(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2019 (25.07.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/143971 A2

(51) International Patent Classification:
A61K 47/69 (2017.01)

(21) International Application Number:
PCT/US2019/014241

(22) International Filing Date:
18 January 2019 (18.01.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/619,019 18 January 2018 (18.01.2018) US

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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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, ST, 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,

(54) Title: FORMULATIONS FOR DERMAL DELIVERY OF POLYMER CONJUGATES OF INDOLOCARBAZOLE COMPOUNDS WITH REDUCED EXPOSURE

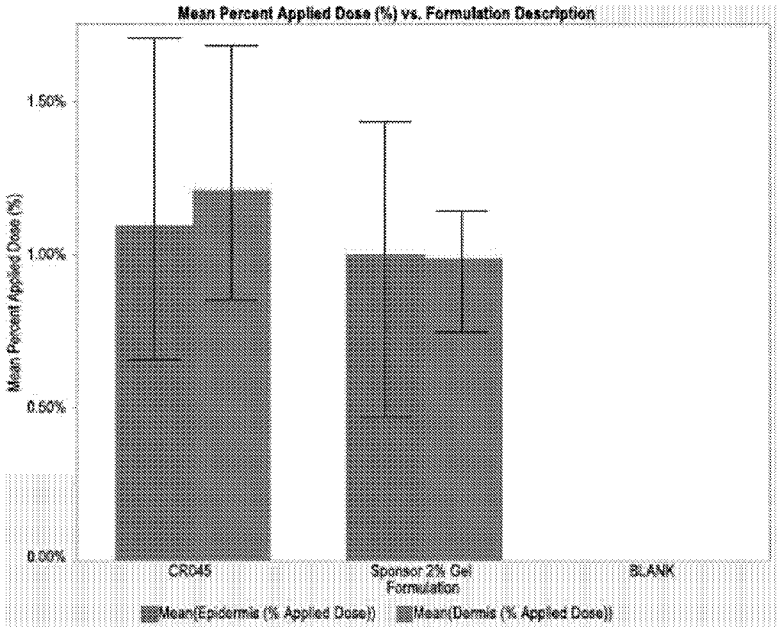


FIGURE 1

(57) Abstract: Topical formulations to treat skin conditions, such as atopic dermatitis, psoriasis, pruritus, are provided in which a polymer conjugate of an indolocarbazole exhibits reduced systemic exposure. An example formulation includes the TrkA/JAK/MAP kinase antagonist, SNA-125, in a cream formulation.

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[Continued on next page]

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).

Published:

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

FORMULATIONS FOR DERMAL DELIVERY OF POLYMER CONJUGATES OF INDOLOCARBAZOLE COMPOUNDS WITH REDUCED EXPOSURE

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/619,019, filed January 18, 2018, the entire content of which is incorporated herein by reference.

BACKGROUND

[0002] Skin care formulations, which include for example, primers, serums, lotions, ointments, gels, creams, foams and other products, are used on the skin for various purposes. Formulations can contain one or more active agents, including in some embodiments, indolocarbazole compounds conjugated to polymer(s).

SUMMARY

[0003] A cream formulation for dermal delivery of a polymer conjugate of an indolocarbazole compound with reduced exposure is disclosed in accordance with one embodiment. The cream formulation includes or consists essentially of, for example a polymer conjugate of an indolocarbazole compound in a solvent system comprising an aqueous phase (containing the indolocarbazole), an oil phase and surfactants.

[0004] In one embodiment of the cream formulation, the polymer conjugate of an indolocarbazole compound is SNA-125. The SNA-125 may be present at about 0.05% to about 25% (w/w) (e.g., 0.05-5%, 5-15%, 15-25%, and overlapping ranges therein). In a variation, the SNA-125 may be present at about 0.05% to about 10% (w/w) of the cream formulation. In another variation, the SNA-125 may be present at about 2% (w/w) of the cream formulation. Other reduced exposure compounds disclosed herein may be used with or instead of SNA-125.

[0005] The aqueous phase of the cream formulation may include solvents, preservatives, solubilizing agents, etc. In some embodiments, the aqueous phase may include, for example, one or more of 2-(2-ethoxyethoxy)ethanol (tradename TRANSCUTOL

P – penetration enhancer), high purity grade, low molecular weight polyethylene glycol 400 (tradename SR (Super Refined)PEG 400 – commonly used as a partitioning agent because it is strongly hydrophilic, purified water, phenoxyethanol (used as a preservative), propylene glycol (water-miscible co-solvent/drug stabilizer), isopropyl alcohol (co-solvent), benzyl alcohol (preservative/solvent), one or more antioxidants, including for example, butylated hydroxyanisole ('BHA'), butylated hydroxytoluene ('BHT'), and propyl gallate, and ethanol (solvent).

[0006] The oil phase of the solvent system for the cream formulation may include, for example, one or more of isopropyl myristate ('IPM' emollient), cetostearyl alcohol (emollient/thickener), Caprylic/Capric Triglyceride ('GTCC' emollient/moisturizer), liquid paraffin and/or white soft paraffin (emollient/skin lubricant), dimethicone 350 (moisturizer/skin protectant), beeswax (skin protectant/thickening agent), stearyl alcohol (skin conditioner/emulsifier), cholesterol (skin conditioner/moisturizer), stearic acid (emulsifier/emollient/lubricant) and castor oil, mineral oil, butyl stearate, IPA and IPP.

[0007] The surfactants used in the cream formulation may be used to stabilize oil-in-water emulsions, and may include, for example, one or more of Brij S2 (polyoxyethylene fatty ethers derived from stearyl alcohols), Brij S20 (polyoxyethylene fatty ethers derived from stearyl alcohols), Span 60 (emulsifier/surfactant derived from stearic acid and used in combination with Tween 60) and Tween 60 (polysorbate emulsifier/surfactant), and Cetomacrogol 1000 (emulsifier/surfactant).

[0008] In one embodiment, a cream formulation for dermal delivery of SNA-125 with reduced exposure is disclosed, wherein the cream formulation includes about 2% w/w SNA-125 and a combination of aqueous phase components, oil phase components and surfactants as set forth below in Table 1.

[0009] A method of treating a skin condition associated with TrkA, Janus Kinase (JAK1, JAK2 and/or JAK3), Tyrosine Kinase 2 (TYK2), Mitogen-Activated Protein Kinase (MAP2K and/or MAP3K) signaling is disclosed in accordance with another embodiment. The method comprises: applying, or instructing application of, a topical cream formulation to a skin region, wherein the cream formulation fully or partially inhibits signaling in the skin region, and thereby treats the skin condition. In one embodiment of the disclosed method,

the cream formulation comprises: a polymer conjugate of an indolocarbazole compound in an oil-in-water emulsion. In one particular embodiment of the disclosed method, the polymer conjugate of an indolocarbazole in the cream formulation is SNA-125 having reduced exposure; examples are set forth below in Table 1. Other reduced exposure compounds disclosed herein may be used with or instead of SNA-125.

SNA-125 CREAM FORMULATIONS

Table 1 provides the compositions of four non-limiting embodiments of SNA-125 cream formulations. Each of the percentages in the table can be adjusted by +/- 20%.

	Component	**CR054 (%w/w)**	**CR058 (%w/w)**	**CR061 (%w/w)**	**CR062 (%w/w)**
Aqueous Phase	SNA-125	2.00	2.00	2.00	2.00
	Transcutol P	15.00	15.00	–	15.00
	SRPEG400	15.95	20.97	15.99	20.97
	Purified Water	30.00	40.00	50.00	40.00
	Benzyl Alcohol	2.00	2.00	2.00	2.00
	BHT or Propyl Gallate	0.05	0.03	0.01	0.03
	Ethanol	–	–	10.00	–
	Subtotal	**65.00**	**80.00**	**80.00**	**80.00**
Oil Phase	IPM	–	7.34	–	8.34
	Cetostearyl alcohol	6.66	3.33	3.33	3.33
	GTCC	–	–	8.34	–
	Liquid paraffin	16.68	–		
	Dimethicone 350	–	1.00	–	–
	Stearic Acid	6.66	3.33	3.33	3.33
	Subtotal	**30.00**	**15.00**	**15.00**	**15.00**
Surfactants	Brij S2	1.31	1.25	1.44	1.04
	Brij S20	3.69	3.75	3.56	3.96
	Subtotal	**5.00**	**5.00**	**5.00**	**5.00**
	Total	**100.00**	**100.00**	**100.00**	**100.00**

[00010] In one embodiment of the disclosed method, the skin condition is inflammation, pain, atopic dermatitis, psoriasis, pruritus associated with psoriasis, or another dermatologic condition.

BRIEF DESCRIPTION OF THE DRAWINGS

[00011] Figure 1 depicts the mean percent applied dose of SNA-125 recovered from epidermis and dermis following application of a representative SNA-125 cream prototype formulation (CR045) and a SNA-125 gel formulation. No formulation was applied to a control blank cell.

[00012] Figure 2 depicts data related to the mean cumulative amount (ng/cm^2) of SNA-125 permeated through the 1 cm^2 skin dosing area (i.e. drug detected in receiver fluid) following application of the ten formulations (n = 5; if Dixon outlier removed, n = 4). Figures 2A and 2B depict the data with error bars (standard deviation) and without error bars, respectively.

[00013] Figure 3 depicts data related to the mean flux ($ng/cm^2/hr$) of SNA-125 permeated through the 1 cm^2 skin dosing area (i.e. drug detected in receiver fluid) following application of ten formulations (n = 5; if Dixon outlier removed, n = 4). Error bars have been removed.

[00014] Figure 4A depicts the mean amount of SNA-125 (ng) recovered from epidermis and dermis following application of the ten prototype formulations. Each bar represents the mean (n = 5; if Dixon outlier removed, n = 4) and error bars represent standard deviation. Figures 4B and 4C depict connecting letters reports summarizing significant differences (Tukey-Kramer, $p < 0.05$) between the formulations with respect to epidermis and dermis, respectively.

[00015] Figure 5A depicts the mean percent of applied dose of SNA-125 recovered from epidermis and dermis (ng) following application of the ten prototype formulations. Each bar represents the mean (n = 5; if Dixon outlier removed, n = 4) and error bars represent standard deviation. Figures 5B and 5C depict connecting letters reports summarizing significant differences (Tukey-Kramer, $p < 0.05$) between the formulations with respect to epidermis and dermis, respectively.

[00016] Figure 6 depicts an individual model graph for BHA (A) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00017] Figure 7 depicts an individual model graph for BHT (B) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00018] Figure 8 depicts an individual model graph for propyl gallate (C) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00019] Figure 9 depicts an individual model graph for ascorbic acid (D) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00020] Figure 10 depicts an individual model graph for ascorbic palmitate (E) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00021] Figure 11 depicts an interaction model graph for BHT and BHA (AB) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00022] Figure 12 depicts an interaction model graph for BHA and propyl gallate (AC) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00023] Figure 13 depicts an interaction model graph for BHT and ascorbic palmitate (BE) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00024] Figure 14 depicts an interaction model graph for propyl gallate and ascorbic palmitate (CE) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00025] Figure 15 depicts an interaction model graph for propyl gallate and alpha tocopherol (CF) in the CR045 solvent system and average percentage recovery (%) of SNA-125 under stress conditions (6% H_2O_2 spiking at 70°C for 24 hours) in the solvent system.

[00026] Figure 16 depicts a design space of the t = 5 day average SNA-125 recovery % w/w from theoretical (%) in a CR045 solvent system that contains propyl gallate (C), alpha tocopherol (F), and BHA (A) at the indicated concentrations.

DETAILED DESCRIPTION

[00027] Effective delivery of pharmacologically active agents may be hindered by unwanted exposure of those agents to non-desired locations (such as the systemic circulation and/or lymphatic system). For example, topical agents useful in treating various skin disorders may result in toxic side effects because of systemic exposure. One issue with delivering compositions comprising one or more active agents topically (or non-topically) is the concern that such agents need to be delivered in an amount and at a location sufficient to have a therapeutic effect. At the same time however, exposure (e.g., absorption or longevity of the composition in the systemic circulation, lymphatic system, or other non-targeted sites) may not be desirable for multiple reasons, including, but not limited to, safety reasons. There remains an unmet need for compounds with reduced exposure at non-target sites that result in a clinically therapeutic effect.

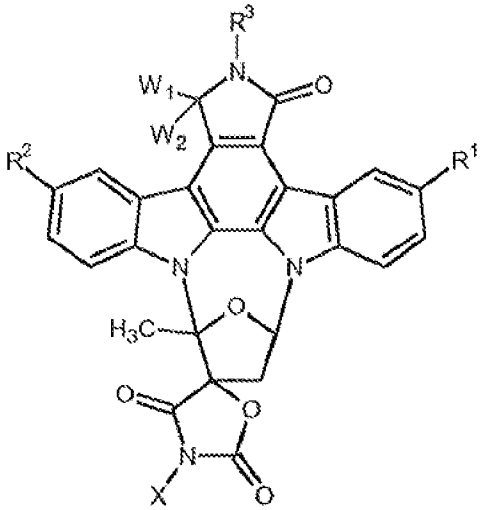
[00028] In several embodiments of the invention, the compositions described herein are both therapeutically efficacious and minimize non-target (e.g., systemic or bloodstream) exposure. In some embodiments, the active agents are PEGylated or otherwise coupled to large molecules, and surprisingly, are effective in crossing biological membranes such that the active agents are effectively delivered to the target location. Inflammatory and non-inflammatory conditions are contemplated herein.

[00029] Reduced exposure compounds and compositions are provided in several embodiments. "Reduced exposure" compounds are those compounds that, when delivered to a target location, are formulated to act at the target location with reduced exposure (e.g., entry and/or longevity) in non-target sites. Exposure is reduced as compared to active agents not formulated according to the embodiments described herein. As a non-limiting example, a

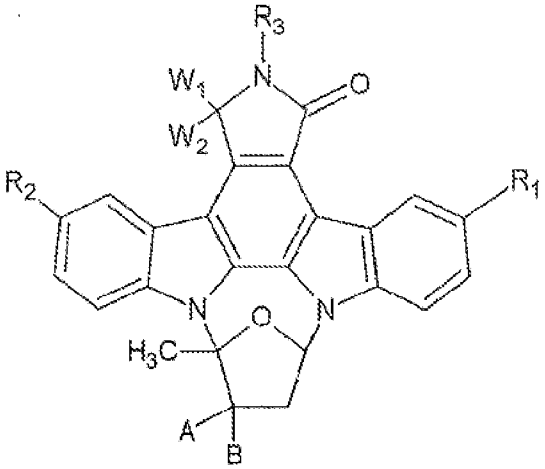
PEGylated topical dermal active agent has reduced exposure to the bloodstream as compared to the active agent alone. Reduced exposure compounds include topical compounds that can be delivered to body surfaces and cavities such as the skin, eyes, ears, nose, mouth, vagina, rectum, etc. Non-desired target sites include, for example, the systemic system, the lymphatic system, non-target tissue, etc. "Reduced exposure compositions" comprise or consist essentially of one or more "reduced exposure compounds."

[00030] Reduced exposure topical compositions are provided in many embodiments. In some cases, less or none of the active agent is absorbed into the non-target site (e.g., systemic circulation and/or lymphatic system). Further, once the composition enters the systemic circulation and/or lymphatic system, clearance (e.g., by the kidney) occurs at a much faster rate. One or more of the advantages of (i) *reduced* absorption into the non-target site (e.g., systemic circulation and/or lymphatic system), (ii) *slower* absorption into the non-target site (e.g., systemic circulation and/or lymphatic system), and (iii) *faster* clearance rates from the non-target site (e.g., systemic circulation and/or lymphatic system) are also achieved when using the compositions (e.g., via dermal topical formulations as described herein) for treating the skin.

[00031] In several embodiments, there is provided in a reduced exposure composition, a polymer conjugate comprising a warhead (e.g., at least one active agent) linked to a polymer, wherein the warhead comprises an indolocarbazole compound. In some embodiments, the polymer conjugate comprises an indolocarbazole compound of formula (I) or of formula (II):



formula (I)



formula (II)

[00032] wherein in formula (I) and (II)

[00033] R^1 and R^2 are the same or a different residue and are each independently selected from the group consisting of:

[00034] (a) hydrogen, halogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, hydroxy, lower alkoxy, carboxy, lower alcoxycarbonyl, acyl, nitro, carbamoyl, lower alkylaminocarbonyl, -NR^5R^6, wherein R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted lower alkylaminocarbonyl, substituted or unsubstituted lower arylaminocarbonyl, alkoxycarbonyl, carbamoyl, acyl or R^5 and R^6 are combined with a nitrogen atom to form a heterocyclic group,

[00035] (b) -$CO(CH_2)_jR^4$, wherein j is 1 to 6, and R^4 is selected from the group consisting of

[00036] (i) hydrogen, halogen, -N_3,

[00037] (ii) -NR^5R^6, wherein R^5 and R^6 are as defined above,

[00038] (iii) -SR^7, wherein R^7 is selected from the group consisting of hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, - $(CH_2)_aCO_2R^{10}$ (wherein a is 1 or 2, and wherein R^{10} is selected from the group consisting of hydrogen and substituted or unsubstituted lower alkyl) and -$(CH_2)_aCO_2NR^5R^6$,

[00039] (iv) -OR^8, -$OCOR^8$, wherein R^8 is selected from hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl

[00040] (c) -$CH(OH)(CH_2)_j$ R^4 wherein j and R^4 are as defined above;

[00041] (d) -$(CH_2)_dCHR^{11}CO_2R^{12}$ or -$(CH_2)_dCHR^{11}CONR^5R^6$, wherein d is 0 to 5, R^{11} is hydrogen, -$CONR^5R^6$, or -CO_2R^{13}, wherein R^{13} is hydrogen or a wherein substituted or unsubstituted lower alkyl, and R^{12} is hydrogen or a substituted or unsubstituted lower alkyl;

[00042] (e) -$(CH_2)_kR^{14}$ wherein k is 2 to 6 and R^{14} is halogen, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -$COOR^{15}$, -OR^{15}, (wherein R^{15} is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or acyl), -SR^7 (wherein R^7 is as defined above), -$CONR^5R^6$, -NR^5R^6 (wherein R^5 and $R^6$are as defined above) or -N_3;

[00043] (f) -$CH=CH(CH_2)_mR^{16}$, wherein m is 0 to 4, and R^{16} is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -$COOR^{15}$, -OR^{15} (wherein R^{15} is as defined above) -$CONR^5R^6$ or -NR^5R^6 (wherein R^5 and R^6 are as defined above);

[00044] (g) -$CH=C(C0_2R^{12})_2$, wherein R^{12} is as defined above;

[00045] (h) -$C\equiv C(CH_2)_nR^{16}$, wherein n is 0 to 4 and R^{16} is as defined above;

[00046] (i) -CH_2OR^{22}, wherein R^{22} is tri-lower alkyl silyl in which the three lower alkyl groups are the same or different or wherein R^{22} has the same meaning as R^8

[00047] (j) $-CH(SR^{23})_2$ and $-CH_2-SR^7$ wherein R^{23} is lower alkyl, lower alkenyl or lower alkynyl and wherein R^7 is as defined above; and

[00048] R_3 is hydrogen, halogen, acyl, carbamoyl, substituted or unsubstituted lower alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted lower alkynyl or amino; and

[00049] W^1 and W^2 are independently hydrogen, hydroxy or W^1 and W^2 together represent oxygen;

[00050] and wherein in formula (I), X is a polymer moiety, either linear or branched,

[00051] and wherein in formula (II), A represents $-L^1-X'$ and B represents $–L^2-Y'$, wherein at least one of X' and Y' is a polymer moiety, either linear or branched, which is bound by L^1 and/or L^2 to the tetrahydrofuran ring of the compound of formula (II); L^1 and/or L^2 are a covalent chemical bond or a linker group;

[00052] when Y' is a polymer moiety, and X' is not a polymer, L^1 is a covalent chemical bond and X' is selected from the group consisting of

[00053] (a) hydrogen, lower hydroxyalkyl, acyl, carboxy, lower alkoxycarbonyl,

[00054] (b) $-CONR^{17a}R^{17b}$, wherein R^{17a} and R^{17b} are each independently selected from

[00055] (i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl,

[00056] (ii) $-CH_2 R^{18}$; wherein R^{18} is hydroxy,

[00057] or (iii) $-NR^{19}R^{20}$, wherein R^{19} or R^{20} are each independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl or R^{19} or R^{20} are independently the residue of an a-amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{19} or R^{20} are combined with a nitrogen atom to form a heterocyclic group; and

[00058] (c) $-CH=N-R^{21}$, wherein R^{21} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

[00059] when X' is a polymer moiety, and Y' is not a polymer, L^2 is a covalent chemical bond and Y' is selected from hydroxy, lower alkoxy, aralkyloxy, or acyloxy;

[00060] or a pharmaceutically acceptable salt of formula (I) and/or (II).

[00061] The polymer moiety X, X' or/and Y' covalently attached to the indolocarbazole compound of formulae (I) and (II) has to be biocompatible, can be of natural or semi-synthetic or synthetic origin and can have a linear or branched structure. In some embodiments, the polymer moiety X, X' or/and Y' is selected from poly(alkylene oxides), in particular from (polyethylene) oxides. However, further exemplary polymers include without limitation polyacrylic acid, polyacrylates, polyacrylamide or N-alkyl derivatives thereof, polymethacrylic acid, polymethacrylates, polyethylacrylic acid, polyethylacrylates, polyvinylpyrrolidone, poly(vinylalcohol), polyglycolic acid, polylactic acid, poly(lactic-co-glycolic) acid, dextran, chitosan, polyaminoacids, hydroxyethyl starch.

[00062] In some embodiments, the polymer moiety X, X' or/and Y' is a polyethylene glycol (PEG) moiety, wherein the terminal OH group can optionally be modified e.g. with C_1-C_5 alkyl or C_1-C_5 acyl groups. In some embodiments, the terminal OH group is optionally modified with C_1-, C_2- or C_3-alkyl groups or C_1-, C_2- or C_3 groups. In some embodiments, the modified polyethylene glycol is a terminally alkoxy-substituted polyethylene glycol. In some embodiments, the polymer moiety is methoxy-polyethylene-glycol (mPEG).

[00063] As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below.

[00064] The term “lower alkyl", when used alone or in combination with other groups, means a straight chained or branched lower alkyl group containing from 1-6 carbon atoms, preferably from 1-5, more preferably from 1-4 and especially preferably 1-3 or 1-2 carbon atoms. These groups include, in some embodiments, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, amyl, isoamyl, neopentyl, 1 -ethylpropyl, hexyl, and the like. The lower alkyl moiety of the "lower alkoxy", the "lower alkoxycarbonyl", the "lower akylaminocarbonyl’, "lower hydroxyalkyl' and of the "tri-lower alkylsilyl’ groups has the same meaning as "lower alkyl” defined above.

[00065] The "lower alkenyl” groups are defined as C_2-C_6 alkenyl groups which may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1 -butenyl, isobutenyl, 2-butenyl, 1 -pentenyl, (Z)-2- pentenyl, (E)-2-pentenyl, (Z)-4-methyl-2-pentenyl, (E)-4-methyl-2-pentenyl, pentadienyl, e.g., 1 , 3 or 2,4-

pentadienyl, and the like. In some embodiments, the C_2-C_6- alkenyl groups are C_2-C_5-, C_2-C_4-alkenyl groups. In other embodiments, the C_2-C_6- alkenyl groups are C_2-C_3-alkenyl groups.

[00066] The term "lower alkynyl" groups refers to C_2-C_6-alkynyl groups which may be straight chained or branched and include ethynyl, propynyl, 1 -butynyl, 2- butynyl, 1 -pentynyl, 2-pentynyl, 3-methyl-1 -pentynyl, 3-pentynyl, 1 -hexynyl, 2-hexynyl, 3-hexynyl and the like. In some embodiments, C_2-C_6-alkynyl groups are C_2-C_5-, C_2-C_4-alkynyl groups. In other embodiments, C_2-C_6-alkynyl groups are C_2-C_3-alkynyl groups.

