

TRANSDERMAL DELIVERY FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/471,487, filed June 6, 2023, and U.S. Provisional Application No. 63/617,608, filed January 4, 2024, the disclosures of which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Systemic delivery of therapeutic agents, drugs, or nutrients are presented with challenges to stability and acceptability. Enteric delivery formulations are exposed to extreme environments, requiring formulations that resist strong acids. Injected formulations are difficult to self-administer and result in biohazardous waste products in the form of used needles. Such challenges affect compliance to therapeutic regimens and increase cost of treatment. Such challenges affect the outcome of treatment. Topical delivery provides for access to the vast absorption area of the skin, is simple to administer, and does not generate hazardous waste. Current topical formulations provide for delivery to the stratum corneum and do not penetrate the stratum corneum to deliver components to the circulatory system. There is a need for systemic delivery formulations that provide for delivery through the stratum corneum to the circulation.

SUMMARY

[0003] The present disclosure fulfills unmet needs in the art for efficient and systemic epicutaneous administration of drugs, nutrients, and other compounds to a human subject; veterinary animal; domesticated or undomesticated animal, plant or insect; or agricultural animal, plant, or insect. The transdermal delivery formulations disclosed herein provide unexpected and surprising advantages over existing technologies for the transdermal delivery of therapeutic agents, drugs, and nutrients, to achieve the efficient and systemic epicutaneous administration of individual compounds and mixtures compounds, including therapeutic agents, drugs, and nutrients,, to a human subjects; veterinary animals; domesticated or undomesticated animals, plants or insects; or agricultural animals, plants, or insects in need thereof.

[0004] Provided herein are transdermal delivery formulations for epicutaneous administration, comprising: (a) a transdermal accelerant comprising: about 600-2000 ml total of one or more weak organic acids comprising lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof; and a carrier comprising: about 400-1000 ml total of one or more emulsifiers; about 400-1000 ml distilled water; and about 400-1000 ml total of one or more oils comprising one or more unsaturated long-chain fatty acids comprising adrenic acid, arachidonic acid, arachidic acid,

behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomog- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof, wherein the transdermal accelerant and the carrier are combined to form a transdermal delivery formulation, wherein epicutaneous application of the transdermal formulation and one or more active agents provides for delivery of the one or more active agents through the stratum corneum.

[0005] Provided herein are transdermal delivery formulations for epicutaneous administration, comprising: (a) a transdermal accelerant comprising at least one weak organic acid having a pKa from about 2.0 to about 6.0; and (b) a carrier comprising one or more emulsifiers, water, and one or more oils comprising an unsaturated long-chain fatty acid, wherein the transdermal delivery formulation comprises: at least about 20% by weight of the transdermal accelerant; and at least about 50% by weight of the carrier, wherein epicutaneous application of the transdermal delivery formulation and one or more active agents provides for delivery of the one or more active agents through the stratum corneum. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant and the carrier are present at a ratio of about 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, or 1:8 by weight. Further provided herein are transdermal delivery formulations, wherein the transdermal delivery formulation comprises about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% (w/w) of the transdermal accelerant. Further provided herein are transdermal delivery formulations, wherein the transdermal delivery formulation comprises about 60%, about 65%, about 70%, about 75%, or about 80% w/w of the carrier. Further provided herein are transdermal delivery formulations, wherein a transdermal delivery formulation of a weight of about 3100 g comprises: a transdermal accelerant of a weight of from about 200 g to about 2480 g; and a carrier of a weight from about 620 g to about 2900 g. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises a weight of about 1050 g and the carrier comprises a weight of about 2050 g. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 weak organic acids. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises 2 weak organic acids. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises 2 weak organic acids at a ratio by weight of about 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7,

1:8, 1:9, 1:10, 1:100 or 1:1000 relative to each other. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises about 80%, about 85%, about 90%, about 95%, about 97%, about 99% (w/w) of one or more weak organic acids. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid has a median pKa of from 3.0 to 5.5. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid has a median pKa of from 4.0 to 5.0. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid has a median pKa of about 4.6. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid comprises a mono, di or tri carbonic acid of chain length (R) between 1-16. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid comprises a mono or poly hydroxy moiety of 0-14. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid comprises a linear, branched, or cyclic structure. Further provided herein are transdermal delivery formulations, wherein the structure is saturated or unsaturated. Further provided herein are transdermal delivery formulations, wherein the at least one weak organic acid comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof. Further provided herein are transdermal delivery formulations, wherein said weak organic acid is citric acid or acetic acid. Further provided herein are transdermal delivery formulations, wherein said transdermal accelerant comprises citric acid and acetic acid. Further provided herein are transdermal delivery formulations, wherein the acetic acid is apple cider vinegar. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises from about 100 g to about 700 g citric acid and from about 300 g to about 1300 g apple cider vinegar. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises about 100 g, about 150 g, about 200 g, about 250 g, about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g citric acid. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g, about 750 g, about 800 g, about 850 g, about 900 g, about 950 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g apple cider vinegar. Further provided herein are transdermal delivery formulations, wherein the carrier comprises at least one emulsifier, at least one oil comprising a long-chain fatty acid, and water at a ratio by weight of about 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:1:5, 1:1:6, 1:2:2, 1:2:3, 1:2:4, 1:2:5, 1:2:6, 1:3:3, 1:3:4, 1:3:5, 1:3:6, 1:4:4, 1:4:5, 1:4:6, 1:5:5, 1:5:6, 1:6:6, 2:2:3, 2:2:4, 2:2:5, 2:2:6, 2:3:3, 2:3:4, 2:3:5, 2:3:6, 2:4:4, 2:4:5, 2:4:6, 2:5:5, 2:5:6, 2:6:6, 3:3:4, 3:3:5, 3:3:6, 3:4:4, 3:4:5, 3:4:6, 3:5:5, 3:5:6, 3:6:6, 4:4:5, 4:4:6, 4:5:5, 4:5:6, 4:6:6, 5:5:6, or 5:6:6. Further provided herein

are transdermal delivery formulations, wherein the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% w/w of one or more emulsifiers. Further provided herein are transdermal delivery formulations, wherein the carrier comprises from about 300 to about 1500 g, from about 500 g to about 1000 g, from about 700 g to about 800 g one or more emulsifiers. Further provided herein are transdermal delivery formulations, wherein the emulsifier comprises a non-ionic emulsifier. Further provided herein are transdermal delivery formulations, wherein said nonionic emulsifier is selected from the group consisting of lecithin, carboxymethylcellulose, a sorbitan ester, and a polysorbate. Further provided herein are transdermal delivery formulations, wherein said nonionic emulsifier is a sorbitan ester selected from the group consisting of sorbitan monolaurate, sorbitan monostearate, sorbitan tristearate, and sorbitan monooleate. Further provided herein are transdermal delivery formulations, wherein said nonionic emulsifier is a polysorbate selected from a class of emulsifiers including but not limited to of polyoxyethylene (20) sorbitan monolaurate (polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (polysorbate 40), polyoxyethylene (20) sorbitan monostearate (polysorbate 60), and polyoxyethylene (20) sorbitan monooleate (polysorbate 80). Further provided herein are transdermal delivery formulations, wherein said polysorbate comprises polysorbate 20, polysorbate 40, polysorbate 60, or polysorbate 80. In some embodiments, the polysorbate is polysorbate 80. Further provided herein are transdermal delivery formulations, wherein the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% w/w water. Further provided herein are transdermal delivery formulations, wherein the carrier comprises from about 300 to about 1500 g, about 500 g to about 1000 g, from about 700 to about 800 g water. Further provided herein are transdermal delivery formulations, wherein said water is distilled water or deionized water. Further provided herein are transdermal delivery formulations, wherein the carrier comprises about 5% (w/w), about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% of at least one oil comprising an unsaturated long-chain fatty acid. Further provided herein are transdermal delivery formulations, wherein the carrier comprises two oils comprising an unsaturated long-chain fatty acid, wherein the two oils are in a ratio by weight of about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:100, 1:1000 relative to each other. Further provided herein are transdermal delivery formulations, wherein the carrier comprises about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g one or more oils comprising an unsaturated long-chain fatty acid. Further provided herein are transdermal delivery formulations, wherein said unsaturated long-chain fatty acid comprises a chain of from 12 to 26 carbons. Further provided herein are

transdermal delivery formulations, wherein said at least one unsaturated long-chain fatty acid comprises one or more double bonds in a cis configuration. Further provided herein are transdermal delivery formulations, wherein said at least one unsaturated long-chain fatty acid comprises adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof. Further provided herein are transdermal delivery formulations, wherein said at least one unsaturated long-chain fatty acid is oleic acid or linoleic acid. Further provided herein are transdermal delivery formulations, wherein said at least one long-chain fatty acid comprises oleic acid and linoleic acid. Further provided herein are transdermal delivery formulations, wherein the one or more oils comprising an unsaturated long-chain fatty acid is one or more plant oils. Further provided herein are transdermal delivery formulations, wherein said one or more plant oils is selected from the group consisting of vegetable oil, nut oil and seed oil. Further provided herein are transdermal delivery formulations, wherein said one or more plant or animal oils comprises macadamia oil, maracuja (passion fruit) oil, safflower oil, sunflower oil, olive oil, avocado oil, canola oil, coconut oil, corn oil, cottonseed oil, flaxseed/linseed oil, grape seed oil, hemp seed oil, palm oil, peanut oil, rice bran oil, sesame oil, soybean oil, Brazil nut oil, almond oil, walnut oil, pecan oil, jojoba oil, chia seed oil, wallflower seed, mustard oil, borage oil, black currant oil, evening primrose oil, chicken fat, cartilage oil, cod liver oil, herring oil, mackerel oil, salmon oil, menhaden oil, sardine oil, or any combination thereof. Further provided herein are transdermal delivery formulations, wherein said one or more plant oils is macadamia oil or maracuja (passion fruit) oil, or a combination thereof. Further provided herein are transdermal delivery formulations, wherein said one or more plant oils comprises macadamia oil and maracuja (passion fruit) oil. Further provided herein are transdermal delivery formulations, wherein the carrier comprises from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g macadamia oil and from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g maracuja oil. Further provided herein are transdermal delivery formulations, wherein the transdermal delivery formulation comprises a lotion, a gel, a cream, an ointment, a liniment, a paste, a film, an encapsulation, or a liquid. Further provided herein are transdermal delivery formulations, wherein said transdermal accelerant further comprises a nitrate source. Further provided herein are transdermal delivery formulations, wherein said nitrate source

is a plant-based nitrate source. Further provided herein are transdermal delivery formulations, wherein said plant-based nitrate source comprises from the group consisting of arugula, spinach, leafy green vegetables, beetroot, or any combination thereof. Further provided herein are transdermal delivery formulations, wherein said plant-based nitrate source is beetroot, and wherein the beetroot is a dried beetroot powder. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises about 2.0%, about 2.5%, about 3.0%, about 3.5%, about 4.0%, about 4.5%, about 5.0%, about 5.5%, about 6.0%, about 6.5%, about 7.0%, about 7.5%, or about 8.0% w/w dried beetroot powder. Further provided herein are transdermal delivery formulations, wherein the transdermal accelerant comprises about 10 g, about 15 g, about 20 g, about 25 g, about 30 g, about 35 g, about 40 g, about 45 g, about 50 g, about 55 g, about 60 g, about 65 g, about 70 g, about 75 g, about 80 g, about 85 g, about 90 g, about 95 g, or about 100 g dried beetroot powder. Further provided herein are transdermal delivery formulations, further comprising a viscosity enhancer, a nutrient, a plant powder or extract, an amino acid, a vitamin, or any combination thereof. Further provided herein are transdermal delivery formulations, wherein said formulation comprises a viscosity enhancer selected from the group consisting of lecithin, aloe vera, glycerin, a plant oil, an animal oil, and collagen. Further provided herein are transdermal delivery formulations, wherein said formulation comprises a nutrient selected from the group consisting of acetyl-L-carnitine, alpha lipoic acid, arginine, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate, calcium carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide. Further provided herein are transdermal delivery formulations, wherein said formulation comprises a plant powder or extract selected from the group consisting of bacopa powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric. Further provided herein are transdermal delivery formulations, wherein said formulation comprises an amino acid selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine. Further provided herein are transdermal delivery formulations, wherein said formulation comprises a vitamin selected from the group consisting of vitamin A, vitamin B-1, vitamin B-2, vitamin B-3, vitamin B-7 & 8 inositol, vitamin B-9 (folic acid), vitamin B-12, vitamin C, vitamin D-3, and vitamin E. Further provided herein are transdermal delivery formulations, wherein said transdermal formulation has a pH of from 2.0 to 6.0. Further provided herein are transdermal delivery formulations, wherein said transdermal formulation has a pH of from 3.0 to 5.0. Further provided herein are transdermal delivery formulations, wherein said transdermal formulation has a pH of from 3.5 to 4.5. Further provided

herein are transdermal delivery formulations, wherein said transdermal formulation has a viscosity at 20°C of from 500 to 10,000 centipoise (cP) or from 1,000 to 5,000 cP, or from 1,500 to 4,000 cP, or from 2,000 to 3,000 cP. Further provided herein are transdermal delivery formulations, wherein said transdermal formulation has a viscosity of about 2,500 cP. Further provided herein are transdermal delivery formulations, wherein the transdermal delivery formulation forms an emulsion comprising a population of droplets from about 10 nm to about 300 nm in diameter.

[0006] Provided herein are transdermal delivery formulations as provided herein, further comprising one or more components for enhancing nutrition and optimizing health, immune support, restful sleep, exercise performance and nitric oxide metabolism, cognitive function, or any combination thereof. Further provided herein are transdermal delivery formulations, further comprising one or more of a hydration electrolyte, cinnamic acid, phenylalanine, resveratrol, and carnitine. Further provided herein are transdermal delivery formulations, further comprising one or more of gamma-aminobutyric acid (GABA), melatonin, and tryptophan. Further provided herein are transdermal delivery formulations, further comprising one or more of vitamin D, vitamin C, citrulline, ribose ATP blood carrier, beetroot, curcumin (turmeric), fish oil, and threonine. Further provided herein are transdermal delivery formulations, further comprising one or more of silicon, leucine, lysine, isoleucine, valine, threonine, phenylalanine, methionine, histidine, tryptophan, vitamin B-5 (pantothenic acid), vitamin B-7 (biotin), vitamin K, acetyl L carnitine, palmitoyl-ethanolamide (PEA), taurine, periwinkle, artichoke, bacopa, ginkgo biloba, nutmeg, alanine, and tyrosine. Further provided herein are transdermal delivery formulations, wherein the formulation comprises: about 12.0% (w/w) citric acid powder; about 20.5% (w/w) apple cider vinegar; about 1.4% (w/w) beetroot powder; about 23.8% (w/w) polysorbate 80; about 22.5% (w/w) distilled water; about 9.9% (w/w) macadamia oil; and about 9.8% (w/w) maracuja oil. Further provided herein are transdermal delivery formulations, wherein the formulation comprises: about 374 g citric acid powder; about 640 g apple cider vinegar; about 44.4 g beetroot powder; about 742 g polysorbate 80; about 700 g distilled water; about 308 g macadamia oil; and about 308 g maracuja oil. Further provided herein are transdermal delivery formulations, further comprising one or more additional ingredients, wherein the additional ingredients comprise: acetyl-L-carnitine (alc), alanine, alpha lipoic acid, arginine, artichoke extract, ashwagandha, bacopa powder, bamboo extract powder, basil powder, beet powder, calcium carbonate, blueberry extract, aloe vera, choline bitartrate, collagen protein peptides, collagen powder, citrulline malate, curcumin powder, creatine, CoQ10, kale powder, folic acid, ginkgo biloba, glutamine, glycerin, ginger, glycine, grape seed extract, green tea, inositol (vitamins B7/B8), histidine, jojoba, pomegranate powder, magnesium glycinate, leucine, lysine, lecithin (sun flower), niacinamide (vitamin B3), nutmeg powder, niacin, methionine, NALT (acetyl tyrosine), NAC, lutein, olive leaf, pea powder,

periwinkle, phenylalanine, potassium, proline, ribose, DAA (d-aspartic acid), serine, hyaluronic acid, taurine, threonine, tryptophan, turmeric, theanine, valine (amino acid), valerian root powder, zinc oxide, vitamin A, vitamin B complex, vitamin B-1, vitamin B-2, vitamin B-5, vitamin B-6 (pyridoxine), vitamin B-7&8, vitamin B-9 (folic acid), vitamin B-12, vitamin C (ascorbic acid), vitamin D-3 (cholecalciferol), vitamin E, vitamin K-2, ginseng, isoleucine, almond oil, broccoli seed oil, collagen liquid, avocado oil, chamomile liquid, vitamin E oil, glycerin (conditioning), grapefruit seed, grape seed oil, gotu kola oil, kava liquid, virgin algae oil (fish oil), jojoba extract oil (organic), lavender oil, macadamia nut oil, meadowfoam seed oil, peppermint oil, maracuja oil (passionfruit), primrose oil, pomegranate oil, BCAA, GABA, collagen oil, virgin algae oil, ashwagandha powder, collagen peptides, guarana powder, and huperzine. Further provided herein are transdermal delivery formulations, wherein the transdermal delivery formulation comprises more than one, more than 2, more than 3, more than 4, more than 5, more than 6, more than 7, more than 8, more than 9, more than 10, more than 11, more than 12, more than 13, more than 14, more than 15, more than 16, more than 17, more than 18, more than 19, more than 20 of the additional ingredients. Further provided herein are transdermal delivery formulations, wherein the one or more active agents comprises a therapeutic agent, a nutraceutical, or a combination thereof. Further provided herein are transdermal delivery formulations, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.

[0007] Provided herein are methods of transdermal delivery, comprising epicutaneous application of the transdermal delivery formulation as described herein. Further provided herein are methods of transdermal delivery, further comprising overlaying an ionized water on to the epicutaneously-applied transdermal delivery formulation.

[0008] Provided herein are methods of manufacture comprising: generating a transdermal accelerant comprising: about 600-2000 ml total of one or more weak organic acids having a pKa from about 2.0 to about 6.0; and generating a carrier comprising: about 400-1000 ml non-ionic surfactant; about 400-1000 ml distilled water; and about 400-1000 ml total of one or more oils comprising one or more of adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof, combining the transdermal

accelerant and the carrier to generate a transdermal delivery formulation; applying an energy to the transdermal delivery formulation to generate an emulsion, wherein the emulsion comprises a population of emulsion droplets from about 10 to about 300 nm in diameter. Further provided herein are methods of manufacture, wherein the one or more weak organic acids comprise mono, di or tri carbonic acids of chain lengths (R) between 1-16. Further provided herein are methods of manufacture, wherein the one or more weak organic acids comprise mono or poly hydroxy moieties of 0-14. Further provided herein are methods of manufacture, wherein the one or more weak organic acids comprise a linear, branched, or cyclic structure. Further provided herein are methods of manufacture, wherein the structure is saturated or unsaturated. Further provided herein are methods of manufacture, wherein the one or more weak organic acids comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof.

[0009] Further provided herein are methods of manufacture, further comprising adding one or more active agents to the transdermal delivery formulation. Further provided herein are methods of manufacture, wherein the one or more active agents comprises a drug, therapeutic agent, a nutraceutical, or a combination thereof. Further provided herein are methods of manufacture, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof. Further provided herein are methods of manufacture, wherein the energy is in the form of a shear force, a cavitation, an impact, or any combination thereof. Further provided herein are methods of manufacture, wherein the energy is applied by vortexing, shearing, stirring, shaking, vortexing, shearing, sonicating, homogenizing, blending, tumbling, extruding, milling, grinding, lyophilization, electrolyzing, heating, cooling, atomizing, or any combination thereof.

