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(54) Title: METHODS AND COMPOSITIONS FOR TRANSDERMAL DELIVERY OF CAFFEINE IN THE FORMS OF SOLUTION OR SUSPENSION

(57) Abstract: One aspect of the invention relates to caffeine-helper compositions comprising caffeine and one or more helper esters. The caffeine-helper compositions disclosed herein can be used for effective transdermal delivery of caffeine to a subject. Another aspect of the invention relates to applications and preparations of the caffeine-helper compositions.

METHODS AND COMPOSITIONS FOR TRANSDERMAL DELIVERY OF CAFFEINE IN THE FORMS OF SOLUTION OR SUSPENSION

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Application Serial No. 61/774,952, filed March 8, 2013; and U.S. Provisional Application Serial No. 61/802,341, filed March 15, 2013, which are incorporated herein by reference in their entireties, as if fully set forth herein.

BACKGROUND

[0002] Caffeine is the world's most commonly consumed psychoactive compound. Caffeine is recognized to have a wide array of physiological and pharmacological effects that include mental stimulation and wakefulness, sustainment of intellectual activity, increased cardiovascular endurance, and increased metabolic function. Therapeutically, caffeine can be employed as an analgesic and a mild diuretic.

[0003] Caffeine has been administered by a variety of routes, but they all have limitations. Consequently, there exists a need for a method for fast and safe delivery of caffeine.

SUMMARY OF THE INVENTION

[0004] One aspect of the invention relates to a caffeine-helper composition comprising caffeine and one or more helper esters.

[0005] Another aspect of the invention relates to a method for transdermal administration of the caffeine-helper composition disclosed herein comprising administering the caffeine-helper composition disclosed herein to a subject via an administration route selected from the group consisting of transdermal administration, transmucosal administration, trans-nasal administration, topical administration, and any combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] **Figure 1:** Effects of caffeine-helper compositions comprising different helper esters as disclosed herein on the human skin penetration rate of caffeine. (A). Effects of caffeine-helper compositions comprising tryptophan esters.HCl at various concentrations; (B). effects of compositions comprising leucine esters.HCl at various concentrations; (C). effects of compositions comprising isoleucine esters.HCl at various concentrations; (D). effects of compositions comprising tyrosine esters.HCl

at various concentrations; (E). effects of compositions comprising phenylalanine esters.HCl at various concentrations; (F). effects of compositions comprising proline esters.HCl at various concentrations; and (G). effects of compositions comprising (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride at various concentrations; and (H). effects of caffeine-helper compositions comprising (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate hydrochloride at various concentrations.

[0007] **Figure 2:** Effects of caffeine-helper compositions comprising different salts of tryptophan isopropyl esters on the human skin penetration rate of caffeine. (A). Control; (B). hydrochloride salt; (C). hydrofluoride salt; (D). hydrobromide salt; (E). hydroiodide salt; (F). citrate salt; (G). acetate salt; (H). benzoate salt; and (I). lactate salt.

DETAILED DESCRIPTION OF THE INVENTION

[0008] One or more embodiments of the invention relate to caffeine-helper compositions that can be delivered via an administration route selected from the group consisting of transdermal administration, transmucosal administration, trans-nasal administration, topical administration, and any combinations thereof, which may provide numerous advantages over alternative administration routes (e.g. oral, injection, etc.).

I) Caffeine-helper compositions

[0009] One aspect of the invention relates to a caffeine-helper composition comprising caffeine and one or more helper esters.

1) Structures of helper esters

[0010] As used herein, a helper ester can include the helper ester, one or more pharmaceutically acceptable solvates thereof, one or more pharmaceutically acceptable salts thereof, one or more pharmaceutically acceptable stereoisomers thereof, and any mixtures thereof in any ratios.

[0011] In certain embodiments, the helper ester comprises a lipophilic portion and a primary, secondary, or tertiary amine group. Optionally, the primary, secondary, or tertiary amine group may form a salt with an acid that is non-toxic to humans and animals (e.g., without limitation, pharmaceutically acceptable acid, such as HF, HCl, HBr, HI, nitric acid, sulfuric acid, bisulfuric acid, phosphoric acid, phosphorous acid, phosphonic acid, isonicotinic acid, acetic acid, lactic acid, salicylic acid, citric acid, tartaric acid, pantothenic acid, bitartaric acid, ascorbic acid, succinic acid, maleic acid, gentisinic acid, fumaric acid, gluconic acid, glucaronic acid,

saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzensulfonic acid, p-toluenesulfonic acid, pamoic acid, etc.).

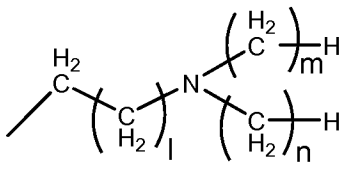
[0012] In certain embodiments, the helper ester comprises a structure of Structure I:

Rx-O-C(=O)-Ry

Structure I,

including pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios, wherein:

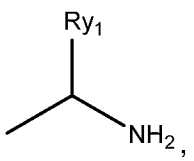
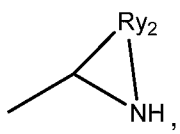
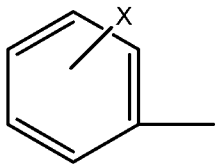
Rx is selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, substituted alkyl halide, and



, wherein any carbon or hydrogen may be further independently replaced with O, S, P, NRz, or any other pharmaceutically acceptable groups;

Rz is selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide;

each l, m, and n is independently selected from the group consisting of 0,1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

Ry is  ,  , or  ;

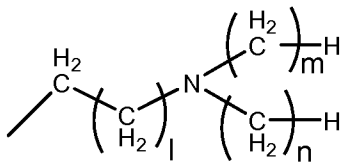
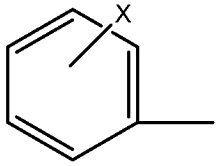
Ry_1 is selected from the group consisting of H, alkyl, alkyl further substituted with aryl, heteroaryl, amino, hydroxide, hydroxide aryl, hydroxide carbonyl, amino carbonyl, thiol, alkyl-S- and guanidinyl group;

Ry_2 is alkyl;

X is selected from the group consisting of H, NH_2, NHR_5, OH, $OCOR_5$, Cl, Br, I, CN, R_5COS, R_5O, R_5OCONH, CH_2NHR_5, R_5SO_2, R_5SO, NH_2SO_2, and NO_2; and

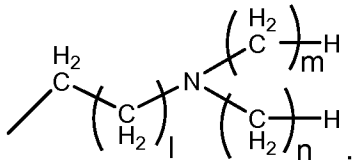
each R_5 is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide, wherein any carbon or hydrogen may be further independently replaced with O, S, P, NRz, or any other pharmaceutically acceptable groups.

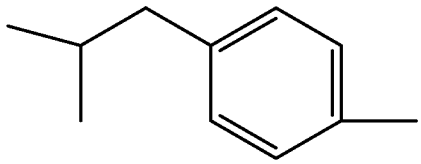
[0013] In certain embodiments, the helper ester comprises a structure of Structure I, including pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios, wherein:

Rx is  , Ry is  ; and

l, m, n, and X are defined the same as supra.