[00067] The term "aryl" group refers to C_6-C_{14}-aryl groups which contain from 6 up to 14 ring carbon atoms. These groups may be mono-, bi- or tricyclic and are fused rings. In some embodiments, the aryl groups include phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl and the like. The aryl moiety of the "arylcarbonyl" and the "arylaminocarbonyl" groups has the same meaning as defined above.

[00068] The term "heteroaryl" groups may contain 1 to 3 heteroatoms independently selected from nitrogen, sulfur or oxygen and refers C_3-C_{13}-heteroaryl groups. These groups may be mono-, bi- or tricyclic. In some embodiments, the C_3-C_{13} heteroaryl groups include heteroaromatics and saturated and partially saturated heterocyclic groups. These heterocyclics may be monocyclic, bicyclic, tricyclic. In some embodiments, the 5 or 6-membered heterocyclic groups are thienyl, furyl, pyrrolyl, pyridyl, pyranyl, morpholinyl, pyrazinyl, methyl pyrrolyl, and pyridazinyl. The C_3-C_{13}-heteroaryl may be a bicyclic heterocyclic group. In some embodiments, the bicyclic heterocyclic groups are benzofuryl, benzothienyl, indolyl, imidazolyl, and pyrimidinyl. In some embodiments, the C_3-C_{13}-heteroaryls are furyl and pyridyl.

[00069] The term "lower alkoxy" includes alkoxy groups containing from 1 to 6 carbon atoms, in some embodiments from 1 to 5, in other embodiments from 1 -4 and in yet other embodiments 1 to 3 or 1 to 2 carbon atoms and may be straight chained or branched. These groups include methoxy, ethoxy, propoxy, butoxy, isopropoxy, tert-butoxy, pentoxy, hexoxy and the like.

[00070] The term "acyl" includes lower alkanoyl containing 1 to 6 carbon atoms, in some embodiments from 1 to 5, from 1 to 4, from 1 to 3 or from 1 to 2 carbon atoms and

may be straight chained or branched. These groups include, in some embodiments, formyl, acetyl, propionyl, butyryl, isobutyryl, tertiary butyryl, pentanoyl and hexanoyl. The acyl moiety of the "acyloxy" group has the same meaning as defined above.

[00071] The term "halogen" includes fluoro, chloro, bromo, iodio, and the like.

[00072] The term "aralkyl' group refers C_7-C_{15}-aralkyl wherein the alkyl group is substituted by an aryl. The alkyl group and aryl may be selected from the C_1-C_6 alkyl groups and the C_6-C_{14}-aryl groups as defined above, wherein the total number of carbon atoms is between 7 and 15. In some embodiments the C_7-C_{15}-aralkyl groups are benzyl, phenylethyl, phenylpropyl, phenylisopropyl, phenylbutyl, diphenylmethyl, 1 ,1 -diphenylethyl, 1 ,2-diphenylethyl. The aralkyl moiety of the "aralkyloxy" groups has the same meaning as defined above.

[00073] The substituted lower alkyl, alkenyl and alkynyl groups have 1 to 3 independently selected substituents, such as lower alkyl, hydroxy, lower alkoxy, carboxyl, lower alkoxycarbonyl, nitro, halogen, amino, mono- or di- lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The lower alkyl substituent moiety of the substituted lower alkyl, alkenyl and alkynyl groups, and the lower alkyl moiety of the lower alkoxy, the lower alkoxycarbonyl, and the mono- or di-lower alkylamino substituents of the substituted lower alkyl, alkenyl and alkynyl groups have the same meaning as "lower alkyl" defined above.

[00074] The substituted aryl, the substituted heteroaryl and the substituted aralkyl groups each has 1 to 3 independently selected substituents, such as lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino, mono- or di-lower alkylamino, and halogen. The lower alkyl moiety of the lower alkyl, the lower alkoxy, the lower alkoxycarbonyl, and the mono- or di- lower alkylamino groups among the substituents has the same meaning as 'lower alkyl' defined above.

[00075] The heterocyclic group formed by R^5 and R^6 combined with a nitrogen atom includes pyrrolidinyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl.

[00076] In some embodiments, R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, nitro, $-CH_2OH$, $-(CH_2)_kR^{14}$, $-CH=CH(CH_2)_mR^{16}$, $-C\equiv C(CH_2)_nR^{15}$, $-CO(CH_2)_jR^4$ wherein R^4 is $-SR^7$, CH_20-(substituted or unsubstituted) lower

alkyl (wherein the substituted lower alkyl is in some embodiments methoxymethyl, methoxyethyl or ethoxymethyl), $-NR^5R^6$. In some embodiments, each of R^1 and R^2 is hydrogen.

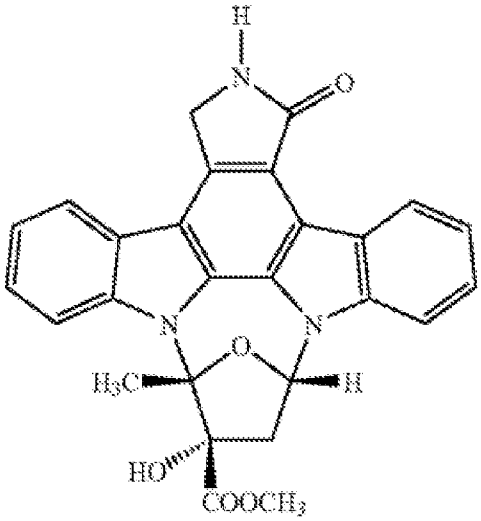
[00077] In some embodiments of R^1 and R^2, the residue R^{14} is selected from phenyl, pyridyl, imidazolyl, thiazolyl, tetrazolyl, $-COOR^{15}$, $-OR^{15}$ (wherein R^{15} is in some embodiments selected from hydrogen, methyl, ethyl, phenyl or acyl), $-SR^7$ (wherein R^7 is in some embodiments selected from substituted or unsubstituted lower alkyl, 2-thiazoline and pyridyl) and $-NR^5R^6$(wherein R^5 and R^6 are in some embodiments selected from hydrogen, methyl, ethyl, phenyl, carbamoyl and lower alkylaminocarbonyl). Moreover, in some embodiments, the residue R^{16} is selected from hydrogen, methyl, ethyl, phenyl, imidazole, thiazole, tetrazole, $-COOR^{15}$, $-OR^{15}$ and $-NR^5R^6$ (wherein the residues R^{15}, R^5 and R^6 have the meanings as described above). In some embodiments of R^1 and R^2, the residue R^7 is selected from the group consisting of substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, thiazole and tetrazole. Further, in some embodiments, k is 2, 3 or 4, j is 1 or 2 and m and n are independently 0 or 1.

[00078] In some embodiments, R^3 is hydrogen or acetyl. Furthermore, in some embodiments, each W^1 and W^2 is hydrogen.

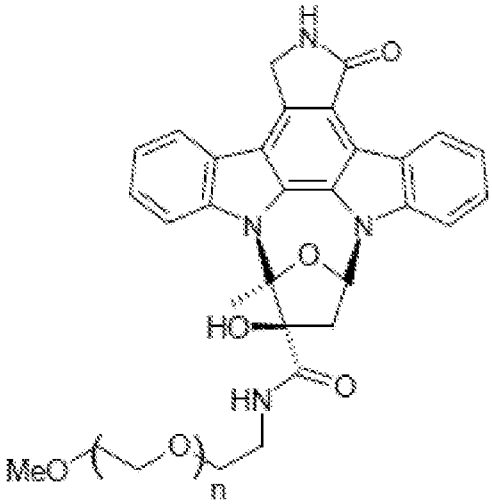
[00079] In some embodiments, when Y' is a polymer moiety and X' is not a polymer moiety, X' is selected from carboxy, hydroxymethyl or a lower alkoxycarbonyl. In some embodiments X' is selected from methoxycarbonyl.

[00080] In some embodiments, when X' is a polymer moiety and Y' is not a polymer moiety, Y' is selected from hydroxy or acetyloxy.

[00081] In some embodiments, the warhead of the polymer conjugate is a derivative of K252a, which has the formula:



[00082] In some embodiments, the polymer conjugate is SNA-125 (also referred to as CT340), wherein the composition has the formula:



SNA-125 (also referred to as CT340)

[00083] The formulas depicted herein are not limited to any particular stereochemistry, and all stereoisomers and enantiomers thereof are included in this disclosure.

[00084] As described above, several embodiments disclosed herein provide reduced or minimized exposure (e.g., entry into and/or longevity in a non-target site such as

the systemic circulation and/or lymphatic system). In some embodiments, exposure at a non-target site is less than 90%, 75%, 50%, 25%, 15%, 10%, 5% or 2% (or less) of the polymer conjugate as compared to a similar active entity that has not been produced according to the embodiments described herein. In some embodiments, desirable rate of clearance from the non-target site (e.g., systemic circulation and/or lymphatic system) for the compositions described herein is increased by at least 10%, 25%, 50%, or 75% or more as compared to non-conjugated controls. As an example, a PEGylated active agent described herein not only penetrates the desired membranes to reach a desired target, but has reduced non-target exposure by at least 20-80% or more as compared to the non-PEGylated active agent. In some embodiments, blood concentrations measured post administration of the compositions described herein are less than about 0.1 ng/ml, less than 1 ng/ml, or less than 10 ng/ml after, e.g., 15 minutes, 30 minutes, 1 hour, 6 hours or 12 hours.

[00085] In some embodiments, reduced exposure at non-target sites contributes to enhanced efficacy. Efficacy may be enhanced because lower concentrations/amounts/dosing schedules are required to achieve the same or similar therapeutic efficacy at the target site (because, for example, the active ingredient stays at the desired target site for a longer time). In one embodiment, concentrations/amounts/dosing schedules are reduced by 25%-75% or more.

[00086] More rapid clearance rates of the active agent once in the non-target site(s) (such as systemic circulation and/or lymphatic system) are also beneficial because this may allow for a *higher* concentration or *more* doses to be delivered. This is especially beneficial for active agents in which a subject would benefit from a higher dose but cannot tolerate the higher dose due to toxicity at the non-target site (e.g., systemic toxicity). Faster clearance rates would permit the desired higher dose to be delivered according to the desired schedule. For example, a subject may be able to tolerate daily doses rather than weekly doses because of the reduced exposure.

[00087] In some embodiments, the active agents of the compositions described herein (e.g., indolocarbazole compounds conjugated e.g., with PEG or other polymers) are measured in non-target sites (e.g., the systemic circulation and/or lymphatic system) at less than amounts found when the active agent is delivered without conjugation (e.g., less than

0.5%, 1% or 2% after 6 or 12 hours, as compared with 3-15% (e.g., 3-6%) when the active agent is delivered without conjugation). In some embodiments, the active agents of the compositions described herein (e.g., indolocarbazole compounds conjugated e.g., with PEG or other polymers) are measured in non-target sites (e.g., the systemic circulation and/or lymphatic system) at less than 0.5%, 1% or 2% after 3-24 hours, as compared to an amount 2-20 times greater when the active agent is delivered without conjugation.

[00088] In some embodiments, clearance of the compositions (e.g., the conjugated polymer compounds) occurs within minutes of exposure to the non-target site (e.g., systemic circulation and/or lymphatic system), as opposed to hours. In other embodiments, 50% clearance of the conjugated polymer compounds occurs in less than 5 minutes, 15 minutes, 30 minutes, 1 hour, 6 hours, and 12 hours of exposure to the systemic circulation and/or lymphatic system. Clearance times of the conjugated polymer compounds are reduced by more than 25%, 50%, 75% and 90%, as compared to the non-conjugated active agents or other formulations. These reduced clearance times are beneficial to reduce toxicity and undesired side effects.

[00089] In some embodiments, an active agent may be increasingly toxic as it is metabolized in the non-target site (e.g., systemic circulation and/or lymphatic system) because the metabolites exhibit more toxicity than the original agent. Thus, faster clearance rates, in some cases even before the toxic metabolites are created, are especially beneficial.

[00090] The term “active entity” or “active agent” as used herein should not be understood as limiting the participation of the polymer itself and/or the chemical linking moiety between the polymer and the warhead in defining the pharmacology of the polymer conjugate. In some embodiments, the polymer influences the selectivity and/or inhibitory activity of the polymer conjugate. In some embodiments, the chemical linking moiety between the polymer and warhead influences the selectivity and/or inhibitory activity of the polymer conjugate. In some embodiments, the polymer conjugates exhibit no change in selectivity or inhibitory activity against the therapeutic target in comparison with the unconjugated active agent. In some embodiments, the polymer conjugates exhibit a significant increase in selectivity against the therapeutic target in comparison with the unconjugated active agent. In some embodiments, the polymer conjugates exhibit a

significant increase in inhibitory activity against the therapeutic target in comparison with the unconjugated active agent. In some embodiments, the polymer conjugates exhibit a significant increase in selectivity and inhibitory activity against the therapeutic target in comparison with the unconjugated active agent. In some embodiments, the increased selectivity and/or inhibitory activity of the polymer conjugate against the therapeutic target in comparison with the unconjugated active agent causes decrease in undesired biological effects. In some embodiments, the increased selectivity of the polymer conjugate is caused by an increase of the hydrodynamic volume resulting from the conjugated polymer chain. In some embodiments, the polymer chain creates a higher steric hindrance which allows discrimination among the diverse shapes and sizes of the binding sites of different proteins, thus improving selectivity with respect to the active agent alone.

[00091] In several embodiments, various inflammatory skin diseases are treated. The inflammatory skin disease comprises, in some embodiments, psoriasis, psoriasis guttata, inverse psoriasis, pustular psoriasis, psoriatic erythroderma, pruritis associated with any of the various forms of psoriasis, acute febrile neutrophilic dermatosis, eczema, xerotic eczema, dyshidrotic eczema, vesicular palmar eczema, acne vulgaris, atopic dermatitis, contact dermatitis, allergic contact dermatitis, dermatomyositis, exfoliative dermatitis, hand eczema, pompholyx, keloids, rosacea, rosacea due to sarcoidosis, rosacea due to scleroderma, rosacea due to Sweet syndrome, rosacea due to systemic lupus erythematosus, rosacea due to urticaria, rosacea due to herpetic pain, Sweet's disease, neutrophilic hydrodenitis, sterile pustule, drug rash, seborrheic dermatitis, pityriasis rosea, Kikuchi's disease of the skin, pruritic urticarial papules and plaques of pregnancy, Stevens-Johnson syndrome and toxic epidermal necrolysis, tattoo reaction, Wells syndrome (eosinophilic cellulitis), reactive arthritis (Reiter syndrome), bowel-associated dermatosis-arthritis syndrome, rheumatoid neutrophilic dermatosis, neutrophilic eccrine hidradenitis, neutrophilic skin disease of dorsum of hand, balanitis circumscripta plasmacellularis, balanoposthitis, Behcet's disease, erythema annulare centrifugum, erythema dyschromicum perstans, erythema multiforme, granuloma annulare, dermatitis of hand, lichen nitidus, lichen planus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen spinulosus, nummular dermatitis, pyoderma

gangrenosum, sarcoidosis, subcorneal pustular dermatosis, urticaria, transient acantholytic dermatosis, vitiligo, prurigo nodularis, and dry skin.

[00092] In several embodiments, various skin neoplasias are treated. The skin neoplasia comprises, in some embodiments, squamous cell carcinoma, basal cell carcinoma, malignant melanoma, malignant cutaneous lymphoma, Kaposi's sarcoma, Merkel cell skin cancer, and non-melanoma skin cancer.

[00093] In several embodiments, various vascular tumors are treated. The vascular tumor comprises, in some embodiments, hemangiomas, Kaposi's sarcoma, lymphangioma, glomangioma, angiosarcoma, hemangioendothelioma, and infantile hemangiomas.

[00094] In several embodiments, various bullous diseases are treated. The bullous disease comprises, in some embodiments, bullous pemphigoid, erythema multiforme, dermatitis herpetiformis, epidermolysis bullosa acquisita, linear Immunoglobulin A disease, mucous membrane pemphigoid, pemphigoid gestationis, pemphigus foliaceus, and pemphigus vulgaris.

[00095] In several embodiments, hair growth and cycling are modulated. In several embodiments, alopecia is treated.

[00096] In several embodiments, the polymer conjugates are administered in combination with UV irradiation therapy.

[00097] Also provided herein, in several embodiments, are polymer conjugates wherein the polymer is polyethylene glycol (PEG) or methoxy-polyethylene glycol (m-PEG). In several embodiments, there is provided a pharmaceutical composition comprising or consisting essentially of a polymer conjugate disclosed herein that is formulated for topical administration. In several embodiments, methods of making and using the compositions described herein are provided.

[00098] In several embodiments, the invention comprises a reduced exposure composition comprising at least one active entity linked to at least one polymer, wherein the composition has reduced exposure at a non-target site as compared to the active entity delivered without the polymer. The non-target site comprises the systemic system, the lymphatic system and/or another non-target tissue site in some embodiments.

[00099] In some embodiments, the active entity binds to a kinase. In some embodiments, the active entity binds to Tropomyosin receptor kinase A (TrkA). In some embodiments, the active entity binds to a Janus Kinase (JAK) family member in some embodiments. In some embodiments, the active entity binds to one or more of Janus Kinase 1 (JAK1), Janus Kinase 2 (JAK2), Janus Kinase 3 (JAK3), and/or Tyrosine kinase 2 (TYK2) in some embodiments. In some embodiments, the active entity binds to mitogen-activated protein kinase kinase 2 (MAP2K) and/or mitogen-activated protein kinase kinase 3 (MAP2K3). Such kinase binding by the active entity may be partially or fully inhibitory or not.

[000100] In some embodiments, the polymer used in the reduced exposure compounds comprises polyethylene glycol (PEG) and/or methoxy-polyethylene glycol (m-PEG). In embodiments where the active entity has one or more carboxyl, hydroxyl, amino and/or sulfhydryl groups, the active entity is PEGylated (or conjugated/coupled to another polymer) at one or more of said carboxyl, hydroxyl, amino and/or sulfhydryl groups.

[000101] The reduced exposure compositions described herein are formulated for topical administration in several embodiments. In several embodiments, methods of treating one or more of the following are provided: inflammatory skin disease, vascular tumors, skin neoplasia, bullous diseases, alopecia, wounds, scars, autoimmune disorders, and cancerous or pre-cancerous lesions. Methods for modulating hair growth and cycling are provided in some embodiments.

[000102] In one embodiment, a method of treating any of the above-mentioned skin diseases or any other skin condition in need of treatment, includes: applying, or instructing application of, a topical formulation to a skin region, wherein the formulation fully or partially inhibits signaling in the skin region, and thereby treats the skin condition, wherein the formulation comprises: a polymer conjugate of an indolocarbazole compound in an oil-in-water emulsion. The topical formulation applied in accordance with the method may be any of the cream formulations of SNA-125 as more fully described herein.

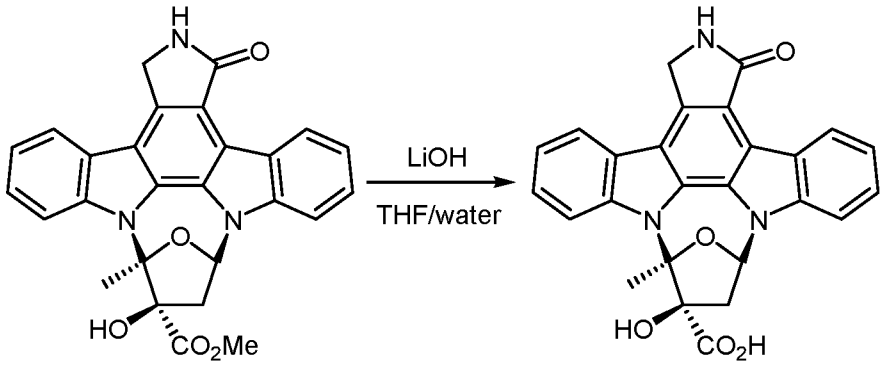
[000103] In some embodiments, the compositions may be administered via at least two routes of administration, either simultaneously or sequentially according to some embodiments. In one embodiment, the composition is administered via a first (e.g. topical

dermal) route to a subject, wherein the subject further receives an additional agent via a second (e.g., non-dermal) route to achieve synergetic effects.

Synthesis of SNA-125 (CT340)

[000104] In some embodiments, the active agent (SNA-125/CT340) may be synthesized as follows:

Step 1: Hydrolysis to K252b



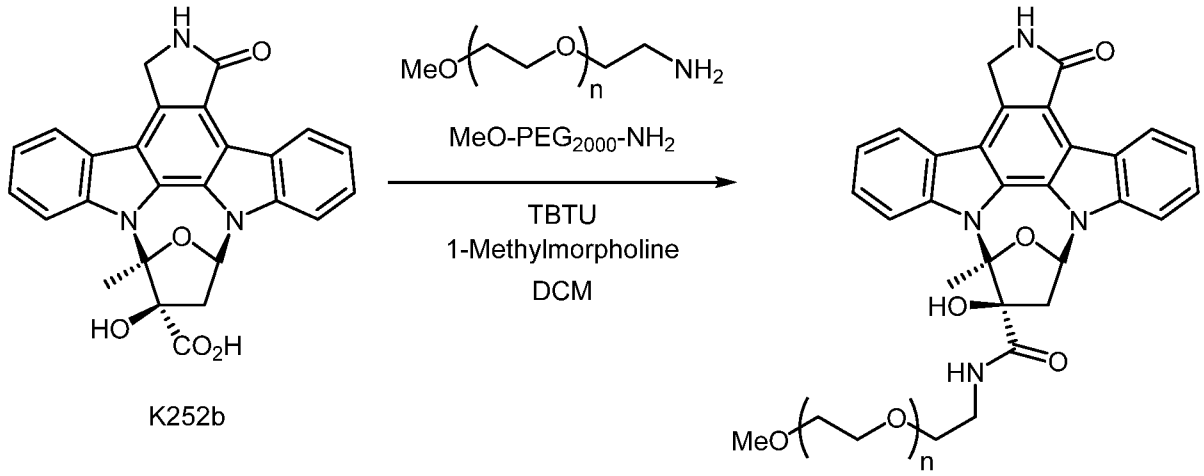
K252a K252b

[000105] 1 molar equivalent of K252a was dissolved in 7.1 vol of THF and the mixture was stirred for at least 30 minutes at ambient temperature (~20°C). A solution of 3 eq. $LiOHxH_2O$ in 4 vol of highly purified water (with respect to K252a) was added to the pale yellow solution over ~ 4 minutes to give a biphasic system which was stirred for ~21 h at ambient temperature, after which an IPC test by HPLC indicated <2% a/a K252a.

[000106] The majority of the solvent was distilled off under reduced pressure at ~30°C. 3 vol of highly purified water were added to the residue and evaporation under reduced pressure at ~30°C was continued to remove the remainder of the solvent, resulting in a thick aqueous mixture. The mixture was cooled to ~20°C and 2N HCl-solution (approximately 3-3.5 vol) was added to adjust the pH to 2-3, affording a white suspension. The suspension was stirred for ~40 minutes at ambient temperature and the solid collected by suction filtration, washing twice with highly purified water. The solid was then tumble-dried on the rotary evaporator at ~25°C under reduced pressure. It was then slurried in 14.2 vol of ethyl acetate for ~ 1 h. The solid was collected by suction filtration, washing twice with

heptane. The solid was then tumble-dried on the rotary evaporator at ~ 25°C under reduced pressure, affording K252b in essentially quantitative (uncorrected) yield.