[0010] Provided herein are methods of treatment of a condition comprising epicutaneous application of a transdermal delivery formulation described herein and one or more active agents. Further provided herein are methods of treatment, wherein the one or more active agents comprises a drug, a therapeutic agent, a nutraceutical, or a combination thereof. Further provided herein are methods of treatment, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.

[0011] Provided herein are methods of enhancing a feature or condition comprising epicutaneous application of a transdermal delivery formulation described herein and one or more active agents. Further provided herein are methods of enhancing a feature or condition, wherein the feature is a cosmetic feature. Further provided herein are methods of enhancing a feature or condition, wherein

the condition is nutrition, general health, quality of sleep, exercise performance, nitric oxide, physiology, metabolism, cognitive function, or any combination thereof.

[0012] Provided herein are methods of systemic delivery of an active agent, comprising epicutaneous application of a transdermal delivery formulation described herein. Further provided herein are methods of systemic delivery, further comprising overlaying an ionized water on to the epicutaneously-applied transdermal delivery formulation. Further provided herein are methods of systemic delivery, wherein the one or more active agents comprises a therapeutic agent, a nutraceutical, or a combination thereof. Further provided herein are methods of systemic delivery, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.

[0013] These and other related aspects of the present disclosure will be better understood in view of the following drawings and detailed description, which exemplify certain aspects of the various embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0015] **FIGURE 1** is a drawing that depicts the major elements of human skin, including, in sequence from outer layer to inner layer, the epidermis, the dermis, and the hypodermis. As shown, the epidermis comprises an outer surface layer of stratum corneum, which covers the stratum lucidum, the stratum granulosum, stratum spinosum, and basal layer at the inner surface of the epidermis. Vascularization originates at the interface between the dermis and hypodermis, and capillaries extend into the dermis.

[0016] **FIGURE 2** is a drawing that depicts liposomes and micelles comprised within cis-unsaturated fatty acid microemulsions and transdermal delivery formulations disclosed herein.

[0017] **FIGURE 3** is a drawing that depicts a Franz diffusion cell for use in in vitro models for testing transdermal delivery formulations as disclosed in Example 3 by, for example, utilizing non-viable skin to measure penetration and permeation only or utilizing fresh, metabolically active skin to simultaneously measure permeation and skin metabolism.

[0018] **FIGURES 4A-4F** provides bar graphs depicting the data presented in Example 5, Table 9. **FIG. 4A** is a bar chart showing subject scores at baseline and after tests 1, 2, and 3 in the Trails A test for Attention. **FIG. 4B** is a bar chart showing subject scores at baseline and after tests 1, 2, and 3 in the Trails B test for Mental Flexibility. **FIG. 4C** is a bar chart showing subject scores at

baseline and after tests 1, 2, and 3 in the Digital Symbol Substitution test for Executive Function. **FIG. 4D** is a bar chart showing subject scores at baseline and after tests 1, 2, and 3 in the Stroop test for Executive Function. **FIG. 4E** is a bar chart showing subject scores at baseline and after tests 1, 2, and 3 in the Immediate Recognition test for Memory. **FIG. 4F** is a bar chart showing subject scores at baseline and after tests 1, 2, and 3 in the Delayed Recognition test for Memory.

[0019] FIGURES 5A-5N illustrate relative amounts of sub-2 micron diameter particles in emulsion formulations as measured by percent intensity: **FIG. 5A** and **FIG. 5B** show size distribution of Batch 1, sample A, diluted to 1:200 and 1:400, respectively. **FIG. 5C** and **FIG. 5D** show size distribution of Batch 1, sample B, diluted to 1:200 and 1:400, respectively. **FIG. 5E** and **FIG. 5F** show size distribution of Batch 2, sample A, diluted to 1:200 and 1:400, respectively. **FIG. 5G** and **FIG. 5H** show size distribution of Batch 2, sample B, diluted to 1:200 and 1:400, respectively. **FIG. 5I** and **FIG. 5J** show size distribution of Batch 3, sample A, diluted to 1:200 and 1:400, respectively. **FIG. 5K** and **FIG. 5L** show size distribution of Batch 3, sample B, diluted to 1:200 and 1:400, respectively. **FIG. 5M** and **FIG. 5N** show size distribution of Batch 1, sample A, diluted in tap or HPLC water to 1:200 and 1:400, respectively.

DETAILED DESCRIPTION

[0020] Provided herein are transdermal delivery formulations that exhibit unexpected and surprising advantages over technologies that are currently available in the art for the efficient systemic epicutaneous administration of therapeutic agents, drugs, and nutrients, to the bloodstream of a human subject; veterinary animal; domesticated or undomesticated animal, plant or insect; or agricultural animal, plant, or insect. Transdermal delivery formulations disclosed herein comprise a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid having a pKa greater than 2.0 and (b) a microemulsion comprising a nonionic emulsifier, distilled water, and a cis-unsaturated long-chain fatty acid.

[0021] Transdermal delivery formulations disclosed herein comprise acidified micelles and/or liposomes that encapsulate a compound or cluster of compounds, such as a therapeutic agent, drug, or nutrient. These transdermal delivery formulations are made by preparing separately (a) a transdermal accelerant comprising a weak organic acid solution having a pKa greater than 2.0 and (b) a microemulsion comprising a nonionic emulsifier, water, and a cis-unsaturated long-chain fatty acid or acids. Those fatty acids microemulsions are combined with the acidified transdermal accelerants having a pH greater than 1.0 (typically from 1.5 to 2.5) to yield a homogenous transdermal delivery formulation comprising fatty acid micelles and/or liposomes that encapsulate one or more compounds, such as a therapeutic agent, a drug or nutrient. Those micelles and/or liposomes incorporate one or more cis-unsaturated fatty acid having a 12 to 26 carbon chain that

includes one or more double bond in a cis configuration. The resulting micelles and/or liposomes yield transdermal delivery formulations that exhibit ideal solubility and absorption properties.

[0022] While oral delivery is the most common route for the enteral administration of therapeutic agents, drugs, and nutrients, it is unsuitable for delivery of therapeutic agents, drugs, and nutrients that are unstable in the acidic environment of the stomach, which can destroy their biological activity or otherwise block bioavailability. Many therapeutic agents, drugs, and nutrients are poorly absorbed in the intestines and/or are subject to first-pass metabolism wherein the concentration of an active drug or nutrient enters the hepatic portal system and is absorbed and/or metabolized in the liver before reaching the site of action or systemic circulation. Therapeutic agents, drugs, or nutrients administered sublingually (i.e. placed under the tongue) diffuse into the capillary network, are rapidly absorbed, and enter systemic circulation directly, thereby avoiding the gastrointestinal tract and are less susceptible to first-pass metabolism. Moreover, oral delivery is impractical for delivery to unconscious patients or when acute onset is required.

[0023] This disclosure will be better understood in view of the following definitions, which are provided for clarification and are not intended to limit the scope of the subject matter that is disclosed herein.

Definitions

[0024] As used herein, the terms “transdermal delivery/administration” and “epicutaneous delivery/administration” refer interchangeably to the non-enteral, parenteral delivery/administration of drugs, nutrients, and other compounds to a subject through the skin to, thereby, avoid the adverse, degradative environment of the stomach and inefficient delivery of biologically active molecules through the small and large intestines in favor of the direct, non-invasive, and efficient delivery of molecules through the skin.

[0025] As used herein, the terms “transdermal delivery” and “transdermal penetration” refer synonymously to the passive diffusion of drugs, nutrients, and other compounds from the outer surface of the skin, through the stratum corneum and epidermis, and into the blood vasculature or via a shunt pathway, such as through hair follicles and associated sebaceous glands and the sweat ducts.

[0026] As used herein, the term “skin” refers primarily to “human skin,” which comprises three distinct but mutually dependent tissues, namely: 1. The stratified, a vascular, cellular epidermis; 2. Underlying dermis of connective tissues; and; 3. Hypodermis.

[0027] As used herein, the term “stratum corneum” refers to the outermost layer of skin. The stratum corneum is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers parallel to the skin surface, which include dying or

dead, keratinized cells, called comeocytes. Stratum corneum is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the stratum corneum depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

[0028] As used herein, the term “epidermis” refers to the multilayered envelope of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin.

[0029] As used herein, the term “viable epidermis” refers to the cell layer that is situated beneath the stratum corneum, which varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it includes various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basale layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

[0030] As used herein, the term “dermis” refers to the 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. The continuous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.

[0031] As used herein, the term “hypodermis” refers to the subcutaneous fat tissue that supports the dermis and epidermis. The hypodermis serves as a fat storage area, which helps to regulate temperature and provides nutritional support and mechanical protection. “Hypodermis” carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

[0032] As used herein, the terms “transcorneal delivery” and “transcorneal penetration” refer synonymously to both the “intracellular” and “intercellular” penetration of a compound past the stratum corneum.

[0033] “Intracellular transcorneal delivery” and “intracellular transcorneal penetration” refer to the passing of a compound, typically a “hydrophilic compound” through the cells of the stratum corneum. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

[0034] “Intercellular transcorneal delivery” and “intercellular transcorneal penetration” refer to the passing of a compound, typically a “hydrophobic compound” through the cells of the stratum corneum by dissolve in and diffuse through the non-aqueous lipid matrix imbibed between the protein filaments.

[0035] As used herein, the terms “transappendageal delivery” and “transappendageal penetration” refer synonymously to the shunt pathway whereby a compound traverses through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus, and/or the aqueous pathway of the salty sweat glands. The transappendageal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). This route is of substantial relevance for the “transappendageal delivery” or “transappendageal penetration” polar, hydrophobic, and/or lipophilic compounds.

[0036] As used herein, the term “unsaturated fatty acid” refers to a fatty acid comprising one or more C=C double bonds. C=C double bonds can adopt either a “cis” or a “trans” configuration and thereby yield either a “cis unsaturated fatty acid” or a “trans unsaturated fatty acid.”

[0037] As used herein, the term “cis unsaturated fatty acid” refers to a fatty acid comprising one or more C=C double bonds in a “cis” configuration, wherein two hydrogen atoms adjacent to the double bond stick out on the same side of the C=C chain. The rigidity of a double bond freezes its conformation and, in the case of the cis isomer, causes the chain to bend and restricts the conformational freedom of the fatty acid. The more double bonds the chain has in the cis configuration, the less flexibility it has. When a chain has many cis bonds, it becomes quite curved in its most accessible conformations.

[0038] For example, oleic acid, with one double bond, has a “kink” in it, whereas linoleic acid, with two double bonds, has a more pronounced “bend.” α -Linolenic acid, with three double bonds, favors a “hooked” shape. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer or triglycerides in lipid droplets, “cis” bonds limit the ability of fatty acids to be closely packed, and therefore can reduce the melting temperature of the membrane or of the fat and, thereby, “cis unsaturated fatty acids” increase cellular membrane

fluidity as compared to the “trans unsaturated fatty acid” comprising the same atomic constituents/primary molecular structure.

[0039] As used herein, the term “trans unsaturated fatty acid” refers to a fatty acid comprising one or more C=C double bonds in a “trans” configuration, wherein two hydrogen atoms adjacent to the double bond lie on opposite sides of the chain. As a result, they do not cause the chain to bend much, and their shape is similar to straight saturated fatty acids. In most naturally occurring unsaturated fatty acids, each double bond has three (n-3), six (n-6), or nine (n-9) carbon atoms after it, and all double bonds have a cis configuration.

[0040] Words and phrases using the singular or plural number also include the plural and singular number, respectively. For example, terms such as “a” or “an” and phrases such as “at least one” and “one or more” include both the singular and the plural. Terms that are intended to be “open” (including, for example, the words “comprise,” “comprising,” “include,” “including,” “have,” and “having,” and the like) are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense. That is, the term “including” should be interpreted as “including but not limited to,” the term “includes” should be interpreted as “includes but is not limited to,” the term “having” should be interpreted as “having at least.”

[0041] The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.”

[0042] Additionally, the terms “herein,” “above,” and “below,” and words of similar import, when used in this application, shall refer to this application as a whole and not to any particular portion of the application.

[0043] It will be further understood that where features or aspects of the disclosure are described in terms of Markush groups, the disclosure is also intended to be described in terms of any individual member or subgroup of members of the Markush group. Similarly, all ranges disclosed herein also encompass all possible sub-ranges and combinations of sub-ranges and that language such as “between,” “up to,” “at least,” “greater than,” “less than,” and the like include the number recited in the range and includes each individual member.

[0044] Unless specifically stated, as used herein, the term “about” in reference to a number or range of numbers is understood to mean the stated number and numbers $\pm 10\%$ thereof, or 10% below the lower listed limit and 10% above the higher listed limit for the values listed for a range.

Transdermal Delivery Formulations

[0045] In some embodiments, a transdermal delivery formulation comprises an emulsion of two immiscible liquids. An emulsion comprises a dispersed phase in a continuous phase. In some

embodiments, an emulsion is stabilized by comprising one or more surfactants. In some embodiments, the liquids comprise an oil and water. In some embodiments, the oil is dispersed in the oil. In some embodiments, the oil is dispersed in the water. In some embodiments, the emulsion further comprises one or more surfactants. A surfactant is a molecule that typically comprises a hydrophilic head and a hydrophobic tail. The surfactant decreases surface tension between two liquids, stabilizing the emulsion.

[0046] In some embodiments, transdermal delivery formulations disclosed herein comprise acidified micelles and/or liposomes that encapsulate a compound, such as a nutrient or a drug. These transdermal delivery formulations are made by preparing separately (a) a transdermal accelerant comprising a weak organic acid solution having a pKa greater than 2.0 and (b) a microemulsion comprising a nonionic emulsifier, water, and a cis-unsaturated long-chain fatty acid. Those fatty acid microemulsions are combined with the acidified transdermal accelerants having a pH greater than 1.0 (typically from 1.5 to 2.5) to yield a homogenous transdermal delivery formulation comprising fatty acid micelles and/or liposomes that encapsulate one or more compound, such as a nutrient or a drug. Those micelles and/or liposomes incorporate one or more cis-unsaturated fatty acid having a 12 to 26 carbon chain that includes one or more double bond in a cis configuration. The resulting micelles and/or liposomes yield transdermal delivery formulations that exhibit ideal solubility and absorption properties in high humidity conditions, such as in a warm to hot shower or sauna.

[0047] Transdermal delivery formulations according to the present disclosure exhibit unexpected and surprising advantages over technologies that are currently available in the art for the administration of drugs, nutrients, and other compounds to a human subject or domestic, veterinary, or agricultural animal -- in particular, over existing technologies of the epicutaneous administration of drugs, nutrients, and other compounds. Within certain aspects, these transdermal delivery formulations comprise a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid having a pKa greater than 2.0 and (b) a microemulsion comprising a nonionic emulsifier, water, and one or more cis-unsaturated long-chain fatty acid.

[0048] The transdermal delivery formulations disclosed herein achieve the efficient and systemic transdermal delivery/permeation of a compound through the stratum corneum and epidermis and into the bloodstream of a human subject or domestic, veterinary, or agricultural animal and facilitate the rapid diffusion of compounds comprised within the transdermal delivery formulation when applied to the outer skin surface through the stratum corneum, viable epidermis, papillary dermis, and into the microcirculation.

[0049] The viable tissue layer and the capillaries are relatively permeable, and the peripheral circulation is sufficiently rapid. Hence, diffusion through the stratum corneum is traditionally the

rate-limiting step, Skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the un-ionized form of the drug is predominant.

[0050] Once applied to the outer surface of the skin, transdermal delivery formulations traverse the skin. Skin permeability is affected by temperature, irradiation, or sun exposure. Absorption occurs through, without limitation, five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. Thus, a compound within the transdermal delivery formulation moves across the skin barrier according to a number of factors. In some embodiments, formulations traverse the skin barrier via passive diffusion. Passive diffusion is calculated following Fick's first law of diffusion, which relates the diffusive flux to the gradient of the concentration. The flux goes from regions of high concentration to regions of low concentration at a rate and magnitude that is proportional to the concentration gradient

[0051] Fick's first law of diffusion:

$$J = -D \frac{d\phi}{dx}$$

where J is the diffusion flux, of which the dimension is the amount of substance per unit area per unit time. J measures the amount of substance that will flow through a unit area during a unit time interval. D is the diffusion coefficient or diffusivity. ϕ (for ideal mixtures) is the concentration, of which the dimension is the amount of substance per unit volume. x is position, the dimension of which is length. D is proportional to the squared velocity of the diffusing particles, which depends on the temperature, viscosity of the fluid, and the size of the particles according to the Stokes-Einstein relation. The driving force for the one-dimensional diffusion is the quantity $-\partial\phi/\partial x$, which for ideal mixtures is the concentration gradient.

[0052] In some embodiments, transdermal delivery formulations for epicutaneous administration of drugs, nutrients, or other compounds to a human subject or domestic, veterinary, or agricultural animal comprise a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid having a pKa greater than 2.0 and (b) a microemulsion comprising a nonionic emulsifier, water, and a cis-unsaturated long-chain fatty acid.

1. Transdermal Accelerants

[0053] The acidity of a molecule is described by the pKa. The pKa value is the negative base -10 logarithm of the acid dissociation constant (Ka) of a solution refers to acid dissociation constant (Ka) of a solution. The pH of a solution can be predicted when the analytical concentration and pKa values of all acids and bases in the solution are known; conversely, it is possible to calculate the equilibrium concentration of the acids and bases in a solution when the pH is known. These

calculations find application in many different areas of chemistry, biology, medicine, and geology. For example, many compounds used for medication are weak acids or bases. The quantitative behavior of acids and bases in solution can be understood only if their pKa values are known. It measures the strength of an acid by how tightly a proton is held by a Bronsted acid. The lower the value of pKa, the stronger the acid and the greater its ability to donate its protons. Description of the acidity of a particular molecule Ka denotes the acid dissociation constant. It measures how completely an acid dissociates in an aqueous solution. The larger the value of Ka, the stronger the acid as acid largely dissociates into its ions and has lower pKa value.

[0054] The relationship between pKa and Ka is described by the following equation:

$$pKa = -\log[Ka]$$

[0055] Acid dissociation constants, or pKa values, are essential for understanding many fundamental reactions in chemistry. These values reveal the deprotonation state of a molecule in a particular solvent. There is great interest in using theoretical methods to calculate the pKa values for many different types of molecules.

[0056] As used herein, the term “weak organic acid” refers to a compound that partially dissociates when dissolved in a solvent, in particular, a fatty acid microemulsion. The strength of a weak acid can be quantified in terms of a dissociation constant, defined as “pH,” which refers to the negative logarithm of the H ion concentration.

[0057] As used herein, the term “strong acids” refers to those acids that exhibit a negative pKa are that are unsuitable for use in the transdermal delivery formulations disclosed herein. Exemplary “strong acids” are presented in **Table 1**.

