for 2.5hrs. A 65.0wt% solution of vinyl functional silsesquioxane resin (68.92g solution, 44.80g solids, 0.0548mols vinyl) in toluene was added at room temperature along with additional toluene (43.08g). The resin had a structure of $M_{0.14}^{Vi}T_{0.26}^{Pr}T_{0.59}^{Ph}$ and an Mw of 1870. The reaction mixture was heated at reflux (110°C) for 1 hour. It was cooled to near room temperature and then a solution (4.39g, 0.0327mols Si-H) of 50wt% tetramethyldisiloxane (DOW CORNING® 3-7010) in toluene was added. The reaction mixture was heated at reflux (110°C) for 2 hours. Cast films (made by pouring the solution in a chase and evaporating the solvent overnight at room temperature) were optically clear.

Formation of ARL-B, C, F, G

[00130] The formation of the samples ARL-B, C, F, G was carried out similarly to the formation of the sample ARL-A, with the weight percentages of the Si-H terminated PDMS, DMAL, and silsesquioxane resin as indicated in Table 1.

Formation of ARL-E (72wt% PDMS, 0wt% DMAL, 28wt% Silsesquioxane-Tg 22°C)

[00131] A 1L 4neck round bottom flask was loaded with 150dp Si-H terminated PDMS (Dow Corning, 115.2g, 0.0206mols Si-H), toluene (Fisher Scientific, 221.6g), and a 70.9wt% solution of vinyl functional silsesquioxane resin (63.2g solution, 44.81g solids, 0.0557mols vinyl) in toluene. The resin had a structure of $M_{0.14}^{Vi}T_{0.26}^{Pr}T_{0.59}^{Ph}$ and an Mw of 2470. The flask was equipped with a stir paddle, thermometer, and a water-cooled condenser. A nitrogen blanket was applied. A 2540ppm solution (1.18g) of Pt (DOW CORNING® 2-0719) in toluene was added at room temperature. The reaction mixture was heated at reflux (110°C) for 1 hour. It was cooled to near room temperature and then a solution (2.59g, 0.00386mols Si-H) of 10wt% tetramethyldisiloxane (DOW CORNING® 3-7010) in toluene was added. The reaction mixture was heated at reflux (110°C) for 2 hours. Cast films (made by pouring the solution in a chase and evaporating the solvent overnight at room temperature) were optically clear.

Formation of RL Copolymers: RL-H and I

Formation of RL Copolymer RL-H

[00132] A 2L 4 neck round bottom flask, equipped with a thermometer, Teflon stir paddle and a Dean Stark apparatus (prefilled with toluene) attached to a water-cooled condenser, was loaded with toluene (Fisher Scientific, 339.3g) and 137.5g of DOW CORNING® 217 flake. A nitrogen blanket was applied. Reaction mixture was heated using heating mantle at reflux for 30 minutes and then cooled to 108°C. A solution of toluene (125.0g) and silanol terminated PDMS (112.5g) capped with MTA/ETA (Methyl triacetoxysilane/Ethyl triacetoxysilane 5/5 wt/wt ratio) was added slowly (for 13 min) at 105-109°C and heated at reflux for 3

hours. The capping of silanol terminated PDMS (112.5g) with 50/50 MTA/ETA (3.71g, 0.0160 mols Si) was carried out separately in a glove box on the same day under nitrogen by mixing those two at room temperature for 30 minutes. The PDMS solution was added to the resin solution slowly (13 min) at 105-109°C and heated at reflux for 3 hours followed by cooling to 108°C and then added with 50/50 MTA/ETA (23.58g, 0.102 mols Si) and heated at reflux for 1hr. The reaction mixture was cooled to 90°C, and then de-ionized water (42.52g). The resulting mixture was further heated at reflux for 1 hr with no water removal, followed by reflux with water removal for the next 2 hours. The volatiles were distilled off to increase the solid content to about ~40% and the reaction mixture was cooled to room temperature and pressure filtered through a 5µm filter.