Step 2: Coupling



[000107] 1 molar equivalent of K252b was pre-dried by suspending in 10 vol of dichloromethane and concentrating to dryness on the rotary evaporator at ~25°C then holding under reduced pressure to afford a yellowish solid. The dried K252b was re-suspended in 160 vol of dichloromethane at ambient temperature (~20°C) and 2 molar equivalents of 4-methylmorpholine were added. The resulting suspension was stirred for ~ 35-45 minutes.

[000108] 1 molar equivalent of PEG-amine was pre-dried by dissolving in dichloromethane (10 vol with respect to K252b) and concentrating to dryness on the rotary evaporator at ~25°C to give a white solid. The dried PEG-amine was dissolved in 50 vol of dichloromethane and this solution was added over ~20 minutes to the K252b/4-methylmorpholine suspension. The reaction mixture was stirred for ~20 minutes at ambient temperature and 1.7 eq. TBTU was then added in one portion. The reaction mixture was stirred for ~18-22h at ambient temperature, after which an IPC test by HPLC indicated <2% K252b.

[000109] Methanol (0.01 vol) was added to quench the reaction and the mixture was stirred for ~1-1.5 hours at ambient temperature. 30 vol of saturated sodium bicarbonate solution were added and the biphasic mixture was then stirred for ~20 minutes. The phases were separated and the lower (organic) phase was washed with 15 vol of saturated sodium

bicarbonate solution. The organic phase was concentrated to dryness under reduced pressure at ~ 25°C, protected from light.

Step 3: Purification and Isolation

[000110] The product from Step 2 is purified by preparative column chromatography using silica gel which has been pretreated with ethyl acetate containing 5% triethylamine. The Step 2 product was dissolved in dichloromethane/ethyl acetate for application to the column. Elution with ethyl acetate enabled residual K252a and UV-inactive species to be eluted (as monitored by TLC). The column was then conditioned with dichloromethane and eluted with dichloromethane/MeOH (98.5:1.5 → 95.5:4.5). Fractions were collected and analyzed by HPLC and TLC, and pooled according to their purity. Evaporation of the combined desired product fractions led to CT340 of purity >95% by HPLC area.

[000111] Although the resulting material is of high chemical purity, a precipitation step is performed to transform it from a semisolid concentrate into a readily handled free-flowing solid.

[000112] The concentrate was therefore dissolved in 4 vol of MeOH and this solution was added to chilled (~0°C) diethyl ether (20 vol) over 40-70 minutes to afford a white suspension that was stirred for further 1-2 hours at ~0°C. The solid product was filtered off, washing with diethyl ether (2 x 2 vol), to give CT340 Drug Substance in a typical yield of ~ 90%.

Formulations for topical delivery

[000113] In some embodiments, the active agent is formulated for topical delivery. The active agent may be a reduced exposure composition. In certain embodiments, the active agent is a polymer conjugate of an indolocarbazole compound, thereby providing a reduced exposure indolocarbazole compound. In one particular embodiment, the polymer conjugate is the indolocabazole depicted in Formula (II). In another particular embodiment, the polymer conjugate is SNA-125 (formerly referred to as CT340; both terms are used interchangeably herein). The topical delivery formulation can be in any form, including for

example, an ointment, a gel, a balm, a cream, a lotion, a primer, a serum, a liquid, a spray, etc. In some embodiments, the topical delivery formulation is a cream.

[000114] The weight percentage (w/w) of active agent to the total weight of the topical delivery formulation may range from about 0.001% to about 20%, from about 0.005% to about 15%, from about 0.01% to about 12%, or from about 0.1% to about 10%, including any weight percentages within the disclosed ranges. In other embodiments, the weight percentage (w/w) of the active agent may be greater than or equal to about 1.00% w/w. In certain embodiments, the weight percentage (w/w) of the active agent to the total weight of the topical delivery formulation may fall within any range defined by any two of the above weight percentages.

[000115] In other embodiments, the weight percentage (w/w) of the active agent may be less than or equal to about 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w. In certain embodiments, the weight percentage (w/w) of the active agent to the total weight of the topical delivery formulation may fall within any range defined by any two of the above weight percentages.

Cream formulation

[000116] A cream formulation is disclosed for dermal delivery of a polymer conjugate of an indolocarbazole compound with reduced exposure. The cream formulation includes a polymer conjugate of an indolocarbazole compound in a solvent system comprising an aqueous phase (containing the indolocarbazole), an oil phase and surfactants. In one embodiment of the cream formulation, the polymer conjugate of an indolocarbazole compound is SNA-125. The SNA-125 may be present at about 0.05% to about 25% (w/w) of the cream formulation. In a variation, the SNA-125 may be present at about 0.05% to about 10% (w/w) of the cream formulation. In one embodiment, a cream formulation for dermal delivery of SNA-125 with reduced exposure is disclosed, wherein the cream formulation includes about 2% w/w SNA-125 and a combination of aqueous phase components, oil phase components and surfactants as set forth below in Table 1 (reproduced again below).

[000117] The aqueous phase may include solvents, preservatives, solubilizing agents, etc. In some embodiments, the aqueous phase may include, for example, one or more of 2-(2-ethoxyethoxy)ethanol (tradename TRANSCUTOL P – penetration enhancer), high purity grade, low molecular weight polyethylene glycol 400 (tradename SR (Super Refined)PEG 400 – commonly used as a partitioning agent because it is strongly hydrophilic, purified water, phenoxyethanol (used as a preservative), propylene glycol (water-miscible co-solvent/drug stabilizer), isopropyl alcohol (co-solvent), benzyl alcohol (preservative/solvent), butylated hydroxytoluene ('BHT' – antioxidant), propyl gallate (antioxidant), and ethanol (solvent).

[000118] The oil phase of the solvent system for the cream formulation may include, for example, one or more of isopropyl myristate ('IPM' emollient), cetostearyl alcohol (emollient/thickener), Caprylic/Capric Triglyceride ('GTCC' emollient/moisturizer), liquid paraffin and/or white soft paraffin (emollient/skin lubricant), dimethicone 350 (moisturizer/skin protectant), beeswax (skin protectant/thickening agent), stearyl alcohol (skin conditioner/emulsifier), cholesterol (skin conditioner/moisturizer), and stearic acid (emulsifier/emollient/lubricant).

[000119] The surfactants used in the cream formulation may be used to stabilize oil-in-water emulsions, and may include, for example, one or more of Brij S2 (polyoxyethylene fatty ethers derived from stearyl alcohols), Brij S20 (polyoxyethylene fatty ethers derived from stearyl alcohols), Span 60 (emulsifier/surfactant derived from stearic acid and used in combination with Tween 60) and Tween 60 (polysorbate emulsifier/surfactant), and Cetomacrogol 1000 (emulsifier/surfactant).

SNA-125 CREAM FORMULATIONS

Table 1 provides the compositions of four non-limiting embodiments of SNA-125 cream formulations. Each of the percentages in the table can be adjusted by +/- 20%.

	Component	**CR054 (%w/w)**	**CR058 (%w/w)**	**CR061 (%w/w)**	**CR062 (%w/w)**
Aqueous Phase	SNA-125	2.00	2.00	2.00	2.00
	Transcutol P	15.00	15.00	–	15.00
	SRPEG400	15.95	20.97	15.99	20.97

	Purified Water	30.00	40.00	50.00	40.00
	Benzyl Alcohol	2.00	2.00	2.00	2.00
	BHT or Propyl Gallate	0.05	0.03	0.01	0.03
	Ethanol	–	–	10.00	–
	Subtotal	**65.00**	**80.00**	**80.00**	**80.00**
Oil Phase	IPM	–	7.34	–	8.34
	Cetostearyl alcohol	6.66	3.33	3.33	3.33
	GTCC	–	–	8.34	–
	Liquid paraffin	16.68	–		
	Dimethicone 350	–	1.00	–	–
	Stearic Acid	6.66	3.33	3.33	3.33
	Subtotal	**30.00**	**15.00**	**15.00**	**15.00**
Surfactants	Brij S2	1.31	1.25	1.44	1.04
	Brij S20	3.69	3.75	3.56	3.96
	Subtotal	**5.00**	**5.00**	**5.00**	**5.00**
	Total	**100.00**	**100.00**	**100.00**	**100.00**

EXAMPLE 1: PHARMACEUTICAL DEVELOPMENT OF A TOPICAL FORMULATION CONTAINING SNA-125

Short-term Formulation Study

[000120] Eighteen prototype formulations (13 cream, 2 ointment and 3 gel formulations) were developed and are described in Table 2 and Table 3. Each of these formulations was assessed by short-term stability testing, where macroscopic and microscopic appearance, physical and chemical stability were tested at t = 0, 2 and 4 weeks at 25°C and 40°C. At each time point, the following parameters were assessed: content of SNA-125 and related substances; apparent pH; microscopic appearance; and macroscopic appearance.

SNA-125 Content and Related Substances

[000121] Table 4 and Table 5 depict the percentage recovery (%) and percentage peak purity (% a/a), respectively, of SNA-125 in the developed active formulations at t=0

and following 2 and 4 weeks storage at 25°C and 40°C. Data are presented as the mean with the range in brackets (n=3).

Apparent pH

[000122] The apparent pH of the assessed formulations at t=0 and following 2 and 4 weeks storage at 25°C and 40°C is presented in Table 6.

Microscopic observations

[000123] Microscopic observations of the assessed formulations at t=0 and following 2 and 4 weeks storage at 25°C and 40°C were made using light microscopy (Table 7). Microscopic observations performed on a Leica DME light microscope with a magnification of 400x (polarized and non-polarized light).

Macroscopic Observations

[000124] Macroscopic observations of the assessed formulations at t=0 and following 2 and 4 weeks storage at 25°C and 40°C are presented in Table 8. The formulations were visually assessed for clarity, color, texture and visual viscosity.

TABLE 2: PROTOTYPE SNA-125 CREAM AND OINTMENT FORMULATIONS

Phase	Excipient Name	Theoretical Composition (% w/w) of the active formulations placed on stability							
		1	2	3	4	5	6	7	8
		CR042	CR043	CR044	CR045	CR047	CR052	CR053	CR054
Solvent System		SS30	SS30	SS30	SS31	SS32	SS34	SS35	SS36
Aqueous Phase	SNA-125	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Transcutol P	-	-	-	15.00	-	-	-	15.00
	SRPEG 400	45.97	45.97	45.97	30.95	30.97	35.95	46.97	15.95
	Water	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
	Phenoxyethanol	-	-	-	-	-	-	1.00	-
	Propylene Glycol	-	-	-	-	15.00	-	-	-
	Benzyl Alcohol	2.00	2.00	2.00	2.00	2.00	2.00	-	2.00
	BHT	0.03	0.03	0.03	0.05	0.03	0.05	0.03	0.05
	Ethanol	-	-	-	-	-	10.00	-	-
	Subtotal	80.00	80.00	80.00	80.00	80.00	80.00	80.00	65.00
Oil Phase	Cetostearyl alcohol	3.33	3.33	3.33	3.33	3.33	3.33	3.33	6.66
	GTCC	8.34	8.34	-	-	8.34	8.34	8.34	-
	Liquid Paraffin	-	-	8.34	8.34	-	-	-	16.68
	Stearic Acid	3.33	3.33	3.33	3.33	3.33	3.33	3.33	6.66
	Subtotal	15.00	15.00	15.00	15.00	15.00	15.00	15.00	30.00
Surfactants	Brij S2	1.44	-	1.31	1.31	1.44	1.44	1.44	1.31
	Brij S20	3.56	-	3.69	3.69	3.56	3.56	3.56	3.69
	Span 60	-	0.85	-	-	-	-	-	-
	Tween 60	-	4.15	-	-	-	-	-	-
	Subtotal	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Total		100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

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TABLE 2 (CONTINUED): PROTOTYPE SNA-125 CREAM AND OINTMENT FORMULATIONS

Phase	Excipient Name	Theoretical Composition (% w/w) of the active formulations placed on stability						
		9	10	11	12	13	14	15
		CR055	CR058	CR060	CR061	CR062	SNA-125 Low BA	SNA-120 Low BA
Solvent System		SS37	SS38	SS29	SS33	SS28	N/A	N/A
Aqueous Phase	SNA-125	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Transcutol P	10.00	15.00	8.00	-	15.00	-	-
	SRPEG 400	25.95	20.97	-	15.99	20.97	-	-
	Water	30.00	40.00	68.00	50.00	40.00	-	-
	Propylene Glycol	-	-	-	-	-	20.00	6.90
	IPA	10.00	-	-	-	-	-	-
	Benzyl Alcohol	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	BHT	0.05	0.03	-	0.01	0.03	-	0.10
	Ethanol	-	-	-	10.00	-	-	-
	Subtotal	80.00	80.00	80.00	80.00	80.00	24.00	13.00
Oil Phase	IPM	-	7.34	-	-	8.34	-	-
	Cetostearyl alcohol	3.33	3.33	3.33	3.33	3.33	-	-
	GTCC	8.34	-	8.34	8.34	-	-	-
	White soft paraffin	-	-	-	-	-	61.72	75.00
	Dimethicone 350	-	1.00	-	-	-	-	-
	Beeswax	-	-	-	-	-	8.16	8.00
	Stearyl Alcohol	-	-	-	-	-	3.06	3.00
	Cholesterol	-	-	-	-	-	3.06	3.00
	Stearic Acid	3.33	3.33	3.33	3.33	3.33	-	-
	Subtotal	15.00	15.00	15.00	15.00	15.00	76.00	87.00
Surfactants	Brij S2	-	1.25	1.44	1.44	1.04	-	-
	Brij S20	-	3.75	3.56	3.56	3.96	-	-
	Cetomacrogol 1000	5.00	-	-	-	-	-	-
	Subtotal	5.00	5.00	5.00	5.00	5.00	0.00	0.00
Total		100.00	100.00	100.00	100.00	100.00	100.00	100.00

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TABLE 3: PROTOTYPE SNA-125 GEL FORMULATIONS

Excipient	Theoretical Composition (% w/w) of the active formulations placed on stability		
	16	17	18
	0.2% Gel	1.0% Gel	2.0% Gel
Purified Water	Q.S	Q.S	Q.S
Benzyl Alcohol	1.00	1.00	1.00
Propylene Glycol	20.00	20.00	20.00
DMSO	20.00	20.00	20.00
Trolamine	Q.S pH 5.0 to 7.5	Q.S pH 5.0 to 7.5	Q.S pH 5.0 to 7.5
Hydroxyethyl cellulose (HEC)	1.25	1.25	1.25
SNA-125	0.2%	1.0%	2.0%
Total	100.00	100.00	100.00

TABLE 4: SNA-125 RECOVERY IN PROTOTYPE FORMULATIONS FOLLOWING STORAGE

Formulation	Theoretical percentage (%) recovery of SNA-125 compared to recovery at T=0					
	T=0	T = 2 weeks		T = 4 weeks		
		25 °C	40 °C	25 °C	40 °C	
CR042	92.86 (87.82 - 96.58)	96.84 (96.16 - 97.73)	97.25 (96.69 - 97.56)	95.40 (94.58 - 96.21)	95.78 (95.55 - 96.02)*	
CR043	97.70 (97.43 - 98.10)	97.87 (97.18 - 98.27)	98.48 (97.68 - 99.95)	91.15 (90.03 - 92.27)	98.47 (96.74 - 100.20)	
CR044	93.49 (90.67 - 95.07)	95.96 (94.54 - 97.35)	96.78 (96.00 - 97.57)	90.09 (89.17 - 91.93)	94.02 (93.71 - 94.32)	
CR045	95.46 (93.96 - 97.28)	97.39 (96.18 - 98.00)	108.36 (107.88 - 108.85)*	94.80 (90.88 - 98.72)	122.91 (121.42 - 125.50)	
CR047	96.76 (94.93 - 97.83)	97.80 (96.44 - 98.63)	99.38 (98.63 - 99.93)	89.69 (89.27 - 90.11)	95.69 (93.80 - 97.18)	
CR052	99.01 (98.63 - 99.32)	97.56 (97.00 - 97.89)	95.38 (94.86 - 95.90)*	95.20 (92.11 - 98.37)	126.02 (125.25 - 127.18)	
CR053	95.86 (92.67 - 97.70)	96.58 (94.08 - 98.13)	100.16 (99.32 - 101.07)	95.60 (94.91 - 96.69)	98.21 (94.91 - 97.50)	
CR054	100.87 (96.70 - 103.06)	100.47 (95.87 - 103.04)	128.80 (126.82 - 130.77)	103.76 (103.14 - 104.64)	163.07 (161.16 - 165.32)	
CR055	99.23 (98.97 - 99.54)	99.54 (99.39 - 99.68)	101.26 (99.14 - 103.38)	98.39 (98.04 - 98.64)	115.17 (114.79 - 115.39)	
CR058	107.55 (107.24 - 107.85)	95.30 (94.32 - 96.29)*	73.62 (45.28 - 101.96)	107.87 (107.64 - 108.23)	146.22 (144.72 - 147.42)	
CR060	97.87 (96.07 - 98.82)	97.77 (95.48 - 101.37)	97.24 (96.78 - 97.57)	96.81 (96.41 - 97.02)	95.87 (93.40 - 98.20)	
CR061	99.14 (98.89 - 99.55)	100.00 (99.68 - 100.38)	99.32 (98.65 - 99.73)	98.87 (98.47 - 99.40)	115.35 (114.88 - 115.72)	
CR062	99.37 (97.31 - 101.18)	91.43 (87.81 - 98.25)	103.22 (102.64 - 103.73)	101.85 (101.36 - 102.34)	104.03 (103.53 - 104.72)	

TABLE 4 (CONTINUED): SNA-125 RECOVERY IN PROTOTYPE FORMULATIONS FOLLOWING STORAGE

Formulation	Theoretical percentage (%) recovery of SNA-125 compared to recovery at T=0					
	T=0	T = 2 weeks		T = 4 weeks		
		25 °C	40 °C	25 °C	40 °C	
SNA-125 (Low BA)	111.66 (83.22 - 140.10)*	71.48 (68.98 - 73.28)	75.07 (74.61 - 75.46)	81.69 (75.60 - 89.97)	80.62 (77.31 - 83.96)	
SNA-120 (Low BA)	95.09 (93.94 - 96.25)*	98.43 (96.00 - 96.93)	93.86 (91.62 - 95.32)	95.06 (94.76 - 95.25)	94.28 (93.06 - 95.20)	
2.0% Sponsor's Gel	96.05 (95.59 - 96.50)	99.07 (98.92 - 99.40)	99.90 (99.66 - 100.13)	103.54 (98.79 - 101.95)	99.46 (98.28 - 99.73)	
1.0% Sponsor's Gel	98.40 (97.63 - 99.24)	98.97 (98.81 - 99.22)	99.99 (99.75 - 100.28)	99.33 (98.65 - 100.02)	98.31 (98.08 - 98.67)	
0.2% Sponsor's Gel	94.38 (91.05 - 96.50)	92.81 (92.64 - 93.03)	94.92 (93.46 - 97.83)	97.35 (96.94 - 97.99)	97.44 (97.28 - 97.64)	

*n=2

TABLE 5: PEAK PURITY OF SNA-125 IN PROTOTYPE FORMULATIONS FOLLOWING STORAGE

Formulation	Percentage purity (% a/a) of SNA-125 at t=0 and following storage at t=2 and 4 weeks at 25 and 40 °C				
	T=0	T = 2 weeks		T = 4 weeks	
		25 °C	40 °C	25 °C	40 °C
CR042	99.64 (99.62 - 99.66)	99.69 (99.61 - 99.73)	99.57 (99.56 - 99.58)	99.65 (99.63 - 99.66)	99.41 (99.33 - 99.46)
CR043	99.64 (99.62 - 99.66)	99.65 (99.51 - 99.74)	99.58 (99.45 - 99.64)	99.65 (99.64 - 99.66)	99.58 (99.55 - 99.60)
CR044	99.65 (99.65 - 99.66)	99.72 (99.71 - 99.73)	99.66 (99.64 - 99.68)	99.66 (99.64 - 99.67)	99.53 (99.50 - 99.55)
CR045	99.65 (99.64 - 99.66)	99.54 (99.17 - 99.72)	99.65 (99.63 - 99.66)	99.66 (99.64 - 99.70)	99.61 (99.60 - 99.62)
CR047	99.68 (99.68 - 99.69)	99.74 (99.72 - 99.75)	99.64 (99.63 - 99.65)	99.66 (99.66 - 99.66)	99.59 (99.59 - 99.60)
CR052	99.66 (99.64 - 99.68)	99.74 (99.73 - 99.75)	99.69 (99.68 - 99.70)	99.65 (99.62 - 99.66)	99.62 (99.60 - 99.63)
CR053	99.63 (99.62 - 99.64)	99.68 (99.67 - 99.69)	99.60 (99.60 - 99.61)	99.65 (99.64 - 99.66)	99.47 (99.43 - 99.51)
CR054	99.52 (99.50 - 99.52)	99.56 (99.53 - 99.58)	99.55 (99.54 - 99.57)	99.37 (99.31 - 99.41)	99.58 (99.57 - 99.58)
CR055	99.67 (99.64 - 99.68)	99.60 (99.28 - 99.76)	99.68 (99.63 - 99.71)	99.57 (99.56 - 99.58)	99.55 (99.53 - 99.56)
CR058	99.49 (99.44 - 99.53)	99.62 (99.60 - 99.64)*	99.57 (99.57 - 99.57)	99.37 (99.32 - 99.41)	99.59 (99.59 - 99.60)
CR060	99.74 (99.73 - 99.75)	99.75 (99.71 - 99.79)	99.52 (99.51 - 99.54)	99.54 (99.53 - 99.55)	99.44 (99.40 - 99.46)
CR061	99.68 (99.65 - 99.74)	99.78 (99.77 - 99.79)	99.52 (99.31 - 99.62)	99.56 (99.49 - 99.60)	99.65 (99.64 - 99.66)
CR062	99.53 (99.51 - 99.54)	99.54 (99.46 - 99.59)	99.52 (99.51 - 99.54)	99.38 (99.35 - 99.42)*	99.54 (99.53 - 99.54)
SNA-125 (Low BA)	99.65 (99.64 - 99.65)	99.67 (99.61 - 99.72)	99.67 (99.64 - 99.69)	99.53 (99.50 - 99.57)	99.45 (99.42 - 99.47)
SNA-120 (Low BA)	99.69 (99.43 - 99.64)	99.80 (99.55 - 100.00)	99.78 (99.59 - 99.89)	99.57 (99.56 - 99.60)	99.50 (99.49 - 99.52)
2.0% Sponsor's Gel	99.66 (99.60 - 99.70)	99.58 (99.58 - 99.59)	99.59 (99.58 - 99.60)	99.51 (99.50 - 99.51)	99.50 (99.49 - 99.51)
1.0% Sponsor's Gel	99.55 (99.53 - 99.56)	99.62 (99.61 - 99.65)	99.59 (99.58 - 99.60)	99.52 (99.50 - 99.55)	99.47 (99.44 - 99.50)
0.2% Sponsor's Gel	99.12 (99.02 - 99.22)	99.59 (99.58 - 99.59)*	99.59 (99.58 - 99.60)*	99.52 (99.52 - 99.53)	99.54 (99.52 - 99.57)

*n=2

TABLE 6: APPARENT PH VALUES OF PLACEBO AND SNA-125 FORMULATIONS FOLLOWING STORAGE

Formulation	Apparent pH of developed formulations											
	T=0		T=2 weeks				T=4 weeks					
			25 °C		40 °C		25 °C		40 °C			
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo		
CR042	5.96	6.12	6.03	5.93	6.06	6.30	5.86	6.05	5.95	6.18		
CR043	5.24	6.51	6.34	6.42	6.23	6.45	6.22	6.64	6.37	6.49		
CR044	6.01	6.12	6.05	6.07	6.10	6.22	5.58	6.20	5.91	6.17		
CR045	5.79	6.11	5.85	5.99	5.82	6.53	5.91	6.09	6.05	6.21		
CR047	5.79	5.88	5.92	5.87	6.01	6.22	5.71	5.86	5.87	5.81		
CR052	6.06	6.20	6.06	6.09	5.93	6.19	5.99	6.06	6.21	6.12		
CR053	5.92	6.14	5.93	6.02	6.07	6.28	5.94	6.12	5.87	6.11		
CR054	5.29	5.36	5.53	5.27	5.50	5.94	5.49	5.17	5.52	5.49		
CR055	6.44	6.41	6.50	6.58	6.13	6.44	6.29	6.34	6.11	6.29		
CR058	5.65	5.59	5.64	5.60	5.74	5.56	5.63	5.44	5.52	5.34		
CR060	4.28	4.20	4.25	4.22	4.24	4.15	4.18	4.16	4.22	4.17		
CR061	5.04	5.05	5.07	5.03	5.04	5.14	4.94	5.05	4.78	4.83		
CR062	5.53	5.53	5.56	5.64	5.60	5.85	5.54	5.45	5.61	5.57		
SNA-125 (Low BA)	6.00	5.41	6.24	5.14	6.27	5.62	6.04	4.83	5.83	4.53		
SNA-120 (Low BA)	6.28	5.54	6.07	6.67	6.87	4.71	4.10	5.36	4.11	4.89		
2.0% Sponsor's Gel	7.58	7.68	7.50	7.67	7.62	7.67	7.72	7.73	7.56	7.71		
1.0% Sponsor's Gel	7.63		7.69		7.73		7.78		7.70			
0.2% Sponsor's Gel	7.79		7.78		7.84		7.62		7.73			

TABLE 7: MICROSCOPIC OBSERVATIONS OF PLACEBO AND SNA-125 FORMULATIONS FOLLOWING STORAGE

Formulation	Microscopic observations of developed formulations															
	T=0				T=2 weeks											
					25 °C						40 °C					
	Active		Placebo		Active		Placebo		Active				Placebo			
	Polarised	Non-Polarised	Polarised	Non-Polarised	Polarised	Non-Polarised	Polarised	Non-Polarised	Polarised	Non-Polarised	Polarised	Non-Polarised	Polarised	Non-Polarised		
CR042	x	x	x	x	x	x	x	x	x	x						
CR043	x	x	x	x	x	x	x	x	x	x						
CR044	x	x	x	x	x	x	x	x	x	x						
CR045	x	x	x	x	x	x	x	x	x	x						
CR047	x	x	x	x	x	x	x	x	x	x						
CR052	x	x	x	x	x	x	x	x	x	x						
CR053	x	x	x	x	x	x	x	x	x	x						
CR054	x	x	x	x	x	x	x	x	x	x						
CR055	x	x	x	x	x	x	x	x	x	x						
CR058	x	x	x	x	x	x	x	x	x	x						
CR060	x	x	x	x	x	x	x	x	x	x						
CR061	x	x	x	x	x	x	x	x	x	x						
CR062	x	x	x	x	x	x	x	x	x	x						
SNA-125 (Low BA)	x	x	x	x	x	x	x	x	x	x						
SNA-120 (Low BA)	x	x	x	x	x	x	x	x	x	x						
2.0% Sponsor's Gel	x	x	x	x	x	x	x	x	x	x						
1.0% Sponsor's Gel	x	x	x	x	x	x	x	x	x	x						
0.2% Sponsor's Gel	x	x	x	x	x	x	x	x	x	x						

x = no SNA-125 crystals present.