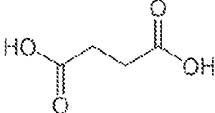
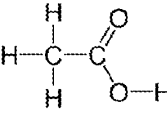
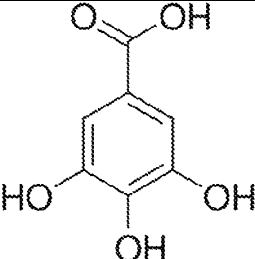
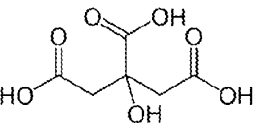
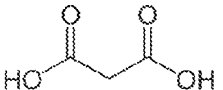
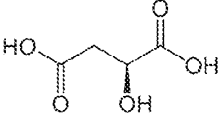
Table 1: Acidic Dissociation Constants (pKa) of Strong Acids

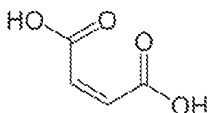
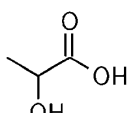
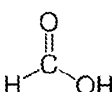
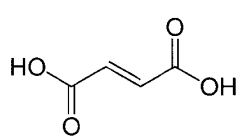
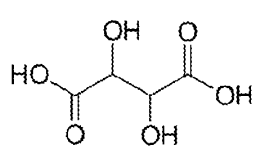
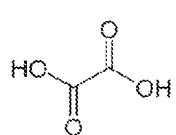
Strong Acids	Formula	pKa (in H ₂ O at ~15-20°C)	
Hydrochloric Acid	HCl	pKa	-5.9
Hydrobromic Acid	HBr	pKa	-8.8
Hydroiodic Acid	HI	pKa	-9.5
Triflic Acid	H[CF ₃ SO ₃]	pKa	-14
Perchloric Acid	H[ClO ₄]	pKa	-15
Nitric Acid	HNO ₃	pKa	-1.6
Sulfuric Acid	H ₂ SO ₄	pKa1	-3

[0058] The epidermis naturally has a slight negative charge, while interior tissues carry a slight positive charge. This potential difference induces movement of ions through the layers in a

unidirectional manner. Under normal conditions, positive ions, for example, sodium (Na^+) are transported toward the outer layers of skin, and negative ions, such as chloride (Cl^-) are transported towards the inner layers. In some embodiments described herein, application of ionic solutions as with a weak acid leverage this charge difference to effect transport across the skin. Transdermal accelerants according to the present disclosure are based upon the observation that weak organic acids, particularly, those having a pK_a at or below the pH of the skin (presented in **Table 2**), when used in combination with a fatty acid microemulsion, as presented herein, greatly enhance skin permeability and delivery of drugs, nutrients, and other compounds through the skin and into the bloodstream.

Table 2: Median Acidic Dissociation Constants (pK_a) of Weak Organic Acids

Weak Organic Acid	Structure	pK_a (in H_2O at $\sim 15\text{-}20^\circ\text{C}$)		Median pK_a (in H_2O at $\sim 15\text{-}20^\circ\text{C}$)
Succinic Acid		pK_{a1}	4.2	4.90
		pK_{a2}	5.6	
Acetic Acid		pK_{a1}	4.756	4.756
Gallic Acid		pK_{a1}	3.13	4.40
		pK_{a2}	8.84	
		pK_{a3}	12.40	
Citric Acid		pK_{a1}	3.128	4.76
		pK_{a2}	4.76	
		pK_{a3}	6.40	
Malonic Acid		pK_{a1}	2.83	4.26
		pK_{a2}	5.69	
		pK_{a2}	5.6	
Malic Acid		pK_{a1}	3.40	3.99
		pK_{a2}	5.20	

Weak Organic Acid	Structure	pKa (in H ₂ O at ~15-20°C)		Median pKa (in H ₂ O at ~15-20°C)
Maleic Acid		pKa1	1.90	3.99
		pKa2	6.07	
Lactic Acid		pKa1	3.86	3.86
Formic Acid		pKa1	3.751	3.751
Fumaric Acid		pKa1	3.03	3.74
		pKa2	4.44	
Tartaric Acid		pKa1	2.89	3.65
		pKa2	4.40	
Oxalic Acid		pKa1	1.25	2.7
		pKa2	4.14	
		pKa2	5.20	
		pKa2	6.07	

[0059] Representative transdermal delivery formulations disclosed herein comprise a transdermal accelerant employing a weak organic acid solution that comprises one or more weak organic acids. In some embodiments, the one or more weak organic acids comprises a mono, di or tri carbonic acid of chain lengths (R) between 1-16. In some embodiments, the weak organic acid comprises mono or poly hydroxy moieties of 0-14. In some embodiments, the organic acid derives from a linear, branched, or cyclic structure. In some embodiments, the structure is saturated or unsaturated. In some embodiments, the one or more weak organic acids comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof. In some embodiments, apple

cider vinegar is provided as a source of acetic acid. Apple cider vinegar is generally about 5% acetic acid, about 94% water, and about 1% carbohydrates.

[0060] Transdermal accelerants suitable for use in the manufacture of these transdermal delivery formulations comprise one or more weak organic acids. In some embodiments, a weak organic acid has a median pKa of from 2.0 to 6.0, from 3.0 to 5.5, from 4.0 to 5.0, or about 4.7. In some embodiments, the one or more weak organic acids comprises a mono, di or tri carbonic acid of chain length (R) between 1-16. In some embodiments, the weak organic acid comprises mono or poly hydroxy moieties of 0-14. In some embodiments, the organic acid derives from a linear, branched, or cyclic structure. In some embodiments, the structure is saturated or unsaturated. In some embodiments, the one or more weak organic acids comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof. Exemplified herein are transdermal accelerants wherein said weak organic acid is citric acid or acetic acid or a combination of both citric acid and acetic acid.

2. Fatty Acid Microemulsions

[0061] Transdermal delivery formulations for epicutaneous administration of a drug, nutrient, or other compound to a human subject or domestic, veterinary, or agricultural animal comprise: a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid (as described herein above) and (b) a microemulsion comprising a nonionic emulsifier, water, and an unsaturated long-chain fatty acid.

[0062] The fatty acid microemulsions according to the present disclosure are based upon the observation that certain unsaturated fatty acids, particularly, those having a C12-C26 carbon chain or a C14-C26 carbon chain or a C16-C26 carbon chain when used in combination with a nonionic emulsifier, particularly, those selected from the group consisting of lecithin, carboxymethylcellulose, a sorbitan ester, and a polysorbate greatly enhance skin permeability and delivery of drugs, nutrients, and other compounds through the skin and into the bloodstream.

[0063] As used herein, the terms “non-ionic surfactant,” “non-ionic emulsifier,” and “non-ionic detergent” refer collectively to compounds that stabilize an emulsion by reducing the oil-water interface tension. Non-ionic surfactants, emulsifiers, and detergents are typically amphiphilic compounds having both a polar, hydrophilic, and water-soluble portion and a non-polar, hydrophobic, and lipophilic portion. Non-ionic surfactants, emulsifiers, and detergents employed in the presently disclosed transdermal delivery formulations include lecithin, carboxymethylcellulose, sorbitan esters, and polysorbates, including polyoxyethylene (20) sorbitan monolaurate (polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (polysorbate

40), polyoxyethylene (20) sorbitan monostearate (polysorbate 60), and polyoxyethylene (20) sorbitan monooleate (polysorbate 80).

[0064] Polysorbate 80, otherwise known as Tween, is a yellow/golden-colored viscous liquid used as an emulsifier or surfactant in foods, medicines, skincare products, and vaccines. Primarily used to solubilize proteins and is widely used in injectable medications, vaccines.

[0065] Polysorbate 80 NF (polyoxyethylene sorbitan monooleate) is derived from RSPO palm oil. It is a non-toxic, nonionic surfactant/emulsifier and a water-soluble yellowish liquid used as a dispersing agent which allows oil and water to mix without the use of alcohol. Polysorbate 80 is a complex mixture consisting of a series of esters and etherates synthesized separately by oleic acid and ethylene oxide with a two-core matrix of sorbitan (Fatty acids in olive oil that are combined with sorbitol. It is plant-derived). Polysorbate 80 helps solubilize ingredients and is considered safe by the FDA for use vitamin and vitamin-mineral preparations which can contain up to 475 milligrams per daily serving of polysorbate 80 (FDA Food Additive Status List).

[0066] Polysorbate 80 has been shown to inhibit reflex pumps involved in the blood-brain barrier (BBB) (e.g., Polysorbate-80 modified neurotoxin microparticles can transport across the BBB). Polysorbate 80 can promote trimethylolpropane phosphate (TMPP) distribution in the brain by increasing drug systemic absorption and then enhanced passive transport of TMPP through the BBB, with the nose-to-brain direct transport percentage decreased to some extent.

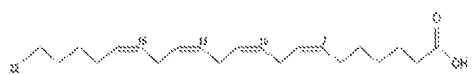
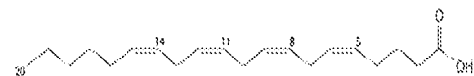
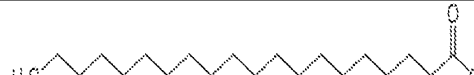
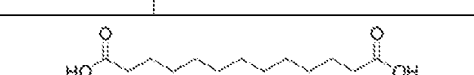
[0067] The geometric differences between the various types of unsaturated fatty acids, as well as between saturated and unsaturated fatty acids, play an important role in biological processes, and in the construction of biological structures (such as cell membranes). Suitable fatty acids for use in the transdermal delivery formulations disclosed herein include unsaturated long-chain fatty acids comprising a chain of from 12 to 26 carbons and one or more double bonds in a cis configuration. As depicted in Table 3, unsaturated long-chain fatty acids comprising a single double bond in a cis configuration (e.g., oleic acid) adopt a “kink” conformation while unsaturated long-chain fatty acids comprising two double bonds in a cis configuration (e.g., linoleic acid) adopt a “bend” conformation, and unsaturated long-chain fatty acids comprising three double bonds in a cis configuration (e.g., Linolenic acid) adopt a “hook” conformation. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer or triglycerides in lipid droplets, cis unsaturated fatty acids increase cellular membrane fluidity by limiting the ability of fatty acids to be closely packed, and thereby reduce the melting temperature of the membrane or of the fat.

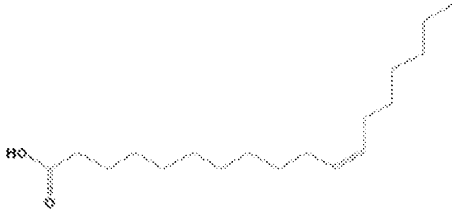
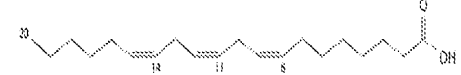
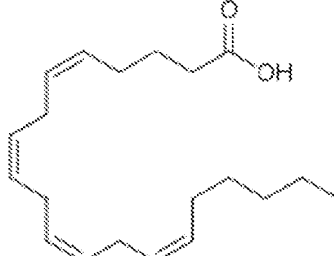
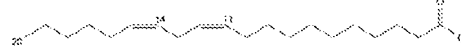
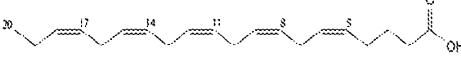
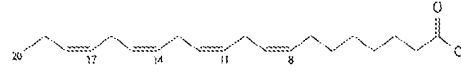
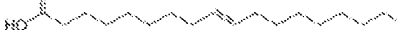
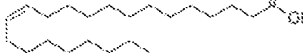
[0068] In contrast, because the adjacent two hydrogen atoms flanking trans double bond lie on opposite sides of the chain, trans unsaturated long-chain fatty acids comprising a chain of from 12 to 26 carbons and one or more double bonds in a trans configuration exhibit little structural

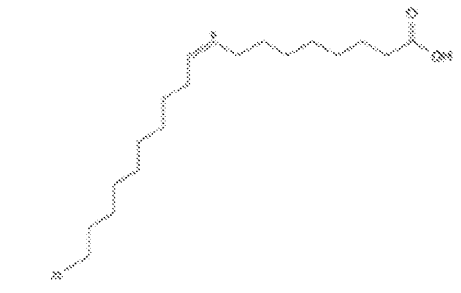
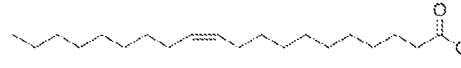
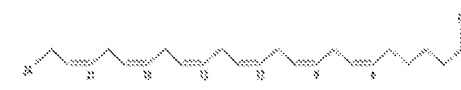
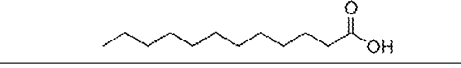
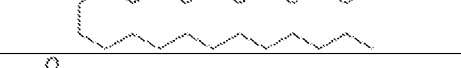
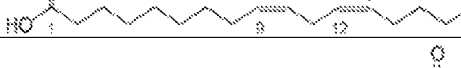
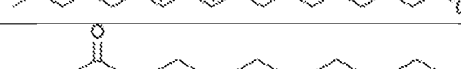
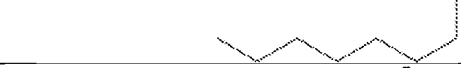
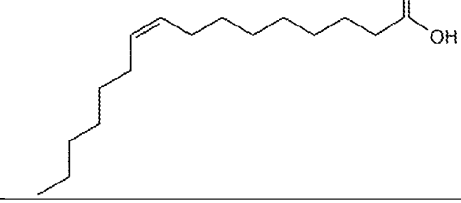
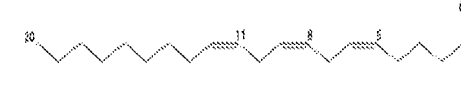
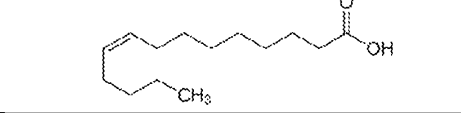
alteration as compared to the corresponding fully-saturated long-chain fatty acid. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer or triglycerides in lipid droplets, trans unsaturated fatty acids decrease cellular membrane fluidity by enhancing the ability of fatty acids to be closely packed, and thereby increase the melting temperature of the membrane or of the fat. See, e.g., **Table 3**, stearic acid (C18:0 saturated), elaidic acid (C18:1 in trans), and linolelaidic acid (C18:2 in trans).

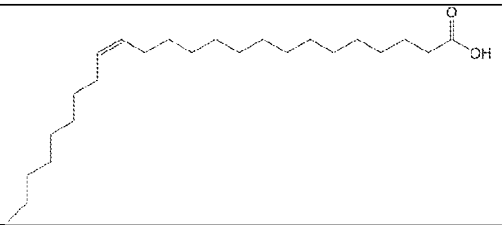
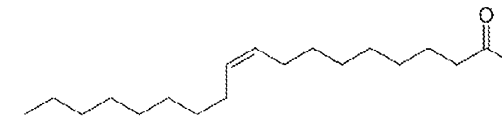
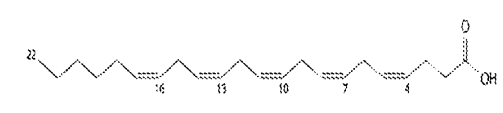
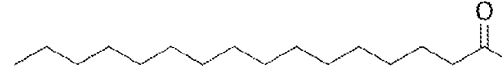
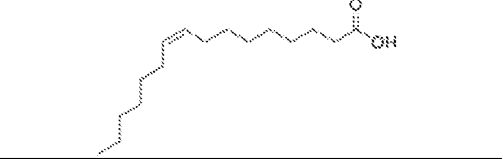
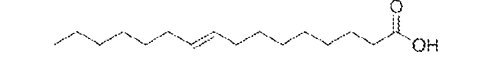
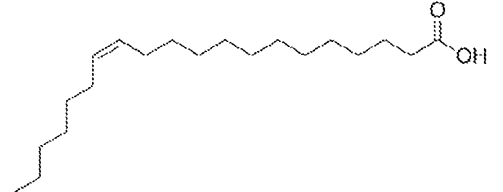
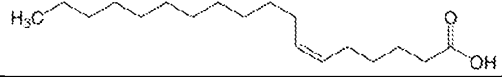
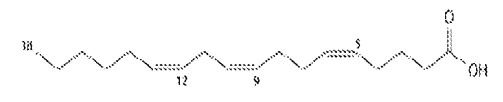
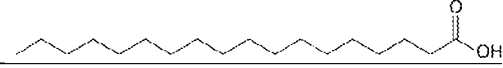
[0069] Thus, disclosed herein are transdermal delivery formulations comprising fatty acid microemulsions comprising one or more 12 to 26 carbon unsaturated long-chain fatty acids. In some embodiments, the one or more 12 to 26 carbon unsaturated long-chain fatty acids comprise adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof. Exemplified herein are transdermal delivery formulations wherein the 12 to 26 carbon unsaturated long-chain fatty acid is oleic acid or linoleic acid as well as transdermal delivery formulations wherein the 12 to 26 carbon unsaturated long-chain fatty acid comprises a combination oleic acid and linoleic acid.

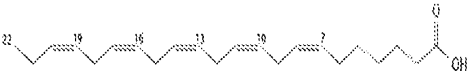
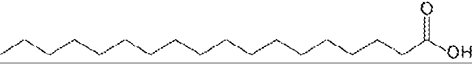
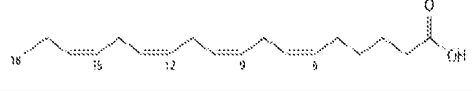
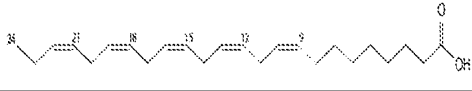
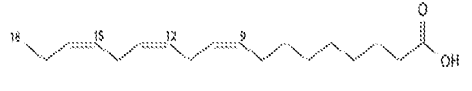
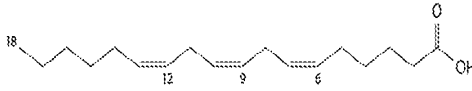
Table 3: Structural and Physical Properties of Unsaturated Long-chain Fatty Acids

Fatty Acid	Naturally Occurring Source	Carbons: Double Bonds	Double Bonds (cis or trans)	Secondary Structure
Adrenic acid	naturally occurring in humans	C22:4	cis	
Arachidonic acid	Various Plant	C20:4	cis	
Arachidic acid	Various Plant	C20:0	saturated	
Behenic acid	drumstick tree (Moringa oleifera)	C22:0	saturated	
Brassidic acid	rapeseed plant oil extracts and canola oil.	C22:1	trans	

Fatty Acid	Naturally Occurring Source	Carbons: Double Bonds	Double Bonds (cis or trans)	Secondary Structure
Cervonic acid	maternal milk, fish oil	C22:6	cis	
Cis-Vaccenic acid	milk, butter, and yogurt.	C18:1	cis	
Dihomo-γ-Linolenic acid	only in trace amounts in animal products	C20:3	cis	
Docosadienoic acid	mushroom	C22:2	cis	
Eicosadienoic acid	Salvia hispanica, Arbutia punctulata	C20:2	cis	
Eicosapentaenoic acid	cod liver, herring, mackerel, salmon, menhaden and sardine	C20:5	cis	
Eicosatetraenoic acid	Mortierella alpina 1S-4 is a fungus	C20:4	cis	
Eicosenoic acid	krill drying oil	C18:3	cis	
Elaidic acid	hydrogenated vegetable oil	C18:1	trans	
Erucic acid	wallflower seed, mustard oil	C22:1	cis	

Fatty Acid	Naturally Occurring Source	Carbons: Double Bonds	Double Bonds (cis or trans)	Secondary Structure
Gadoleic acid	Cod Liver Oil, marine animal oils	C20:1	cis	
Gondoic acid	jojoba oil (edible but non-caloric and non-digestible)	C20:1	cis	
Herring acid	herring oil	C24:6	cis	
Lauric acid	coconut oil	C12:0	saturated	
Lignoceric acid	peanut oil	C24:0	saturated	
Linoleic acid	peanut oil, chicken fat, olive oil	C18:2	cis	
Linolelaidic acid	partially hydrogenated vegetable oils	C18:2	trans	
Margaric acid	fat, milkfat of ruminants	C17:0	saturated	
Margoleic acid	olive oil	C17:1	cis	
Mead acid	cartilage	C20:3	cis	
Myristoleic acid	Saw palmetto	C14:1	cis	

Fatty Acid	Naturally Occurring Source	Carbons: Double Bonds	Double Bonds (cis or trans)	Secondary Structure
Nervonic acid	King salmon, flaxseed, sockeye salmon, sesame seed, macadamia nuts	C24:1	cis	
Oleic acid	olive oil, pecan oil, canola oil	C18:1	cis	
Ozubondo acid	plants and mice	C22:5	cis	
Palmitic acid	olive oil	C16:0	saturated	
Palmitoleic acid	macadamia nuts	C16:1	cis	
trans-Palmitoleic acid	milk, cheese, yogurt, and butter.	C16:1	trans	
trans-Vaccenic acid	Agaricus blazei, Allamanda cathartica,	C18:1	trans	
Paullinic acid	guarana	C20:1	cis	
Petroselinic acid	vegetable oil of Coriandrum sativum fruits	C18:1	cis	
Pinolenic acid	pine nut oil	C18:3	cis	
Sapienic acid	human skin	C16:1	cis	

Fatty Acid	Naturally Occurring Source	Carbons: Double Bonds	Double Bonds (cis or trans)	Secondary Structure
Sardine acid	sardines	C22:5	cis	
Stearic acid	olive oil	C18:0	saturated	
Stearidonic acid	seed oils of hemp, blackcurrant, corn gromwell	C18:4	cis	
Tetracosapentaenoic acid	salmon	C24:5	cis	
α -Linolenic acid	flaxseeds, chia seeds, walnuts, lin seed	C18:3	cis	
γ -Linolenic acid	borage oil, black currant oil, evening primrose oil and safflower oil	C18:3	cis	

[0070] In related embodiments, the presently disclosed transdermal delivery formulations for epicutaneous administration of a therapeutic agent, drug, nutrient, or other compound to a human subject; veterinary animal; domesticated or undomesticated animal, plant or insect; or agricultural animal, plant, or insect comprise: a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid (as described herein above) and (b) a microemulsion comprising a nonionic emulsifier, water, and plant or animal oil.