Formation of RL Copolymer RL-I

[00133] The formulation of the sample RL-I was carried out similarly to the formation of the sample RL-H above, except OH terminated poly phenylmethyl siloxane (PhMe) was used in place of the OH-terminated PDMS, with the weight percentage indicated in Table 1.

Formulation Examples Using Ibuprofen

Preparation of Stock Solutions with ARL-A to RL-I

[00134] A stock solution with each one of the polymers ARL-A to RL-I was made by dissolving each polymer in ethyl acetate (EA, USP/FCC grade, Fisher Scientific, Fair Lawn, NJ). The concentration (or the % solids) of the stock solution of the polymer samples ARL-A to RL-I ranged from between about 38-77% w/w. The exact % solids corresponding to each polymer was used when determining the amount of each polymer ARL-A to RL-I required to make each particular formulation.

Preparation of Trimethylated Silica Resin Solution

[00135] A stock solution of trimethylated silica resin (MQ resin) (Dow Corning, Midland, MI) was made by dissolving the MQ resin in EA. The concentration was about 50% w/w. Appropriate amount of this solution was used to incorporate the MQ resin into each one of the formulation examples below.

Formulation Examples 1-9

[00136] Formulation example 1 was prepared by weighing 0.2544 g of ibuprofen (IBP, USP grade, Spectrum Chemical Manuf. Corp., New Brunswick, NJ) in a scintillation vial followed by the addition of 0.2267 g of dipropylene glycol (DPG, USP/FCC grade, Fisher Scientific, Fair Lawn, NJ), 0.0252 g of oleic acid (OLAC, NF/FCC grade, Fisher Scientific, Fair Lawn, NJ) and 3.0010 g of the MQ resin stock solution (from 50% w/w stock solution in EA as discussed above). The vial was closed with a lid and was mixed using a vortex mixer until the IBP was completely dissolved or well dispersed. To this vial, 1.5994 g of the stock solution of ARL-A (38% w/w stock solution of ARL-A in EA as described above) was added.

The vial was closed and mixed using a vortex mixer. Thus obtained was a slightly viscous liquid formulation. When applied on a surface (e.g., skin), the formulation forms a film after the evaporation of EA. Formulation examples 2-9 were prepared using a similar procedure to that described above by changing the amount of individual components according to the compositions shown below in Table 2. The concentrations (% w/w solids) of the stock solutions of all ARLs/RLs were different and hence the amount needed for each formulation was calculated accordingly. The composition of each one of the formulations 1-9 is the same; however, each formulation includes a different ARL/RL. The objective was to find out the effect of different ARLs/RLs in delivering the drug.

[00137] Table 2. Composition of formulation examples 1-9.

Ingredients	Formulation examples								
	1	2	3	4	5	6	7	8	9
	% (w/w)								
ARL-A	11.9	-	-	-	-	-	-	-	-
ARL-B	-	11.8	-	-	-	-	-	-	-
ARL-C	-	-	11.8	-	-	-	-	-	-
ARL-D	-	-	-	11.7	-	-	-	-	-
ARL-E	-	-	-	-	11.8	-	-	-	-
ARL-F	-	-	-	-	-	11.8	-	-	-
ARL-G	-	-	-	-	-	-	11.8	-	-
RL-H								11.8	-
RL-I								-	11.9
MQ Resin	29.4	29.4	29.4	29.5	29.5	29.5	29.5	29.5	28.7
DPG	4.4	4.4	4.6	4.6	4.4	4.5	4.6	4.4	4.3
OLAC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
EA	48.8	48.8	48.7	48.7	48.7	48.8	48.7	48.9	49.6
IBP	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Formulations examples using ARL-C with changes in the composition:

[00138] Formulation example 10 was prepared by weighing 0.2546 g of IBP in a scintillation vial followed by the addition of 0.2399 g of DPG, 0.0267 g of OLAC and 1.5025 g of the MQ resin solution (from 50% w/w stock solution in EA as described above). The vial was closed with a lid and was mixed using a vortex mixer until the IBP was completely dissolved or well dispersed. To this vial, 1.4645 g of the stock solution of ARL-C (41% stock solution of ARL-C in EA as described above) was added. The vial was closed and mixed using a vortex mixer. Thus obtained was a slightly viscous liquid formulation. When applied on a surface (e.g., skin), the formulation forms a film after the evaporation of EA. Formulation examples 10-16 were prepared using a similar procedure to that described above by changing the amount of individual components as shown in Table 3 below. Formulation example 13 was prepared using a non-silicone polymer, poly(n-butyl methacrylate) (poly(n-BMA)); SP²

Scientific Polymer Products Inc., Ontario, NY) in place of ARL. Isopropyl alcohol (IPA, HPLC grade, Fisher Scientific, Fair Lawn, NJ) was also used in formulation example 16 in addition to EA. The compositions of formulations 10-16 are different. The objective was to find out the effect of changes made in the formulations in delivering the drug using the same ARL.

[00139] Table 3. Composition of formulation examples 10-16.

Ingredients	Formulation examples						
	10	11	12	13	14	15	16
	% (w/w)						
ARL-C	11.8	11.2	18.1	-	-	11.8	11.8
Poly(n-BMA)	-	-	-	11.8	-	-	-
IPA	-	-	-	-	-	-	17.1
MQ Resin	14.7	27.9	22.6	29.4	29.4	-	29.4
DPG	4.7	8.7	3.5	4.6	4.6	4.6	4.6
OLAC	0.5	1.0	0.4	0.5	0.5	0.5	0.5
EA	63.3	46.2	50.4	48.7	60.5	78.1	31.6
IBP	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Permeability experiments using human cadaver skin epidermis

[00140] The permeability behavior, the flux (or the amount of IBP delivered through skin per unit area per unit time, ($\mu\text{g}/\text{cm}^2/\text{hr}$)) of the IBP from the above formulations was determined using Franz cell permeability experiment set-up at 32°C and using epidermis of human cadaver skin. In the Franz cell set-up, initially the bottom compartment of a cell was placed in the unit and filled with 3 mL of phosphate buffered saline (PBS, pH 7.4). A small magnetic stir bar was added to the cell. The permeation area in the Franz cell was 0.63 cm². The thawed epidermis of skin membrane (as a circle, 1.5875 cm diameter, 1.98 cm² area) was now carefully transferred to the top of the bottom compartment. The top compartment (cap) of the Franz cell was attached now on top of the skin and both the top and bottom compartments were clamped together. For each formulation, 3 cells (triplicate) were prepared. A known amount of the formulation was taken using positive displacement pipette and applied on the skin. PBS was added to the right volume (~5 mL) of the cell and now the permeability experiment was started. Being a fluid, the formulation covered the permeation area well and formed a thin coating (film) after the evaporation of the volatile solvent. The experiment was carried out for 8 hours. During the 8 hours period, 1 mL of sample was collected from the bottom compartment and replaced with fresh PBS solution at 0.5, 1, 2, 4, 6 and 8 hours. The experiment was stopped after collecting the sample after 8 hours. All samples collected were taken for ultra performance liquid chromatography (UPLC) analysis to determine the IBP concentration using an appropriate UPLC method.

[00141] The flux profiles of formulation examples 1-9 are provided in FIGs. 1-3. The flux profiles of formulation examples 10-16 are provided in the FIGs. 4 and 5.