TABLE 7 (CONTINUED): MICROSCOPIC OBSERVATIONS OF PLACEBO AND SNA-125 FORMULATIONS FOLLOWING STORAGE

Formulation	Microscopic observations of developed formulations													
	T=0				T=4 weeks									
					25 °C						40 °C			
	Active		Placebo		Active		Placebo		Active		Placebo			
	Polarised	Non-Polarised	Polarised	Non-polarised	Polarised	Non-polarised	Polarised	Non-polarised	Polarised	Non-polarised	Polarised	Non-polarised		
CR042	x	x	x	x	x	x	x	x	x	x	x	x		
CR043	x	x	x	x	x	x	x	x	x	x	x	x		
CR044	x	x	x	x	x	x	x	x	x	x	x	x		
CR045	x	x	x	x	x	x	x	x	x	x	x	x		
CR047	x	x	x	x	x	x	x	x	x	x	x	x		
CR052	x	x	x	x	x	x	x	x	x	x	x	x		
CR053	x	x	x	x	x	x	x	x	x	x	x	x		
CR054	x	x	x	x	x	x	x	x	x	x	x	x		
CR055	x	x	x	x	x	x	x	x	x	x	x	x		
CR058	x	x	x	x	x	x	x	x	x	x	x	x		
CR060	x	x	x	x	x	x	x	x	x	x	x	x		
CR061	x	x	x	x	x	x	x	x	x	x	x	x		
CR062	x	x	x	x	x	x	x	x	x	x	x	x		
SNA-125 (Low BA)	x	x	x	x	x	x	x	x	x	x	x	x		
SNA-120 (Low BA)	x	x	x	x	x	x	x	x	x	x	x	x		
2.0% Sponsor's Gel	x	x	x		x	x	x		x	x	x			
1.0% Sponsor's Gel	x	x		x		x		x		x		x		
0.2% Sponsor's Gel	x	x			x	x			x	x				

x = no SNA-125 crystals present.

TABLE 8: MACROSCOPIC APPEARANCE OF PLACEBO AND SNA-125 FORMULATIONS FOLLOWING STORAGE

Formulation	Macroscopic appearance of developed formulations									
	T=0		T=2 weeks				T=4 weeks			
			25 °C		40 °C		25 °C		40 °C	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
CR042	Opaque, off white, smooth application, high viscosity	Opaque, off white, smooth application, high viscosity	As T=0				As T=0			
CR043	Opaque, off white, smooth application, high viscosity	Opaque, off white, smooth application, high viscosity								
CR044	Opaque, off white, smooth	Opaque, off white, smooth								

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	application , high viscosity										
CR045	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity									
CR047	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity								
CR052	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity								

CR053	Opaque, off white, smooth application, high viscosity	Opaque, off white, smooth application, high viscosity			
CR054	Opaque, off white, smooth application, high viscosity	Opaque, off white, smooth application, high viscosity			
CR055	Opaque, off white, smooth application, high viscosity	Opaque, off white, smooth application, high viscosity			
CR058	Opaque, off white, smooth	Opaque, off white, smooth			

	application , high viscosity										
CR060	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity									
CR061	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity								
CR062	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity								

SNA-125 (Low BA)	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity			
SNA-120 (Low BA)	Opaque, off white, smooth application , high viscosity	Opaque, off white, smooth application , high viscosity			
2.0 % Sponsor's Gel	Clear, colourless, smooth application , medium viscosity	Clear, colourless, smooth application , medium viscosity			
10 % Sponsor's Gel	Clear, colourless, smooth				

	0.2 % Sponsor's Gel	Clear, colourless, smooth application, medium viscosity	application, medium viscosity	

Maximum Feasible Drug Concentration

[000125] The maximal feasible concentration of the SNA-125 that can be incorporated into the 10 formulations selected for *ex vivo* permeation and penetration experiments (described in detail below) was assessed. Maximal feasible concentration was assessed by drug solubility limit testing of SNA-125 in the formulation solvent system. The saturated solubility of SNA-125 in these formulations is detailed in Table 9 (with the data presented as the mean with the range in brackets (n=3) unless otherwise stated).

TABLE 9: SATURATED SOLUBILITY (% W/W) OF SNA-125 FORMULATIONS

Formulation	Saturated solubility (% w/w)
CR042	> 20.00 (visual observation)
CR043	> 20.00 (visual observation)
CR045	> 20.00 (visual observation)
CR047	> 20.00 (visual observation)
CR053	> 20.00 (visual observation)
CR054	> 20.00 (visual observation)
CR058	> 20.00 (visual observation)
CR061	> 20.00 (visual observation)
CR062	> 20.00 (visual observation)
SNA-125 (Low BA)	16.72 (16.42 - 16.99)

[000126] While the target preferred maximum feasible dose is 5% (based on a clinical concentration of 2% w/w SNA-125), the data in Table 9 highlights that all the cream formulations had a SNA-125 solubility of >20% w/w (therefore 4 times the target preferred maximum feasible dose). Further, the SNA-125 ointment formulation (low BA) had a saturated solubility of 16.72%, which is still significantly higher than the preferred maximum feasible dose.

[000127] In some embodiments, SNA-125 cream formulations have a maximum feasible concentration of less than 20% (w/w). In several embodiments, SNA-125 cream formulations have a maximum feasible concentration of about 10% to about 15% (w/w). In several embodiments, SNA-125 cream formulations have a maximum feasible concentration of about 5% to about 10% (w/w). In several embodiments, SNA-125 cream formulations have a maximum feasible concentration of less than 5%. In some embodiments, the CR062

and CR054 formulations have a maximum feasible concentration of less than 20% (w/w). Table 10 depicts the composition of manufactured formulations for evaluation of the maximum feasible concentration of CR054 and CR062. Table 11 depicts the characterization of the manufactured formulations for evaluation of the maximum feasible concentration of CR054 and CR062.

Ex Vivo Skin Permeation and Penetration Testing

[000128] The ten prototype formulations depicted in Table 12 were selected for further analysis by *ex vivo* permeation and penetration testing. *Ex vivo* skin penetration and permeation studies were performed with the MedFlux-HT continuous flow system as outlined below.

TABLE 10: COMPOSITION OF MANUFACTURED FORMULATIONS FOR EVALUATION OF THE MAXIMUM FEASIBLE CONCENTRATION OF CR054 AND CR062.

Phase	Excipient Name	Composition of formulation (% w/w)										
		CR054								CR062		
		Original 2%	10% Option 1	8% Option 1	8% Option 2	8% Option 3	6% Option 1	5% Option 1	4% Option 1	Original 2%	8% Option 1	6% Option 1
Aqueous Phase	SNA-125	2.00	10.00	8.00	8.00	8.00	6.00	5.00	4.00	2.00	8.00	6.00
	Transcutol P	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
	SRPEG 400	15.95	15.95	15.95	12.95	14.60	15.95	15.95	15.95	20.97	20.97	20.97
	Water	30.00	22.00	24.00	27.00	27.63	28.00	27.00	29.00	40.00	34.00	36.00
	Benzyl Alcohol	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	BHT	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.03	0.03	0.03
	Subtotal	65.00	65.00	65.00	65.00	67.37	65.00	65.00	65.00	80.00	80.00	80.00
Oil Phase	IPM	-	-	-	-	-	-	-	-	8.34	8.34	8.34
	Cetostearyl alcohol	6.66	6.66	6.66	6.66	6.13	6.66	6.66	6.66	3.33	3.33	3.33
	Liquid Paraffin	16.68	16.68	16.68	16.68	15.36	16.68	16.68	16.68	-	-	
	Stearic Acid	6.66	6.66	6.66	6.66	6.13	6.66	6.66	6.66	3.33	3.33	3.33
	Subtotal	30.00	30.00	30.00	30.00	27.63	30.00	30.00	30.00	15.00	15.00	15.00
Surfactants	Brij S2	1.31	1.31	1.31	1.31	1.31	1.31	1.31	1.31	1.04	1.04	1.04
	Brij S20	3.69	3.69	3.69	3.69	3.69	3.69	3.69	3.69	3.96	3.96	3.96
	Subtotal	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Total		100.00	100.00	100.00	100.00	100.00	100.00	100.00	100	100.00	100.00	100.00
Comments		N/A	P/S	Grainy and lumpy	Grainy and lumpy	Grainy and lumpy	Grainy and lumpy	Grainy and lumpy	MFC	N/A	Grainy and lumpy	MFC

P/S = Phase separated.

Option 1: Remove % difference from the water.
Option 2: Remove % difference from water and SRPEG 400
Option 3: Remove % difference from SRPEG 400, water, cetostearyl alcohol, liquid paraffin and stearic acid.

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TABLE 11: CHARACTERIZATION OF THE MANUFACTURED FORMULATIONS FOR EVALUATION OF THE MAXIMUM FEASIBLE CONCENTRATION OF CR054 AND CR062

Formulation	Physical stability*	Macroscopic Appearance	Microscopic Observation		Comment
			Polarised	Non-polarised	
CR054 10% Active (Option 1)	Separation observed	n/a	n/a	n/a	Failed
CR054 8% Active (Option 1)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR054 8% Active (Option 2)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR054 8% Active (Option 3)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR054 6% Active (Option 1)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR054 5% Active (Option 1)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR054 4% Active (Option 1)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation
CR062 8% Active (Option 1)	No separation	Grainy and lumpy formulation.	No API crystals	Irregular droplets, coalescence observed.	Failed
CR062 6% Active (Option 1)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation
CR054 2% Active (back-up formulation)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation
CR062 2% Active (back-up formulation)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation
CR054 2% Active (Re-manufactured)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation
CR062 2% Active (Re-manufactured)	No separation	Opaque, white, smooth application, not stringy.	No API crystals	Small and medium sized droplets evenly dispersed.	Acceptable formulation

*Physical stability was performed *via* centrifugation at 16,060 g-force for 20 mins (in 2 min intervals).

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TABLE 12: COMPOSITION (% W/W) OF SNA-125 FORMULATIONS ASSESSED IN THE *EX VIVO* PERMEATION AND PENETRATION EXPERIMENTS

Phase	Excipient Name	Theoretical Composition (% w/w) of the active formulations assessed in the *ex vivo* permeation experiments									
		CR042	CR043	CR045	CR047	CR053	CR054	CR058	CR061	CR062	SNA-125 Low BA
Aqueous Phase	SNA-125	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Transcutol P	-	-	15.00	-	-	15.00	15.00	-	15.00	-
	SRPEG 400	45.97	45.97	30.95	30.97	46.97	15.95	20.97	15.99	20.97	-
	Water	30.00	30.00	30.00	30.00	30.00	30.00	40.00	50.00	40.00	-
	Phenoxyethanol	-	-	-	-	1.00	-	-	-	-	-
	Propylene Glycol	-	-	-	15.00	-	-	-	-	-	20.00
	Benzyl Alcohol	2.00	2.00	2.00	2.00	-	2.00	2.00	2.00	2.00	2.00
	BHT	0.03	0.03	0.05	0.03	0.03	0.05	0.03	0.01	0.03	-
	Ethanol	-	-	-	-	-	-	-	10.00	-	-
	Subtotal	80.00	80.00	80.00	80.00	80.00	65.00	80.00	80.00	80.00	24.00
Oil Phase	IPM	-	-	-	-	-	-	7.34	-	8.34	-
	Cetostearyl alcohol	3.33	3.33	3.33	3.33	3.33	6.66	3.33	3.33	3.33	-
	GTCC	8.34	8.34	-	8.34	8.34	-	-	8.34	-	-
	Liquid Paraffin	-	-	8.34	-	-	16.68	-	-	-	-
	White soft paraffin	-	-	-	-	-	-	-	-	-	61.34
	Dimethicone 350	-	-	-	-	-	-	1.00	-	-	-
	Beeswax	-	-	-	-	-	-	-	-	-	8.37
	Stearyl Alcohol	-	-	-	-	-	-	-	-	-	3.14
	Cholesterol	-	-	-	-	-	-	-	-	-	3.14
	Stearic Acid	3.33	3.33	3.33	3.33	3.33	6.66	3.33	3.33	3.33	-
	Subtotal	15.00	15.00	15.00	15.00	15.00	30.00	15.00	15.00	15.00	76.00
Surfactants	Brij S2	1.44	-	1.31	1.44	1.44	1.31	1.25	1.44	1.04	-
	Brij S20	3.56	-	3.69	3.56	3.56	3.69	3.75	3.56	3.96	-
	Span 60	-	0.85	-	-	-	-	-	-	-	-
	Tween 60	-	4.15	-	-	-	-	-	-	-	-
	Subtotal	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	0.00
Total		100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

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Study Design

[000129] Human skin from cosmetic reduction surgery (dermatomed to 500 ± 50 μm thickness) from one skin donor was mounted between the donor and receptor compartment of the MedFlux-HT diffusion cell (with an exposed dosing surface area of ~1 cm^2 for each replicate). The skin was dosed with about 10 mg of each of the prototype formulations described in Table 12 to achieve a dose of ~10 mg/cm^2. A flow-through cell was also set up (cell contains no skin or formulation), and skin was also mounted in a blank cell to which no formulation was applied. The pump of the MedFluxHT™ system was adjusted to maintain a continuous receiver fluid flow-rate of approximately 10 μL/min (600 μL/hr) directly under the skin. Receiver fluid was automatically collected into a 96-well plate at 2 hour intervals over the course of 24 hours and analyzed using a single HPLC-FLD analytical method.

[000130] Following the 24 hour period, the residual formulation was removed from the surface of the skin and then the skin surface was taped striped up to 5 times to remove the skin surface layers (*Stratum Corneum*). The epidermis was then heat-separated from the dermis by placing the skin into an incubator at 60°C for 2 min, followed by manual separation using curved forceps. The amount of drug delivered to epidermis and dermis was then determined by HPLC-FLD.

[000131] Prior to performing the full scale study of the ten formulations, a small scale study was performed comparing a representative prototype cream formulation (CR045) and the SNA-125 gel formulation. As shown in Figure 1, both formulations achieved similar epidermal and dermal levels of SNA-125 (~1%).

Results

[000132] The mean cumulative amount (ng/cm^2) of SNA-125 that permeated through the 1 cm^2 skin dosing area (i.e. drug detected in receiver fluid) following application of the ten formulations was evaluated (Figure 2). Based on cumulative amount at 24 hours, there was no significant difference between any of the tested formulations ($p < 0.05$, Tukey-Kramer). The receiver fluid employed in these experiments was PBS with 0.01% Brij.

[000133] The effect of the different prototype formulations on drug flux across the skin was next evaluated. As with the last experiment, the receiver fluid employed was PBS

with 0.01% Brij. Figure 3 depicts the mean flux (ng/cm^2/hr) of SNA-125 permeated through the 1 cm^2 skin dosing area (i.e. drug detected in receiver fluid) following application of each of the ten prototype formulations. A difference in flux profiles between the low-BA ointment formulation and the cream formulation was observed. While the low-BA ointment formulation exhibited a maximum flux at about 4 hours, the cream formulations tended to have bi-phasic flux patterns with maxima near 4 hours and after about 18 hours.

[000134] A wide range of epidermal and dermal levels of SNA-125 were observed across prototype formulations. Figure 4 depicts the mean amount of SNA-125 (ng) recovered from epidermis and dermis following application of the ten prototype formulations, while Figure 5 depicts the mean percent of applied dose of SNA-125 recovered from epidermis and dermis (ng) following application of the ten formulations. CR045 showed comparable epidermal (~3%) & dermal levels (~1%) as observed in the small-scale study described above. Creams CR061 and CR062 delivered the greatest amount of SNA-125 to both epidermis and dermis based both on amount (ng) and percent applied dose (%). These two creams showed statistically significant increases in the active delivered to the both epidermis and dermis with respect to creams CR042, CR043, CR045, and CR053 as well as the low-BA ointment formulation. CR054 was found to be statistically similar to CR062 (epidermis) and CR061 (dermis).

Ranking of Prototype Formulations Based Upon the Short-Term Stability Assessment

[000135] Based upon the characteristics assessed in the short-term stability experiments and *ex vivo* permeation and penetration experiments described above, the prototype formulations were ranked according to the following five sets of criteria.

First Criterion: Recovery after 4 Weeks (25°C and 40°C)

[000136] This criterion is based upon change in percentage recovery from initial testing. Formulations with a SNA-125 percentage recovery of 95-105% after 4 weeks storage were scored 1, formulations with a percentage recovery of 90-95% or 105-110% SNA-125 were scored 2, and formulations with a recovery <90 or >110 % SNA-125 were scored 3.

Second Criterion: Purity after 4 Weeks (25°C and 40°C)

[000137] This criterion is based upon change in percentage purity from initial testing. All formulations had a percentage purity of 99%, therefore all formulations were scored 1.

Third Criterion: Physical Stability after 4 Weeks (25°C and 40°C)

[000138] This criterion is based upon the apparent pH and the microscopic and macroscopic observations of the formulations after 4 weeks storage. The cream and ointment formulations all had an initial pH between 5.04 and 6.51, with the exception of CR060 which had an apparent pH of 4.28 and 4.20 (active and placebo, respectively). No change in macroscopic appearance was noted from initial testing, with all cream and ointment formulations being opaque, off white, smooth application and high in visual viscosity. For all the formulations no SNA-125 crystals were observed under the microscope at any of the conditions or time points. During manufacture for stability it was noted that CR054 had a slightly oily feel in a larger batch size due to the higher oil phase composition in the formulation; however, further development of the formulation could be performed if necessary.

Fourth Criterion: Ease of Manufacturing Formulation

Cream Formulation

[000139] All cream formulations assessed had 9-11 excipients (excluding SNA-125) in the composition. The formulations containing Transcutol P (CR045, CR054, CR058 and CR062) dissolve the BHT quicker as compared to dissolving the antioxidant in SRPEG 400. Dimethicone is incorporated in the oil phase of the formulation CR058, and the addition of the dimethicone during homogenization of the formulation is an additional step in the formulation manufacture that is not required during the manufacture of the remaining formulations.

Ointment Formulation

[000140] The SNA-125 ointment formulation (low BA) has fewer excipients (6 excipients) as compared to the prototype cream formulations; however, the ointments take longer on average to stir to cool. In addition, small particles of cholesterol were initially

observed in the ointment formulation due to the high melting point of the excipients. During manufacture of the formulation on a 50 g scale for stability testing, the small particles of cholesterol sat at the bottom of the vessel; while these particles were later solubilized by the benzyl alcohol in the liquid phase, this may be an issue with a larger batch size.

Fifth Criterion: Penetration into the Epidermis and Dermis

[000141] This criterion is based upon the delivery of SNA-125 into the epidermal/dermal layers, measured as amount (ng) recovered from the epidermis/dermis after 24 hours following application of the formulation. The epidermal and dermal delivery has been ranked via absolute values. The statistical analyses depicted in Figures 4B-4C and Figures 5B-5C indicate which formulations are statistically similar to each other. Rankings of numbers which are not connected by the same number are significantly different.

Conclusions

[000142] A decision matrix summary of the above criteria is depicted in Table 13. The formulations were ranked in order to identify suitable candidates for scale up and process development.

[000143] Using the ranking employed for each formulation, the formulations can be ranked from most to least favorable as follows: (1) CR061 and CR062; (3) CR054; (4) CR047 and SNA-125 ointment (Low BA); (6) CR053 and CR058; (8) CR045; (9) CR042; (10) CR043. Table 14 depicts the top four top 4 SNA-125 formulations under consideration when incorporating an aesthetic preference (e.g., ethanol content) criterion.