[0014] In certain embodiments, the helper ester comprises a structure of Structure I, including pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios,

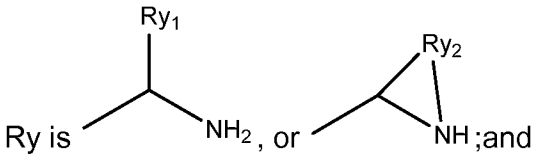
wherein Rx is  ;

Ry is  ; and

l, m, and n are defined the same as supra.

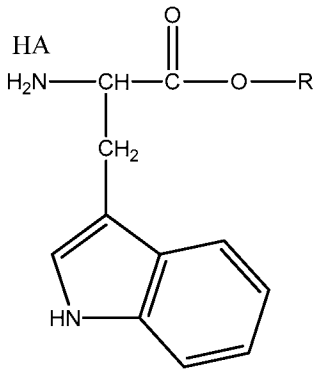
[0015] In certain embodiments, the helper ester comprises a structure of Structure I, including pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios, wherein:

Rx is selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide, wherein any carbon or hydrogen may be further independently replaced with O, S, P, NRz, or any other pharmaceutically acceptable groups;

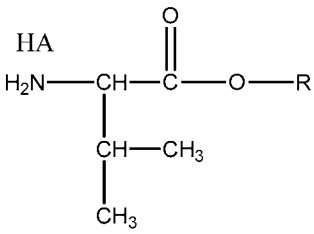


Ry_1,Ry_2 and Rz are defined the same as supra.

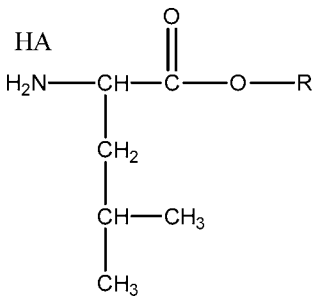
[0016] In certain embodiments of the invention, the helper esters are selected from the group consisting of Structure 1, Structure 2, Structure 3, Structure 4, Structure 5, Structure 6, Structure 7, Structure 8, Structure 9, Structure 10, Structure 11, Structure 12, Structure 13, Structure 14, Structure 15, Structure 16, and Structure 17:



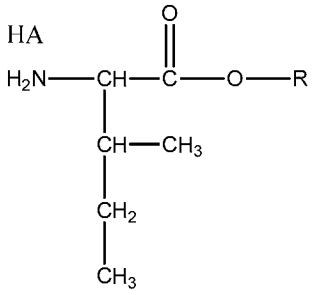
Structure 1



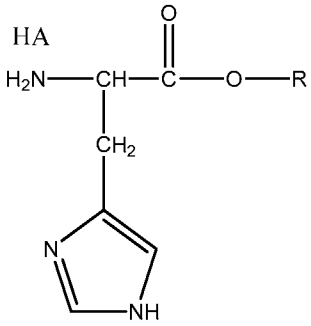
Structure 2



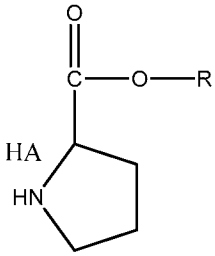
Structure 3



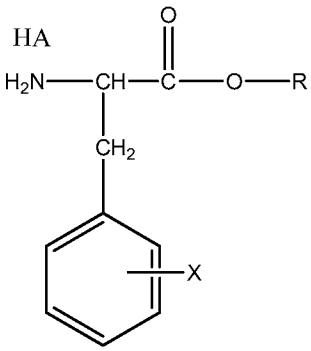
Structure 4



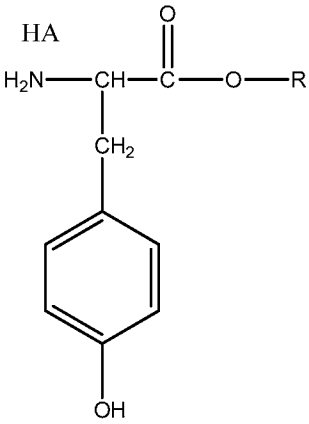
Structure 5



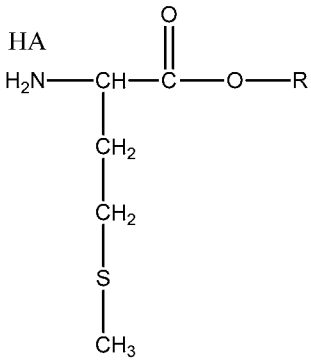
Structure 6



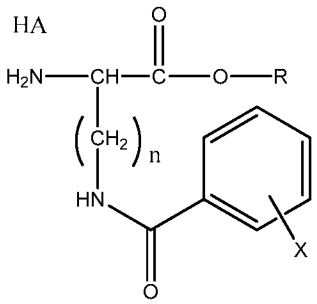
Structure 7



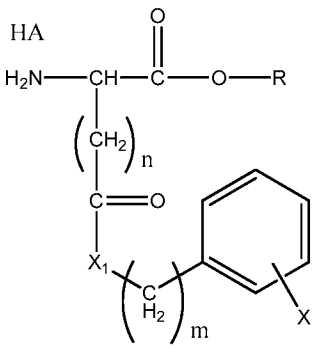
Structure 8



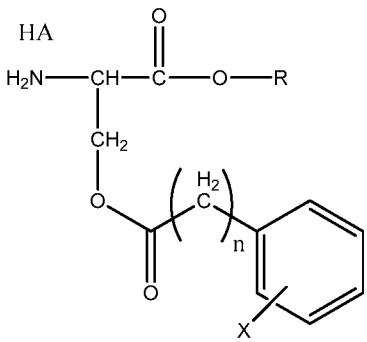
Structure 9



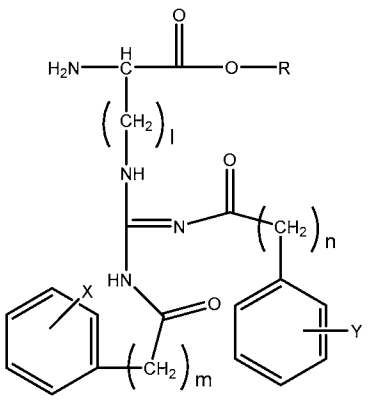
Structure 10



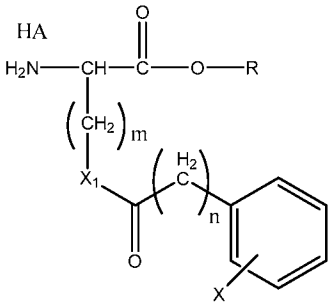
Structure 11



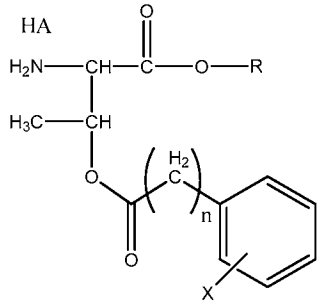
Structure 12



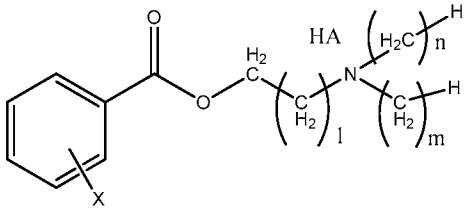
Structure 13



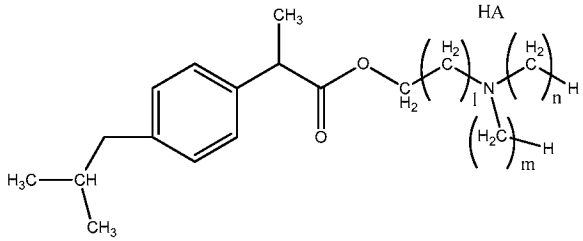
Structure 14



Structure 15



Structure 16



Structure 17,

wherein:

each X and Y are independently selected from the group consisting of H, NH_2, NHR_5, OH, $OCOR_5$, Cl, Br, I, CN, R_5COS, R_5O, R_5OCONH, CH_2NHR_5, R_5SO_2, R_5SO, NH_2SO_2, and NO_2;

each X_1 is independently selected from the group consisting of O, S, NH_2, and NHR_5;

each R_1, R_5 and R is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide, wherein any carbon or hydrogen may be further independently replaced with O, S, P, NRz, or any other pharmaceutically acceptable groups;

each HA is independently a suitable organic acid or a suitable inorganic acid as described below, or independently selected from the group consisting of HF, HCl,

HBr, HI, acetic acid, citric acid, benzoic acid, lactic acid, nitric acid, sulfuric acid, bisulfuric acid, phosphoric acid, phosphorous acid, phosphonic acid, isonicotinic acid, acetic acid, lactic acid, salicylic acid, citric acid, tartaric acid, pantothenic acid, bitartaric acid, ascorbic acid, succinic acid, maleic acid, gentisinic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzensulfonic acid, p-toluenesulfonic acid, pamoic acid and any other acid that is non-toxic to humans and animals;

each l, m, and n is independently selected from the group consisting of 0,1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

each Rz is defined the same as supra.

[0017] In certain embodiments, the helper esters selected from the group consisting of Structure 1, Structure 2, Structure 3, Structure 4, Structure 5, Structure 6, Structure 7, Structure 8, Structure 9, Structure 10, Structure 11, Structure 12, Structure 13, Structure 14, Structure 15, Structure 16, and Structure 17 as described supra may further include pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios.

[0018] Examples of the helper esters disclosed herein include, without limitation, L-tryptophan esters, L-leucine esters, L-isoleucine esters, L-proline esters, L-tyrosine esters, L-phenylalanine esters, L-arginine esters, L-alanine esters, L-asparagine esters, L-aspartic acid esters, L-cysteine esters, L-glutamine esters, L-histidine esters, L-lysine esters, L-methionine esters, L-serine esters, L-threonine esters, L-valine esters, D-tryptophan esters, D-leucine esters, D-isoleucine esters, D-proline esters, D-tyrosine esters, D-phenylalanine esters, D-arginine esters, D-alanine esters, D-asparagine esters, D-aspartic acid esters, D-cysteine esters, D-glutamine esters, D-histidine esters, D-lysine esters, D-methionine esters, D-serine esters, D-threonine esters, D-valine esters, glycine esters, esters of (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate (and salts thereof, e.g. hydrochloride), and esters of (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride (and salts thereof, e.g. hydrochloride), pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, further including mixtures thereof in all ratios.

[0019] In certain embodiments, the molar ratio of the one or more helper esters to caffeine in the caffeine-helper composition is about 10:1 to about 1:10, or about 10:1.

[0020] In certain embodiments, the amount of caffeine ranges from about 1 percent to about 20 percent, from about 2 percent to about 12 percent, from about 3 percent to about 10 percent, and from about 4 percent to about 7 percent of the caffeine-helper compositions. Generally, out of 100 percent by weight, the amount of salts of esters of amino acids and other acids present in the caffeine-helper compositions will range from about 1 percent to about 50 percent, from about 2 percent to about 25 percent, from about 3 percent to about 10 percent, or from about 4 percent to about 7 percent of the caffeine-helper compositions by weight.

[0021] In certain embodiments, the amount of the helper esters ranges from about 1 percent to about 50 percent, from about 2 percent to about 25 percent, from about 3 percent to about 10 percent, or from about 4 percent to about 7 percent of the caffeine-helper composition by weight.

2) Solvent

[0022] In certain embodiments, the caffeine-helper compositions disclosed herein further comprise a pharmaceutically acceptable solvent. The pharmaceutically acceptable solvent may be a pure chemical compound or a mixture of multiple chemical compounds. For example, the pharmaceutically acceptable solvent may comprise water, alcohol, glycine, acetone dimethyl sulfoxide, and any mixtures thereof.

[0023] In certain embodiments, the solvent is water. Generally, the amount of water ranges from about 1 percent to about 99 percent, from about 50 percent to about 95 percent, from about 70 percent to about 90 percent, or from about 75 percent to about 88 percent of the caffeine-helper composition by weight.

[0024] In certain embodiments, the solvent comprises water and one or more alcohols (e.g. ethanol, propanol, isopropanol, and butanol). The use of alcohols as a solvent may increase the evaporation rate of the caffeine-helper composition, consequently decrease the amount of time the caffeine-helper composition is noticeably wet on the skin. Generally, the amount of the alcohols ranges from about 1 percent to about 99 percent, from about 5 percent to about 75 percent, from about 10 percent to about 50 percent, or from about 10 percent to about 25 percent of the caffeine-helper compositions by weight.

[0025] In certain embodiments, the solvent comprises glycerin, and water and/or one or more alcohols as described supra.

[0026] In certain embodiments, the solvent comprises dimethyl sulfoxide (DMSO), and water and/or one or more alcohols as described supra. Generally, the amount of DMSO ranges from about 1 percent to about 80 percent, from about 5 percent to about 70 percent, from about 10 percent to about 50 percent, or from about 20 percent to about 30 percent of the caffeine-helper compositions by weight.

3) Other additives

[0027] In certain embodiments, the caffeine-helper compositions disclosed herein further comprise one or more additives. Examples of additives include, without limitation, menthol, one or more amino acids (e.g. L-tryptophan, L-leucine, L-isoleucine, L-proline, L-tyrosine, L-phenylalanine, L-arginine, L-alanine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamine, L-histidine, L-lysine, L-methionine, L-serine, L-threonine, L-valine, D-tryptophan, D-leucine, D-isoleucine, D-proline, D-tyrosine, D-phenylalanine, D-arginine, D-alanine, D-asparagine, D-aspartic acid, D-cysteine, D-glutamine, D-histidine, D-lysine, D-methionine, D-serine, D-threonine, D-valine, and glycine), one or more adjuvants (e.g. preservatives, wetting agents, emulsifying agents, and dispersing agents), and antibacterial and antifungal agents (e.g. paraben, chlorobutanol, and phenol sorbic acid).