[00142] As shown in FIGs. 1 and 2, formulation examples 1-5 delivered very similar amounts of IBP to the skin. Formulations 2, 3, 5, and 6 started delivering IBP to the skin after about 30 minutes. Formulations 1, 4, and 7 started delivering the IBP to the skin after about 1 hour. Formulations 3 and 5 resulted in delivering about $0.8 \mu\text{g}/\text{cm}^2/\text{hr}$ of IBP to the skin after 1 hour. Formulations 1, 2, 4, 5, and 6 delivered about $0.8 \mu\text{g}/\text{cm}^2/\text{hr}$ of IBP to the skin after about 1.5 hours. After about 1 or 1.5 hours, all the formulations started delivering the IBP to the skin at a steady rate.

[00143] Referring now to FIG. 3, formulation example 8 started delivering the IBP to the skin after about 1 hour, and the formulation example 9 started delivering the IBP to the skin after about 2 hours. Formulation examples 8 and 9 exhibited a highest rate of delivery of the IBP to the skin between about 2 and 4 hours. After 4 hours, formulation example 8 started delivering the IBP steadily to the skin. After 4 hours, formulation example 9 delivered about $2 \mu\text{g}/\text{cm}^2$ to the skin, and after 6 hours – about $3 \mu\text{g}/\text{cm}^2$. For formulation example 9, the concentration of the IBP slightly declined between 6 and 8 hours.

[00144] Referring now to FIG. 4, formulation example 14 delivered the highest amount of IBP to the skin, with no decline in flux even at 8 hours. Formulation example 15 delivered the lowest amount of IBP to the skin, but the formulation kept delivering IBP to the skin steadily at 8 hours.

[00145] Referring now to FIG. 5, formulation examples 11 and 16 delivered the lowest amount of IBP to the skin out of all the formulation examples 1-16. However, at 8 hours the two formulation examples 11 and 16 continued to deliver IBP to the skin.

[00146] In general, the formulations prepared using ARLs delivered the drug through the skin. Depending on the ARL/RL used in the formulations, the amount of drug delivered varied (FIG. 2, formulations 5 & 7). Similarly, depending on changes (ingredients, quantity, etc.) made in the formulations using a particular ARL/RL, the amount of drug delivered varied (FIG. 4, formulations 12 & 15). The permeability experiment was carried out for 8 hours only. However, the drug delivery profile did not show a trend of decline in delivering the IBP in this 8 hours period. This indicated that the IBP was not depleted and ARL/RL formulations could deliver it for longer than 8 hours.

[00147] Hence, ARL/RLs are useful as a drug delivery platform in topical pharmaceutical formulations to deliver the drug through the skin.

[00148] While the invention is susceptible to various modifications and alternative forms, specific embodiments have been shown by way of example in the examples and described in detail herein. It should be understood, however, that the invention is not intended to be limited to the particular forms disclosed. Rather, the invention is to cover all modifications,

equivalents, and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

Claims:

1. A drug delivery formulation comprising:
 - (a) an organosiloxane copolymer wherein the organosiloxane copolymer is
 - (i) an amphiphilic resin-linear organosiloxane block copolymer;
 - (ii) a resin-linear organosiloxane block copolymer;
 - (iii) or a combination of (i) and (ii) ;
 - (b) a first solvent, wherein the first solvent is configured to dissolve the amphiphilic resin-linear organosiloxane block copolymer or the resin-linear organosiloxane block copolymer;
 - (c) at least one active ingredient configured to be topically delivered through skin for an intended therapeutic application; and
 - (d) at least one penetration enhancer or penetration excipient.
2. The drug delivery formulation of claim 1, further comprising:
 - (e) a solid silicone resin in
 - (f) a second solvent, wherein the second solvent is configured to dissolve the solid silicone resin.
3. The formulation of claim 2, wherein the solid silicone resin comprises a trimethylsiloxysilicate resin and resins comprising:

disiloxy units of the formula $R^x_3SiO_{1/2}$, wherein R^x is independently selected from monovalent hydrocarbon groups; and