TABLE 13: SNA-125 PROTOTYPE FORMULATIONS DECISION MATRIX SUMMARY

Formulations	Criteria Assessed						
	Percentage Recovery (%)	Percentage Purity (% a/a)	Physical stability	Ease of manufacture	Amount of excipients in composition	Penetration into Epidermal layer	Penetration into Dermal layer
CR042	1	1	1	1	9	9	9
CR043	1	1	1	1	9	10	10
CR045	2	1	1	1	10	6	7
CR047	2	1	1	1	10	7	4
CR053	1	1	1	1	9	8	6
CR054	3	1	2	1	10	3	3
CR058	3	1	1	2	11	4	5
CR061	1	1	1	1	10	1	2
CR062	1	1	1	1	10	2	1
SNA-125 (Low BA)	3	1	1	3	6	5	8

TABLE 14: TOP 4 PROTOTYPE SNA-125 FORMULATIONS FROM SKIN PERMEATION STUDY

Formulation	Aesthetic Preference	Skin Permeation Results	Epidermis (% applied dose)	Dermis (% applied dose)	Formulation Notes
CR061	2nd tier	Top 2	22.63%	2.73%	10% ethanol, 50% water
CR062	1st tier	Top 2	18.73%	4.00%	15% Transcutol P, 40% water (almost identical to CR058 except for 1% Dimethicone 350)
CR054	1st tier	3rd	12.10%	1.82%	15% Transcutol P, 30% water, 17% liquid paraffin
CR058	1st tier	4th	6.95%	1.54%	15% Transcutol P, 40% water, 1% Dimethicone 350

EXAMPLE 2: ANTIOXIDANT SCREENING STUDY

Introduction

[000144] Based on testing of the chemical stability of SNA-125 in excipients and solvent systems it was determined that SNA-125 may undergo oxidative degradation. A set of antioxidants was selected for incorporation into the solvent system from formulation CR045 to determine the optimal antioxidant/stabilizer combination that would prevent SNA-125 degradation and improve chemical stability.

Antioxidant Preliminary Study

[000145] From the 15 formulations developed for short-term stability testing the formulation CR045 was selected for the antioxidant screening study as a representative formulation with 30% w/w water content in the formulation (adjusted to 37.50% w/w in the solvent system). In addition, the CR045 solvent system could solubilize all the antioxidants selected for investigation (BHA, BHT, propyl gallate, ascorbic acid, ascorbyl palmitate and alpha tocopherol). Table 15 depicts the theoretical composition (% w/w) of the solvent system from formulation CR045, which is adjusted to total 100%.

TABLE 15: THEORETICAL COMPOSITION (% W/W) OF THE SOLVENT SYSTEM FROM FORMULATION CR045

Excipient Name	Theoretical composition (% w/w) of the solvent system
	CR045
Transcutol P	18.75
SR-PEG 400	41.25
Water	37.50
Benzyl Alcohol	2.50
Total	100.00

[000146] A preliminary investigation was then performed to determine the conditions that degrade SNA-125 to a suitable level (5-20% degradation) such that oxidation products observed during long-term storage can be detected. A CR045 solvent system containing 0.5% w/w SNA-125 was prepared and subjected to 6% and 12% hydrogen peroxide (H_2O_2) treatment while heating at 70°C to the increase degradation. The degradation of SNA-125 was investigated at t=0, 6 and 24 hours. Table 16 depicts the percentage recovery of SNA-125 in formulation CR045 after stress with peroxide spiking and high temperature (70°C) at t=0, 6 and 24 hours. The data of Table 16 is presented as the mean with the range in brackets (n=3).

TABLE 16: PERCENTAGE RECOVERY OF SNA-125 IN FORMULATION CR045 AFTER STRESS WITH PEROXIDE SPIKING AND HIGH TEMPERATURE

Formulation	Peroxide Spiking	Percentage (%) Recovery of SNA-125		
		T=0	T=6 h	T=24 h
CR045	Control	100.00 (99.17–100.64)	103.46 (103.44–103.49)	100.53 (100.43–100.63)
	6 % H_2O_2		99.84 (99.38–100.65)	85.98 (85.08–86.71)
	12 % H_2O_2		95.81 (95.35–96.26)	81.81 (81.01–82.63)

[000147] Table 17 depicts the percentage peak purity (% a/a) of SNA-125 in formulation CR045 after stress with peroxide spiking and high temperature (70°C) at t=0, 6 and 24 hours (data is presented as n=1).

TABLE 17: PERCENTAGE PEAK PURITY OF SNA-125 IN FORMULATION CR045 AFTER STRESS WITH PEROXIDE SPIKING AND HIGH TEMPERATURE

Formulation	Peroxide Spiking	Percentage peak purity (% a/a) Recovery of SNA-125		
		T=0	T=6 h	T=24 h
CR045	Control	99.52	99.45	99.40
	6 % H_2O_2		97.45	89.27
	12 % H_2O_2		96.36	87.98

[000148] The H_2O_2 spiking resulted in SNA-125 degrading to <90% after t=24 hours with both 6% and 12% H_2O_2. The stress conditions selected as degrading SNA-125 to a suitable level for determining antioxidant selection were spiking with 6% H_2O_2 at 70°C;

after 24 hours, these conditions yield a SNA-125 percentage recovery of 85.98% and percentage peak purity of 89.27% a/a.

Design of Experiment Antioxidant Screening Study

[000149] Once the stress conditions degrading SNA-125 to a suitable level were identified, a statistical Design of Experiment (DoE) study was performed with the aim of determining the optimal antioxidant combination to prevent SNA-125 degradation and improve drug chemical stability under the stress conditions determined (6% H_2O_2 spiking at 70°C). Table 18 depicts the antioxidants assessed along with their symbols and their corresponding concentrations (% w/w) in the antioxidant screening study.

TABLE 18: ANTIOXIDANTS ASSESSED IN DOE INVESTIGATION

Antioxidant	Concentration (% w/w)
BHA (A)	0.05
BHT (B)	0.05
Propyl gallate (C)	0.05
Ascorbic acid (D)	0.10
Ascorbic palmitate (E)	0.02
Alpha tocopherol (F)	0.002

[000150] A two-level fractional factorial that ensured that main factors and two-factor interactions were not confounded was designed. The factors and their levels are detailed in Table 19.

TABLE 19: ANTIOXIDANT SYSTEMS INVESTIGATED

Antioxidant System Run	Theoretical concentration of antioxidants (% w/w)					
	BHA	BHT	Propyl gallate	Ascorbic acid	Ascorbyl palmitate	α-Tocopherol
1	-	-	0.05	0.10	-	0.002
2	0.05	0.05	0.05	0.10	-	0.002
3	0.05	-	0.05	0.10	0.02	0.002
4	-	-	0.05	-	0.02	0.002
5	0.05	-	-	-	-	-
6	-	0.05	-	0.10	0.02	-
7	-	0.05	0.05	-	-	0.002
8	-	-	-	0.10	-	-
9	-	-	-	0.10	0.02	0.002
10	0.05	0.05	0.05	0.10	0.02	-
11	0.05	0.05	0.05	-	0.02	0.002
12	0.05	-	0.05	-	-	-
13	0.05	0.05	-	-	-	-
14	-	-	0.05	0.10	0.02	-
15	-	-	-	-	0.02	-
16	0.05	-	-	0.10	-	-
17	0.05	-	-	-	0.02	-
18	-	-	0.05	-	-	-
19	0.05	0.05	-	0.10	0.02	0.002
20	-	0.05	0.05	0.10	-	-
21	-	0.05	-	0.10	-	0.002
22	-	0.05	-	-	-	-
23	0.05	-	-	-	-	0.002
24	-	-	-	-	-	0.002
25	-	0.05	-	-	0.02	0.002
26	-	0.05	0.05	-	0.02	-
27	0.05	0.05	0.05	0.10	0.02	0.002
28	-	0.05	0.05	0.10	0.02	0.002

(-) not included

[000151] The antioxidants were assessed in the CR045 solvent system containing 0.5% w/w SNA-125 at t=0, 24 hours, and 5 days. The recovery (% w/w) of SNA-125 (with the inclusion of antioxidant systems Run 1-28) was investigated after the being stored in the stress conditions determined in the preliminary study above (6% H_2O_2 spiking at 70°C). Table 20 depicts the percentage recovery of SNA-125 in the CR045 solvent system (0.5%

w/w SNA-125) following t=0, 24 hours and 5 days storage at 70°C with 6% H_2O_2 spiking. Data is presented as the mean with the range in brackets (n=3). Table 21 depicts percentage peak purity (% a/a) of SNA-125 in the CR045 solvent system (0.5% w/w SNA-125) at t=0, 24 hours and 5 days following storage at 70°C with 6% H_2O_2 spiking. Data presented as the mean with the range in brackets (n=3).

TABLE 20: SNA-125 PERCENTAGE RECOVERY IN ANTIOXIDANT SYSTEMS

Antioxidant System Run	Percentage (%) recovery of SNA-125 in the antioxidant systems.		
	T=0	T= 24 h	T=5 days
1	105.00 (104.66 - 105.42)	102.39 (101.58 - 102.92)	95.14 (94.82 - 95.59)
2	101.64 (101.18 - 102.44)	98.67 (98.12 - 99.06)	98.42 (98.05 - 98.88)
3	99.37 (99.30 - 99.44)	93.82 (93.62 - 94.08)	94.98 (94.53 - 95.62)
4	98.66 (98.46 - 98.83)	99.39 (98.71 - 99.78)	93.87 (92.84 - 94.15)
5	103.85 (103.55 - 104.35)	104.66 (104.48 - 104.78)	105.15 (104.91 - 105.34)
6	101.43 (101.01 - 102.20)	95.86 (95.76 - 95.92)	91.38 (91.07 - 91.54)
7	100.79 (100.59 - 101.05)	105.22 (104.99 - 105.41)	99.25 (97.76 - 100.58)
8	102.18 (101.91 - 102.53)	88.60 (87.85 - 89.03)	45.05 (44.67 - 45.67)
9	99.62 (99.25 - 99.96)	89.26 (89.16 - 89.44)	53.81 (53.69 - 54.05)
10	99.84 (99.52 - 100.18)	94.53 (94.35 - 94.64)	87.35 (86.79 - 87.73)
11	100.65 (100.07 - 101.42)	98.79 (97.98 - 99.39)	93.46 (93.31 - 93.69)
12	100.17 (99.68 - 100.56)	101.90 (101.46 - 102.60)	99.00 (98.36 - 99.79)
13	102.44 (101.11 - 103.99)	100.35 (100.01 - 100.54)	101.41 (101.13 - 101.66)
14	99.02 (98.39 - 99.58)	90.85 (90.22 - 91.47)	84.54 (84.40 - 84.70)
15	101.77 (100.78 - 103.54)	92.39 (92.22 - 92.65)	38.98 (38.88 - 39.17)
16	100.78 (99.47 - 102.32)	99.62 (99.58 - 99.66)	94.76 (94.04 - 95.45)
17	101.23 (100.14 - 103.15)	99.83 (99.64 - 100.18)	96.76 (96.61 - 97.05)
18	101.14 (100.98 - 101.38)	103.45 (102.94 - 104.46)	98.19 (97.57 - 99.31)
19	98.85 (98.58 - 99.12)	96.16 (95.42 - 96.62)	93.01 (92.65 - 93.37)
20	100.75 (100.38 - 101.16)	100.90 (100.57 - 101.09)	89.95 (88.91 - 90.48)
21	100.28 (99.91 - 100.74)	91.96 (91.70 - 92.32)	52.29 (52.27 - 52.30)
22	102.87 (102.30 - 103.44)	95.97 (95.71 - 96.11)	33.00 (32.95 - 33.05)
23	101.64 (101.30 - 101.82)	103.26 (102.96 - 103.76)	100.13 (98.87 - 100.94)
24	99.65 (99.39 - 100.07)	93.20 (92.87 - 93.43)	40.29 (40.11 - 40.59)
25	101.17 (100.75 - 101.63)	94.82 (94.66 - 95.06)	41.09 (40.83 - 41.34)
26	100.82 (100.22 - 101.50)	102.65 (102.49 - 102.94)	96.98 (96.23 - 97.83)
27	98.72 (97.89 - 99.37)	97.67 (97.49 - 97.84)	88.92 (87.84 - 89.52)
28	102.66 (101.82 - 103.54)	103.02 (102.64 - 103.41)	94.83 (94.59 - 95.12)
Control (without H_2O_2)	101.03 (100.59 - 101.38)	101.06 (100.76 - 101.53)	99.86 (99.42 - 100.49)
Control (with H_2O_2)		91.63 (91.15 - 92.01)	38.85 (38.72 - 38.93)

TABLE 21: SNA-125 PERCENTAGE PEAK PURITY IN ANTIOXIDANT SYSTEMS

Antioxidant System Run	Percentage peak purity (% a/a) of SNA-125 in the antioxidant systems.		
	T=0	T= 24 h	T= 5 days
1	99.01 (98.54 - 99.25)	94.41 (94.39 - 94.42)	91.63 (91.54 - 91.68)
2	99.26 (99.25 - 99.27)	94.89 (94.87 - 94.92)	94.33 (94.14 - 94.51)
3	99.23 (99.22 - 99.23)	93.91 (93.86 - 93.97)	92.39 (92.32 - 92.43)
4	99.31 (99.29 - 99.33)	99.27 (99.25 - 99.30)	95.46 (95.32 - 95.56)
5	99.25 (99.21 - 99.28)	99.20 (99.18 - 99.22)	98.18 (98.06 - 98.27)
6	98.67 (98.38 - 99.23)	93.31 (93.27 - 93.37)	91.82 (91.75 - 91.90)
7	99.32 (99.23 - 99.37)	99.44 (99.42 - 99.46)	98.13 (97.93 - 98.34)
8	99.22 (99.21 - 99.24)	87.79 (87.47 - 88.03)	52.16 (52.11 - 52.22)
9	99.22 (99.21 - 99.23)	92.10 (92.08 - 92.12)	61.94 (61.92 - 61.95)
10	99.12 (99.08 - 99.15)	94.82 (94.81 - 94.84)	91.57 (91.55 - 91.59)
11	99.35 (99.34 - 99.36)	99.31 (99.30 - 99.32)	96.73 (96.59 - 96.83)
12	99.37 (99.36 - 99.40)	99.44 (99.44 - 99.45)	98.00 (97.95 - 98.07)
13	99.37 (99.36 - 99.39)	99.37 (99.36 - 99.38)	98.31 (98.22 - 98.38)
14	99.18 (99.17 - 99.19)	93.24 (93.21 - 93.27)	87.32 (87.18 - 87.41)
15	99.29 (99.28 - 99.29)	94.14 (94.13 - 94.15)	47.18 (47.12 - 47.28)
16	99.17 (99.14 - 99.23)	97.61 (97.57 - 97.63)	94.23 (94.16 - 94.27)
17	99.34 (99.34 - 99.34)	99.20 (99.18 - 99.23)	97.04 (96.74 - 97.33)
18	99.33 (99.27 - 99.37)	99.21 (99.14 - 99.28)	96.87 (96.84 - 96.90)
19	99.31 (99.28 - 99.36)	99.05 (99.01 - 99.08)	96.55 (96.42 - 96.82)
20	99.19 (99.12 - 99.25)	94.58 (94.53 - 94.65)	91.55 (91.51 - 91.57)
21	99.11 (99.08 - 99.13)	90.66 (90.60 - 90.70)	59.15 (59.07 - 59.25)
22	99.35 (99.33 - 99.36)	93.83 (93.79 - 93.88)	40.35 (40.17 - 40.52)
23	99.35 (99.35 - 99.36)	99.06 (99.02 - 99.13)	98.41 (98.37 - 98.45)
24	99.36 (99.36 - 99.37)	93.79 (93.73 - 93.83)	48.15 (49.11 - 49.18)
25	99.35 (99.35 - 99.37)	94.33 (94.29 - 94.38)	49.78 (49.72 - 49.85)
26	99.30 (99.27 - 99.33)	96.52 (95.87 - 97.77)	98.35 (98.35 - 98.36)*
27	99.17 (99.11 - 99.22)	92.49 (92.11 - 92.77)	93.20 (93.20 - 93.21)*
28	99.19 (99.17 - 99.22)	94.51 (94.43 - 94.56)	93.07 (93.04 - 93.09)
Control (without H_2O_2)	99.36 (99.36 - 99.36)	99.45 (99.40 - 99.47)	98.56 (98.47 - 98.65)
Control (with H_2O_2)		93.10 (93.06 - 93.17)	47.57 (47.47 - 47.73)

*n=2

[000152] The results show that a percentage recovery (%) of SNA-125 of ≥ 99% was observed with Run 5, 7, 12, 13 and 23 after 5 days; all of these systems, with the exception of Run 7, contained 0.5% w/w BHA. The use of propyl gallate as an antioxidant also showed good percentage recovery of SNA-125, with a percentage recovery of 103.45% and 98.19% after t=24 hours and 5 days, respectively, in Run 18 (propyl gallate control).

[000153] From the DoE investigation, it was observed that antioxidants systems with ascorbic acid present displayed the lowest percentage recovery; for example, Run 8 had a percentage recovery of 88.60% after 24 hours, then degraded further to 45.05% after 5 days. Ascorbyl palmitate and alpha tocopherol offered no significant protection against oxidation.

[000154] The peak purity data (Table 20) was consistent with the SNA-125 recoveries observed (Table 21), with decreases in recovery accompanied by a corresponding decrease in peak purity for the majority of samples across the experimental time frame and conditions. Following 24 hour storage at 70°C in 6% H_2O_2, SNA-125 peak purities of between 87.79 and 99.44% a/a were observed for all systems investigated.

[000155] Individual and interaction model graphs generated by DoE software analysis of the data were also prepared to further determine which antioxidants (in combination or used separately) in CR045 increases the percentage (%) recovery of SNA-125 when subjected to the stress conditions of 6% H_2O_2 spiking at 70°C for 24 hours. The individual model graph for BHA (Figure 6) indicates that having BHA in the solvent system resulted in an increase in the average percentage recovery (%) of SNA-125 under the stress conditions. Figure 7 depicts the individual model graph for BHT, showing that having BHT in the solvent system resulted in a small increase in the average percentage recovery (%) of SNA-125 under the stress conditions. Figure 8 shows individual model graph for propyl gallate, indicating that its presence in the solvent system resulted in an increase in the average percentage recovery (%) of SNA-125 under the stress conditions. The individual model graph for ascorbic acid (Figure 9) indicates that having this antioxidant in the solvent system resulted in a decrease in the average percentage recovery (%) of SNA-125 under the stress conditions. The individual model graph for ascorbic palmitate (Figure 10) indicates that this antioxidant resulted in a slight decrease in the average percentage recovery (%) of SNA-125 under the stress conditions.

[000156] Figure 11 depicts the interaction model graph for BHT and BHA (AB), indicating there is an interaction between BHA and BHT. When there is BHA in the solvent system, the average percentage recovery (%) of SNA-125 is higher without BHT. When there is no BHA in the solvent system, the average percentage recovery (%) of SNA-125 is

higher with BHT. The average percentage recovery (%) of API is highest when there is BHA and no BHT.

[000157] The interaction model graph for BHA and propyl gallate (Figure 12; AC) indicates there is an interaction between BHA and propyl gallate. When there is propyl gallate in the solvent system, the average percentage recovery (%) of SNA-125 remains constant with and without BHA. The combination of BHA without propyl gallate, BHA with propyl gallate and propyl gallate without BHA all yielded similar results of percentage recovery (%) of SNA-125. The average percentage recovery (%) of SNA-125 is slightly higher with BHA alone. When neither BHA nor propyl gallate are in the solvent system, the average percentage recovery (%) of SNA-125 is lower.

[000158] Figure 13 depicts the interaction model graph for BHT and ascorbic palmitate (BE), which indicates there is an interaction between BHT and ascorbic palmitate. When ascorbic palmitate is in the solvent system, the average percentage recovery (%) of SNA-125 is highest with BHT, but lowest without BHT. When ascorbic palmitate is not in the solvent system, the average percentage recovery (%) of SNA-125 remains similar with and without BHT. The combination of BHT and ascorbic palmitate results in the highest average percentage recovery (%) of SNA-125.

[000159] The interaction model graph for propyl gallate and ascorbic palmitate (Figure 14; CE) indicates there is an interaction between propyl gallate and ascorbic palmitate. When ascorbic palmitate is in the solvent system, the average percentage recovery (%) of SNA-125 is lower than when it is not. When propyl gallate is in the solvent system, the average percentage recovery (%) of SNA-125 is much higher without ascorbic palmitate. The combination of propyl gallate without ascorbic palmitate results in the highest average percentage recovery (%) of SNA-125.

[000160] Figure 15 depicts the interaction model graph for propyl gallate and alpha tocopherol (CF), which indicates there is an interaction between propyl gallate and alpha tocopherol. When there is no propyl gallate in the solvent system, the average percentage recovery (%) of SNA-125 is similar with and without alpha tocopherol. When propyl gallate is in the solvent system the average percentage recovery (%) of SNA-125 is higher when

alpha tocopherol is included. The combination of propyl gallate and alpha tocopherol results in the highest average percentage recovery (%) of SNA-125.

Conclusions

[000161] Table 22 depicts the general trend observed regarding the effect of the six selected antioxidants on SNA-125 percentage recovery following 24 hours and 5 days storage with 6% H_2O_2 spiking at 70°C.

TABLE 22: GENERAL TREND OF ANTIOXIDANT EFFECT ON SNA-125 PERCENTAGE RECOVERY

Antioxidant	T = 24 h	T = 5 day
BHA (A)	Increase	Increase
BHT (B)	Small Increase	Non-Significant
Propyl Gallate (C)	Increase	Increase
Ascorbic Acid (D)	Decrease	Non-Significant
Ascorbic Palmitate (E)	Small Decrease	Non-Significant
Alpha Tocopherol (F)	Non-Significant	Non-Significant

[000162] Uses of BHA and propyl gallate in the solvent system of CR045 were both found to increase the average percentage recovery of SNA-125. BHA and propyl gallate can be used alone, and can also be used in combination to achieve the best outcome. In some embodiments, the SNA-125 formulation contains at least one of BHA and propyl gallate. Additionally, alpha tocopherol was found to increase the effectiveness of propyl gallate. Figure 16 depicts a design space of the t = 5 day average SNA-15 recovery % w/w in a CR045 solvent system with antioxidants propyl gallate, alpha tocopherol, and BHA at the indicated concentrations.

In conclusion, incorporation of BHA and propyl gallate (in combination or separately) in CR045 increases the percentage (%) recovery of SNA-125 when the formulation is subjected to stress conditions. Therefore, in some embodiments, BHA and/or propyl gallate is incorporated in the SNA-125 formulations. Both BHA and propyl gallate have USP and EU monographs available.

CLAIMS

WHAT IS CLAIMED IS:

1. A topical cream formulation for dermal delivery of polymer conjugates of indolocarbazole compounds with reduced exposure, the formulation comprising:

a polymer conjugate of an indolocarbazole compound;

an aqueous phase, comprising one or more compounds;

an oil phase, comprising one or more compounds; and

a surfactant.

2. The cream formulation of Claim 1, wherein the polymer conjugate of an indolocarbazole compound is SNA-125.

3. The cream formulation of Claim 2, wherein the SNA-125 is present at about 0.05% to about 25% (w/w) of the cream formulation.

4. The cream formulation of Claim 2, wherein the SNA-125 is present at about 0.05% to about 10% (w/w) of the cream formulation.

5. The cream formulation of Claim 2, wherein the SNA-125 is present at about 2% (w/w) of the cream formulation.

6. The cream formulation according to any one of Claims 1 to 5, wherein the one or more aqueous phase compounds are selected from the group consisting of 2-(2-ethoxyethoxy)ethanol (tradename TRANSCUTOL P), high purity grade, low molecular weight polyethylene glycol 400 (tradename SRPEG 400), purified water, phenoxyethanol, propylene glycol, isopropyl alcohol, benzyl alcohol, butylated hydroxyanisole ('BHA'), butylated hydroxytoluene (BHT), propyl gallate, and ethanol.

7. The cream formulation of Claim 6, wherein the one or more aqueous phase compounds are present in the following concentrations:

TRANSCUTOL P from about 0% to about 15% (w/w) of the cream formulation;

SRPEG400 from about 15% to about 21% (w/w) of the cream formulation;

Purified water from about 30% to about 50% (w/w) of the cream formulation;

Benzyl alcohol at about 2% (w/w) of the cream formulation;

BHA, BHT or propyl gallate from about 0.01% to about 0.05% (w/w) of the cream formulation; and

Ethanol from about 0% to about 10% (w/w) of the cream formulation;

8. The cream formulation according to any one of Claims 1 to 7, wherein the aqueous phase comprises about 65% to about 80% (w/w) of the cream formulation.