[0028] In one example, the additive comprises menthol. In certain embodiments, one or more agents selected from the group consisting of alcohols, acetones, DMSO, and salts of the helper esters disclosed herein may be used to increase the solubility of menthol. The use of menthol may have the additional benefit of eliciting a cooling sensation when applied, which may provide feedback to the user as to where of the body the caffeine-helper composition has been administered to. Generally, the amount of menthol ranges from about 0.01 percent to about 20 percent, from about 0.1 percent to about 10 percent, from about 1 percent to about 5 percent, or from about 1 percent to about 3 percent of the caffeine-helper compositions by weight.

[0029] In another example, the additive comprises scent agent (e.g. peppermint) to provide a desired scent.

[0030] In another example, the additive comprises citric acid and/or other suitable acids to improve the solubilities of caffeine.

[0031] The additional amino acids presented in the caffeine-helper compositions may be beneficial to the skin (if applied to the skin), especially for amino acids that can act as anti-oxidants (e.g. histidine, cysteine, and tyrosine) to protect the skin from oxidative damage. Generally, the amount of amino acids ranges from about 0.001 percent to about 50 percent, from about 0.01 percent to about 20 percent, from about 0.1 percent to about 10 percent, or from about 0.1 percent to about 2 percent of the caffeine-helper compositions by weight.

4) Examples of caffeine-helper compositions

[0032] In certain embodiments, the caffeine-helper composition disclosed herein comprises caffeine, one or more solvents, and one or more helper esters, such as esters of amino acids (e.g. L-tryptophan esters, L-leucine esters, L-isoleucine esters, L-proline esters, L-tyrosine esters, L-phenylalanine esters, L-arginine esters, L-alanine esters, L-asparagine esters, L-aspartic acid esters, L-cysteine esters, L-glutamine esters, L-histidine esters, L-lysine esters, L-methionine esters, L-serine esters, L-threonine esters, L-valine esters, D-tryptophan esters, D-leucine esters, D-isoleucine esters, D-proline esters, D-tyrosine esters, D-phenylalanine esters, D-arginine esters, D-alanine esters, D-asparagine esters, D-aspartic acid esters, D-cysteine esters, D-glutamine esters, D-histidine esters, D-lysine esters, D-methionine esters, D-serine esters, D-threonine esters, D-valine esters, glycine esters, etc.), and/or esters of other acids (e.g. 2-(dialkylamino)ethyl 2-(4-isobutylphenyl)propionate hydrochloride, 2-(dialkylamino)alkyl 2-acetoxybenzoate hydrochloride, etc.).

[0033] In certain embodiments, the caffeine-helper composition comprises caffeine, tryptophan isopropyl ester, and water.

[0034] In certain embodiments, the caffeine-helper composition comprising D-amino acid esters or L-amino acid esters.

5) Definitions

[0035] As used herein, a compound or a composition that is "pharmaceutically acceptable" is suitable for use in contact with the tissue or organ of a biological subject without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. If said compound or composition is to be used with other ingredients, said compound or composition is also compatible with said other ingredients.

[0036] As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (e.g., the helper esters disclosed herein) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, aqueous solution (e.g. buffer), methanol, ethanol and acetic acid. Preferably, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, aqueous solution (e.g. buffer), ethanol and acetic acid. Most preferably, the solvent used is water or aqueous solution (e.g. buffer). Examples for suitable solvates are the mono- or dihydrates or alcoholates of the compound according to the invention.

[0037] As used herein, pharmaceutically acceptable salts of a compound refers to any pharmaceutically acceptable acid and/or base additive salt of the compound (e.g. the helper esters disclosed herein). Suitable acids include organic and inorganic acids. Suitable bases include organic and inorganic bases. Examples of suitable inorganic acids include, but are not limited to: hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, bisulfuric acid, phosphoric acid, phosphorous acid, phosphonic acid, and boric acid. Examples of suitable organic acids include but are not limited to: isonicotinic acid, acetic acid, bitartaric acid, trifluoroacetic acid, formic acid, oxalic acid, malonic acid, pantothenic acid, succinic acid, tartaric acid, ascorbic acid, maleic acid, gentisinic acid, saccharic acid, fumaric acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, gluconic acid, glucaronic acid, lactic acid, salicylic acid, citric acid, mandelic acid, benzensulfonic acid, p-toluenesulfonic acid, pamoic acid. Examples of suitable inorganic bases include, but are not limited to: ammonia, hydroxyethylamine and hydrazine. Examples of suitable organic bases include, but are not limited to, methylamine, ethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. The invention further provides for the hydrates and polymorphs of all of the helper esters described herein.

[0038] The helper esters disclosed herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the helper esters disclosed herein include mixtures of stereoisomers or mixtures of enantiomers, as well as purified stereoisomers, purified enantiomers, stereoisomerically enriched

mixtures, or enantiomerically enriched mixtures. The helper esters disclosed herein also include the individual isomers of the helper esters as well as any wholly or partially equilibrated mixtures thereof. The helper esters disclosed herein also cover the individual isomers of the helper esters as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the helper esters are included within the scope of the helper esters and preferably the structures corresponding thereto.

[0039] Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent. The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

[0040] It is also possible to obtain optically active helper esters by the methods described above by using starting materials which are already optically active.

[0041] As used herein, unless specified otherwise, the term “alkyl" means a branched or unbranched, saturated or unsaturated, monovalent or multivalent hydrocarbon group, including saturated alkyl groups, alkenyl groups and alkynyl groups. Examples of alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, ethenyl, propenyl, butenyl, isobutenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, ethynyl, propynyl, butynyl, isobutynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene, undecylene, and dodecylene. In certain embodiments, the hydrocarbon group contains 1 to 20 carbons. In certain embodiments, the hydrocarbon group contains 1 to 10 carbons. In certain embodiments, the hydrocarbon group contains 1 to 8 carbons.

[0042] As used herein, unless specified otherwise, the term "cycloalkyl" means an alkyl that contains at least one ring and no aromatic rings. In certain

embodiments, a cycloalkyl is a saturated cycloalkyl group. In certain embodiments, a cycloalkyl group comprises unsaturated bonds. Examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl. In certain embodiments, the hydrocarbon chain contains 1 to 30 carbons. In certain embodiments, the hydrocarbon group contains 1 to 20 carbons. In certain embodiments, the hydrocarbon group contains 1 to 12 carbons. In certain embodiments, the hydrocarbon group contains 1 to 6 carbons.

[0043] As used herein, unless specified otherwise, the term "heterocycloalkyl" means a cycloalkyl wherein at least one ring atom is a non-carbon atom. Examples of the non-carbon ring atom include, but are not limited to, S, O and N.

[0044] As used herein, unless specified otherwise, the term "alkoxyl" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more oxygen atoms. Examples of alkoxyl include, but are not limited to, -CH_2-OH, -OCH_3, -O-alkyl, -alkyl-OH, -alkyl-O-alkyl-, wherein the two alkyls can be the same or different.

[0045] As used herein, unless specified otherwise, the term "alkyl halide" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more halogen atoms, wherein the halogen atoms can be either the same or different. The term "halogen" means fluorine, chlorine, bromine or iodine. Examples of alkyl halides include, but are not limited to, -alkyl-F, -alkyl-Cl, -alkyl-Br, -alkyl-I, -alkyl(F)-, -alkyl(Cl)-, -alkyl(Br)- and –alkyl(I)-.