tetrafunctional units of the formula $SiO_{4/2}$.
4. The formulation according to any one of claims 2-3, further configured to form a film that temporarily adheres to an area of the skin where the formulation is applied, wherein an amount of the solid silicone resin in the formulation determines tackiness of the film and a length of time that the film remains on the skin, the solid silicone resin being configured to improve transfer and wash-off resistance and remain intact on the skin for a time period ranging from 1 hour to 24 hours and resist formation of cracks on the surface of the film.
5. The drug delivery formulation of any one of claims 2-4, wherein the first solvent and the second solvent are independently selected from ethyl acetate, dimethylsulfoxide, isododecane, siloxane fluids, cyclosiloxanes, alcohols, alkanes, or any combination thereof.

6. The drug delivery formulation of any one of the preceding claims, wherein the amphiphilic resin-linear organosiloxane block copolymer comprises:

i) a linear block of repeating units having the formula $B-[AB]_n$,

wherein

B is a diorganopolysiloxane having an average of from 10 to 400 disiloxy units of the formula $[R^1_2SiO_{2/2}]$;

A is a divalent organic group comprising at least one polyether group; and

$n \geq 1$;

ii) a resinous block of repeating units of the formula $[R^2SiO_{3/2}]$ arranged in non-linear blocks having a molecular weight of at least 500 g/mol,

wherein

each R^1 is independently selected from C_1 to C_{30} hydrocarbyls;

each R^2 is independently selected from C_1 to C_{20} hydrocarbyls;

each linear block is linked to at least one non-linear block by a divalent C_2 to C_{12} hydrocarbon group; and

the amphiphilic resin-linear organosiloxane block copolymer has a molecular weight of at least about 20,000 g/mole.

7. The drug delivery formulation of claim 6, wherein the linear block has the formula:

$-R^1_2SiO(R^1_2SiO)_xSiR^1_2[[R^5(C_mH_{2m}O)_yR^5][R^1_2SiO(R^1_2SiO)_x]R^1_2Si]_n-$

wherein $x \geq 0$, m is from 2 to 4 inclusive, $y \geq 3$, $n \geq 1$;

each R^1 is independently selected from monovalent hydrocarbon groups including 1 to 30 carbons; and

each R^5 is independently selected from divalent hydrocarbons including 2 to 30 carbons.

8. The drug delivery formulation of any one of claims 1-5, wherein the resin-linear organosiloxane block copolymer comprises:

40 to 90 mole percent disiloxy units of the formula $[R^1_2SiO_{2/2}]$;

10 to 60 mole percent trisiloxy units of the formula $[R^2SiO_{3/2}]$;

0.5 to 35 mole percent silanol groups $[≡SiOH]$,

wherein each R^1 is independently selected from C_1 to C_{30} hydrocarbyls;

each R^2 is independently selected from C_1 to C_{20} hydrocarbyls;

the disiloxy units $[R^1_2SiO_{2/2}]$ are arranged in linear blocks having an average of from 10 to 400 disiloxy units $[R^1_2SiO_{2/2}]$ per linear block;

the trisiloxy units $[R^2SiO_{3/2}]$ are arranged in non-linear blocks having a molecular weight of at least 500 g/mol, and at least 30% of the non-linear blocks are crosslinked with each other;

each linear block is linked to at least one non-linear block; and
the organosiloxane block copolymer has an average molecular weight (M_w) of at least about 20,000 g/mole.

9. The drug delivery formulation of any one of the preceding claims, wherein at least one penetration enhancer or penetration excipient is selected from propylene glycol, butylene glycol, dipropylene glycol, polyethylene glycol-20, oleic acid, oleyl alcohol, isopropyl myristate, dimethylisobornide, isopropyl alcohol, ethyl alcohol, dimethylsulfoxide, or any combination thereof.

10. The drug delivery formulation any one of the preceding claims, wherein the at least one active ingredient is selected from a non-steroidal anti-inflammatory drug, a steroid, a retinoid, traditional Chinese medicines, anti-acne, anti-fungal, antibiotics, or any combination thereof.