[0071] Suitable plant or animal oils for use in the microemulsions disclosed herein include vegetable oils, nut oils, seed oils or animal oils comprising from 50%-100%, or from 60%-90%, or from 70%-90%, or from 80%-90% of the total unsaturated fatty acid content as long-chain unsaturated fatty acids comprising one or more cis double bonds. Representative suitable plant or animal oils are selected from the group consisting of macadamia oil, maracuja (passion fruit) oil, safflower oil, sunflower oil, olive oil, avocado oil, canola oil, coconut oil, corn oil, cottonseed oil, flaxseed/linseed oil, grape seed oil, hemp seed oil, palm oil, peanut oil, rice bran oil, sesame oil, soybean oil, Brazil nut oil, almond oil, walnut oil, pecan oil, jojoba oil, chia seed oil, wallflower seed, mustard oil, borage oil, black currant oil, evening primrose oil, chicken fat, cartilage oil, cod liver oil, herring oil, mackerel oil, salmon oil, menhaden oil, sardine oil, or any combination thereof.

[0072] Exemplified herein are transdermal delivery formulations comprising one or more plant oils as presented in **Table 4** “Plant and Animal Oil Unsaturated Fatty Acid Profiles.” In some embodiments, plant or animal oils comprise macadamia oil, maracuja (passion fruit) oil, safflower oil, sunflower oil, olive oil, and almond oil, fish oil, chicken fat, or any combination thereof. In certain aspects, the transdermal delivery formulation comprises macadamia oil or maracuja (passion fruit) oil. In other aspects, the plant or animal oil comprises a combination of macadamia oil and maracuja (passion fruit) oil.

Table 4: Plant and Animal Oil Unsaturated Fatty Acid Profiles

Macadamia Oil			
Fatty Acid	Average Fatty Acid Content	Primary Structure (Carbons: Double Bonds)	Double Bonds (cis or trans)
Palmitoleic Acid	19.5%	C16:1	cis Omega-7 Fatty Acid
Oleic Acid	61.0%	C18:1	cis Omega-9 Fatty Acid
Linoleic Acid	2.2%	C18:2	cis Essential omega-6 Fatty Acid
Eicosenoic	2.8%	C20:1	cis Omega-3 and -6 Fatty Acids
Total % Unsaturated Fatty Acids	85.5%		
Salmon Oil			
Fatty Acid	Average Fatty Acid Content	Primary Structure (Carbons: Double Bonds)	Double Bonds (cis or trans)
Palmitoleic Acid	8.7%	C16:1	cis Omega-7 Fatty Acid
Oleic Acid	18.6%	C18:1	cis Omega-9 Fatty Acid
Linoleic Acid	1.2%	C18:2	cis Essential omega-6 Fatty Acid
Eicosenoic	8.4%	C20:1	cis Omega-3 and -6 Fatty Acids
Erucic	5.5%	C22:1	cis Omega-3 and -6 Fatty Acid
Eicosapentaenoic	5.0%	C20:5	cis Essential omega-3 Fatty Acid
Docosahexaenoic	13.8%	C22:6	cis Essential omega-3 Fatty Acid
Stearidonic	2.1%	C18:4	cis Essential omega-3 Fatty Acid
Docosapentaenoic	2.9%	C22:5	cis Essential omega-3 Fatty Acid
Linolenic	0.6%	C18:3	cis Essential omega-3 Fatty Acid
Arachidonic	0.9%	C20:4	cis Essential omega-3 Fatty Acid

Total % Unsaturated Fatty Acids	74.7%	
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<u>Sardine Oil</u>			
Fatty Acid	Average Fatty Acid Content	Primary Structure (Carbons: Double Bonds)	Double Bonds (cis or trans)
Palmitoleic Acid	9.2%	C16:1	cis Omega-7 Fatty Acid
Oleic Acid	11.4%	C18:1	cis Omega-9 Fatty Acid
Linoleic Acid	0.9%	C18:2	cis Essential omega-6 Fatty Acid
Eicosenoic	3.2%	C20:1	cis Omega-3 and -6 Fatty Acids
Erucic	3.8%	C22:1	cis Omega-3 and -6 Fatty Acid
Eicosapentaenoic	16.9%	C20:5	cis Essential omega-3 Fatty Acid
Docosahexaenoic	21.9%	C22:6	cis Essential omega-3 Fatty Acid
Stearidonic	2.0%	C18:4	cis Essential omega-3 Fatty Acid
Docosapentaenoic	2.5%	C22:5	cis Essential omega-3 Fatty Acid
Linolenic	1.3%	C18:3	cis Essential omega-3 Fatty Acid
Arachidonic	1.6%	C20:4	cis Essential omega-3 Fatty Acid
Total % Unsaturated Fatty Acids	74.7%		

<u>Tallow</u>			
Fatty Acid	Average Fatty Acid Content	Primary Structure (Carbons: Double Bonds)	Double Bonds (cis or trans)
Palmitoleic Acid	3.0%	C16:1	cis Omega-7 Fatty Acid
Oleic Acid	47.0%	C18:1	cis Omega-9 Fatty Acid
Linoleic Acid	3.0%	C18:2	cis Essential omega-6 Fatty Acid
Linolenic	1.0%	C18:3	cis Omega-9 Fatty Acids
Total % Unsaturated Fatty Acids	54.0%		

<u>Herring Oil</u>			
Fatty Acid	Average Fatty Acid Content	Primary Structure (Carbons: Double Bonds)	Double Bonds (cis or trans)
Palmitoleic Acid	7.5%	C16:1	cis Omega-7 Fatty Acid

Oleic Acid	12.9%	C18:1	cis Omega-9 Fatty Acid
Linoleic Acid	1.1%	C18:2	cis Essential omega-6 Fatty Acid
Eicosenoic	15.1%	C20:1	cis Omega-3 and -6 Fatty Acids
Erucic	22.0%	C22:1	cis Omega-3 and -6 Fatty Acid
Eicosapentaenoic	6.8%	C20:5	cis Essential omega-3 Fatty Acid
Docosahexaenoic	5.8%	C22:6	cis Essential omega-3 Fatty Acid
Stearidonic	1.4%	C18:4	cis Essential omega-3 Fatty Acid
Docosapentaenoic	0.8%	C22:5	cis Essential omega-3 Fatty Acid
Linolenic	0.7%	C18:3	cis Essential omega-3 Fatty Acid
Arachidonic	0.3%	C20:4	cis Essential omega-3 Fatty Acid
Total % Unsaturated Fatty Acids	74.4%		

3. Composition of Exemplary Transdermal Delivery Formulation

[0073] In some embodiments, a transdermal delivery formulation as provided herein comprises a transdermal accelerant and a carrier. In some embodiments, the transdermal accelerant and the carrier are present in the transdermal delivery formulation at a ratio of about 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, or 1:8 by weight. In some embodiments, the transdermal delivery formulation comprises about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% weight/weight (w/w) of the transdermal accelerant. In some embodiments, a transdermal delivery formulation of about 3100 g comprises about 200 g, about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g, about 1600 g, about 1700 g, about 1800 g, about 1900 g, or about 2050 g of the transdermal accelerant.

[0074] In some embodiments, the transdermal delivery formulation comprises about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% weight/weight (w/w) of the carrier. In some embodiments, a transdermal delivery formulation of about 3100 g comprises about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g, about 1600 g, about 1700 g, about 1800 g, about 1900 g, about 2000 g, about 2100 g, about 2200 g, about 2300 g, or about 2400 g of the carrier.

[0075] In some embodiments, the transdermal accelerant comprises one or more weak organic acids. In some embodiments, the transdermal accelerant comprises 2, 3, 4, 5, 6, 7, 9, 9 or 10 weak organic acids. In some embodiments, the transdermal accelerant comprises two or more weak organic acids. In some embodiments, the transdermal accelerant comprises 2 weak organic acids at a ratio by weight of about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:9, or 1:10 relative to each other. In some embodiments, the transdermal accelerant comprises 3 weak organic acids in equal amounts by weight. In some embodiments, the transdermal accelerant comprises 3 weak organic acids at a ratio by weight of X:Y:Z, wherein X = 1-5, Y=1-6, and Z=1-6. In some embodiments, the ratio is about 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:1:5, 1:1:6, 1:2:2, 1:2:3, 1:2:4, 1:2:5, 1:2:6, 1:3:3, 1:3:4, 1:3:5, 1:3:6, 1:4:4, 1:4:5, 1:4:6, 1:5:5, 1:5:6, 1:6:6, 2:2:3, 2:2:4, 2:2:5, 2:2:6, 2:3:3, 2:3:4, 2:3:5, 2:3:6, 2:4:4, 2:4:5, 2:4:6, 2:5:5, 2:5:6, 2:6:6, 3:3:4, 3:3:5, 3:3:6, 3:4:4, 3:4:5, 3:4:6, 3:5:5, 3:5:6, 3:6:6, 4:4:5, 4:4:6, 4:5:5, 4:5:6, 4:6:6, 5:5:6, or 5:6:6. In some embodiments, the transdermal accelerant comprises about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, about 99% (w/w) of one or more weak organic acids. In some embodiments, the transdermal delivery formulation comprises about 5% (w/w), about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% of one or more weak organic acids. In some embodiments, the weak organic acids comprise citric acid and apple cider vinegar.

[0076] In some embodiments, a transdermal accelerant of about 1050 g comprises one or more weak organic acids by weight in a range of about 400 g to about 1050 g. In some embodiments, a transdermal accelerant of about 1050 g comprises from about 400 g to about 1500 g, from about 1000 g to about 1500 g. In some embodiments, a transdermal accelerant of about 1050 g comprises about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g of one or more weak organic acids.

[0077] In some embodiments, the weak organic acids comprise citric acid and apple cider vinegar. In some embodiments, a transdermal accelerant of about 1050 g comprises from about 100 g to about 700 g, from about 200 g to about 500 g, from about 300 g to about 400 g citric acid. In some embodiments, a transdermal accelerant of about 1050 g comprises about 100 g, about 150 g, about 200 g, about 250 g, about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g citric acid. In some embodiments, a transdermal accelerant of about 1050 g comprises from about 300 g to about 1300 g, from about 400 g to about 900 g, from about 600 g to about 700 g apple cider vinegar. In some embodiments, a transdermal accelerant of about 1050 g comprises about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g, about 750 g, about 800 g, about 850 g, about 900 g, about 950 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g apple cider

vinegar. In some embodiments, a transdermal accelerant of about 1050 g comprises about 374 g citric acid and about 640 g apple cider vinegar.

[0078] In some embodiments, the transdermal accelerant further comprises a nitrate source. In some embodiments the nitrate source is a plant-based nitrate source. In some embodiments, the plant-based nitrate source comprises arugula, spinach, leafy green vegetables, beetroot, or any combination thereof. In some embodiments, the plant-based nitrate source is a dried powder. In some embodiments, the transdermal accelerant comprises about 2.0%, about 2.5%, about 3.0%, about 3.5%, about 4.0%, about 4.5%, about 5.0%, about 5.5%, about 6.0%, about 6.5%, about 7.0%, about 7.5%, or about 8.0% w/w of a nitrate source. In some embodiments, a transdermal accelerant of about 1050 g comprises from about 10 g to about 100 g, from about 30 g to about 70 g, from about 40 g to about 50 g of a nitrate source. In some embodiments, a transdermal accelerant of about 1050 g comprises about 10 g, about 15 g, about 20 g, about 25 g, about 30 g, about 35 g, about 40 g, about 45 g, about 50 g, about 55 g, about 60 g, about 65 g, about 70 g, about 75 g, about 80 g, about 85 g, about 90 g, about 95 g, or about 100 g of a nitrate source. In some embodiments, the transdermal delivery formulation comprises about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.5%, about 2.0%, about 2.5%, about 3.0% w/w of a nitrate source. In some embodiments, the plant-based nitrate source is beetroot powder. In some embodiments, a transdermal accelerant of about 1050 g comprises 44.4 g beetroot powder.

[0079] In some embodiments, the carrier as provided herein comprises at least one emulsifier, at least one oil comprising a long-chain fatty acid, and water. In some embodiments, the carrier comprises equal parts by weight of the emulsifier, oil, and water. In some embodiments, the carrier comprises an emulsifier, an oil, and water at a ratio by weight of X:Y:Z, wherein X = 1-5, Y=1-6, and Z=1-6. In some embodiments, about 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:1:5, 1:1:6, 1:2:2, 1:2:3, 1:2:4, 1:2:5, 1:2:6, 1:3:3, 1:3:4, 1:3:5, 1:3:6, 1:4:4, 1:4:5, 1:4:6, 1:5:5, 1:5:6, 1:6:6, 2:2:3, 2:2:4, 2:2:5, 2:2:6, 2:3:3, 2:3:4, 2:3:5, 2:3:6, 2:4:4, 2:4:5, 2:4:6, 2:5:5, 2:5:6, 2:6:6, 3:3:4, 3:3:5, 3:3:6, 3:4:4, 3:4:5, 3:4:6, 3:5:5, 3:5:6, 3:6:6, 4:4:5, 4:4:6, 4:5:5, 4:5:6, 4:6:6, 5:5:6, or 5:6:6.

[0080] In some embodiments, the carrier comprises about 5% (w/w), about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% of at least one oil comprising a long-chain fatty acid. In some embodiments, the carrier comprises two oils comprising a long-chain fatty acid. In some embodiments, the carrier comprises two oils comprising a long-chain fatty acid in a ratio by weight of about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:9, 1:10, 1:100 or 1:1000 relative to each other.

[0081] In some embodiments, a carrier of about 2050 g comprises about 300-1500 g one or more oils comprising a long-chain fatty acid. In some embodiments, a carrier of about 2050 g comprises

about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g one or more oils comprising a long-chain fatty acid.

[0082] In some embodiments, the one or more oils comprise macadamia oil and maracuja oil. In some embodiments, a carrier of about 2050 g comprises from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g macadamia oil. In some embodiments, a carrier of about 2050 g comprises about 100 g, about 150 g, about 200 g, about 250 g, about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, or about 600 g macadamia oil. In some embodiments, a carrier of about 2050 g comprises from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g maracuja oil. In some embodiments, a carrier of about 2050 g comprises about 100 g, about 150 g, about 200 g, about 250 g, about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, or about 600 g maracuja oil. In some embodiments, a carrier of about 2050 g comprises about 308 g macadamia oil and about 308 g maracuja oil.

[0083] In some embodiments, the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% w/w of one or more emulsifiers. In some embodiments, the carrier comprises two emulsifiers. In some embodiments, the carrier comprises two emulsifiers in a ratio by weight of about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:9, or 1:10 relative to each other.

[0084] In some embodiments, a carrier of about 2050 g comprises from about 300 to about 1500 g, from about 500 g to about 1000 g, from about 700 g to about 800 g one or more emulsifiers. In some embodiments, a carrier of about 2050 g comprises about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g one or more emulsifiers. In some embodiments, the emulsifier comprises a nonionic emulsifier. In some embodiments, the emulsifier comprises polysorbate 80. In some embodiments, a carrier of about 2050 g comprises about 742 g polysorbate 80.

[0085] In some embodiments, the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% w/w water. In some embodiments, a carrier of about 2050 g comprises from about 300 to about 1500 g, about 500 g to about 1000 g, from about 700 to about 800 g water. In some embodiments, a carrier of about 2050 g comprises about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, or about 1500 g water. In some embodiments, the water is distilled water. In some embodiments, the water is deionized water.

[0086] In some embodiments, a transdermal delivery formulation described herein comprises a formulation as described **Table 5**.

Table 5

Transdermal Accelerant	Volume added (ml)	Density (g/ml)	Calculated weight (g)	Percentage (wt/wt)
Citric Acid Powder	340	1.1	374	12.0%
Apple Cider Vinegar	800	0.8	640	20.5%
Beetroot Powder	60	0.74	44.4	1.4%
Carrier				
Polysorbate 80	700	1.06	742	23.8%
Distilled Water	700	1	700	22.5%
Macadamia Oil	350	0.88	308	9.9%
Maracuja Oil	350	0.88	308	9.9%
Total			3116.4	

Emulsions

[0087] Emulsions are a dispersion of droplets of a first liquid in an immiscible second liquid. In some embodiments, the emulsion provided herein is an oil in water emulsion. In some embodiments, the emulsion provided herein is a water in oil emulsion. In some embodiments, a transdermal accelerant described herein is combined with a carrier described herein.

[0088] In some embodiments, emulsions are generated by applying an energy to disperse a first phase of the emulsion in a second phase. In some embodiments, the energy is applied by vortexing, shearing, stirring, shaking, vortexing, shearing, sonicating, homogenizing, blending, tumbling, extruding, milling, grinding, lyophilization, electrolyzing, heating, cooling, atomizing, or any combination thereof. In some embodiments, the emulsion is generated using a paddle mixer, a rotor-stator mixer, a blender, a homogenizer, a sonicator, a vortexer, a high pressure homogenizer, or a microfluidizer.