9. The cream formulation according to any one of Claims 1 to 8, wherein the one or more oil phase compounds are selected from the group consisting of isopropyl myristate (IPM), cetostearyl alcohol, Caprylic/Capric Triglyceride (GTCC), liquid paraffin and/or white soft paraffin, dimethicone 350, beeswax, stearyl alcohol, cholesterol and stearic acid.

10. The cream formulation of Claim 9, wherein the one or more oil phase compounds are present in the following concentrations:

IPM from about 0% to about 9% (w/w) of the cream formulation;

Cetostearyl alcohol from about 3% to about 7% (w/w) of the cream formulation;

GTCC from about 0% to about 8% (w/w) of the cream formulation;

Liquid paraffin from about 0% to about 17% (w/w) of the cream formulation;

Dimethicone 350 from about 0% to about 1% (w/w) of the cream formulation; and

Stearic acid from about 3% to about 7% (w/w) of the cream formulation;

11. The cream formulation according to any one of Claims 1 to 10, wherein the oil phase comprises about 15% to about 30% (w/w) of the cream formulation.

12. The cream formulation according to any one of Claims 1 to 11, wherein the one or more surfactants are selected from the group consisting of Brij S2 (polyoxyethylene fatty ethers derived from stearyl alcohols), Brij S20 (polyoxyethylene fatty ethers derived from stearyl alcohols), Span 60

(emulsifier/surfactant derived from stearic acid and used in combination with Tween 60) and Tween 60 (polysorbate emulsifier/surfactant), and Cetomacrogol 1000.

13. The cream formulation of Claim 12, wherein the one or more surfactants are present in the following concentrations:

Brij S2 from about 1% to about 1.5% (w/w) of the cream formulation; and

Brij S20 from about 3.5% to about 4% (w/w) of the cream formulation.

14. The cream formulation according to any one of Claims 1 to 13, wherein the surfactant comprises about 5% (w/w) of the cream formulation.

15. A method of treating a skin condition associated with kinase signaling, the method comprising:

applying, or instructing application of, a topical formulation to a skin region, wherein said formulation inhibits kinase signaling in said skin region, and thereby treats the skin condition;

wherein said topical formulation is the cream formulation of any one of Claims 1 to 14.

16. The method of Claim 15, wherein the polymer conjugate of an indolocarbazole is SNA-125.

17. The method of Claim 15 or 16, wherein the kinase is TrkA, a JAK kinase selected from JAK1, JAK2 or JAK3, a tyrosine kinase 2 (TYK2), or a mitogen-activated protein kinase kinase selected from MAP2K or MAP2K3.

18. The method according to any one of Claims 15 or 17, wherein the skin condition is atopic dermatitis, psoriasis, pruritus or any other dermatologic condition.

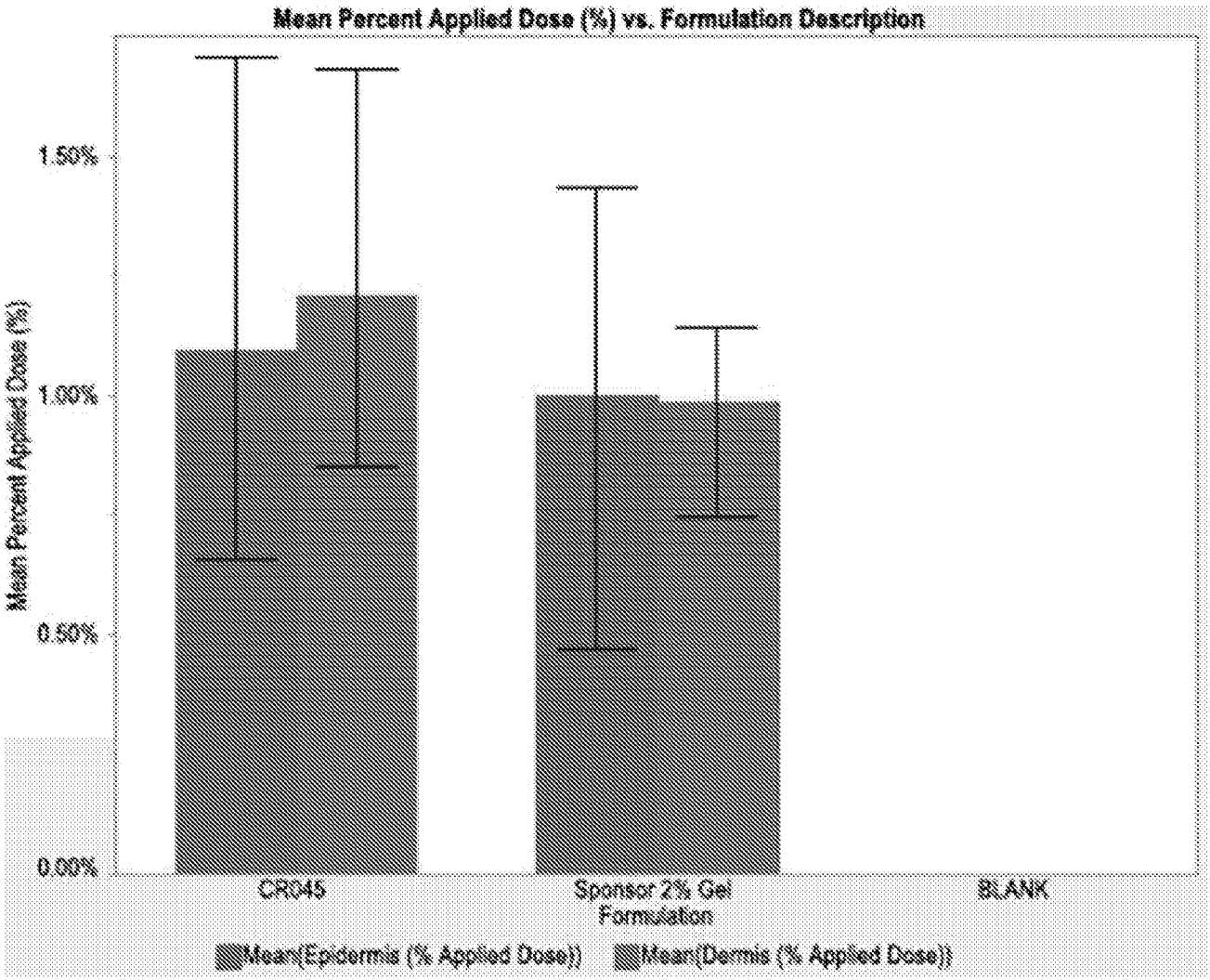
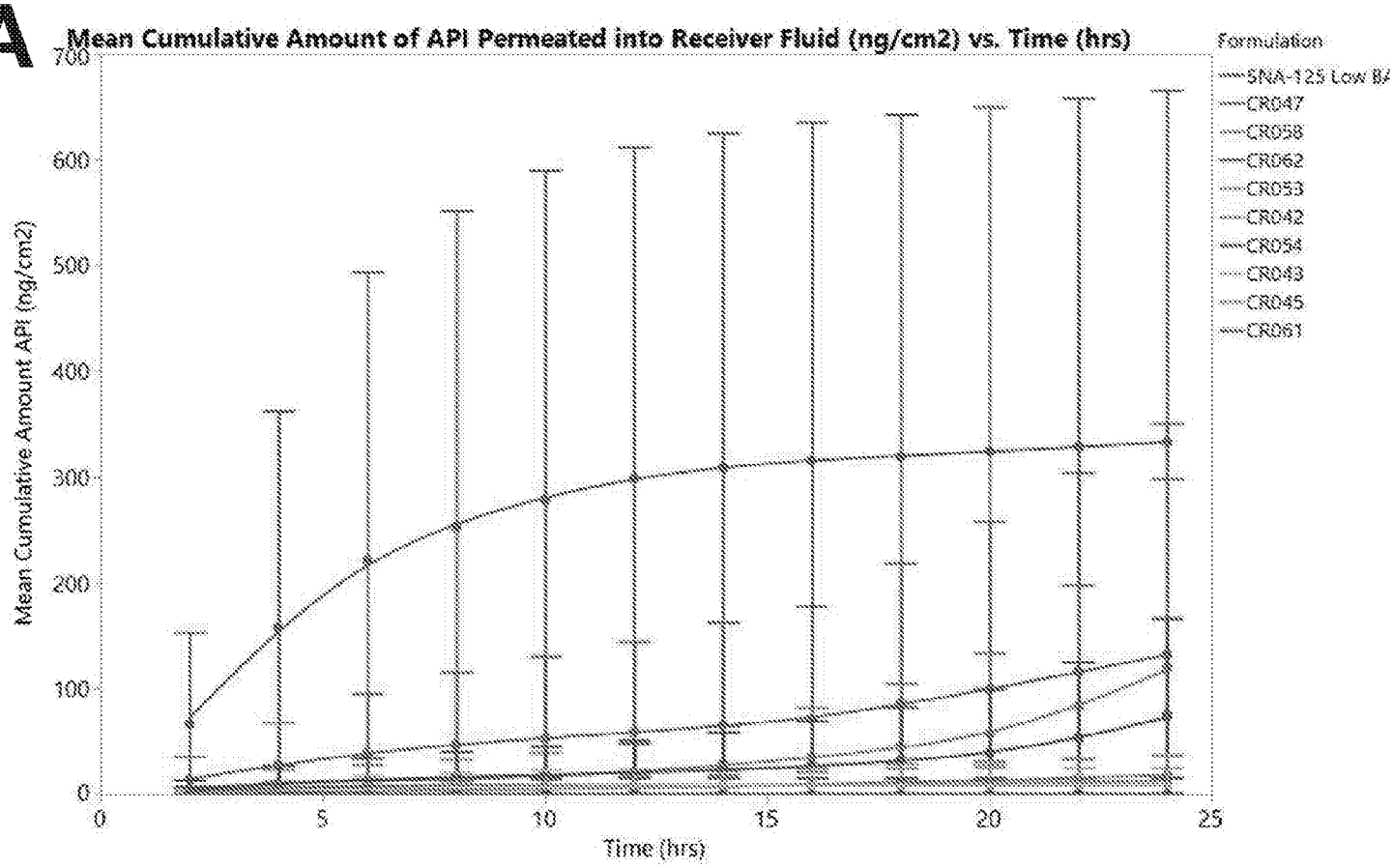

Mean Percent Applied Dose (%) vs. Formulation Description
Mean Percent Applied Dose (%)
1.50%
1.00%
0.50%
0.00%
CR045
Sponsor 2% Gel Formulation
BLANK
Mean(Epidermis (% Applied Dose))
Mean(Dermis (% Applied Dose))

FIGURE 1

A


Mean Cumulative Amount of API Permeated into Receiver Fluid (ng/cm2) vs. Time (hrs)
Mean Cumulative Amount API (ng/cm2)
Time (hrs)
Formulation
SNA-125 Low BA
CR047
CR058
CR062
CR053
CR042
CR054
CR043
CR045
CR061

B

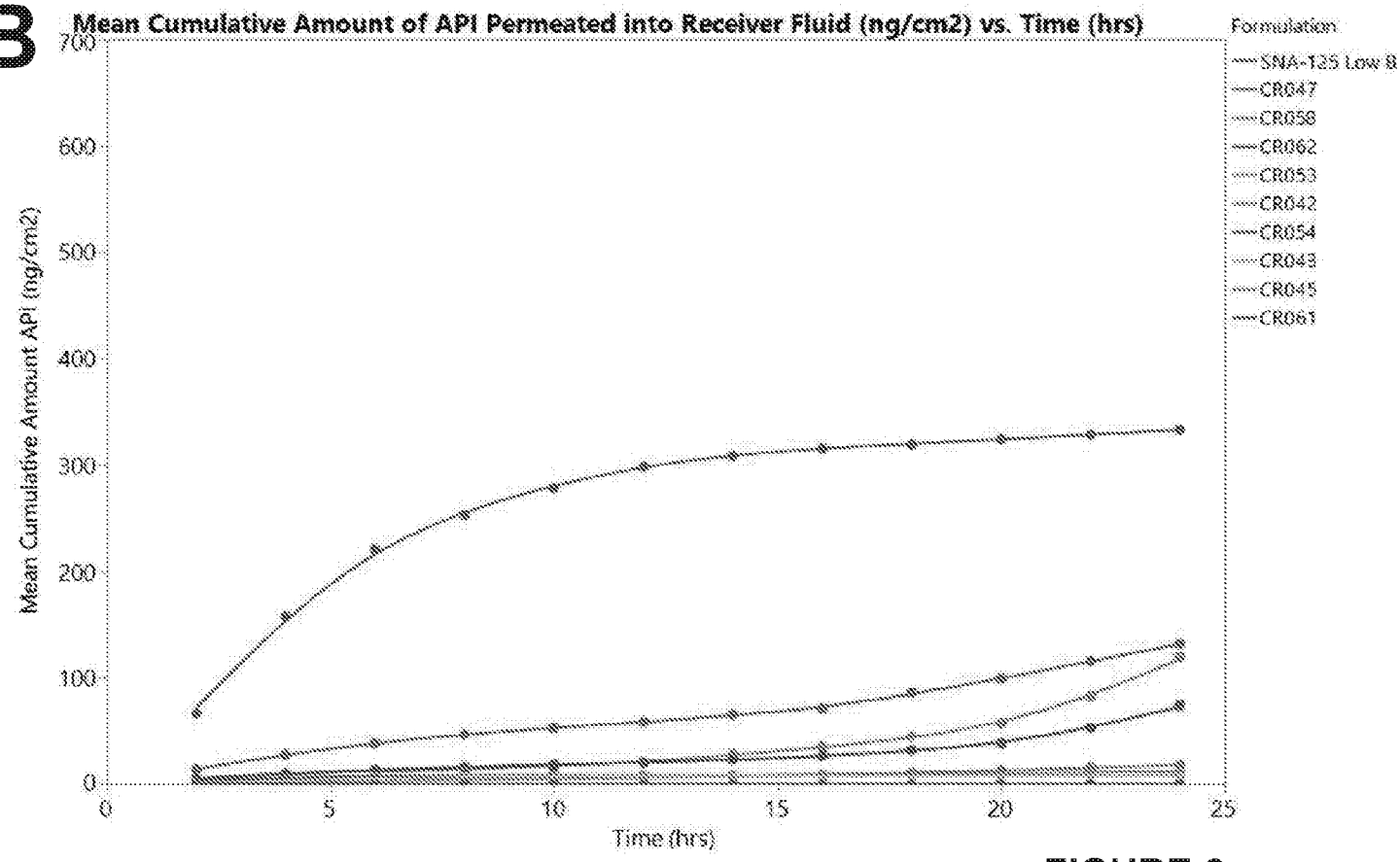

Mean Cumulative Amount of API Permeated into Receiver Fluid (ng/cm2) vs. Time (hrs)
Mean Cumulative Amount API (ng/cm2)
Time (hrs)
Formulation
SNA-125 Low B
CR047
CR058
CR062
CR053
CR042
CR054
CR043
CR045
CR061

FIGURE 2

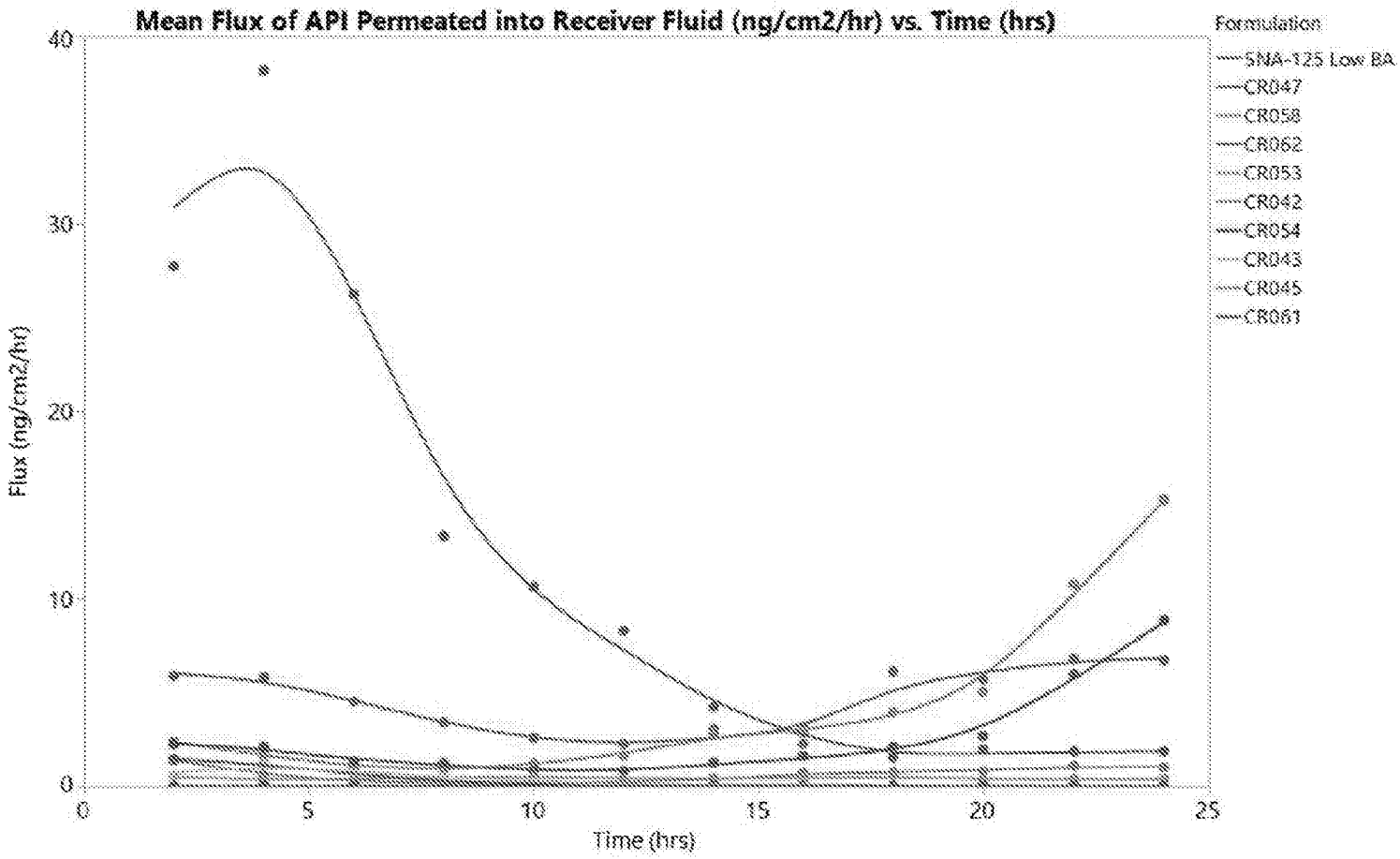
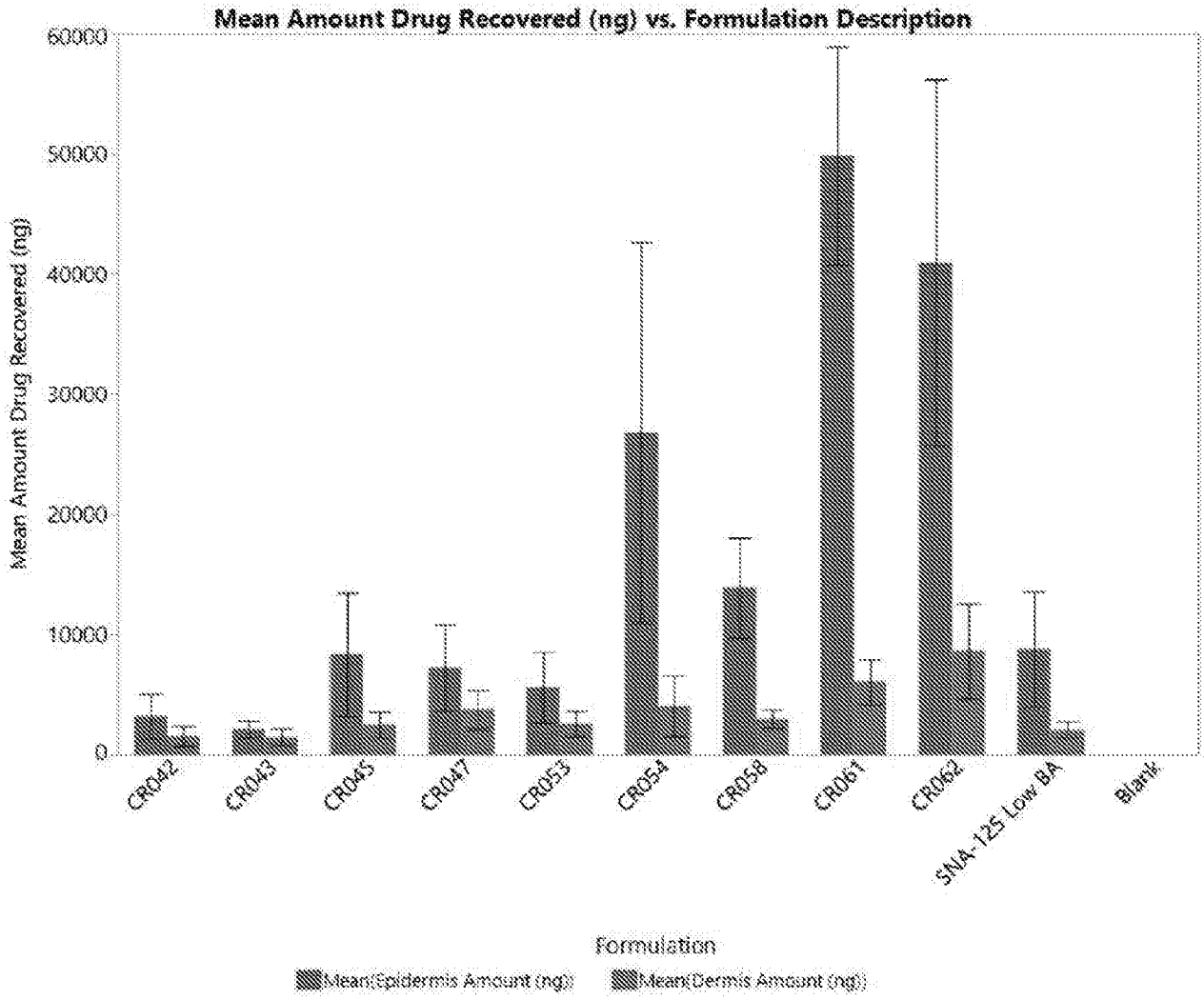

Mean Flux of API Permeated into Receiver Fluid (ng/cm2/hr) vs. Time (hrs)
Flux (ng/cm2/hr)
Time (hrs)
0
10
20
30
40
0
5
10
15
20
25
Formulation
SNA-125 Low BA
CR047
CR058
CR062
CR053
CR042
CR054
CR043
CR045
CR061

FIGURE 3

A



B

Connecting Letters Report

Level		Mean
CR061	A	49844
CR062	A B	40921
CR054	B C	26791
CR058	C D	13854
SNA-125 Low BA	D	8769
CR045	D	8304
CR047	D	7202
CR053	D	5567
CR042	D	3165
CR043	D	2080

Epidermis

Levels not connected by same letter are significantly different.