[0046] As used herein, unless specified otherwise, the term "alkylthio" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more sulfur atoms. Examples of alkylthios include, but are not limited to, -CH_2-SH, -SCH_3, -S-alkyl, -alkyl-SH, -alkyl-S-alkyl-, wherein the two alkyls can be either the same or different.

[0047] As used herein, unless specified otherwise, the term "alkylamino" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more nitrogen atoms. Examples of alkylaminos include, but are not limited to, -CH_2-NH, -NCH_3, -N(alkyl)-alkyl, -N-alkyl, -alkyl-NH_2, -alkyl-N-alkyl and -alkyl-N(alkyl)-alkyl wherein the alkyls can be either the same or different.

[0048] As used herein, unless specified otherwise, the term "alkylcarbonyl" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more carbonyl groups. Examples of alkylcarbonyl groups include, but are not limited to, the aldehyde group (-R'-C(O)-H), the ketone group (-R'-C(O)-R"), the carboxylic acid

group (R'-COOH), the ester group (-R''-COO-R'), carboxamide, (-R'''-COO-N(R')R''), the enone group (-R''''-C(O)-C(R')=C(R'')R'''), the acyl halide group (-R'-C(O)-X) and the acid anhydride group (-R''-C(O)-O-C(O)-R'), wherein R', R'', R''' and R'''' are either the same or different alkyls, cycloalkyls, or heterocycloalkyls.

[0049] As used herein, unless specified otherwise, the term "perfluoroalkyl" means an alkyl, cycloalkyl, or heterocycloalkyl, which contains one or more fluoro groups, including, without limitation, perfluoromethyl, perfluoroethyl, and perfluoropropyl.

[0050] As used herein, unless specified otherwise, the term “aryl” means a chemical structure comprising one or more aromatic rings. In certain embodiments, the ring atoms are all carbon. In certain embodiments, one or more ring atoms are non-carbon, e.g. oxygen, nitrogen, or sulfur ("heteroaryl"). Examples of aryls include, without limitation, phenyl, benzyl, naphthalenyl, anthracenyl, pyridyl, quinoyl, isoquinoyl, pyrazinyl, quinoxalinyl, acridinyl, pyrimidinyl, quinazolinyl, pyridazinyl, cinnolinyl, imidazolyl, benzimidazolyl, purinyl, indolyl, furanyl, benzofuranyl, isobenzofuranyl, pyrrolyl, indolyl, isoindolyl, thiophenyl, benzothiophenyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, thiaxolyl, quanidino, and benzothiazolyl.

II) Properties of the caffeine-helper composition disclosed herein

[0051] A reasonable skilled in the art would be able to test various helper esters, solvents, additives, and concentrations thereof for optimal results.

[0052] The caffeine-helper compositions disclosed herein have shown significantly improved transdermal delivery of caffeine, compared to aqueous solution/suspension of caffeine absent the helper esters, pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof as disclosed herein.. For example, when applying about the same mole of caffeine to a skin of a subject, the subject’s caffeine plasma level can maintain for about 8 hours or more, with a caffeine plasma level about 5 to about 10 times higher than the subject applied with caffeine absent the helper esters.

[0053] The caffeine-helper compositions can also increase caffeine solubility and/or caffeine skin penetration rate compared to those absent the helper esters, pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof as disclosed herein.

[0054] Solubility of caffeine in water at 20 °C is about 2 g/100 mL (i.e. about 103 mM, and 2% (w/v)). In certain embodiments, the presence of helper esters can increase the caffeine solubilities to about 3 to about 10 g/100 mL, more than about 3 g/100 mL, more than about 10 g/100 mL, more than about 10 g/100 mL, or more than about 10 g/100 mL, depending on the concentration of the helper esters (e.g. about 150 mM to about 500 mM, or higher) and the temperature (e.g. at 20 °C or at 10 °C). A reasonable skilled in the art would be able to test various helper esters and concentrations thereof for optimal results.

[0055] Skin penetration rates of caffeine in the presence of helper esters also increase. For example, at 20 °C, such increase can be by about 2 folds or more, about 3 folds or more, about 4 folds or more, or about 2~4 folds, or about 3~4 folds, depending on the concentration of the helper esters (e.g. about 150 mM to about 500 mM, or higher), and the concentration of caffeine (e.g. about 3 mg/100 mL or higher, about 5 mg/100 mL or higher, about 3 mg/100 mL to about 5 mg/100 mL, or about 6 mg/100 mL or higher). A reasonable skilled in the art would be able to test various helper esters and concentrations thereof for optimal results.

[0056] In certain embodiments, the caffeine-helper composition comprising caffeine and one or more helper esters, e.g. esters of amino acids (e.g. L-tryptophan esters, L-leucine esters, L-isoleucine esters, L-proline esters, L-tyrosine esters, L-phenylalanine esters, L-arginine esters, L-alanine esters, L-asparagine esters, L-aspartic acid esters, L-cysteine esters, L-glutamine esters, L-histidine esters, L-lysine esters, L-methionine esters, L-serine esters, L-threonine esters, L-valine esters, D-tryptophan esters, D-leucine esters, D-isoleucine esters, D-proline esters, D-tyrosine esters, D-phenylalanine esters, D-arginine esters, D-alanine esters, D-asparagine esters, D-aspartic acid esters, D-cysteine esters, D-glutamine esters, D-histidine esters, D-lysine esters, D-methionine esters, D-serine esters, D-threonine esters, D-valine esters, glycine esters, etc.), and/or esters of other acids (e.g. 2-(dialkylamino)ethyl 2-(4-isobutylphenyl)propionate hydrochloride, 2-(dialkylamino)alkyl 2-acetoxybenzoate hydrochloride, etc.), and one or more solvents, wherein the caffeine solubility and/or the caffeine penetration rate (through, e.g. skin) in such composition have increased significantly compared to those in water absent the helper esters, in various temperatures (e.g. at room temperature) (See, e.g. Tables 1-16).

[0057] In certain embodiments, the caffeine-helper composition comprises caffeine, tryptophan isopropyl ester, and water. The caffeine solubility in such composition has increased significantly from that in pure water.

[0058] In certain embodiments, the caffeine-helper composition comprising D-amino acid esters or L-amino acid esters may provide similar improvements of the solubility and skin penetration rates of caffeine. In certain embodiments, the caffeine-helper composition comprising D-amino acid esters or L-amino acid esters may provide different improvements of the solubility and skin penetration rates of caffeine.

III) Preparation of the caffeine-helper composition disclosed herein

[0059] Another aspect of the invention relates to a method for synthesizing the helper esters disclosed herein comprising reacting a suitable acid and a suitable alcohol in the presence of one or more catalyzers, such as HCl, HBr, oxalyl chloride, sulfone dichloride, etc. Examples of specific ester preparations of one or more embodiments are disclosed below.