[0089] In some embodiments, emulsions described herein comprise particles from about 10 nm to about 300 nm, from about 20 nm to about 500 nm, from about 500 nm to about 100 μ m. In some embodiments, an emulsion described herein comprises a mean particle size of about 10 nm, about 50 nm, about 100 nm, about 200 nm, about 300 nm, about 400 nm, about 500 nm, about 600 nm, about 700 nm, about 800 nm, about 900 nm, about 1000 nm, about 5 μ m, about 10 μ m, about 15 μ m, about 20 μ m, about 25 μ m, about 30 μ m, about 35 μ m, about 40 μ m, about 45 μ m, about 50 μ m, about 60 μ m, about 70 μ m, about 80 μ m, about 90 μ m, or about 100 μ m. A “micro-emulsion,” as provided herein, comprises an emulsion comprising a median particle size from about 10 nm to about 300 nm. A “nano-emulsion” comprises an emulsion comprising a median particle size from

about 20 nm to about 500 nm. A “macro-emulsion” comprises an emulsion comprising a median particle size from about 500 nm to about 100 μ m.

[0090] Emulsion stability is measured by the growth in median particle size of the emulsion over a period of time. In some embodiments, the median particle size is measured over one hour, one day, one week, two weeks, one month, two months, three months, six months, nine months, or one year. In some embodiments, the median particle size increases less than about 10%, about 20%, about 30%, about 40%, about 50%, or about 60% over the period of time.

Application

[0091] In some embodiments, a transdermal delivery formulation described herein is applied directly to a skin surface. In some embodiments, the transdermal delivery formulation is applied to a mucosal surface. In some embodiments, the transdermal delivery formulation is applied as a lotion, a gel, a cream, an ointment, a liniment, a paste, a film, an encapsulation, or a liquid.

[0092] Ionization of the skin surface, in some embodiments, increases the conductivity of the skin. In some embodiments, increasing conductivity of the skin improves penetration of a transdermal delivery formulation as described herein. In some embodiments, an ionic solution is applied to the skin after application of the transdermal delivery formulation. In some embodiments, a further overlay of an ionized water is applied following application of the transdermal delivery formulation. In some embodiments, the ionized water is in a liquid form. In some embodiments, the ionized water is in a gaseous form. In some embodiments, the ionized water is applied as a wash, a spray, a steam, or any other form to provide contact with the skin.

Additional additives

[0093] Transdermal delivery formulations may further comprise one or more active agents. In some embodiments, an active agent comprises a therapeutic agent, a drug, a nutraceutical, a nutrient, and/or other compound. In some embodiments, the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof. In some embodiments, the nutraceutical comprises a compound or food product with an additional pharmaceutical effect.

[0094] Transdermal delivery formulations may alternatively or additionally comprise one or more viscosity enhancer, nutrient, plant powder or extract, amino acid, a vitamin, or any combination thereof. Representative viscosity enhancers may be selected from the group consisting of lecithin, aloe vera, glycerin, plant oil, animal oil, and collagen.

[0095] Representative nutrients may be selected from the group consisting of acetyl-L-carnitine, alpha lipoic acid, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate,

calcium carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide.

[0096] Representative plant powders or extracts may be selected from the group consisting of bacopa powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric.

[0097] Representative amino acids may be selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine.

[0098] Within other embodiments, the presently disclosed transdermal delivery formulations comprise a transdermal accelerant wherein the nitrate source is a plant-based nitrate source, such as an arugula, spinach, leafy green vegetables, or beetroot nitrate source.

[0099] Within related aspects, the presently disclosed transdermal delivery formulations comprise a carrier serum that comprises a nitrate source, such as a plant-based nitrate source, such as an arugula, spinach, leafy green vegetables, or beetroot nitrate source.

[0100] As used herein, the terms “nitrate” and “NO₃-” refer interchangeably to an inorganic precursor of “nitric oxide.” Laue, Ullmann’s Encyclopedia of Industrial Chemistry (Ed. Weinheim, Wiley-VCH 2006). Plant sources that are especially high in inorganic nitrate include leafy green vegetables, such as spinach and arugula, and beetroot. Dietary nitrate supplementation has been shown to increase endurance exercise performance.

[0101] Within yet other aspects, the transdermal delivery formulation further comprises viscosity enhancer, nutrient, plant powder or extract, amino acid, a vitamin, or any combination thereof. As used herein, the term “viscosity” and “thickness” refers interchangeably to the resistance of a fluid, compound, serum, composition, or formulation to deformation at a given rate. “Viscosity enhancer” refers to compounds that are added to increase the “viscosity” and “thickness” of a composition or formulation. “Viscosity” and “thickness” of a fluid, compound, serum, composition, or formulation typically decreases with increasing temperature. “Viscosity” can be measured with a viscometer, a rheometer, a Zahn cup, or a Ford viscosity cup. For example, oil “viscosity” can be determined using a Cannon-Fenske capillary viscometer, after calibration with 60% sucrose solution in a constant temperature bath regulated to +/-0.05°C. The SI unit of viscosity is the newton-second per square meter (N.s/m²), pascal.second (Pa.s), kilogram per meter per second (kg.m⁻¹.s⁻¹), and Poiseuille (PI). The CGS unit is the poise (P, or g.cm⁻¹.s⁻¹ = 0.1 Pa.s).

[0102] Certain core transdermal delivery formulations comprise a viscosity enhancer that is selected from the group consisting of lecithin, aloe vera, glycerin, plant oil, animal oil, and collagen. Other transdermal delivery formulations comprise a nutrient that is selected from the

group consisting of acetyl-L-carnitine, alpha lipoic acid, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate, calcium carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide.

[0103] Further core transdermal delivery formulations comprise a plant powder, oil, or extract that is selected from the group consisting of bacopa powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric. Other core transdermal delivery formulations comprise an amino acid that is selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine. Yet other core transdermal delivery formulations comprise a vitamin that is selected from the group consisting of vitamin A, vitamin B-1, vitamin B-2, vitamin B-3, vitamin B-7 & 8 inositol, vitamin B-9 (folic acid), vitamin B-12, vitamin C, vitamin D-3, and vitamin E.

[0104] Also provided herein are transdermal delivery formulations that are enriched with one or more components for enhancing nutrition and optimizing health (“Core”), immune support, restful sleep (“Sleep”), exercise performance (“Exercise”) and nitric oxide metabolism (“iNOS”), cognitive function (“Cognition”), or any combination thereof. Those transdermal delivery formulations are exemplified by the representative transdermal delivery formulations presented in **Table 6**.

[0105] Transdermal delivery formulations for enhancing exercise performance may comprise one or more of a hydration electrolyte, cinnamic acid, phenylalanine, resveratrol, and carnitine.

[0106] Electrolytes comprise positively and negatively charged ions that conduct electrical activity to perform various functions within the body. Electrolyte concentrations in vivo are regulated to maintain fluid balance, muscle contraction, and neural activity, which are all essential to high levels of exercise performance and basic daily functions. Electrolytes that are lost through sweating include sodium (Na⁺), and chloride (Cl⁻), potassium (K⁺), Magnesium (Mg²⁺), and Calcium (Ca²⁺). Peak exercise performance, therefore, requires replenishment of hydration electrolytes. Athletes exercising in extreme conditions (for three or more hours continuously) must consume electrolytes to prevent dehydration and/or hyponatremia.

[0107] Arginine a basic amino acid which is a constituent of most proteins. It is an essential nutrient in the diet of vertebrates. Chemical formula: $\text{HN}=\text{C}(\text{NH}_2)\text{NH}(\text{CH}_2)_3\text{CH}(\text{NH}_2)\text{COOH}$.

[0108] Cinnamic acid plays key roles in the formation of complex phenolic compounds, which occur primarily as esters of quinic acid or esterified to malic or tartaric acids, or sugars. Chlorogenic acid (5-caffeoylquinic acid) is an important cinnamic acid that is observed in fruits and contributes 25% of the dry weight of the bilberry (*Vaccinium*) fruit. Chlorogenic acid can be

isolated from green coffee beans, and forms a black compound with iron, believed to be responsible for the blackening of cut or cooked potatoes. Anthocyanin and flavonoid glycosides are also acylated by cinnamic acids through sugar hydroxyl groups, with p-coumaric acid the most common acylating agent. In addition to forming esters, hydroxylated cinnamic acids also form glycosides with sugars.

[0109] Phenylalanine stimulates plasma cholecystokinin (CCK) and pyloric pressures, both of which are important in the regulation of energy intake and gastric emptying. Gastric emptying is a key determinant of postprandial blood glucose.

[0110] Resveratrol is a plant polyphenol micronutrient found in peanuts, blueberries, red grapes, and wine. Resveratrol has antioxidant, anti-inflammatory, immunomodulatory, glucose and lipid regulatory, neuroprotective, and cardiovascular protective effects, therefore, can protect against diverse chronic diseases, such as cardiovascular diseases (CVDs), cancer, liver diseases, obesity, diabetes, Alzheimer's disease.

[0111] Coenzyme Q10 ("CoQ10") is a ubiquinone, which is an essential component of the energy-generating machinery within the mitochondria. The safety and efficacy of CoQ10 in prolonging exercise performance has been reported

[0112] CoQ10 participates in redox reactions within the electron transport chain at the mitochondrial level facilitating the production of adenosine triphosphate (ATP) to a mobile redox agent shuttling electrons and protons in the electron transport chain. CoQ10 also has a lipophilic antioxidant effect that protects the DNA, the phospholipids and the mitochondrial membrane proteins against the lipid peroxidation. CoQ10 acts as an antioxidant in both the mitochondria and lipid membranes by scavenging reactive oxygen species (ROS), either directly or in conjunction with α -tocopherol (vitamin E).

[0113] L-carnitine ("carnitine") is used by highly competitive and trained athletes to affect physical performance. The primary function of carnitine is the transport of long-chain fatty acids into the mitochondrial matrix for their conversion in energy, via β -oxidation process. Carnitine reacts with acetyl-CoA and maintains the acetyl-CoA/CoA ratio in the cell to, thereby, regulate pyruvate dehydrogenase activity. Carnitine also plays an important role in the regulation of metabolic pathways involved in skeletal muscle protein balance: proteolysis and protein synthesis.

[0114] Transdermal delivery formulations for enhancing restful sleep may comprise one or more of gamma-aminobutyric acid (GABA), melatonin, and tryptophan.

[0115] GABA is the main inhibitory neurotransmitter of the CNS. It is well established that activation of GABAA receptors favors sleep. GABA is a non-proteinogenic amino acid and is the main inhibitory neurotransmitter in the mammalian brain. GABA's stress-reducing and sleep enhancing effects are well established.

[0116] Melatonin is a hormone (an “indoleamine”) that the brain produces in response to darkness. Melatonin affects synchronizing of circadian rhythms, timing of sleep-wake cycling, and regulation of blood pressure. Many of its effects are through activation of the melatonin receptors, while others are due to its role as an antioxidant. Mitochondria are the main cell organelles that produce the antioxidant melatonin, which indicates that melatonin is an ancient molecule that primarily provided the earliest cells protection from the destructive actions of oxygen. Melatonin is commonly used as a dietary supplement and medication in the treatment of sleep disorders such as insomnia and circadian rhythm sleep disorders.

[0117] Tryptophan is an amino acid that produces an increase in rated subjective sleepiness and a decrease in sleep latency (time to sleep). Tryptophan may also have additional effects such as decrease in total wakefulness and/or increase in sleep time. Tryptophan is more effective in subjects having mild insomnia or in normal subjects reporting a longer-than-average sleep latency.

[0118] Transdermal delivery formulations for enhancing nitric oxide metabolism may comprise one or more of vitamin D, vitamin C, citrulline, ribose ATP blood carrier, beetroot, curcumin (turmeric), fish oil, and threonine.

[0119] Nitric oxide is a small molecule gas that is produced in vivo by epithelial cells (e.g., the inner lining of blood vessels, the blood-brain barrier, and barriers in the gut and around reproductive structures). Nitric oxide is a universal messenger, which is made ubiquitously and is involved in detoxification and the urea cycle, tissue regeneration, blood flow, prevention of atherosclerosis, and regulation of inflammation and oxidation. Maintaining a large reservoir of nitric oxide through its in vivo intake or via the uptake of nitric oxide precursors (e.g., arginine, citrulline, and carnitine) is important to health and wellness.

[0120] Beetroot possesses high nutritional value and is a primary dietary source of nitrate. The effects of beetroot intake on cardiovascular health with respect to nitric oxide production and blood pressure are well established.

[0121] Citrulline is an α -amino acid that is a key intermediate in the urea cycle, the pathway by which mammals excrete ammonia by converting it into urea. Citrulline is also produced as a byproduct of the enzymatic production of nitric oxide from the amino acid arginine, catalyzed by nitric oxide synthase.

[0122] Curcumin (turmeric) is a naturally occurring, dietary polyphenolic phytochemical having anti-inflammatory properties. Curcumin (as well as demethoxycurcumin, bisdemethoxycurcumin, and diacetylcurcumin) inhibits activation of free radical-activated transcription factors, such as nuclear factor κ B and AP-1, and reduces production of pro-inflammatory cytokines such as tumor necrosis factor- α , interleukin-1 β , and interleukin-8. Inducible nitric oxide synthase (iNOS) is an inflammation-induced enzyme that catalyzes the production of nitric oxide.

[0123] Vitamin D is a group of lipid-soluble secosteroids that are responsible for increasing intestinal absorption of Ca^{2+} , Mg^{2+} , and PO_4^{3-} . Vitamin D encompasses cholecalciferol (vitamin D_3), which is synthesized in the lower layers of skin epidermis through a photo-chemical reaction of UVB light from sun exposure and is obtained dietarily in fish oil. The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR) located in the nuclei of target cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as Transient Receptor Potential Cation Channel Subfamily V Member 6 (TRPV6) and calbindin), which are involved in calcium absorption in the intestine. VDR regulates cell proliferation and differentiation and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione.

[0124] Vitamin C (ascorbic acid) is a water-soluble vitamin found in citrus and other fruits and vegetables. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. Vitamin C also restores the nitric oxide synthase inhibitory effects of N-methylarginine.

[0125] Transdermal delivery formulations for enhancing cognitive performance may comprise one or more of silicon, leucine, lysine, isoleucine, valine, threonine, phenylalanine, methionine, histidine, tryptophan, vitamin B-5 (pantothenic acid), vitamin B-7 (biotin), vitamin K, acetyl L carnitine, palmitoyl-ethanolamide (PEA), taurine, periwinkle, artichoke, bacopa, ginkgo biloba, nutmeg, alanine, and tyrosine.

[0126] The B vitamins comprise a group of eight water soluble vitamins that perform essential, closely inter-related roles in cellular functioning. In particular, the collective effects of B vitamins are critical to numerous aspects of brain function, including energy production, DNA and RNA synthesis and repair, genomic and non-genomic methylation, and the synthesis of numerous neurochemicals and signaling molecules.

[0127] Pantothenic acid (vitamin B5) is a substrate for the synthesis of the ubiquitous coenzyme A (CoA). Beyond its role in oxidative metabolism, CoA contributes to the structure and function of brain cells via its involvement in the synthesis of cholesterol, amino acids, phospholipids, and fatty acids. Pantothenic acid is also involved in the synthesis of multiple neurotransmitters and steroid hormones via pathways involving CoA.

[0128] Vitamin B-7 (biotin), vitamin B-12, and thiamine, play unique, intersecting, essential roles in mitochondrial metabolism of glucose, fatty acids, and amino acids, respectively, thereby contributing substrates to the citric acid cycle.

[0129] Vitamin K is a fat-soluble nutrient mainly found in green leafy vegetables as phyloquinone (Vitamin K1). This vitamin is widely known for its procoagulant effect. It acts as a cofactor for the enzyme that allows the activation of vitamin K-dependent factors (II, VII, IX, X, protein C, and

protein S). Vitamin K is involved in the metabolism of the central nervous system (CNS), suggesting the possibility that a vitamin K deficiency might be related to the onset of cognitive impairment.

[0130] Moreover, vitamin K is involved in the metabolism of sphingolipids, which participate in the proliferation, differentiation, and survival of brain cells. An altered expression in sphingolipid profile is associated with neuroinflammation and neurodegeneration. Evidence of a direct correlation between vitamin K levels and cognitive performance (including visual memory, verbal fluency, and brain volume) have been reported.

[0131] Palmitoyl-ethanolamide (PEA) has been associated with neuroprotective and anti-inflammatory properties. Studies conducted in animal models of neurodegeneration demonstrate that PEA improves neurobehavioral functions, including memory and learning, by reducing oxidative stress and pro-inflammatory and astrocyte marker expression as well as rebalancing glutamatergic transmission. PEA promotes neurogenesis, especially in the hippocampus, neuronal viability and survival, and microtubule associated protein and brain derived neurotrophic factor expression, while inhibiting mast cell infiltration/degranulation and astrocyte activation.

[0132] Taurine is a key functional amino acid with many functions in the nervous system. The effects of taurine on cognitive function have aroused increasing attention. First, the fluctuations of taurine and its transporters are associated with cognitive impairments in physiology and pathology. Taurine supplements in cognitive impairment of different physiologies, pathologies, and toxicologies have been demonstrated to significantly improve and restore cognition.