C

Connecting Letters Report

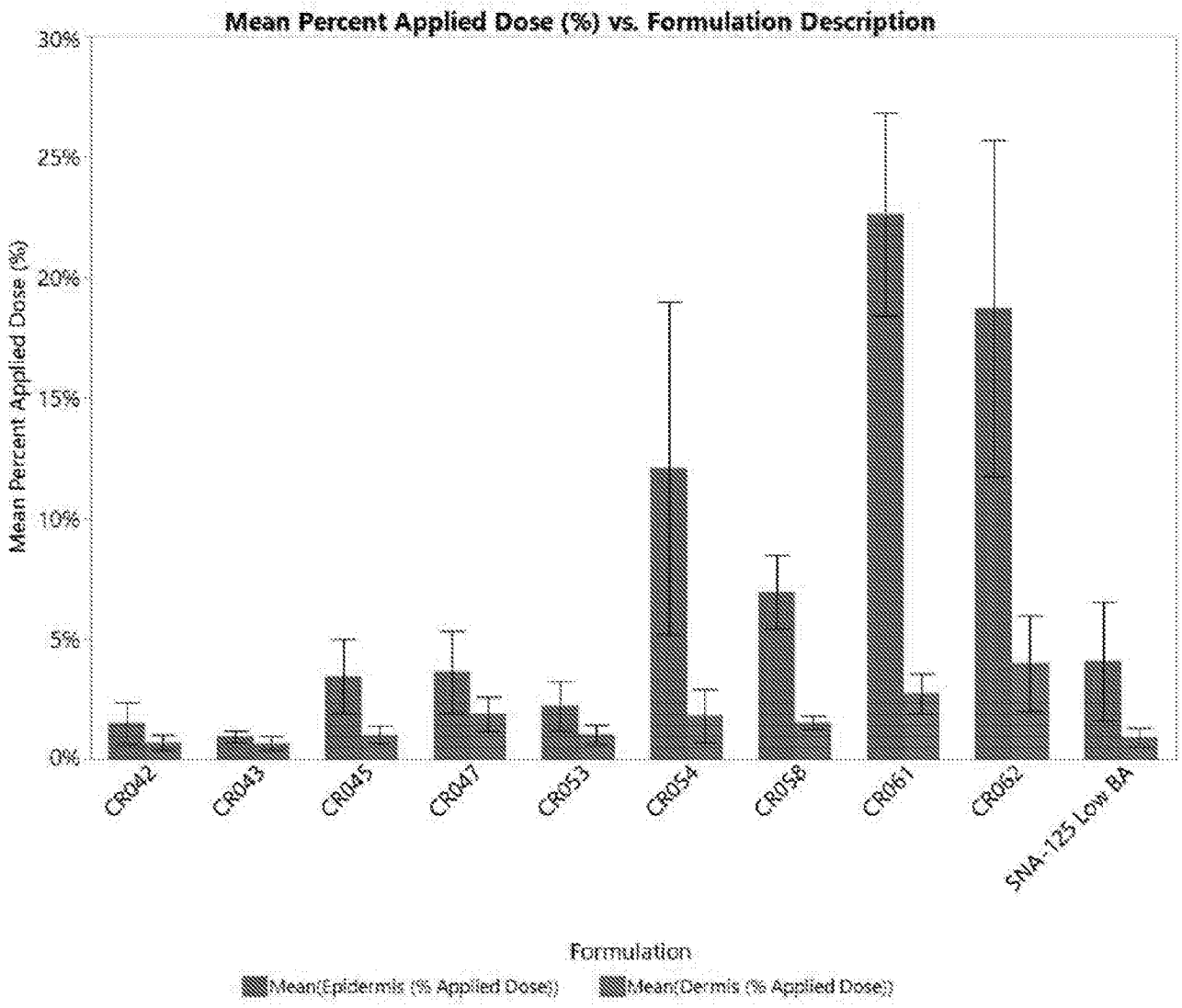
Level		Mean
CR062	A	8586
CR061	A B	6040
CR054	B C	4033
CR047	B C	3742
CR058	B C	2942
CR053	B C	2546
CR045	B C	2416
SNA-125 Low BA	C	2045
CR042	C	1497
CR043	C	1444

Dermis

Levels not connected by same letter are significantly different.

FIGURE 4

A



B

Connecting Letters Report

Level		Mean
CR061	A	22.63%
CR062	A B	18.73%
CR054	B C	12.10%
CR058	C D	6.95%
SNA-125 Low BA	D	4.08%
CR047	D	3.64%
CR045	D	3.46%
CR053	D	2.23%
CR042	D	1.51%
CR043	D	0.96%

Epidermis

Levels not connected by same letter are significantly different.

C

Connecting Letters Report

Level		Mean
CR062	A	4.00%
CR061	A B	2.73%
CR047	B C	1.90%
CR054	B C	1.82%
CR058	B C	1.54%
CR053	C	1.04%
CR045	C	1.03%
SNA-125 Low BA	C	0.92%
CR042	C	0.70%
CR043	C	0.67%

Dermis

Levels not connected by same letter are significantly different.

FIGURE 5

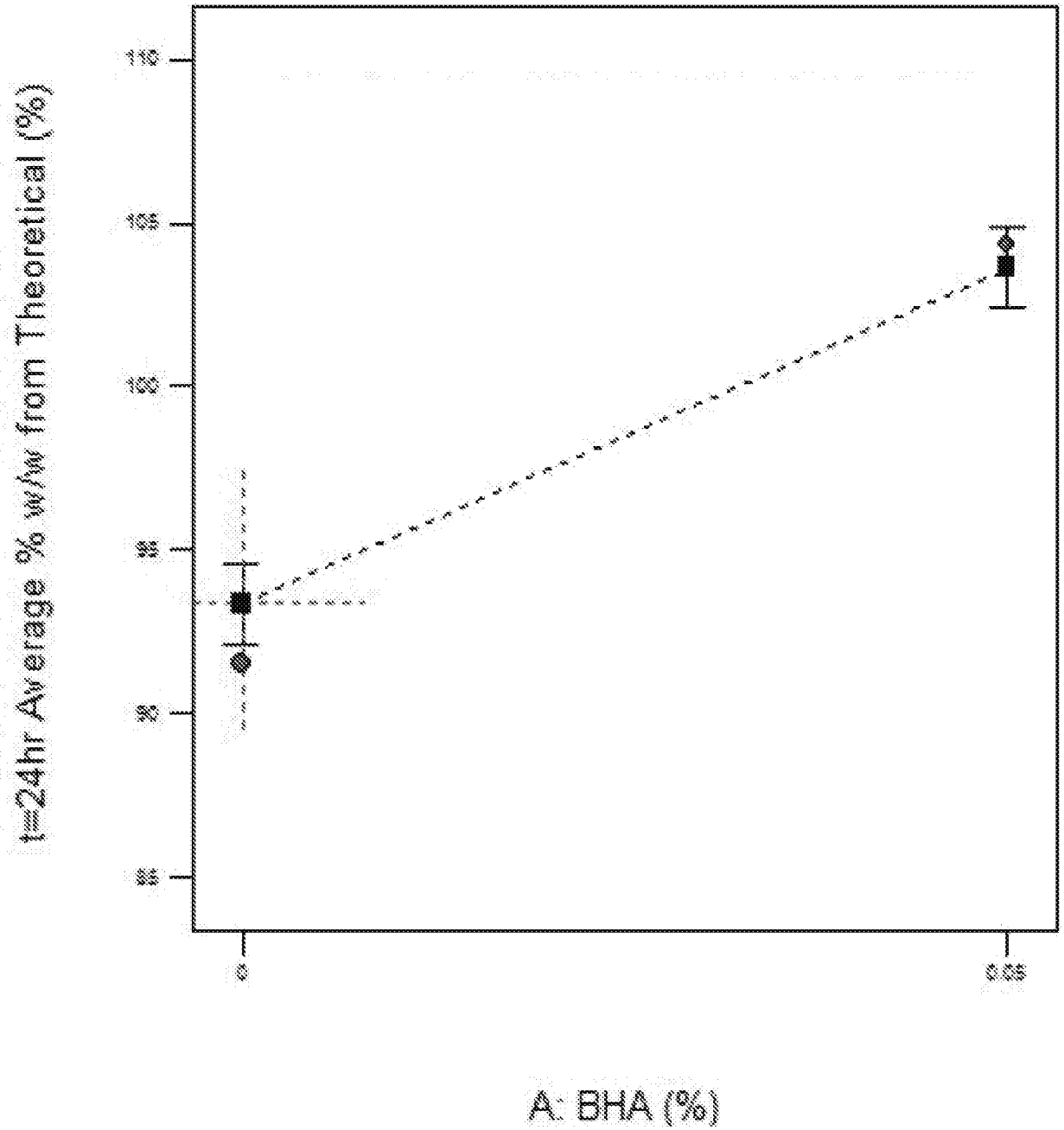


FIGURE 6

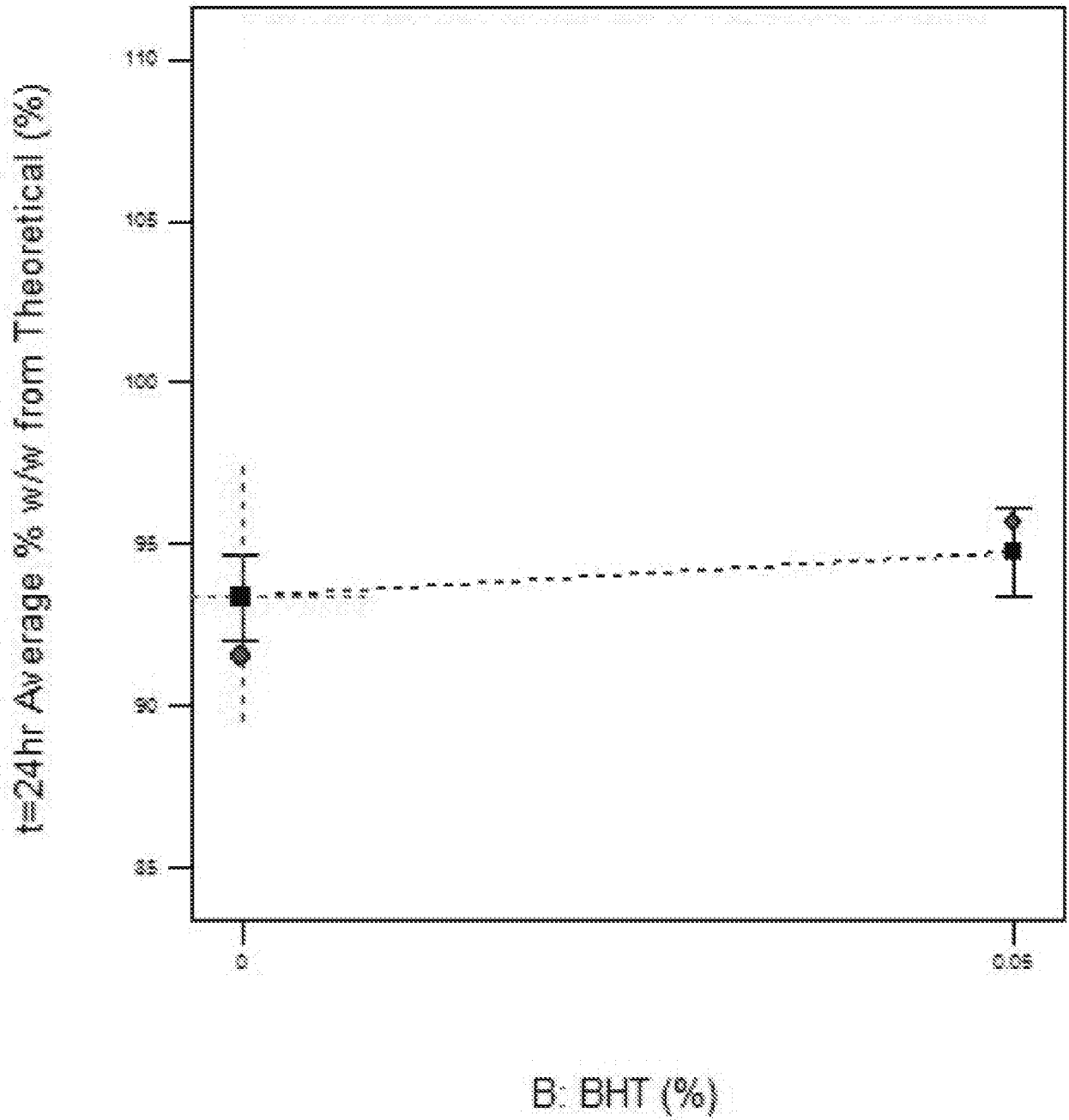


FIGURE 7

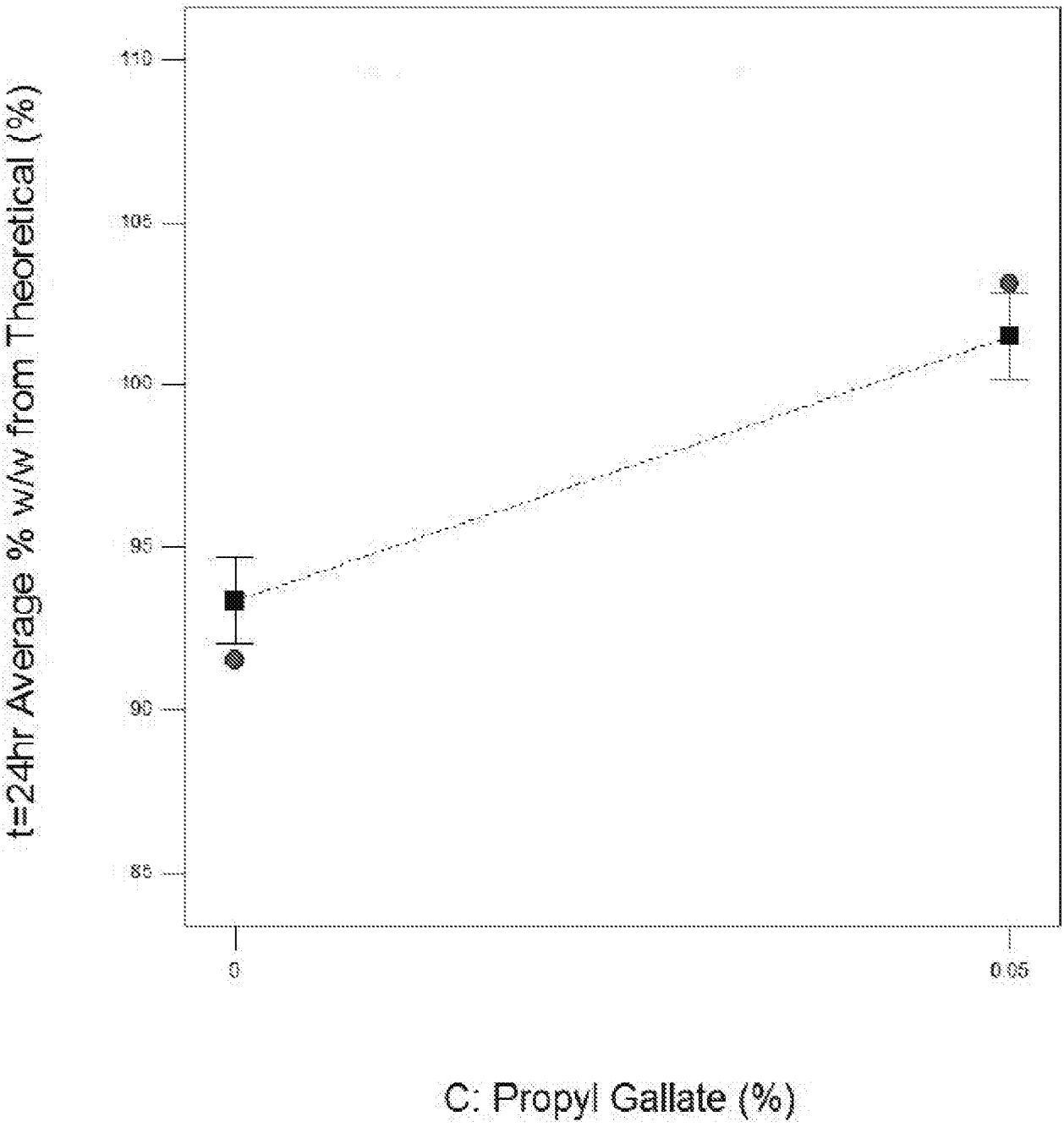

t=24hr Average % w/w from Theoretical (%)
110
105
100
95
90
85
0
0.05
C: Propyl Gallate (%)

FIGURE 8

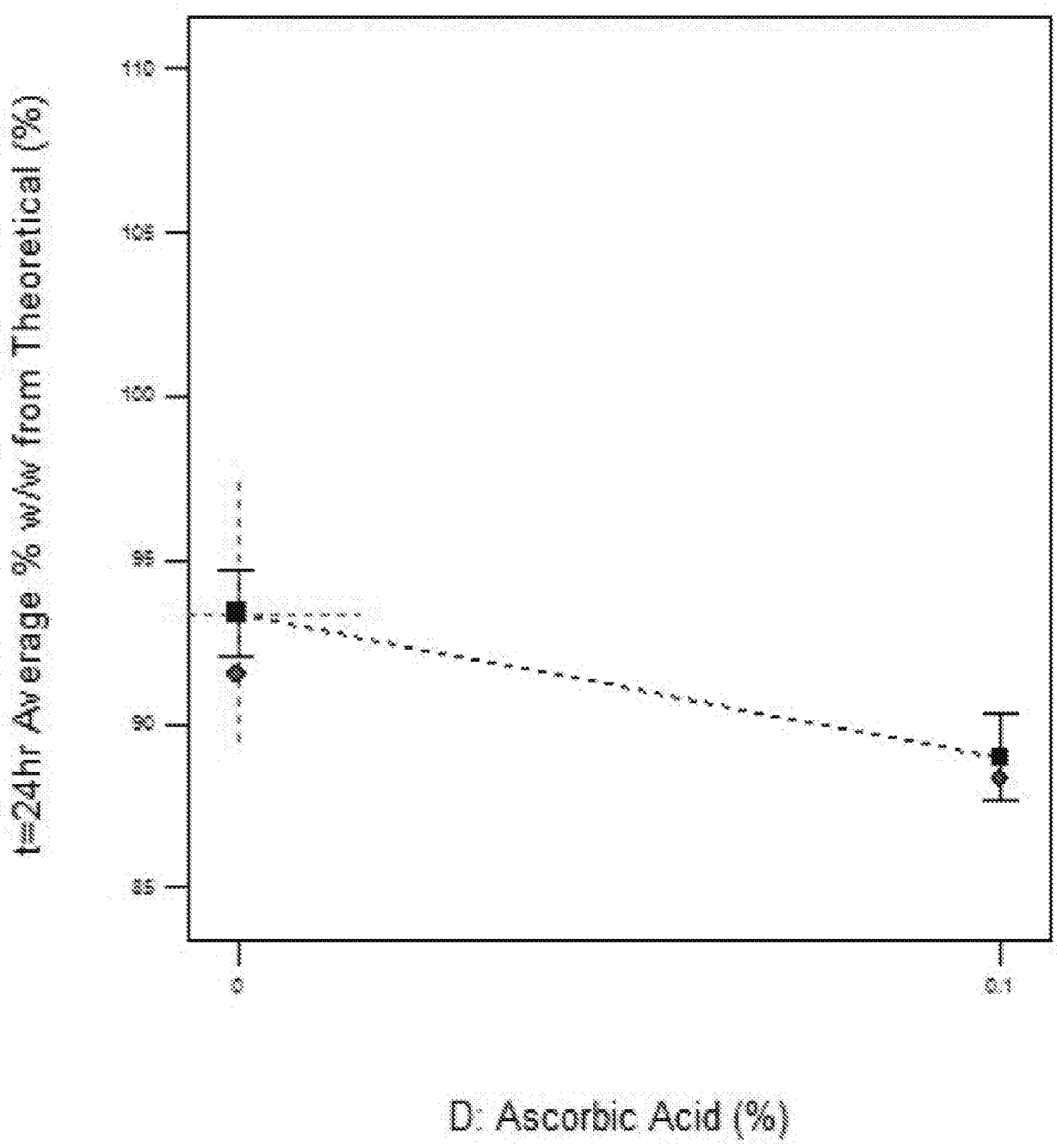


FIGURE 9

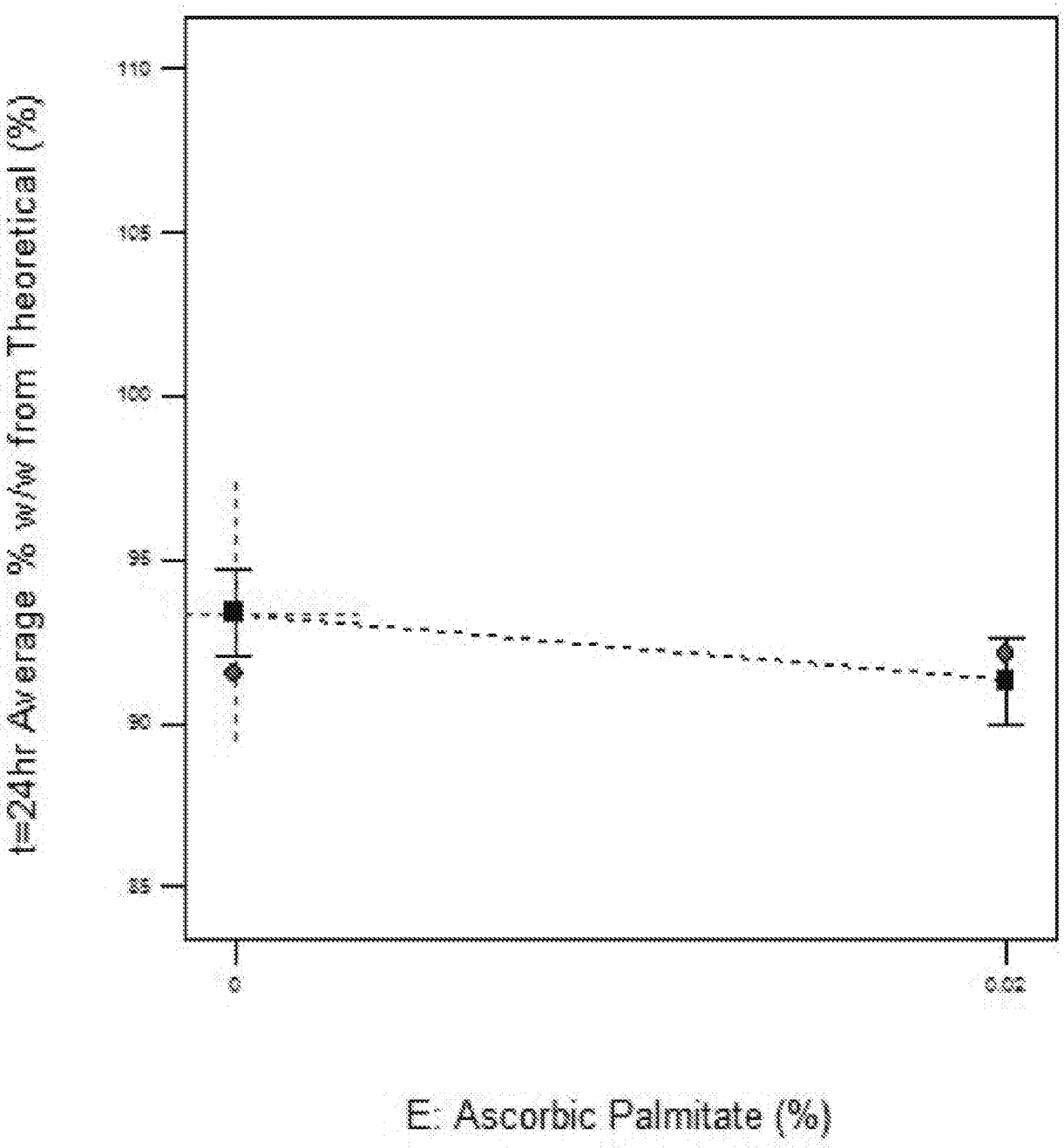

t=24hr Average % w/w from Theoretical (%)
115
110
105
100
95
0
0.5
E: Ascorbic Palmitate (%)