11. The drug delivery formulation of any one of the preceding claims, further comprising an occlusivity agent configured to provide occlusivity when the formulation is applied to the skin.

12. The drug delivery formulation of any one of the preceding claims, wherein the formulation is, a gel, a liquid, or an aerosol.

13. The drug delivery formulation of any one of the preceding claims, wherein the formulation is anhydrous and/or free of preservatives.

14. The drug delivery formulation of any one of the preceding claims, wherein the formulation is configured to form a film on a substrate, the film being configured to resist formation of cracks on a surface of the film for an entire duration of the intended therapeutic application.

15. The formulation of any one of the preceding claims, further comprising a pressure sensitive adhesive.

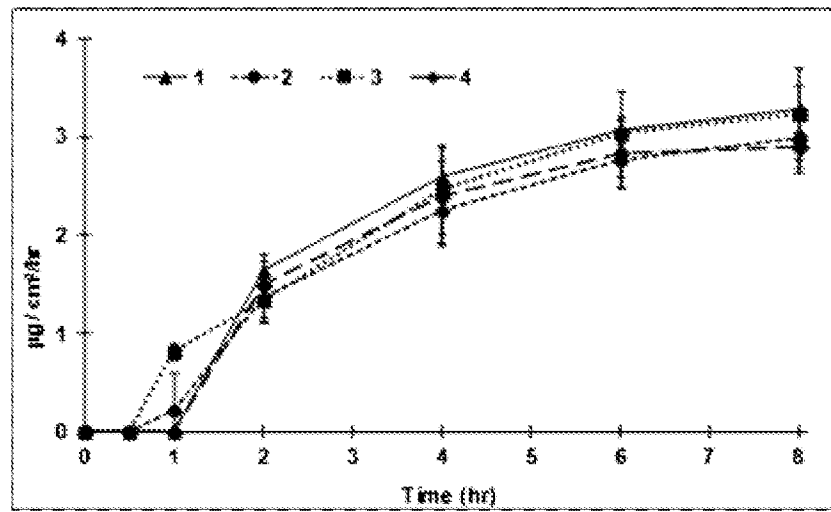


FIG. 1

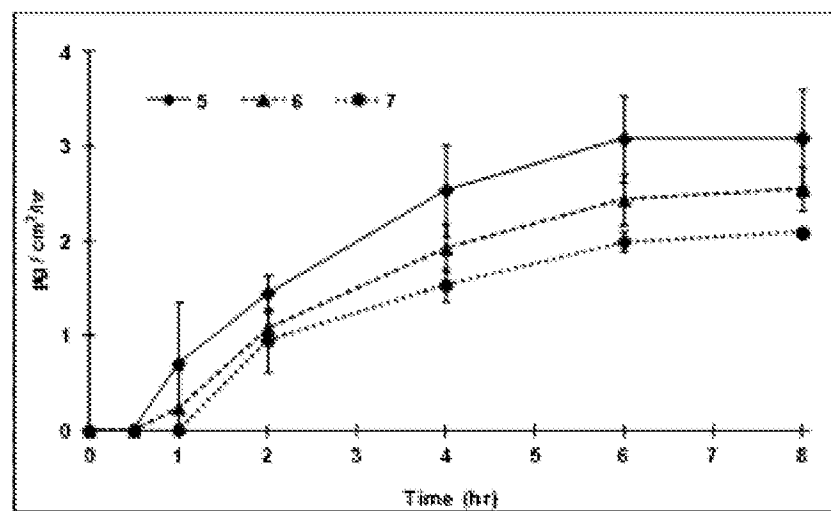


FIG. 2

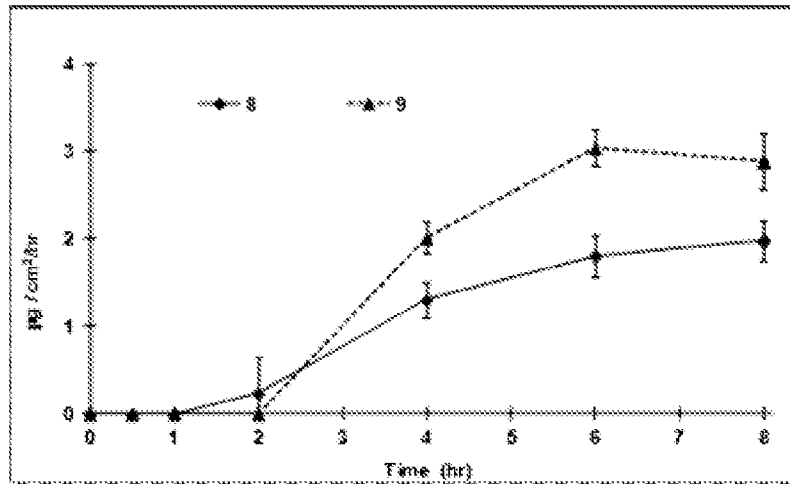


FIG. 3

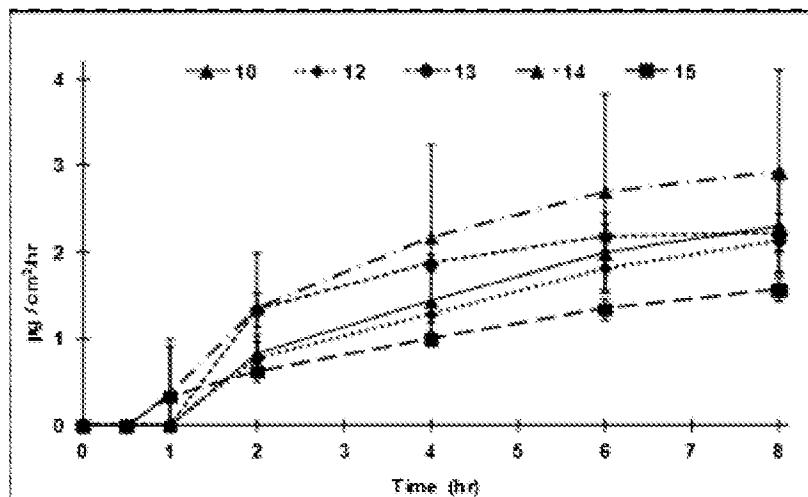


FIG. 4

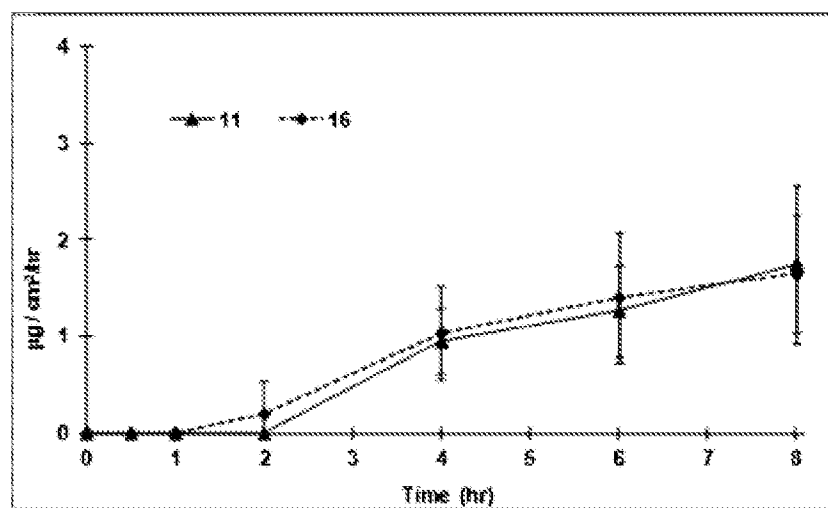


FIG. 5