Table 6: Representative Components within Distinct Transdermal Delivery Formulations

CATEGORY	COMPONENT	TRANSDERMAL DELIVERY FORMULATION				
		CORE	EXERCISE	SLEEP	iNOS	COGNITION
Energy Enhancement & Exercise Performance	Hydration	--	++++	--	--	--
	Electrolytes	--	++++	--	--	--
	Olive	--	++++	--	--	--
	Cinnamic Acid (Cinnamon)	--	++++	--	--	--
	Phenylalanine	--	++++	--	--	--
	CoQ10	--	++++	--	--	--
	Resveratrol	++	++++	++	++	++
Sleep Enhancement	Carnitine	++	++++	++	++	++
	Bamboo	++	++++	++	++	++
	Gamma-Aminobutyric Acid (GABA)	--	--	++++	--	--
	Melatonin	--	--	++++	--	--
iNOS Enhancement	Tryptophan	++	++	++++	++	++
	Vitamin D	--	--	--	++++	--
	Citrulline	++	++	++	++++	++
	Ribose ATP Blood Carrier	++	++	++	++++	++
	Beetroot	++	++	++	++++	++
	Curcumin (Turmeric)	++	++	++	++++	++

CATEGORY	COMPONENT	TRANSDERMAL DELIVERY FORMULATION				
		CORE	EXERCISE	SLEEP	iNOS	COGNITION
	Fish Oil	++	++	++	++++	++
	Threonine	++	++	++	++++	++
	Vitamin C (Ascorbic Acid)	++	++	++	++++	++
Cognitive Enhancement	silicon	--	--	--	--	++++
	Amino acids	--	--	--	--	++++
	Vitamin B-5 (Pantothenic Acid)	--	--	--	--	++++
	Vitamin B-7 (Biotin)	--	--	--	--	++++
	Vitamin K	--	--	--	--	++++
	Acetyl L Carnitine	++	++	++	++	++++
	Palmitoyl- ethanolamide (PEA)	++	++	++	++	++++
	Taurine	++	++	++	++	++++
	Periwinkle	++	++	++	++	++++
	Artichoke	++	++	++	++	++++
	Bacopa	++	++	++	++	++++
	Ginkgo Biloba	++	++	++	++	++++
	Nutmeg	++	++	++	++	++++
	Alanine	++	++	++	++	+
	Tyrosine	++	++	++	++	++++
	Vitamin C Serum	++	++	++	++	++++

-- absent from a Transdermal Delivery Formulation

++ present in a Transdermal Delivery Formulation

++++ unique to (or at an elevated concentration relative to "core") in a Transdermal Delivery Formulation

[0133] In some embodiments, a transdermal delivery formulation described herein further comprises one or more additional ingredients comprising acetyl-l-carnitine (alc), alanine, alpha lipoic acid, arginine, artichoke extract, ashwagandha, bacopa powder, bamboo extract powder, basil powder, beet powder, calcium carbonate, blueberry extract, aloe vera, choline bitartrate, collagen protein peptides, collagen powder, citrulline malate, curcumin powder, creatine, CoQ10, kale powder, folic acid, ginkgo biloba, glutamine, glycerin, ginger, glycine, grape seed extract, green tea, inositol (vitamin B8), histidine, jojoba, pomegranate powder, magnesium glycinate, leucine, lysine, lecithin (sun flower), niacinamide (vitamin B3), nutmeg powder, niacin, methionine, NALT (acetyl tyrosine), NAC, lutein, olive leaf, pea powder, periwinkle, phenylalanine, potassium, proline, ribose, DAA (d-aspartic acid), serine, hyaluronic acid, taurine, threonine, tryptophan, turmeric, theanine, valine (amino acid), valerian root powder, zinc oxide, vitamin A, vitamin B complex, vitamin B-1, vitamin B-2, vitamin B-5, vitamin B-6 (pyridoxine), vitamin B-7&8, vitamin B-9 (folic acid), vitamin B-12, vitamin C (ascorbic acid), vitamin D-3 (cholecalciferol), vitamin E, vitamin K-2, ginseng, isoleucine, almond oil, broccoli seed oil, collagen liquid, avocado oil, chamomile liquid, vitamin E oil, glycerin (conditioning), grapefruit seed, grape seed oil, gotu kola oil, kava liquid, virgin algae oil (fish oil), jojoba extract oil (organic),

lavender oil, macadamia nut oil, meadowfoam seed oil, peppermint oil, maracuja oil (passionfruit), primrose oil, pomegranate oil, BCAA, GABA, collagen oil, virgin algae oil, ashwagandha powder, collagen peptides, guarana powder, and huperzine. In some embodiments, the transdermal delivery formulation comprises more than one, more than 2, more than 3, more than 4, more than 5, more than 6, more than 7, more than 8, more than 9, more than 10, more than 11, more than 12, more than 13, more than 14, more than 15, more than 16, more than 17, more than 18, more than 19, more than 20 supplemental ingredients.

[0134] Other embodiments on the present disclosure provides methods for the manufacture of transdermal delivery formulations as disclosed herein for the epicutaneous administrations of drugs, nutrients, and/or other compounds to a human subject or domestic, veterinary, or agricultural animal.

Exemplary Embodiments

[0135] 1. A transdermal delivery formulation comprising: a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid and (b) a microemulsion comprising a nonionic emulsifier, water, and a cis-unsaturated long-chain fatty acid.

[0136] 2. The transdermal delivery formulation of embodiment 1 wherein said weak organic acid has a median pKa greater than 2.0.

[0137] 3. The transdermal delivery formulation of any of embodiments 1-2 wherein said weak organic acid has a median pKa of from 3.0 to 5.5.

[0138] 4. The transdermal delivery formulation of any of embodiments 1-3 wherein said weak organic acid has a median pKa of from 4.0 to 5.0.

[0139] 5. The transdermal delivery formulation of any of embodiments 1-4 wherein said weak organic acid has a median pKa of about 4.7.

[0140] 6. The transdermal delivery formulation of any of embodiments 1-5 wherein said weak organic acid is selected from the group consisting of mono, di or tri carbonic acids of chain lengths (R) between 1-16, optionally comprising a mono or poly hydroxy moieties of 0-14. In some embodiments, the organic acid derives from a linear, branched, or cyclic structure. In some embodiments, the structure is saturated or unsaturated. In some embodiments, the weak organic acid comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, g acid, malic acid, maleic acid, tartaric acid, malonic acid, succinic acid, and fumaric acid.

[0141] 7. The transdermal delivery formulation of any of embodiments 1-6 wherein said weak organic acid is citric acid or acetic acid.

[0142] 8. The transdermal delivery formulation of any of embodiments 1-7 wherein said transdermal accelerant comprises citric acid and acetic acid.

[0143] 9. The transdermal delivery formulation of any of embodiments 1-8 wherein said nonionic emulsifier is selected from the group consisting of lecithin, carboxymethylcellulose, a sorbitan ester, and a polysorbate.

[0144] 10. The transdermal delivery formulation of any of embodiments 1-9 wherein said nonionic emulsifier is a sorbitan ester selected from the group consisting of sorbitan monolaurate, sorbitan monostearate, sorbitan tristearate, and sorbitan monooleate.

[0145] 11. The transdermal delivery formulation of any of embodiments 1-10 wherein said nonionic emulsifier is a polysorbate selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate (Polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (Polysorbate 40), polyoxyethylene (20) sorbitan monostearate (Polysorbate 60), and polyoxyethylene (20) sorbitan monooleate (Polysorbate 80).

[0146] 12. The transdermal delivery formulation of any of embodiments 1-11 wherein said polysorbate is Polysorbate 80.

[0147] 13. The transdermal delivery formulation of any of embodiments 1-12 wherein said water is distilled water.

[0148] 14. The transdermal delivery formulation of any of embodiments 1-13 wherein said cis-unsaturated long-chain fatty acid comprises a chain of from 16 to 26 carbons.

[0149] 15. The transdermal delivery formulation of any of embodiments 1-14 wherein said 16 to 26 carbon cis-unsaturated long-chain fatty acid comprises one or more double bond at position 4-9, or at position 5-8, or at position 6-7.

[0150] 16. The transdermal delivery formulation of any of embodiments 1-15 wherein said 16 to 26 carbon unsaturated long-chain fatty acid is selected from the group consisting of Sapienic Acid, Palmitoleic Acid, Margoleic acid, Cis-Vaccenic Acid, Oleic Acid, Petroselinic Acid, Linoleic Acid, Eicosenoic Acid, Gadoleic Acid, Eicosadienoic acid, Erucic acid, Docosadienoic Acid, and Nervonic acid.

[0151] 17. The transdermal delivery formulation of any of embodiments 1-16 wherein said 16 to 26 carbon unsaturated long-chain fatty acid is Oleic Acid or Linoleic Acid.

[0152] 18. The transdermal delivery formulation of any of embodiments 1-17 wherein said 16 to 26 carbon unsaturated long-chain fatty acid comprises Oleic Acid and Linoleic Acid.

[0153] 19. The transdermal delivery formulation of any of embodiments 1-18 wherein said unsaturated long-chain fatty acid is comprised within a plant oil. 20. The transdermal delivery formulation of any of embodiments 1-19 wherein said plant oil is selected from the group consisting of vegetable oil, nut oil and seed oil.

[0154] 20. The transdermal delivery formulation of any of embodiments 1-19 wherein said plant oil is selected from the group consisting of Macadamia Oil, Maracuja (Passion Fruit) Oil, Safflower

Oil, Sunflower Oil, Olive Oil, Avocado Oil, Canola Oil, Coconut Oil, Corn Oil, Cottonseed Oil, Flaxseed/Linseed Oil, Grape Seed Oil, Hemp Seed Oil, Palm Oil, Peanut Oil, Rice Bran Oil, Sesame Oil, Soybean Oil, Brazil Nut Oil, Almond Oil, Walnut Oil, and Pecan Oil.

[0155] 21. The transdermal delivery formulation of any of embodiments 1-20 wherein said plant oil is selected from the group consisting of Macadamia Oil, Maracuja (Passion Fruit) Oil, Safflower Oil, Sunflower Oil, Olive Oil, and Almond Oil.

[0156] 22. The transdermal delivery formulation of any one of embodiments 1-21 wherein said plant oil is Macadamia Oil or Maracuja (Passion Fruit) Oil.

[0157] 23. The transdermal delivery formulation of any one of embodiments 1-22 wherein said plant oil comprises Macadamia Oil and Maracuja (Passion Fruit) Oil.

[0158] 24. The transdermal delivery formulation of any one of embodiments 1-23 wherein said microemulsion is selected from the group consisting of a cream, an ointment, a liniment, a paste, a film, and a liquid.

[0159] 25. The transdermal delivery formulation of any one of embodiments 1-24 wherein said transdermal accelerant comprises a nitrate source.

[0160] 26. The transdermal delivery formulation of any one of embodiments 1-25 wherein said nitrate source is a plant-based nitrate source.

[0161] 27. The transdermal delivery formulation of any one of embodiments 1-26 wherein said plant-based nitrate source is selected from the group consisting of arugula, spinach, and beetroot.

[0162] 28. The transdermal delivery formulation of any one of embodiments 1-27 wherein said plant-based nitrate source is beetroot.

[0163] 29. The transdermal delivery formulation of any one of embodiments 1-28, further comprising a (a) a viscosity enhancer, (b) a nutrient, (c) a plant powder or extract, (d) an amino acid, and a (e) vitamin.

[0164] 30. The transdermal delivery formulation of any one of embodiments 1-29 wherein said formulation comprises a viscosity enhancer selected from the group consisting of lecithin, aloe vera, glycerin, a plant oil, an animal oil, and collagen.

[0165] 31. The transdermal delivery formulation of any one of embodiments 1-30 wherein said formulation comprises a nutrient selected from the group consisting of acetyl-L-carnitine, alpha lipoic acid, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate, calcium carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide.

[0166] 32. The transdermal delivery formulation of any one of embodiments 1-31 wherein said formulation comprises a plant powder or extract selected from the group consisting of bacopa

powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric.

[0167] 33. The transdermal delivery formulation of any one of embodiments 1-32 wherein said formulation comprises an amino acid selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine.

[0168] 34. The transdermal delivery formulation of any one of embodiments 1-33 wherein said formulation comprises a vitamin selected from the group consisting of vitamin A, vitamin B, vitamin B-3, vitamin B-7 & 8 inositol, vitamin B-9 (folic acid), vitamin B-12, vitamin C, vitamin D-3, and vitamin E.

[0169] 35. The transdermal delivery formulation of any one of embodiments 1-34 wherein said transdermal formulation has a pH of from 2.0 to 6.0.

[0170] 36. The transdermal delivery formulation of any one of embodiments 1-35 wherein said transdermal formulation has a pH of from 3.0 to 5.0.

[0171] 37. The transdermal delivery formulation of any one of embodiments 1-36 wherein said transdermal formulation has a pH of from 3.5 to 4.5.

[0172] 38. The transdermal delivery formulation of any one of embodiments 1-37 wherein said transdermal formulation has a viscosity at 20°C of from 500 to 10,000 centipoise (cP) or from 1,000 to 5,000 cP, or from 1,500 to 4,000 cP, or from 2,000 to 3,000 cP.

[0173] 39. The transdermal delivery formulation of any one of embodiments 1-38 wherein said transdermal formulation has a viscosity of about 2,500 cP.

[0174] 40. A transdermal delivery formulation comprising: a homogenous mixture of (a) a transdermal accelerant comprising a weak organic acid and (b) a microemulsion comprising a nonionic emulsifier, water, and a plant oil comprising an unsaturated long-chain fatty acid.

[0175] 41. The transdermal delivery formulation of any one of embodiment 40 wherein said weak organic acid has a median pKa of from 2.0 to 6.0.

[0176] 42. The transdermal delivery formulation of any one of embodiments 40-41 wherein said weak organic acid has a median pKa of from 3.0 to 5.5.

[0177] 43. The transdermal delivery formulation of any one of embodiments 40-42 wherein said weak organic acid has a median pKa of from 4.0 to 5.0.

[0178] 44. The transdermal delivery formulation of any one of embodiments 40-43 wherein said weak organic acid has a median pKa of about 4.6.

[0179] 45. The transdermal delivery formulation of any one of embodiments 40-44 wherein said weak organic acid is selected from the group consisting of lactic acid, acetic acid, formic acid,

citric acid, oxalic acid, uric acid, malic acid, maleic acid, tartaric acid, malonic acid, succinic acid, and fumaric acid.

[0180] 46. The transdermal delivery formulation of any one of embodiments 40-45 wherein said weak organic acid is citric acid or acetic acid.

[0181] 47. The transdermal delivery formulation of any one of embodiments 40-46 wherein said transdermal accelerant comprises citric acid and acetic acid.

[0182] 48. The transdermal delivery formulation of any one of embodiments 40-47 wherein said nonionic emulsifier is selected from the group consisting of lecithin, carboxymethylcellulose, a sorbitan ester, and a polysorbate.

[0183] 49. The transdermal delivery formulation of any one of embodiments 40-48 wherein said nonionic emulsifier is a sorbitan ester selected from the group consisting of sorbitan monolaurate, sorbitan monostearate, sorbitan tristearate, and sorbitan monooleate.

[0184] 50. The transdermal delivery formulation of any one of embodiments 40-49 wherein said nonionic emulsifier is a polysorbate selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate (Polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (Polysorbate 40), polyoxyethylene (20) sorbitan monostearate (Polysorbate 60), and polyoxyethylene (20) sorbitan monooleate (Polysorbate 80).

[0185] 51. The transdermal delivery formulation of any one of embodiments 40-50 wherein said polysorbate is Polysorbate 80.

[0186] 52. The transdermal delivery formulation of any one of embodiments 40-51 wherein said water is distilled water.

[0187] 53. The transdermal delivery formulation of any one of embodiments 40-52 wherein said unsaturated long-chain fatty acid comprises a chain of from 16 to 26 carbons.

[0188] 54. The transdermal delivery formulation of any one of embodiments 40-53 wherein said 16 to 26 carbon unsaturated long-chain fatty acid comprises one or more double bond in a cis configuration.

[0189] 55. The transdermal delivery formulation of any one of embodiments 40-54 wherein said 16 to 26 carbon unsaturated long-chain fatty acid is selected from the group consisting of Sapienic Acid, Palmitoleic Acid, Margoleic acid, Cis-Vaccenic Acid, Oleic Acid, Petroselinic Acid, Linoleic Acid, Eicosenoic Acid, Gadoleic Acid, Eicosadienoic acid, Erucic acid, Docosadienoic Acid, and Nervonic acid.

[0190] 56. The transdermal delivery formulation of any one of embodiments 40-55 wherein said 16 to 26 carbon unsaturated long-chain fatty acid is Oleic Acid or Linoleic Acid.

[0191] 57. The transdermal delivery formulation of any one of embodiments 40-56 wherein said 16 to 26 carbon unsaturated long-chain fatty acid comprises Oleic Acid and Linoleic Acid.

[0192] 58. The transdermal delivery formulation of any one of embodiments 40-57 wherein said plant oil is selected from the group consisting of vegetable oil, nut oil and seed oil.

[0193] 59. The transdermal delivery formulation of any one of embodiments 40-58 wherein said plant oil is selected from the group consisting of Macadamia Oil, Maracuja (Passion Fruit) Oil, Safflower Oil, Sunflower Oil, Olive Oil, Avocado Oil, Canola Oil, Coconut Oil, Corn Oil, Cottonseed Oil, Flaxseed/Linseed Oil, Grape Seed Oil, Hemp Seed Oil, Palm Oil, Peanut Oil, Rice Bran Oil, Sesame Oil, Soybean Oil, Brazil Nut Oil, Almond Oil, Walnut Oil, and Pecan Oil.

[0194] 60. The transdermal delivery formulation of any one of embodiments 40-59 wherein said plant oil is selected from the group consisting of Macadamia Oil, Maracuja (Passion Fruit) Oil, Safflower Oil, Sunflower Oil, Olive Oil, and Almond Oil.

[0195] 61. The transdermal delivery formulation of any one of embodiments 40-60 wherein said plant oil is Macadamia Oil or Maracuja (Passion Fruit) Oil.

[0196] 62. The transdermal delivery formulation of any one of embodiments 40-61 wherein said plant oil comprises Macadamia Oil and Maracuja (Passion Fruit) Oil.

[0197] 63. The transdermal delivery formulation of any one of embodiments 40-62 wherein said microemulsion is selected from the group consisting of a cream, an ointment, a liniment, a paste, a film, and a liquid.

[0198] 64. The transdermal delivery formulation of any one of embodiments 40-63 wherein said transdermal accelerant comprises a nitrate source.

[0199] 65. The transdermal delivery formulation of any one of embodiments 40-64 wherein said nitrate source is a plant-based nitrate source.

[0200] 66. The transdermal delivery formulation of any one of embodiments 40-65 wherein said plant-based nitrate source is selected from the group consisting of arugula, spinach, and beetroot.

[0201] 67. The transdermal delivery formulation of any one of embodiments 40-66 wherein said plant-based nitrate source is beetroot.

[0202] 68. The transdermal delivery formulation of any one of embodiments 40-67, further comprising a (a) a viscosity enhancer, (b) a nutrient, (c) a plant powder or extract, (d) an amino acid, I/or a (e) vitamin.

[0203] 69. The transdermal delivery formulation of any one of embodiments 40-68 wherein said formulation comprises a viscosity enhancer selected from the group consisting of lecithin, aloe vera, glycerin, a plant oil, an animal oil, and collagen.

[0204] 70. The transdermal delivery formulation of any one of embodiments 40-69 wherein said formulation comprises a nutrient selected from the group consisting of acetyl-L-carnitine, alpha lipoic acid, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate, calcium

carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide.

[0205] 71. The transdermal delivery formulation of any one of embodiments 40-70 wherein said formulation comprises a plant powder or extract selected from the group consisting of bacopa powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric.

[0206] 72. The transdermal delivery formulation of any one of embodiments 40-71 wherein said formulation comprises an amino acid selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine.

[0207] 73. The transdermal delivery formulation of any one of embodiments 40-72 wherein said formulation comprises a vitamin selected from the group consisting of vitamin A, vitamin B, vitamin B-3, vitamin B-7 & 8 inositol, vitamin B-9 (folic acid), vitamin B-12, vitamin C, vitamin D-3, and vitamin E.

[0208] 74. The transdermal delivery formulation of any one of embodiments 40-73 wherein said transdermal formulation has a pH of from 2.0 to 6.0.

[0209] 75. The transdermal delivery formulation of any one of embodiments 40-74 wherein said transdermal formulation has a pH of from 3.0 to 5.0.

[0210] 76. The transdermal delivery formulation of any one of embodiments 40-75 wherein said transdermal formulation has a pH of from 3.5 to 4.5.

[0211] 77. The transdermal delivery formulation of any one of embodiments 40-76 wherein said transdermal formulation has a viscosity at 20°C of from 500 to 10,000 centipoise (cP) or from 1,000 to 5,000 cP, or from 1,500 to 4,000 cP, or from 2,000 to 3,000 cP.

[0212] 78. The transdermal delivery formulation of any one of embodiments 40-77 wherein said transdermal formulation has a viscosity at 20°C of about 2,500 cP.

[0213] 79. The transdermal delivery formulation of any of embodiments 1-78 for epicutaneous administration of a drug, nutrient, or other compound to a human subject or domestic, veterinary, or agricultural animal.

[0214] 80. A transdermal delivery formulation of any of embodiments 1-79 further comprising one or more components for enhancing (1) exercise performance, (2) restful sleep, (3) nitric oxide metabolism, and/or (4) cognitive function.

[0215] 81. The transdermal delivery formulation for enhancing exercise performance of embodiment 80 further comprising one or more of (1) a hydration electrolyte, (2) cinnamic acid, (3) phenylalanine, (4) resveratrol, and (5) carnitine.