IV) Applications of the caffeine-helper composition disclosed herein

[0060] Another aspect of this invention relates to a method for using the caffeine-helper compositions disclosed herein for one or more purposes e.g., without limitation, increasing mental stimulation, increasing wakefulness, increasing cardiovascular endurance, increasing metabolic function, sustaining intellectual activity, as an analgesic, as a mild diuretic, protecting skin from sunlight, and/or treating Herpes simplex virus infections. In certain embodiments, the caffeine-helper composition comprises a therapeutically effective amount of caffeine for the purpose desired.

[0061] Another aspect of the invention relates to a method for delivering caffeine to a subject (e.g. human or animals) comprising applying the caffeine-containing composition disclosed herein to the subject.

1) Transdermal administration of the caffeine-containing composition disclosed herein

[0062] In one embodiment, the caffeine-containing composition is applied transdermally (e.g. via applying to the skin).

[0063] For example, the caffeine-containing composition may be applied via a fine mist or stream of liquid dispensed via a spray bottle to various locations on the skin (e.g. neck, upper arms, back, wrists, hip, etc.). In another example, the

caffeine-helper composition is administered transdermally via a roll-on bottle. This method of administration allows for application of the caffeine-helper composition to a more exact region of the skin.

[0064] In certain embodiments, the caffeine-helper composition is administered by employing a cotton swab soaked with the caffeine-helper composition. A cotton swab may be dabbed in the caffeine-helper composition, which is held in a reservoir, and then applied directly to the skin, and this procedure may be repeated as many times as necessary until the desired amount of caffeine composition has been dispensed.

[0065] Several advantages are shared by transdermal administration of the caffeine-helper composition. Transdermal delivery of a caffeine composition presents multiple advantages over other topical caffeine products. It is quick and easy to use without the bitter taste, and such use can be inconspicuous and invisible to others. This provides multiple advantages, e.g. allowing the caffeine-helper composition to be applied in the most desirable locations physiologically speaking, such as the neck, where it is closest to blood circulation in the brain.

[0066] In comparison with oral ingestion, transdermal composition application eliminates aversion caused by the bitter taste of caffeine. The elimination of taste also allows the product to be delivered without unnecessary additives to make the product more palatable. There is also no need to drink a large amount of liquid along with the caffeine, hence no longer limiting one's caffeine intake to one's thirst or desire to drink. Furthermore, transdermal administration avoids teeth staining and halitosis, which is often a concern with coffee, tea, and other caffeine containing oral products.

2) Administration methods of the caffeine-helper composition disclosed herein

[0067] In certain embodiments, the caffeine-helper composition disclosed herein is applied to the subject via transdermal administration, transmucosal administration, trans-nasal administration, topical administration, and any combinations thereof.

VI). A kit comprising one or more caffeine-helper compositions disclosed herein

[0068] Another aspect of the invention relates to a kit comprising one or more caffeine-helper compositions disclosed herein. In certain embodiments, the kit

further comprising articles used to apply the caffeine-helper compositions to a subject.

V). ADVANTAGES

[0069] In certain embodiments, the solubility and/or skin penetration rate of caffeine in the caffeine-helper compositions are greatly increased compared to those of caffeine in aqueous solution absent the helper esters. Thus, a caffeine composition having higher caffeine concentration may be prepared to allows more caffeine to be applied to a target region of skin than an aqueous caffeine composition without the helper esters disclosed herein. Higher skin penetrate rates of caffeine in the caffeine-helper compositions further facilitates the delivery of caffeine to a user. These improvements to the solubility and skin penetration rate of caffeine make the caffeine-helper compositions viable to a wide range of users.

[0070] In certain embodiments, the caffeine-helper compositions may be applied transdermally with the benefits discussed supra.

[0071] In certain embodiments, administration (e.g. transdermal administration) of the caffeine composition to a subject has provided a relatively steady caffeine plasma level for about 8 hours or more, or about 4 hours or more. This prevents the disadvantage of oral or intravenous ingestion of caffeine, where a large amount of the caffeine is absorbed into the body at the same time. Having a steady rate of permeation as opposed to absorbing all the caffeine at once is desirable as it helps deliver the stimulatory effects of caffeine smoothly over several hours, at once prolonging the effect of the caffeine and also mitigating the risk of overdose from absorbing more caffeine than desirable at one time.

[0072] In certain embodiments, the administration methods disclosed herein allow the user to control the amount of caffeine applied by varying the number of administrations. Unlike caffeine containing drinks, which encourage the imbiber to consume a set amount of liquid and caffeine, the methods disclosed herein encourage the user to regulate each dose so that they only receive the amount of stimulation they desire from the caffeine, and do not overdose.

[0073] The following examples are intended to illustrate various embodiments of the invention. As such, the specific embodiments discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of invention, and it is understood that such

equivalent embodiments are to be included herein. Further, all references cited in the disclosure are hereby incorporated by reference in their entirety, as if fully set forth herein.

VII). EXAMPLES

[0074] Example 1. Caffeine-helper composition compositions showed higher caffeine solubility compared and skin higher penetration rate to caffeine solubility absent the helper esters.

[0075] Solubility was tested by adding small amounts of caffeine to a set volume of a caffeine-helper composition at a certain temperature until the caffeine-helper composition was saturated with caffeine, and measuring the amount of caffeine added to calculate the solubility of caffeine in the caffeine-helper composition at the temperature.

[0076] Penetration rates of caffeine in the caffeine-helper composition through human skin were measured in vitro by modified Franz cells. A Franz cell had two chambers: the top sample chamber and the bottom receiving chamber. The human skin tissue (450-500 μm thick) that separated the top and the receiving chambers was isolated from the anterior or posterior thigh areas.

Table 1 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising a tryptophan ester hydrochloride (D- or L-isomer) and water

Tryptophan ester	Isomer	Concentration of tryptophan ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (%, w/v)
Tryptophan isopropyl ester	L-	6	20	>6
Tryptophan isopropyl ester	D-	6	20	>6
Tryptophan isopropyl ester	L-	10	20	>10
Tryptophan isopropyl ester	D-	10	20	>10
Tryptophan ethyl ester	L-	10	20	>10
Tryptophan ethyl ester	D-	10	20	>10
Tryptophan butyl ester	L-	10	20	>8
Tryptophan butyl ester	D-	10	20	>8
Tryptophan	L-	6	10	>5

isopropyl ester				
Tryptophan isopropyl ester	D-	6	10	>5
Tryptophan isopropyl ester	L-	10	10	>8
Tryptophan isopropyl ester	D-	10	10	>8
Tryptophan ethyl ester	L-	10	10	>8
Tryptophan ethyl ester	D-	10	10	>8
Tryptophan butyl ester	L-	10	10	>7
Tryptophan butyl ester	D-	10	10	>7

Table 2 Skin penetration rates of caffeine in caffeine-helper compositions further comprising a tryptophan ester hydrochloride (D- or L-isomer) and water at 20°C