FIGURE 10

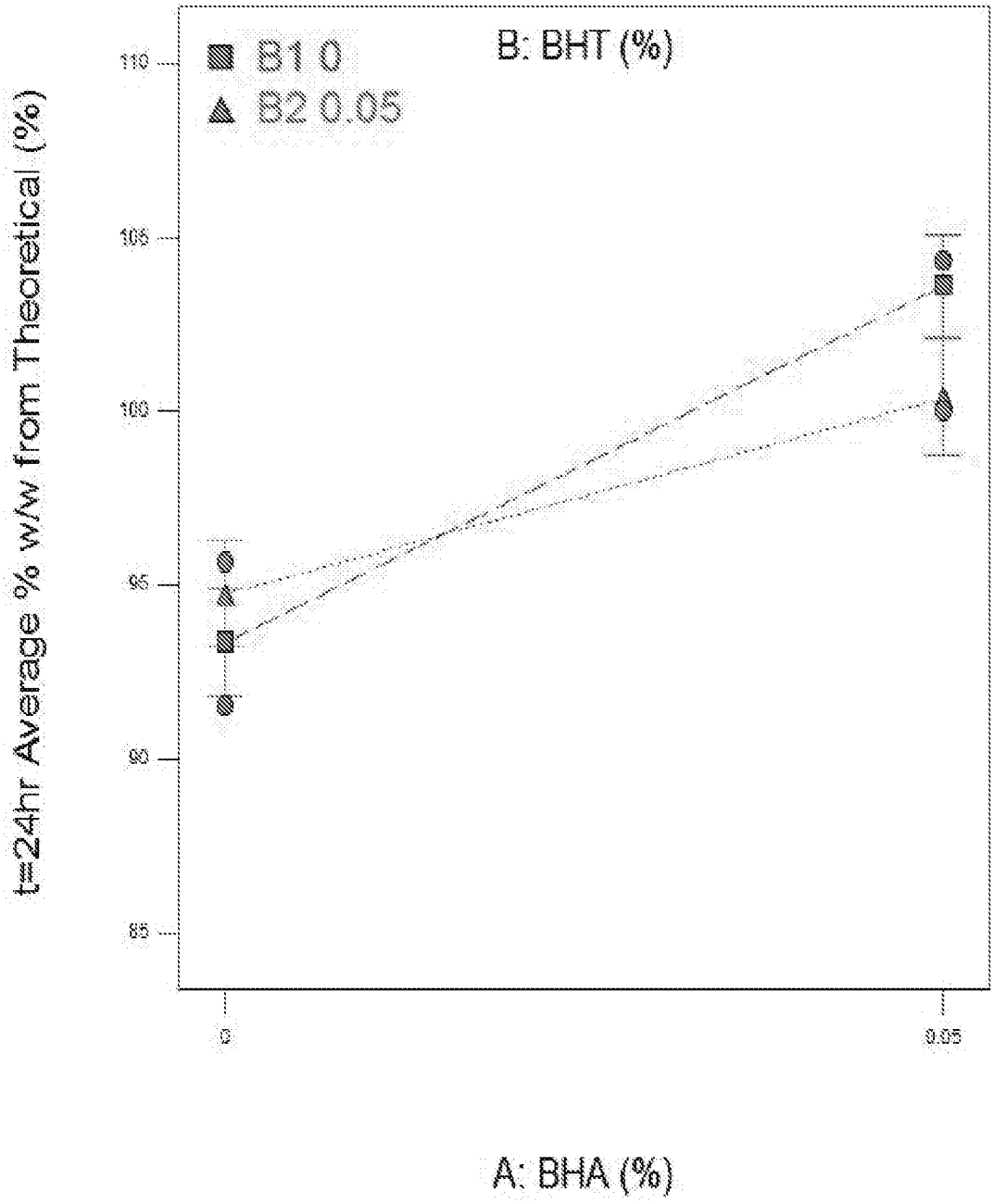

B: BHT (%)
B1 0
B2 0.05
110
105
100
95
90
85
t=24hr Average % w/w from Theoretical (%)
0
0.05
A: BHA (%)

FIGURE 11

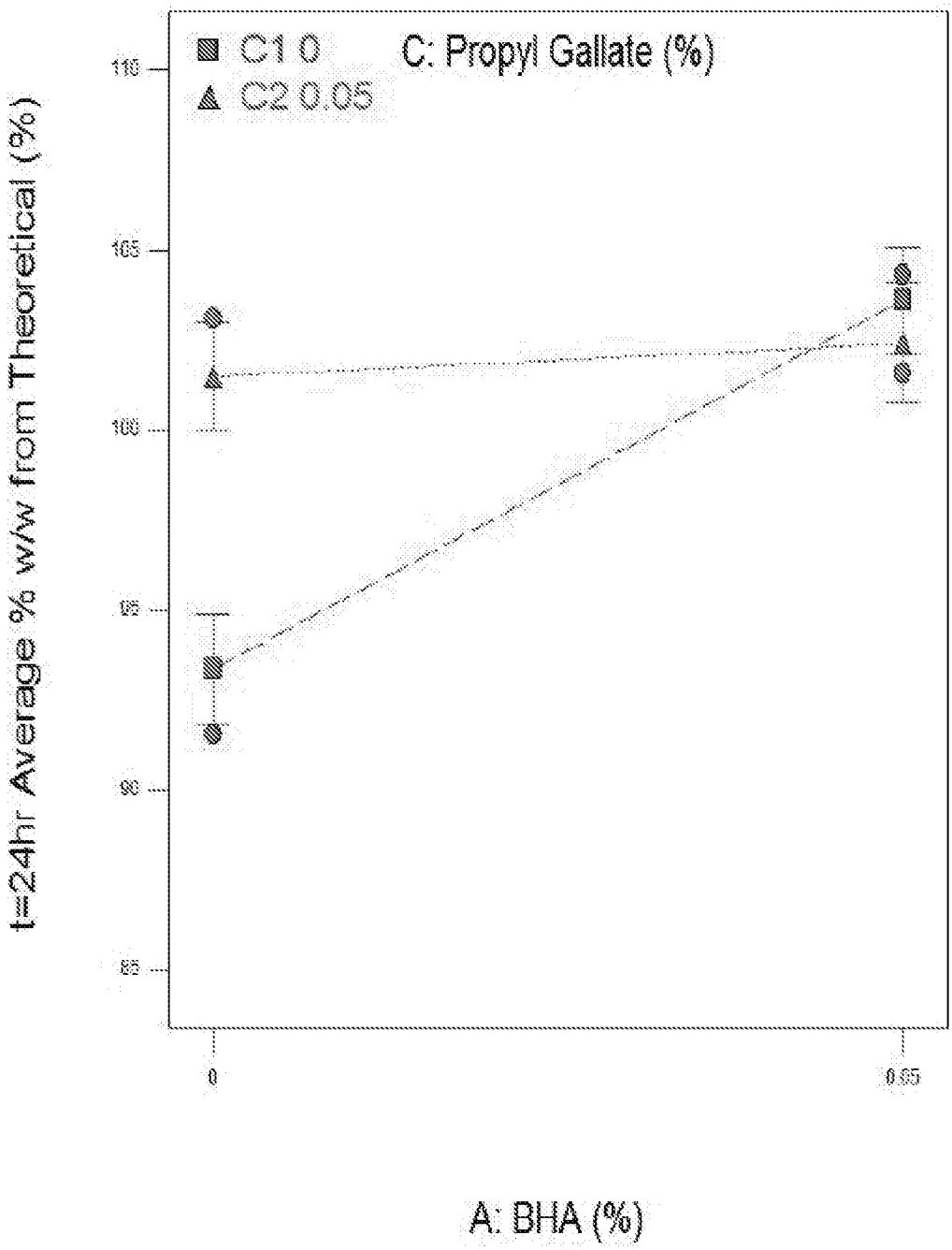

C1 0
C2 0.05
C: Propyl Gallate (%)
t=24hr Average % w/w from Theoretical (%)
110
105
100
95
90
85
0
0.05
A: BHA (%)

FIGURE 12

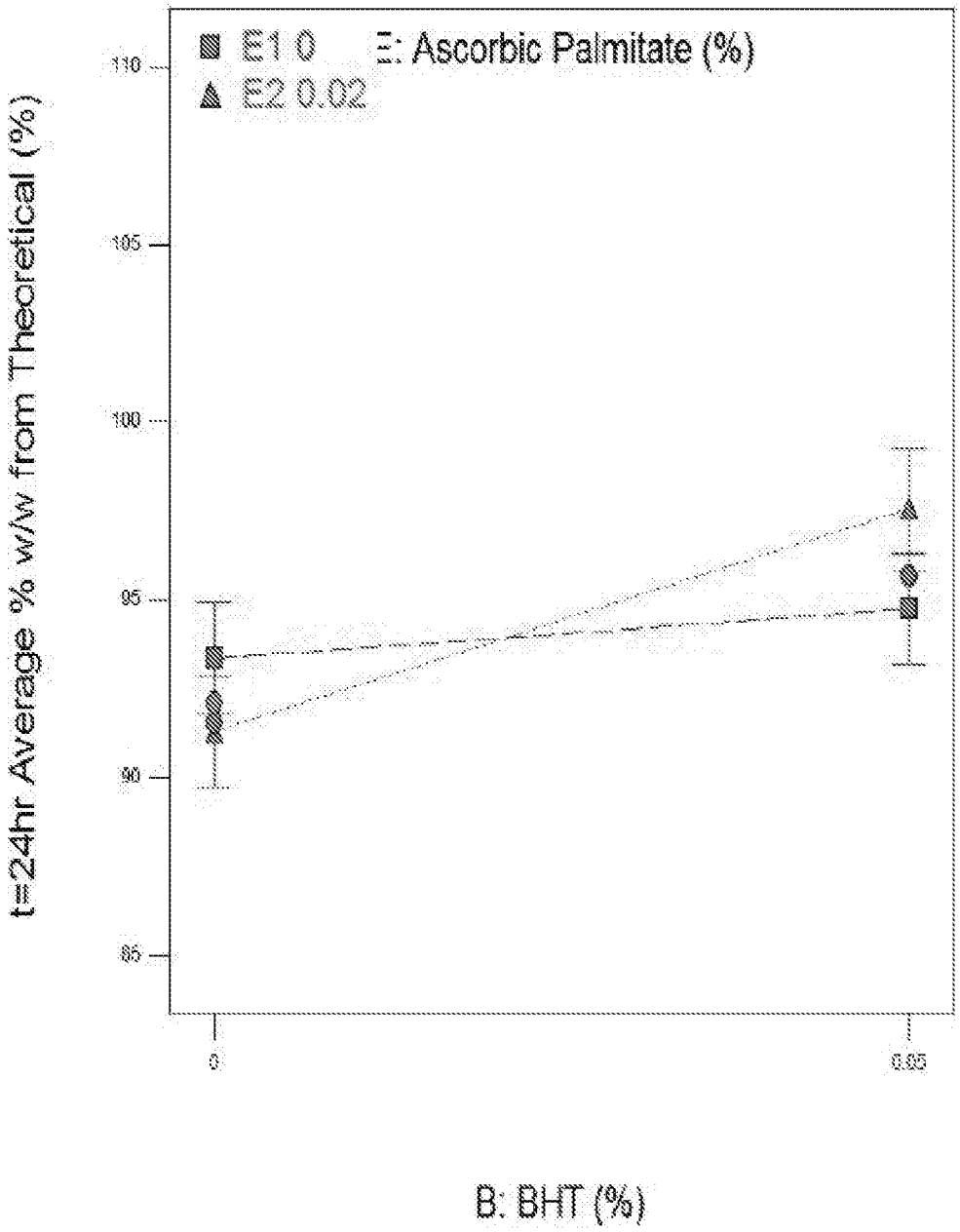

E1 0
E2 0.02
E: Ascorbic Palmitate (%)
t=24hr Average % w/w from Theoretical (%)
110
105
100
95
90
85
0
0.05
B: BHT (%)

FIGURE 13

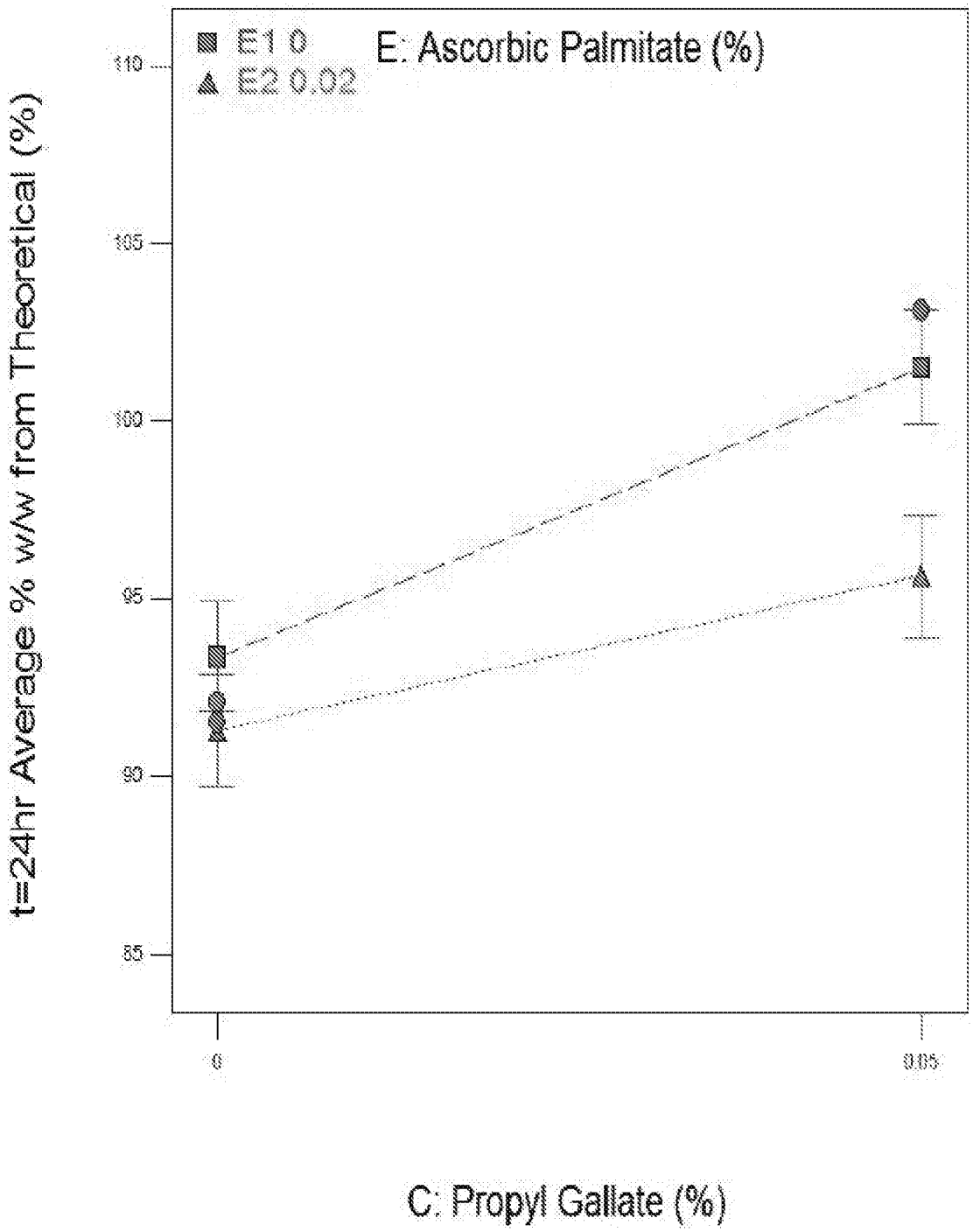

E1 0
E2 0.02
E: Ascorbic Palmitate (%)
110
105
100
95
90
85
t=24hr Average % w/w from Theoretical (%)
0
0.05
C: Propyl Gallate (%)

FIGURE 14

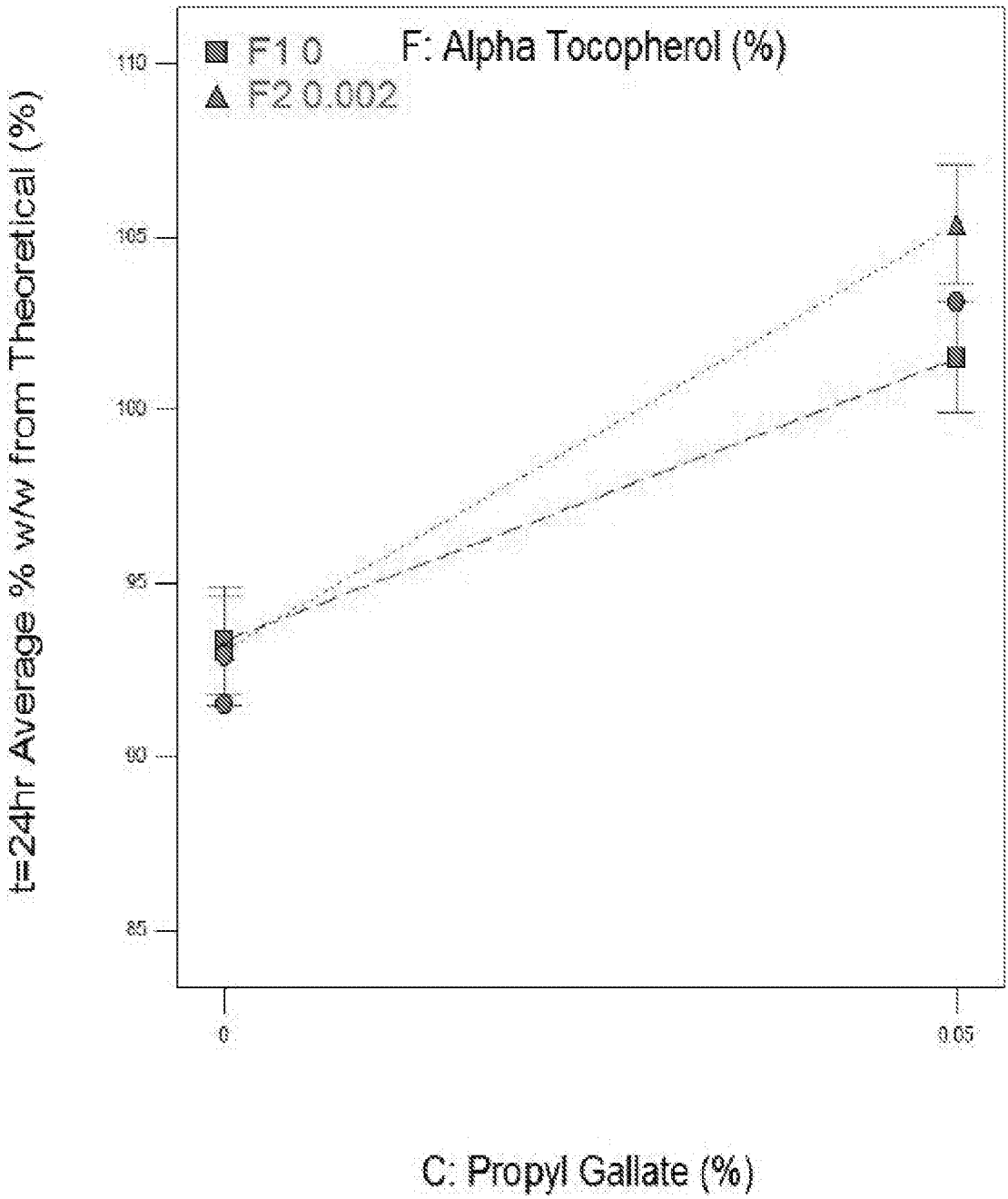

F: Alpha Tocopherol (%)
F1 0
F2 0.002
t=24hr Average % w/w from Theoretical (%)
110
105
100
95
90
85
0
0.05
C: Propyl Gallate (%)

FIGURE 15

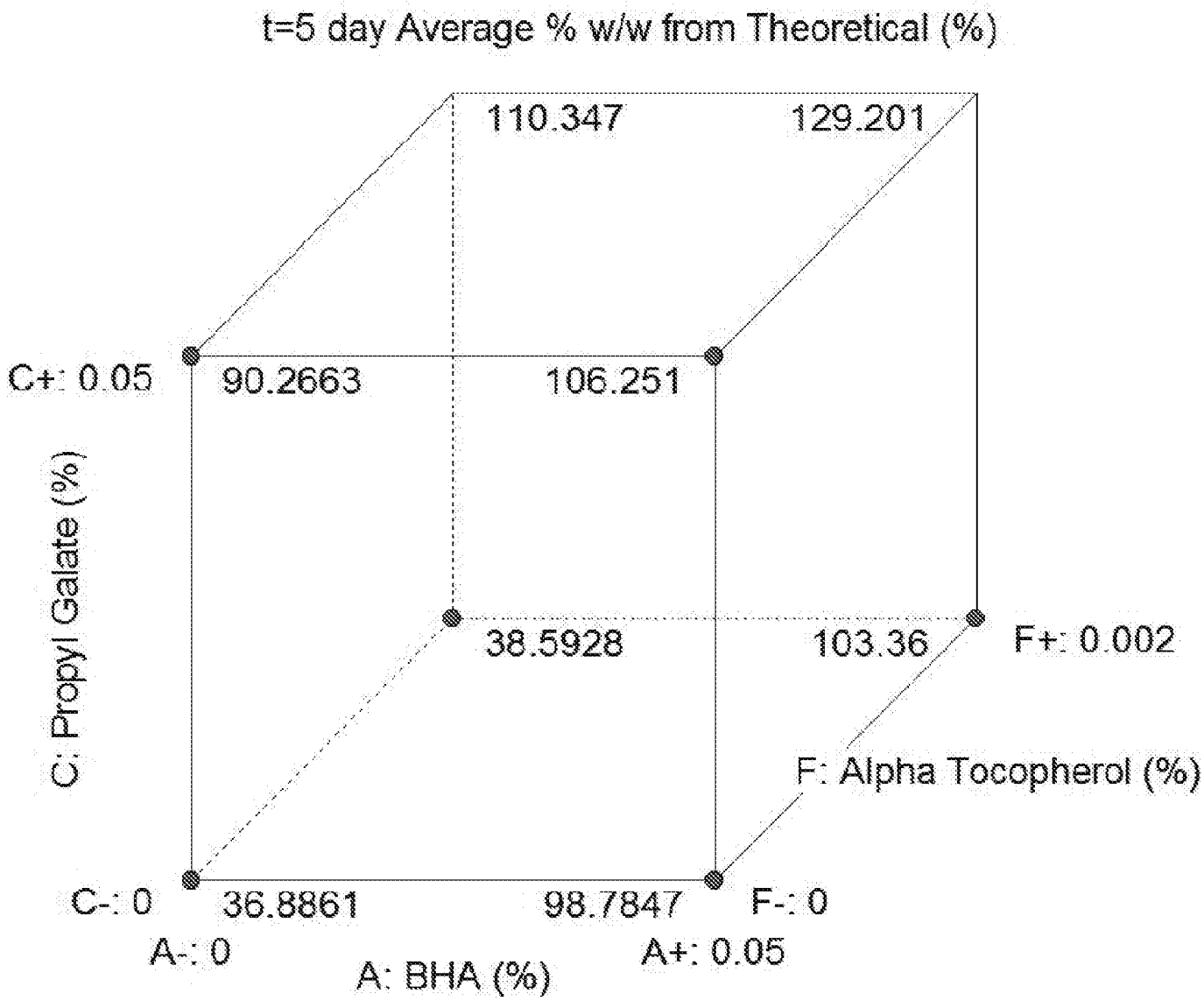

t=5 day Average % w/w from Theoretical (%)
110.347
129.201
C+: 0.05
90.2663
106.251
C: Propyl Galate (%)
38.5928
103.36
F+: 0.002
F: Alpha Tocopherol (%)
C-: 0
36.8861
98.7847
F-: 0
A-: 0
A+: 0.05
A: BHA (%)

FIGURE 16