[0216] 82. The transdermal delivery formulation for enhancing restful sleep of embodiment 80 further comprising one or more of (1) gamma-aminobutyric acid (GABA), (2) melatonin, and (3) tryptophan.

[0217] 83. The transdermal delivery formulations for enhancing nitric oxide metabolism of embodiment 80 further comprising one or more of (1) vitamin D, (2) vitamin C, (3) citrulline, (4) ribose ATP blood carrier, (5) beetroot, (6) curcumin (turmeric), (7) fish oil, and (8) threonine.

[0218] 84. The transdermal delivery formulations for enhancing cognitive performance of claim 80 further comprising one or more of silicon, leucine, lysine, isoleucine, valine, threonine, phenylalanine, methionine, histidine, tryptophan, vitamin B-5 (pantothenic acid), vitamin B-7 (biotin), vitamin K, acetyl L carnitine, palmitoyl-ethanolamide (PEA), taurine, periwinkle, artichoke, bacopa, ginkgo biloba, nutmeg, alanine, and tyrosine.

EXAMPLES

Example 1: Manufacture of Transdermal Delivery Formulation

[0219] An emulsified formulation was generated by combining an acidic composition with oil, water and surfactant. A Polypeptide Transdermal Accelerant (PTA) was made by combining 340 ml (374 g) citric acid powder, 800 ml (640 g) apple cider vinegar, and 60 ml (44.4 g) beetroot powder. A Carrier Formulation was made by combining 700 ml polysorbate 80 (742 g), 700 ml (700 g) distilled water, and, 350 ml (308 g) macadamia oil, and 350 ml (308g) maracuja oil. The PTA and Carrier Formulation were poured together and mixed for 60 – 180 minutes at 70-85°F. The pH was checked to confirm acidity of pH 4.5-5.5. Viscosity was confirmed at 2,000-3,000 centipoise (cP). The emulsion was poured in to a fine micro-mesh filter (mesh #325/44 microns) suspended over a 150 oz vat. Emulsion was incubated at room temperature without agitation for 24-36 hours. Surface impurities were skimmed of liquid surface using a 44 micron micro mesh filter.

[0220] The emulsion was drained from vat. The pH was measured to confirm pH 3.5-5.5. Viscosity was confirmed at 2,000-3,000 cP.

[0221] The Transdermal Delivery Formulation was placed in a refrigerated/cooling storage area, in a range between 37-45 degrees Fahrenheit, until and up to 60 days.

Example 2: Application of Transdermal Delivery Formulation

[0222] A 0.35 oz dose of transdermal delivery formulation as described in Example 1 is applied to an area of skin of a subject. The area of skin to which the formulation is applied is overlaid with ionized water, in liquid or gas form.

Example 3: In Vitro Models for Testing Transdermal Delivery Formulations

[0223] This Example provides *in vitro* model systems that may be adapted and employed for the testing various aspects of the transdermal delivery formulations disclosed herein.

[0224] *In vitro* methods are designed to measure the penetration of compounds, including drugs and nutrients, into the skin and permeation through the stratum comeum and epidermis to the site of vascularization. The Franz diffusion cell (see, **FIG. 3**) can utilize non-viable skin to measure penetration and permeation only or fresh, metabolically active skin to simultaneously measure permeation and skin metabolism.

[0225] Such experiments offer a number of advantages over whole-animal or human volunteer experiments, including saving in time and costs, better reproducibility of results, and less restricted parameter variations. Additional advantages of the *in vitro* method over the *in vivo* method are that it can be used equally well with skin from humans and other species, several replicate measurements can be made from the same or number of different subjects, non-radio-labeled test substances which are extensively metabolized can be studied.

[0226] *In vitro* testing is carried out in accordance with "OECD Guideline for the Testing of Chemicals. Draft New Guideline 428: Skin Absorption *in vitro* method" and Scientific Committee on Consumer Products (SCCP) guidelines.

[0227] The *in vitro* measurement of skin penetration of transdermal delivery formulations includes the application of a test substance in an appropriate formulation (may be radiolabeled) to the surface of a skin sample, which is mounted as a barrier between the donor compartment and the receptor compartment of a diffusion cell. **FIG. 3**

[0228] The majority of skin absorption studies are conducted using horizontal cells, with the skin surface open to the air. The use of vertical (or side-by-side) cells is more common when evaluating drug delivery systems, such as sonophoresis, iontophoresis or electroporation and requires immersion of both surfaces of the skin preparation, which may result in excessive hydration and possibly skin damage.

[0229] Diffusion cells include an inert non-adsorbing material with receptor chamber volumes of about 0.5 – 10 ml and surface areas of exposed membranes of about 0.2 – 2 cm². Testing is performed with an appropriate number (*i.e.* minimum six) skin samples.

[0230] The receptor fluid, which must have an adequate capacity to solubilize the test substance, is maintained in contact with underside of the skin from the time of application of a transdermal delivery formulation until the end of the collection of the receptor fluid. Temperature control of the receptor fluid is maintained and monitored throughout the testing. The skin surface temperature in the diffusion cell should be kept at the *in vivo* skin temperature of 32 ± 1°C. The receptor fluid in static cells is well-stirred throughout the study.

Example 4: Observational Study with Metabolic Transdermal Delivery Formulation

[0231] This Example provides evidence for the therapeutic benefits of a metabolic transdermal delivery formulation through *in vivo* data presented in Tables 7 and 8 that demonstrate improvements in three key indicia of human health: weight, heart rate, and blood pressure following administration of a transdermal delivery formulation as disclosed herein. Five (5) participants applied to their umbilicus (navel area) approximately 0.35 oz of a Metabolic Transdermal Delivery Formulation twice daily for 21 consecutive days. Each participant's weight, heart rate, and blood pressure were measured on days 0, 7, 14, and 21 and Blood Pressure and Heart Rate were measured.

Table 7

	Blood Pressure			
Timing	Part 1	Part 2	Part 3	Part 4
Day 0	175/86	107/72	126/76	145/75
Day 7	153/98	94/69	113/74	128/78
Day 14	153/87	113/79	102/66	145/79
Day 21	153/98	117/69		134/74

Table 8

	Heart Rate			
Timing	Part 1	Part 2	Part 3	Part 4
Day 0	57	68	61	58
Day 7	70	72	61	52
Day 14	64	73	58	58
Day 21	64	61		57

Example 5: Observational Study with a Transdermal Delivery Formulation

[0232] This Example provides evidence for the therapeutic benefits of a transdermal delivery formulation as disclosed herein though *in vivo* data that demonstrates cognitive improvements in five (5) participants from 60 to 79 years of age and with no previous diagnosis of dementia who applied a transdermal delivery formulation to the nape (nucha) of the neck and around the entirety of the neck area approximately 0.25 oz of a Focus™ Transdermal Delivery Formulation (or Placebo Control), as described in Table 6, once daily for 28 consecutive days.

[0233] Improved cognitive function and performance were demonstrated through studies performed by BrainCheck, Inc. (Austin, TX). Two protocols are used during the study: (1) TNS Studies' FOCUS Serum, (2) BrainCheck's online cognitive assessment.

[0234] Baseline testing is captured using BrainCheck's online cognitive assessment tool. BrainCheck performed an online cognitive assessment one each participant and provided testing results.

[0235] The results of this study are presented in **Table 9** and **FIGs. 4A-4F**. The average change in Total Score from baseline to Test 3, as reported by BrainCheck, was 10% (data not shown). Improvements in executive function were demonstrated by a 27% improvement from baseline for Stroop Color Interference measurements of the ability of a human subject or domestic, veterinary, or agricultural animal to inhibit reactions and control impulses.

[0236] As depicted in **FIGs. 4A-F**, all test groups shows an increase in score over baseline. Test subjects in the 51-60 age range showed the greatest improvement in Total Score, 19.5%. Attention improved by 29%, Mental Flexibility improved by 4% (Ages 71-80), Executive Function (digital symbol substitution) improved by 15.5% (Ages 41-50), Executive Function (stroop) improved by 44% (Ages 41-50), Immediate Memory improved by 16.6% (Ages 51-60), and Delayed Memory improved by 27% (Ages 71-80).

Table 9

Attention	
Trails A	
Baseline	67
Test 1	100
Test 2	106
Test 3	106
Mental Flexibility	
Trails B	
Baseline	103
Test 1	107
Test 2	108
Test 3	107
Executive Function	
Digital Symbol Substitution	
Baseline	100
Test 1	107
Test 2	111.5
Test 3	115.5
Executive Function	
Stroop	
Baseline	76
Test 1	89
Test 2	89
Test 3	109.5
Memory	
Immediate Recognition	

Baseline	99.5
Test 1	116
Test 2	107
Test 3	116
Memory	
Delayed Recognition	
Baseline	84
Test 1	118
Test 2	118
Test 3	107

Example 6: Observational Study with a Transdermal Delivery Formulation

[0237] This Example provides evidence for the therapeutic benefits of a transdermal delivery formulation as disclosed herein though *in vivo* data that demonstrates cognitive improvements in eight (8) participants from 34 to 72 years of age and with no previous diagnosis of dementia who applied to the nape of the neck area approximately 0.25 oz of a Focus™ Transdermal Delivery Formulation (or Placebo Control), as described in Table 6, once daily for 28 consecutive days.

[0238] Improved cognitive function and performance were demonstrated through studies performed using RC21X by Home Base Impairment Company, Inc. (Coraopolis, PA). Two protocols were used during the study: (1) TNS Studies' FOCUS Serum, and (2) RC21X's ROBERTO mobile application.

[0239] Baseline testing was captured using RC21X's ROBERTO mobile application. RC21X provided testing results on each participants' test.

[0240] with the Roberto App (RC21X, Coraopolis, PA). Testing scores were tracked and indicators of improvement were assessed in the following areas: (1) mental focus, (2) hand/eye coordination, (3) eye tracking, (4) auditory and visual recognition & recollection, and (5) reduction in stress and mental fatigue. 100% of Study Participants reported improved or less stress during the Study. 83% of Study Participants' sleep was improved. 66% of Study Participants reported feeling calmer while on the Serum.

[0241] The results of this study are presented in **Table 10**. Improvements in average scores across five (5) of the six (6) tests were demonstrated from baseline to the last test performed. Visual discrimination and impulse control (Base-Stealing Game) showed the greatest overall improvement as an average of all participant scores. The 61 – 70 age group demonstrated improvement in four (4) of the five (5) tests. Visual memory delayed recall (Video Recognition) demonstrated a 38% increase in the 41 – 50 age group. Audio memory delayed recall (Audio Recognition), Bilateral finger motor speed (Finger Tapping), Working memory and visual attention (Shape Memory) and Visual discrimination and impulse control (Base-Stealing Game) demonstrated 56%, 46%, 126% and 375% respectively, improvement from baseline to last test in

the 61-70 age group. Working memory/visual attention (Number Memory), a 29% improvement, was demonstrated in the 71 – 80 age group.

Table 10. Results of ROBERTO test.

<u>Visual Memory Delayed Recall</u>			
<u>(Video Recognition)</u>			
Part #	Baseline	Last Test	% Change
4150-JM	63	87	38.10%
<u>Audio Memory Delayed Recall</u>			
<u>Audio Recognition</u>			
Part #	Baseline	Last Test	% Change
6170-LI	23	42	82.61%
6170-IC	26	48	84.62%
6170-LaI	41	42	2.44%
<u>Bilateral Finger Motor Speed</u>			
<u>Finger Tapping</u>			
Part #	Baseline	Last Test	% Change
6170-LI	57	118	107.02%
6170-IC	57	62	8.77%
6170-LaI	59	72	22.03%
<u>Working Memory and Visual Attention</u>			
<u>Shape Memory</u>			
Part #	Baseline	Last Test	% Change
6170-LI	15	70	366.67%
6170-IC	49	52	6.12%
6170-LaI	45	48	6.67%
<u>Working Memory and Visual Attention</u>			
<u>Number Memory</u>			
Part #	Baseline	Last Test	% Change
7180-JH	45	70	55.56%
7180-RH	52	71	36.54%
7180-SF	71	67	-5.63%
<u>Visual Discrimination and Impulse Control</u>			
<u>Base-Stealing</u>			
Part #	Baseline	Last Test	% Change
6170-LI	6	71	1083.33%
6170-IC	56	72	28.57%
6170-LaI	71	81	14.09%

Example 7: Characterization of Transdermal Delivery Formulation

[0242] Transdermal Delivery Formulation was characterized using emulsion droplet size and zeta sizer analysis. Three batches of emulsion (designated batch 1, 2, and 3) were generated as described in Example 1. Emulsion was held for 24 hours at 37-45 degrees C. Duplicate samples (designated A and B) were taken from each batch for testing.

Zetasizer analysis

[0243] Samples were diluted in HPLC-grade water at 1:200 and 1:400. Additionally, to compare results from samples diluted in local (Mobile, AL) tap water, a sample from Batch A was prepared by diluting 1:1 in tap water, then further diluted in tap water or HPLC-grade water to a final dilution of 1:200 or 1:400.

[0244] Sizing measurements were made using a Zetasizer Nano series instrument (Malvern Panalytical Inc., Westborough, MA). Three measurements were carried out for each sample. Eleven runs or cycles were completed for each replicate. Each run had a duration of 10 seconds. Zetasizer settings were as follows:

Temperature: 25°C
 Material: Nanoparticles
 Material refractive index (RI): 1.00
 Dispersant name: Water
 Dispersant RI: 1.330
 Viscosity (cP): 0.8888
 Equilibration time: 1 min
 Cell Description: Disposable sizing cuvette

Zetapotential analysis and count rate

[0245] Zeta potential and count rate were measured using a Zetaview® instrument (Particle Metrix, Ammersee, Germany). Samples were diluted 1:100,000 in water. Analysis was performed with the following settings:

Temperature: 25°C
 Electrolyte: Water
 Laser: 488 nm
 Filter Wavelength: Scatter
 Cell S/N: ZNTA
 Sensed Electric Field: 3.39 V/cm (pulse)
 Measurement Mode: Stationary 3 cycles

[0246] Size, countrate, and zeta potential data are shown in Table 11.

Table 11: Characterization data from batches of Transdermal Delivery Formulation

Sample	Dilution ratios (Formulation: HPLC H ₂ O)	Size distributions (nm)	Mode (nm)	Figure	Count rate (kilo counts per second - kcps)	Zeta potential (mV) 1:100,000 dilution
Batch 1 - A	1:200	68-255	164	FIG. 5A	280.83	-16.6
		255-5560	955			

	1:400	68-255	142	FIG. 5B	200.43	
		255-3580	825			
		3580-5560	5560			
Batch 1 - B	1:200	68-220	141	FIG. 5C	327.03	-21.32
		220-2669	825			
		2669-4801	4801			
	1:400	68-295	164	FIG. 5D	357.43	
		295-3580	825			
		3580-5560	5560			
Batch 2 – A	1:200	68-122	91	FIG. 5E	440.73	-17.19
		141-615	255			
		712-5560	2305			
	1:400	51-190	91	FIG. 5F	340.56	
		190-825	459			
		825-4145	1990			
		4145-5560	5560			
Batch 2 - B	1:200	91-358	141	FIG. 5G	329.36	-27.59
		358-4145	1718			
		4145-5560	5560			
	1:400	190-531	342	FIG. 5H	287.43	
		712-5560	2305			
Batch 3 – A	1:200	79-190	122	FIG. 5I	265.93	-21.45
		190-3091	712			
		3091-5560	5560			
	1:400	122-396	220	FIG. 5J	231.63	
		396-5560	1281			
Batch 3 – B	1:200	122-3580	955	FIG. 5K	430.66	-23.95
		3580-5560	5560			
	1:400	79-5560	1106	FIG. 5L	275.53	
Dilutions in tap water						

Batch 1- A	1:200 dilution in TW from 1:1 (F:TW)	68-295	220	FIG. 5M	206.53	
		295-4145	825			
		4145-5560	5560			
	1:400 dilution in TW from 1:1 (F:TW)	91-295	164	FIG. 5N	129.26	
		295-4145	1106			
	1:200 dilution in HW from 1:1 (F:TW)	79-164	141	FIG. 5M	216.93	
		164-4145	825			
		4145-5560	5560			
	1:400 dilution in HW from 1:1 (F:TW)	43-91	68	FIG. 5N	118.66	
		91-5560	1281			
	1:200 dilution in HW from 1:1 (F:HW)	91-295	142	N/S	227.06	
		295-3091	825			

[0247] Line graphs showing size distribution in the sub-2 micron range of each sample preparation are provided in **FIGs. 5A-5N**. As shown in the figures, all samples comprised a population of emulsion droplets with a diameter from about 10 nm to about 300 nm.

[0248] The foregoing description and accompanying drawings set forth a number of representative embodiments at the present time. Various modifications, additions, and alternative designs will, of course, become apparent to those skilled in the art in light of the foregoing teachings without departing from the scope hereof, which is indicated by the following claims rather than by the foregoing description. All changes and variations that fall within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

WHAT IS CLAIMED IS:

1. A transdermal delivery formulation for epicutaneous administration, comprising:
 - (a) a transdermal accelerant comprising:

about 600-2000 ml total of one or more weak organic acids comprising lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof; and
 - (b) a carrier comprising:

about 400-1000 ml total of one or more emulsifiers;
about 400-1000 ml distilled water; and
about 400-1000 ml total of one or more oils comprising one or more unsaturated long-chain fatty acids comprising adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof,wherein the transdermal accelerant and the carrier are combined to form a transdermal delivery formulation,
wherein epicutaneous application of the transdermal formulation and one or more active agents provides for delivery of the one or more active agents through the stratum corneum.
2. A transdermal delivery formulation for epicutaneous administration of an active agent, comprising:
 - (a) a transdermal accelerant comprising at least one weak organic acid having a pKa from about 2.0 to about 6.0; and
 - (b) a carrier comprising one or more emulsifiers, water, and one or more oils comprising at least one unsaturated long-chain fatty acid,

wherein the transdermal delivery formulation comprises:

at least about 20% by weight of the transdermal accelerant; and

at least about 50% by weight of the carrier.

wherein epicutaneous application of the transdermal delivery formulation and one or more active agents provides for delivery of the one or more active agents through the stratum corneum.

3. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal accelerant and the carrier are present at a ratio of about 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, or 1:8 by weight.
4. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal delivery formulation comprises about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% (w/w) of the transdermal accelerant.
5. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal delivery formulation comprises about 60%, about 65%, about 70%, about 75%, or about 80% w/w of the carrier.
6. The transdermal delivery formulation of claim 1 or 2, wherein a transdermal delivery formulation of a weight of about 3100 g comprises:
 - a transdermal accelerant of a weight of from about 200 g to about 2480 g; and
 - a carrier of a weight from about 620 g to about 2900 g.
7. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal accelerant comprises a weight of about 1050 g and the carrier comprises a weight of about 2050 g.
8. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal accelerant comprises 2, 3, 4, 5, 6, 7, 8, 9 or 10 weak organic acids.
9. The transdermal delivery formulation of claim 8, wherein the transdermal accelerant comprises 2 weak organic acids.
10. The transdermal delivery formulation of claim 9, wherein the transdermal accelerant comprises 2 weak organic acids at a ratio by weight of about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:100 or 1:1000 relative to each other.

11. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal accelerant comprises about 80%, about 85%, about 90%, about 95%, about 97%, about 99% (w/w) of one or more weak organic acids.
12. The transdermal delivery formulation of claim 1 or 2, wherein the at least one weak organic acid has a median pKa of from 3.0 to 5.5.
13. The transdermal delivery formulation of claim 1 or 2, wherein the at least one weak organic acid has a median pKa of from 4.0 to 5.0.
14. The transdermal delivery formulation of claim 1 or 2, wherein the at least one weak organic acid has a median pKa of about 4.6.
15. The transdermal delivery formulation of claim 2, wherein the at least one weak organic acid comprises a mono, di or tri carbonic acid of chain length (R) between 1-16.
16. The transdermal delivery formulation of claim 2, wherein the at least one weak organic acid comprises a mono or poly hydroxy moiety of 0-14.
17. The transdermal delivery formulation of claim 2, wherein the at least one weak organic acid comprises a linear, branched, or cyclic structure.
18. The transdermal delivery formulation of claim 2, wherein the structure is saturated or unsaturated.
19. The transdermal delivery formulation of claim 2, wherein the at least one weak organic acid comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof.
20. The transdermal delivery formulation of claim 19, wherein said weak organic acid is citric acid or acetic acid.
21. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal accelerant comprises citric acid and acetic acid.
22. The transdermal delivery formulation of claim 21, wherein the acetic acid is apple cider vinegar.

23. The transdermal delivery formulation of claim 22, wherein the transdermal accelerant comprises from about 100 g to about 700 g citric acid and from about 300 g to about 1300 g apple cider vinegar.
24. The transdermal delivery formulation of claim 23, wherein the transdermal accelerant comprises about 100 g, about 150 g, about 200 g, about 250 g, about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g citric acid.
25. The transdermal delivery formulation of claim 23, wherein the transdermal accelerant comprises about 300 g, about 350 g, about 400 g, about 450 g, about 500 g, about 550 g, about 600 g, about 650 g, about 700 g, about 750 g, about 800 g, about 850 g, about 900 g, about 950 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g apple cider vinegar.
26. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises at least one emulsifier, at least one oil comprising a long-chain fatty acid, and water at a ratio by weight of about 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:1:5, 1:1:6, 1:2:2, 1:2:3, 1:2:4, 1:2:5, 1:2:6, 1:3:3, 1:3:4, 1:3:5, 1:3:6, 1:4:4, 1:4:5, 1:4:6, 1:5:5, 1:5:6, 1:6:6, 2:2:3, 2:2:4, 2:2:5, 2:2:6, 2:3:3, 2:3:4, 2:3:5, 2:3:6, 2:4:4, 2:4:5, 2:4:6, 2:5:5, 2:5:6, 2:6:6, 3:3:4, 3:3:5, 3:3:6, 3:4:4, 3:4:5, 3:4:6, 3:5:5, 3:5:6, 3:6:6, 4:4:5, 4:4:6, 4:5:5, 4:5:6, 4:6:6, 5:5:6, or 5:6:6.
27. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% w/w of one or more emulsifiers.
28. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises from about 300 to about 1500 g, from about 500 g to about 1000 g, from about 700 g to about 800 g of one or more emulsifiers.
29. The transdermal delivery formulation of claim 1 or 2, wherein the emulsifier comprises a non-ionic emulsifier.
30. The transdermal delivery formulation of claim 29, wherein said nonionic emulsifier is selected from the group consisting of lecithin, carboxymethylcellulose, a sorbitan ester, and a polysorbate.

31. The transdermal delivery formulation of claim 30, wherein said nonionic emulsifier is a sorbitan ester selected from the group consisting of sorbitan monolaurate, sorbitan monostearate, sorbitan tristearate, and sorbitan monooleate.
32. The transdermal delivery formulation of claim 30, wherein said nonionic emulsifier is a polysorbate selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate (polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (polysorbate 40), polyoxyethylene (20) sorbitan monostearate (polysorbate 60), and polyoxyethylene (20) sorbitan monooleate (polysorbate 80).
33. The transdermal delivery formulation of claim 32, wherein said polysorbate is polysorbate 80.
34. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% w/w water.
35. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises from about 300 to about 1500 g, about 500 g to about 1000 g, from about 700 to about 800 g water.
36. The transdermal delivery formulation of claim 1 or 2, wherein said water is distilled water or deionized water.
37. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises about 5% (w/w), about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% of at least one oil comprising an unsaturated long-chain fatty acid.
38. The transdermal delivery formulation of claim 1 or 2, wherein the carrier comprises two oils comprising an unsaturated long-chain fatty acid, wherein the two oils are in a ratio by weight of about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:100 or 1:1000 relative to each other.
39. The transdermal delivery formulation of claim 1, wherein the carrier comprises about 300 g, about 400 g, about 500 g, about 600 g, about 700 g, about 800 g, about 900 g, about 1000 g, about 1100 g, about 1200 g, about 1300 g, about 1400 g, about 1500 g one or more oils comprising an unsaturated long-chain fatty acid.

40. The transdermal delivery formulation of claim 2, wherein said at least one unsaturated long-chain fatty acid comprises a chain of from 12 to 26 carbons.
41. The transdermal delivery formulation of claim 40, wherein said at least one unsaturated long-chain fatty acid comprises one or more double bonds in a cis configuration.
42. The transdermal delivery formulation of claim 40, wherein said at least one unsaturated long-chain fatty acid comprises adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof.
43. The transdermal delivery formulation of claim 42, wherein said at least one unsaturated long-chain fatty acid is oleic acid or linoleic acid.
44. The transdermal delivery formulation of claim 42, wherein said at least one long-chain fatty acid comprises oleic acid and linoleic acid.
45. The transdermal delivery formulation of claim 1 or 2, wherein the one or more oils comprising an unsaturated long-chain fatty acid is one or more plant or animal oils.
46. The transdermal delivery formulation of claim 45, wherein said one or more plant oils is selected from the group consisting of vegetable oil, nut oil and seed oil.
47. The transdermal delivery formulation of claim 45, wherein said one or more plant or animal oils comprises macadamia oil, maracuja (passion fruit) oil, safflower oil, sunflower oil, olive oil, avocado oil, canola oil, coconut oil, corn oil, cottonseed oil, flaxseed/linseed oil, grape seed oil, hemp seed oil, palm oil, peanut oil, rice bran oil, sesame oil, soybean oil, brazil nut oil, almond oil, walnut oil, pecan oil, jojoba oil, chia seed oil, wallflower seed, mustard oil, borage oil, black currant oil, evening primrose oil, chicken fat, cartilage oil, cod liver oil, herring oil, mackerel oil, salmon oil, menhaden oil, sardine oil, or any combination thereof.

48. The transdermal delivery formulation of claim 47, wherein said one or more plant or animal oils is macadamia oil or maracuja (passion fruit) oil, or a combination thereof.
49. The transdermal delivery formulation of claim 47, wherein said one or more plant or animal oils comprises macadamia oil and maracuja (passion fruit) oil.
50. The transdermal delivery formulation of claim 49, wherein the carrier comprises from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g macadamia oil and from about 100 to about 600 g, from about 200 g to about 500 g, from about 300 g to about 400 g maracuja oil.
51. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal delivery formulation comprises a lotion, a gel, a cream, an ointment, a liniment, a paste, a film, an encapsulation, or a liquid.
52. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal accelerant further comprises a nitrate source.
53. The transdermal delivery formulation of claim 52, wherein said nitrate source is a plant-based nitrate source.
54. The transdermal delivery formulation of claim 53, wherein said plant-based nitrate source comprises from the group consisting of arugula, spinach, leafy green vegetables, beetroot, or any combination thereof.
55. The transdermal delivery formulation of claim 54, wherein said plant-based nitrate source is beetroot, and wherein the beetroot is a dried beetroot powder.
56. The transdermal delivery formulation of claim 55, wherein the transdermal accelerant comprises about 2.0%, about 2.5%, about 3.0%, about 3.5%, about 4.0%, about 4.5%, about 5.0%, about 5.5%, about 6.0%, about 6.5%, about 7.0%, about 7.5%, or about 8.0% w/w dried beetroot powder.
57. The transdermal delivery formulation of claim 55, wherein the transdermal accelerant comprises about 10 g, about 15 g, about 20 g, about 25 g, about 30 g, about 35 g, about 40 g, about 45 g, about 50 g, about 55 g, about 60 g, about 65 g, about 70 g, about 75 g, about 80 g, about 85 g, about 90 g, about 95 g, or about 100 g dried beetroot powder.

58. The transdermal delivery formulation of claim 1 or 2, further comprising a viscosity enhancer, a nutrient, a plant powder or extract, an amino acid, a vitamin, or any combination thereof.
59. The transdermal delivery formulation of claim 58, wherein said formulation comprises a viscosity enhancer selected from the group consisting of lecithin, aloe vera, glycerin, a plant oil, an animal oil, and collagen.
60. The transdermal delivery formulation of claim 58, wherein said formulation comprises a nutrient selected from the group consisting of acetyl-L-carnitine, alpha lipoic acid, arginine, potassium, NALT-Acetyl Tyrosine, NAC, PEA, resveratrol, taurine, palmitate, calcium carbonate, choline bitartrate B-4, creatine, resveratrol, citrulline malate, taurine, magnesium glycinate, carnitine, CoQ10, humic, hyaluronic acid, magnesium, selenium, and zinc oxide.
61. The transdermal delivery formulation of claim 58, wherein said formulation comprises a plant powder or extract selected from the group consisting of bacopa powder, bamboo extract powder, beet powder, blueberry extract, ginkgo biloba, ginger, grape seed extract, green tea, jojoba, nutmeg, olive leaf, pomegranate, and turmeric.
62. The transdermal delivery formulation of claim 58, wherein said formulation comprises an amino acid selected from the group consisting of alanine, arginine, leucine, isoleucine, valine, glutamine, glycine, histidine, leucine, lysine, methionine, proline, serine, threonine, and valine.
63. The transdermal delivery formulation of claim 58, wherein said formulation comprises a vitamin selected from the group consisting of vitamin A, vitamin B-1, vitamin B-2, vitamin B-3, vitamin B-7 & 8 inositol, vitamin B-9 (folic acid), vitamin B-12, vitamin C, vitamin D-3, and vitamin E.
64. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal formulation has a pH of from 2.0 to 6.0.
65. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal formulation has a pH of from 3.0 to 5.0.
66. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal formulation has a pH of from 3.5 to 4.5.

67. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal formulation has a viscosity at 20°C of from 500 to 10,000 centipoise (cP) or from 1,000 to 5,000 cP, or from 1,500 to 4,000 cP, or from 2,000 to 3,000 cP.
68. The transdermal delivery formulation of claim 1 or 2, wherein said transdermal formulation has a viscosity of about 2,500 cP.
69. The transdermal delivery formulation of claim 1 or 2, wherein the transdermal delivery formulation forms an emulsion comprising a population of droplets from about 10 nm to about 300 nm in diameter.
70. The transdermal delivery formulation of any of claims 1-69, further comprising one or more components for enhancing nutrition and optimizing health, immune support, restful sleep, exercise performance and nitric oxide metabolism, cognitive function, or any combination thereof.
71. The transdermal delivery formulation of claim 70, further comprising one or more of a hydration electrolyte, cinnamic acid, phenylalanine, resveratrol, carnitine.
72. The transdermal delivery formulation of claim 71, further comprising one or more of gamma-aminobutyric acid (GABA), melatonin, and tryptophan.
73. The transdermal delivery formulation of claim 71, further comprising one or more of vitamin D, vitamin C, citrulline, ribose ATP blood carrier, beetroot, curcumin (turmeric), fish oil, and threonine.
74. The transdermal delivery formulation of claim 71, further comprising one or more of silicon, leucine, lysine, isoleucine, valine, threonine, phenylalanine, methionine, histidine, tryptophan, vitamin B-5 (pantothenic acid), vitamin B-7 (biotin), vitamin K, acetyl L carnitine, palmitoyl-ethanolamide (PEA), taurine, periwinkle, artichoke, bacopa, ginkgo biloba, nutmeg, alanine, and tyrosine.
75. The transdermal delivery formulation of claim 1 or 2, wherein the formulation comprises:
 - about 12.0% (w/w) citric acid powder;
 - about 20.5% (w/w) apple cider vinegar;
 - about 1.4% (w/w) beetroot powder;
 - about 23.8% (w/w) polysorbate 80;
 - about 22.5% (w/w) distilled water;

about 9.9% (w/w) macadamia oil; and
about 9.8% (w/w) maracuja oil.

76. The transdermal delivery formulation of claim 1 or 2, wherein the formulation comprises:
about 374 g citric acid powder;
about 640 g apple cider vinegar;
about 44.4 g beetroot powder;
about 742 g polysorbate 80;
about 700 g distilled water;
about 308 g macadamia oil; and
about 308 g maracuja oil.
77. The transdermal delivery formulation of claim 1 or 2, further comprising one or more additional ingredients, wherein the additional ingredients comprise: acetyl-L-carnitine (alc), alanine, alpha lipoic acid, arginine, artichoke extract, ashwagandha, bacopa powder, bamboo extract powder, basil powder, beet powder, calcium carbonate, blueberry extract, aloe vera, choline bitartrate, collagen protein peptides, collagen powder, citrulline malate, curcumin powder, creatine, CoQ10, kale powder, folic acid, ginkgo biloba, glutamine, glycerin, ginger, glycine, grape seed extract, green tea, inositol (vitamins B7/B8), histidine, jojoba, pomegranate powder, magnesium glycinate, leucine, lysine, lecithin (sun flower), niacinamide (vitamin B3), nutmeg powder, niacin, methionine, NALT (acetyl tyrosine), NAC, lutein, olive leaf, pea powder, periwinkle, phenylalanine, potassium, proline, ribose, DAA (d-aspartic acid), serine, hyaluronic acid, taurine, threonine, tryptophan, turmeric, theanine, valine (amino acid), valerian root powder, zinc oxide, vitamin A, vitamin B complex, vitamin B-1, vitamin B-2, vitamin B-5, vitamin B-6 (pyridoxine), vitamin B-7&8, vitamin B-9 (folic acid), vitamin B-12, vitamin C (ascorbic acid), vitamin D-3 (cholecalciferol), vitamin E, vitamin K-2, ginseng, isoleucine, almond oil, broccoli seed oil, collagen liquid, avocado oil, chamomile liquid, vitamin E oil, glycerin (conditioning), grapefruit seed, grape seed oil, gotu kola oil, kava liquid, virgin algae oil (fish oil), jojoba extract oil (organic), lavender oil, macadamia nut oil, meadowfoam seed oil, peppermint oil, maracuja oil (passionfruit), primrose oil, pomegranate oil, BCAA, GABA, collagen oil, virgin algae oil, ashwagandha powder, collagen peptides, guarana powder, and huperzine.
78. The transdermal delivery formulation of claim 77, wherein the transdermal delivery formulation comprises more than one, more than 2, more than 3, more than 4, more than 5, more than 6, more than 7, more than 8, more than 9, more than 10, more than 11, more

than 12, more than 13, more than 14, more than 15, more than 16, more than 17, more than 18, more than 19, more than 20 of the additional ingredients.

79. The transdermal delivery formulation of claim 1 or 2, wherein the one or more active agents comprises a therapeutic agent, a nutraceutical, or a combination thereof.
80. The transdermal delivery formulation of claim 79, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.
81. A method of transdermal delivery, comprising epicutaneous application of the transdermal delivery formulation of any one of claims 1-80.
82. The method of claim 81, further comprising overlaying an ionized water on to the epicutaneously-applied transdermal delivery formulation.
83. A method of manufacture comprising:
- (a) generating a transdermal accelerant comprising:
about 600-2000 ml total of one or more weak organic acids having a pKa from about 2.0 to about 6.0; and
 - (b) generating a carrier comprising:
about 400-1000 ml non-ionic surfactant;
about 400-1000 ml distilled water; and
about 400-1000 ml total of one or more oils comprising one or more of adrenic acid, arachidonic acid, arachidic acid, behenic acid, brassidic acid, cervonic acid, cis-vaccenic acid, dihomo- γ -linolenic acid, docosadienoic acid, eicosadienoic acid, eicosapentaenoic acid, eicosatetraenoic acid, eicosenoic acid, elaidic acid, erucic acid, gadoleic acid, gondoic acid, herring acid, lauric acid, lignoceric acid, linoleic acid, linolelaidic acid, margaric acid, margoleic acid, mead acid, myristoleic acid, nervonic acid, oleic acid, ozubondo acid, palmitic acid, palmitoleic acid, trans-palmitoleic acid, paullinic acid, petroselinic acid, pinolenic acid, sapienic acid, sardine acid, stearic acid, stearidonic acid, tetracosapentaenoic acid, α -linolenic acid, γ -linolenic acid, or any combination thereof,
 - (c) combining the transdermal accelerant and the carrier to generate a transdermal delivery formulation;

- (d) applying an energy to the transdermal delivery formulation to generate an emulsion, wherein the emulsion comprises a population of emulsion droplets from about 10 nm to about 300 nm in diameter.
84. The method of claim 83, wherein the one or more weak organic acids comprise mono, di or tri carbonic acids of chain lengths (R) between 1-16.
85. The method of claim 83, wherein the one or more weak organic acids comprise mono or poly hydroxy moieties of 0-14.
86. The method of claim 83, wherein the one or more weak organic acids comprise a linear, branched, or cyclic structure.
87. The method of claim 86, wherein the structure is saturated or unsaturated.
88. The method of claim 83, wherein the one or more weak organic acids comprises lactic acid, acetic acid, formic acid, citric acid, oxalic acid, gallic acid, malic acid, maleic acid, malonic acid, succinic acid, tartaric acid, fumaric acid, or any combination thereof.
89. The method of claim 83, further comprising adding one or more active agents to the transdermal delivery formulation.
90. The method of claim 89, wherein the one or more active agents comprises a drug, a therapeutic agent, a drug, a nutraceutical, or a combination thereof.
91. The method of claim 90, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.
92. The method of claim 83, wherein the energy is in the form of a shear force, a cavitation, an impact, or any combination thereof.
93. The method of claim 83, wherein the energy is applied by vortexing, shearing, stirring, shaking, vortexing, shearing, sonicating, homogenizing, blending, tumbling, extruding, milling, grinding, lyophilization, electrolyzing, heating, cooling, atomizing, or any combination thereof.
94. A method of treatment of a disease or condition comprising epicutaneous application of the transdermal delivery formulation of any one of claims 1-78 and one or more active agents.

95. The method of claim 94, wherein the one or more active agents comprises a therapeutic agent, a nutraceutical, or a combination thereof.
96. The method of claim 95, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.
97. A method of enhancing a feature or condition comprising epicutaneous application of the transdermal delivery formulation of any one of claims 1-80.
98. The method of claim 97, wherein the feature is a cosmetic feature.
99. The method of claim 97, wherein the condition is nutrition, general health, quality of sleep, exercise performance, nitric oxide metabolism, cognitive function, or any combination thereof.
100. A method of systemic delivery of an active agent, comprising epicutaneous application of the transdermal delivery formulation of any one of claims 1-78, and one or more active agents.
101. The method of systemic delivery of claim 100, further comprising overlaying an ionized water on to the epicutaneously-applied transdermal delivery formulation.
102. The method of claim 100, wherein the one or more active agents comprises a therapeutic agent, a nutraceutical, or a combination thereof.
103. The method of claim 100, wherein the therapeutic agent comprises a biologic, a protein, a peptide, a small molecule, a macromolecule, a nucleic acid, another pharmaceutically or physiologically active ingredient, or any combination thereof.