Tryptophan ester	Isomer	Concentration of tryptophan ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Tryptophan isopropyl ester	L-	6	5	0.6678±0.0567
Tryptophan isopropyl ester	D-	6	5	0.6487±0.0478
Tryptophan ethyl ester	L-	6	5	0.6498±0.0526
Tryptophan ethyl ester	D-	6	5	0.6478±0.0481
Tryptophan butyl ester	L-	6	5	0.6056±0.0642
Tryptophan butyl ester	D-	6	5	0.5967±0.0528
Tryptophan pentyl ester	L-	6	5	0.5879±0.0465
Tryptophan pentyl ester	D-	6	5	0.5870±0.0389
None	N/A	N/A	5	0.1797±0.0131

Table 3 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising leucine ester hydrochloride (D- or L-isomer) and water

Leucine ester	Concentration of leucine ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
Leucine isopropyl ester	6	20	>3%
Leucine isopropyl ester	10	20	>4%
Leucine methyl ester	10	20	>4%
Leucine hexyl ester	10	20	>3%
Leucine isopropyl ester	6	10	>2.5%
Leucine isopropyl ester	10	10	>3%
Leucine methyl ester	10	10	>3%
Leucine hexyl ester	10	10	>2.5%

Table 4 Skin penetration rates of caffeine in caffeine-helper compositions further comprising a leucine ester hydrochloride and water at 20°C

Leucine ester	Concentration of leucine ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Leucine isopropyl ester	6	3	0.3535±0.0178
Leucine ethyl ester	6	3	0.3321±0.0169
Leucine methyl ester	6	3	0.3246±0.0138
Leucine hexyl ester	6	3	0.3012±0.0111
None	N/A	3 (a suspension)	0.1567±0.0241

Table 5 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising an isoleucine ester chloride and water

Isoleucine ester	Concentration of isoleucine ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
Isoleucine isopropyl ester	6	20	>3%
Isoleucine isopropyl ester	10	20	>4%
Isoleucine methyl ester	10	20	>4%
Isoleucine hexyl ester	10	20	>3%
Isoleucine isopropyl ester	6	10	>2.5%
Isoleucine isopropyl ester	10	10	>3%
Isoleucine methyl ester	10	10	>3%
Isoleucine hexyl ester	10	10	>2.5%

Table 6 Skin penetration rates of caffeine in caffeine-helper compositions further comprising an isoleucine ester hydrochloride and water at 20°C

Isoleucine ester	Concentration of isoleucine ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Isoleucine isopropyl ester	6	3	0.3535±0.0178
Isoleucine isopropyl ester	6	3	0.3321±0.0169
Isoleucine isopropyl ester	6	3	0.3246±0.0138
Isoleucine isopropyl ester	6	3	0.2945±0.0139
None	N/A	3 (suspension)	0.1567±0.0241

Table 7 Solubility of caffeine (%, w/v) in in caffeine-helper compositions further comprising a tyrosine ester hydrochloride and water

Tyrosine ester	Concentration of tyrosine ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
Tyrosine isopropyl ester	6	20	>5%
Tyrosine isopropyl ester	10	20	>9%
Tyrosine ethyl ester	10	20	>9%
Tyrosine propyl ester	10	20	>9%
Tyrosine pentyl ester	10	20	>9%
Tyrosine hexyl ester	10	20	>8%
Tyrosine isopropyl ester	6	10	>4%
Tyrosine isopropyl ester	10	10	>7%
Tyrosine ethyl ester	10	10	>7%
Tyrosine propyl ester	10	10	>7%
Tyrosine pentyl ester	10	10	>7%
Tyrosine hexyl ester	10	10	>6%

Table 8 Skin Penetration rates of caffeine in in caffeine-helper compositions further comprising a tyrosine ester hydrochloride (D- or L-isomer) and water at 20°C

Tyrosine ester	Isomer	Concentration of tyrosine ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Tyrosine isopropyl ester	L-	6	5	0.6678±0.0567
Tyrosine isopropyl ester	D-	6	5	0.6598±0.0412
Tyrosine ethyl ester	L-	6	5	0.6411±0.0578
Tyrosine	D-	6	5	0.6372±0.0457

ethyl ester				
Tyrosine pentyl ester	L-	6	5	0.5951±0.0431
Tyrosine pentyl ester	D-	6	5	0.5913±0.0409
Tyrosine hexyl ester	L-	6	5	0.5112±0.0351
Tyrosine hexyl ester	D-	6	5	0.5015±0.0416
None	N/A	N/A	5 (suspension)	0.1797±0.0131

Table 9 Solubility of caffeine (%, w/v) in in caffeine-helper compositions further comprising a phenylalanine ester hydrochloride and water

Phenylalanine ester	Concentration of phenylalanine ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
Phenylalanine isopropyl ester	6	20	>3%
Phenylalanine isopropyl ester	10	20	>4%
Phenylalanine methyl ester	10	20	>4%
Phenylalanine octyl ester	10	20	>3%
Phenylalanine isopropyl ester	6	10	>2.5%
Phenylalanine isopropyl ester	10	10	>3%
Phenylalanine methyl ester	10	10	>3%
Phenylalanine octyl ester	10	10	>2.5%

Table 10 Skin penetration rates of caffeine in in caffeine-helper compositions further comprising a phenylalanine ester hydrochloride and water at 20°C

Phenylalanine ester	Concentration of phenylalanine ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Phenylalanine isopropyl ester	6	3	0.3411±0.0213
Phenylalanine ethyl ester	6	3	0.3321±0.0158

Phenylalanine methyl ester	6	3	0.3047±0.0218
Phenylalanine pentyl ester	6	3	0.2889±0.0234
None	N/A	3 (suspension)	0.1567±0.0241

Table 11 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising a proline ester hydrochloride and water

Proline ester	Concentration of proline ester hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
Proline isopropyl ester	6	20	>3%
Proline isopropyl ester	10	20	>4%
Proline isopropyl ester	10	20	>4%
Proline isopropyl ester	10	20	>3%
Proline isopropyl ester	6	10	>2.5%
Proline isopropyl ester	10	10	>3%
Proline isopropyl ester	10	10	>3%
Proline isopropyl ester	10	10	>3%

Table 12 Skin penetration rates of caffeine in caffeine-helper compositions further comprising a proline ester hydrochloride and water at 20°C

Proline ester	Concentration of proline ester hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
Proline isopropyl ester	6	3	0.3215±0.0153
Proline ethyl ester	6	3	0.3236±0.0201
Proline methyl ester	6	3	0.3272±0.0185
Proline pentyl ester	6	3	0.2748±0.0172
None	N/A	3 (suspension)	0.1567±0.0241

Table 13 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising a (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride (non-amino acid ester) and water

(Dialkylamino)alkyl 2-acetoxybenzoate	Concentration of (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
3-(Diethylamino)propyl 2-acetoxybenzoate	6	20	>5%
3-(Diethylamino)propyl 2-acetoxybenzoate	10	20	>9%
6-(Dimethylamino) hexyl 2-acetoxybenzoate	10	20	>9%
2-(Dibutylamino)ethyl 2-acetoxybenzoate	10	20	>9%
3-(Diethylamino)propyl 2-acetoxybenzoate	6	10	>4%
3-(Diethylamino)propyl 2-acetoxybenzoate	10	10	>7%
2-(Diethylamino)ethyl 2-acetoxybenzoate	10	10	>7%
2-(Dimethylamino)ethyl 2-acetoxybenzoate	10	10	>7%
2-(Dibutylamino)ethyl 2-acetoxybenzoate	10	10	>7%

Table 14 Skin Penetration rates of caffeine in caffeine-helper compositions further comprising a (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride and water at 20°C

(Dialkylamino)alkyl 2-acetoxybenzoate	Concentration of (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride (%, w/v)	Concentration of caffeine (%, w/v)	Skin penetration rate of caffeine (mg/cm^2/h)
3-(Diethylamino)propyl 2-acetoxybenzoate	6	5	0.6012±0.0521
6-(Dimethylamino)hexyl 2-acetoxybenzoate	6	5	0.5898±0.0478
2-(Dibutylamino)ethyl 2-acetoxybenzoate	6	5	0.5795±0.0395
4-(Dibutylamino)butyl 2-acetoxybenzoate	6	5	0.5598±0.0410
None	N/A	5 (suspension)	0.1797±0.0131

Table 15 Solubility of caffeine (%, w/v) in caffeine-helper compositions further comprising a (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate hydrochloride (non-amino acid ester) and water

(Dialkylamino)alkyl 2-(4-isobutylphenyl)propionate	Concentration of (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate hydrochloride (%, w/v)	Temperature (°C)	Solubility of caffeine (w/v)
5-(Diethylamino)pentyl 2-(4-isobutylphenyl)propionate	6	20	>3%
5-(Diethylamino)pentyl 2-(4-isobutylphenyl)propionate	10	20	>4%
2-(Dimethylamino)ethyl 2-(4-isobutylphenyl)propionate	10	20	>4%
(Dipentylamino)methyl 2-(4-isobutylphenyl)propionate	10	20	>3%
2-(Diethylamino)ethyl 2-(4-isobutylphenyl)propionate	6	10	>2.5%
4-(Diethylamino)butyl 2-(4-isobutylphenyl)propionate	10	10	>3%
3-(Dimethylamino)propyl 2-(4-isobutylphenyl)propionate	10	10	>3%
2-(Dipentylamino)ethyl 2-(4-isobutylphenyl)propionate	10	10	>2.5%

Table 16 Skin penetration rates of caffeine in caffeine-helper compositions further comprising a dialkylaminoalkyl 2-(4-isobutylphenyl)propionate hydrochloride and water at 20°C

Dialkylaminoalkyl 2-(4-isobutylphenyl)propionate	Concentration of dialkylaminoalkyl 2-(4-isobutylphenyl)propionate hydrochloride (%, w/v)	Concentration of Caffeine (%, w/v)	Skin penetration rate of caffeine ($mg/cm^2/h$)
5-(Diethylamino)pentyl 2-(4-isobutylphenyl)propionate	6	3	0.3137±0.0216
2-(Dimethylamino)ethyl 2-(4-isobutylphenyl)propionat	6	3	0.3427±0.0188

e			
(Dipentylamino)methyl 2-(4-isobutylphenyl)propionate	6	3	0.2987±0.0156
4-(Diethylamino)butyl 2-(4-isobutylphenyl)propionate	6	3	0.3145±0.0174
None	N/A	3 (suspension)	0.1567±0.0241

[0077] Although data shown in Tables 1-16 related to hydrochloride salts of certain helper esters as examples, salts of other acids of helper esters achieved similar effects without significantly altering caffeine's solubility or skin penetration rates in the helper ester composition (Tables 17 and 18).

Table 17 Solubility of caffeine in a caffeine-helper composition comprising water and a salt of helper esters with different acids (HA) at 20°C

Different HA salts of tryptophan isopropyl ester		
HA	**Concentration of tryptophan isopropyl ester·HA (%, w/v)**	**Solubility of caffeine (w/v)**
HCl	10	>10%
HF	10	>10%
HBr	10	>10%
HI	10	>10%
Citric acid	10	>9%
acetic acid	10	>9%
benzoic acid	10	>9%
lactic acid	10	>10%
butyric acid	10	>9%
$1/2H_2SO_4$	10	>9%
H_2SO_4	10	>9%
$1/3H_3PO_4$	10	>9%
$2/3H_3PO_4$	10	>9%
Different HA salts of tyrosine isopropyl ester		
HA	**Concentration of tyrosine isopropyl ester·HA (%, w/v)**	**Solubility of caffeine (w/v)**
HCl	10	>9%
HF	10	>9%
HBr	10	>9%
HI	10	>8%

citric acid	10	>8%
acetic acid	10	>9%
benzoic acid	10	>8%
lactic acid	10	>9%
butyric acid	10	>8%
$1/2H_2SO_4$	10	>9%
H_2SO_4	10	>9%
$1/3H_3PO_4$	10	>9%
$2/3H_3PO_4$	10	>9%

Table 18 Skin penetration rate of caffeine (5%, w/v) in a caffeine-helper composition comprising various salts of helper esters (6%, w/v) and water at 20°C

Tryptophan isopropyl ester·HA	
HA	**Skin penetration rate of caffeine ($mg/cm^2/h$)**
HCl	0.6678±0.0567
HF	0.6475±0.0579
HBr	0.6554±0.0538
HI	0.6379±0.0237
Citric acid	0.6174±0.0386
Acetic acid	0.6483±0.0476
Benzoic acid	0.6581±0.0513
Lactic acid	0.5979±0.0418
Butyric acid	0.6071±0.0386
$1/2H_2SO_4$	0.6174±0.0386
H_2SO_4	0.6312±0.0472
$1/3H_3PO_4$	0.6571±0.0678
$2/3H_3PO_4$	0.5937±0.0537
Tryptophan isopropyl ester·HA	
HA	**Skin penetration rate of caffeine ($mg/cm^2/h$)**
HCl	0.6179±0.0389
HF	0.6321±0.0515
HBr	0.6278±0.0571
HI	0.6472±0.0723
Citric acid	0.6071±0.0348
Acetic acid	0.5833±0.0471
Benzoic acid	0.6341±0.0501
Lactic acid	0.6103±0.0613
Butyric acid	0.5941±0.0321
$1/2H_2SO_4$	0.6412±0.0391
H_2SO_4	0.5903±0.0417
$1/3H_3PO_4$	0.6601±0.0765
$2/3H_3PO_4$	0.6279±0.0631
5% caffeine (a suspension) without	**Skin penetration rate of caffeine**

helper esters	(mg/cm^2/h)
	0.1797±0.0131

[0078] The ability for a concentrated caffeine composition to stay entirely dissolved even at cold temperatures (e.g. 10 °C and 20 °C)·allowed the caffeine-helper composition to be used in a wide variety of everyday situations.

[0079] Example 2. Transdermal delivery of caffeine using examples of caffeine-helper compositions disclosed herein.

[0080] Control compositions (1.05 ml of 2% caffeine in water) were applied to a skin on the neck of a subject (20cm x 20 cm). Various caffeine-helper compositions having 7% helper esters and various caffeine concentrations (depending on the composition volume applied to maintain the total mole of caffeine applied being the same as that of the control compositions) were applied to a skin on the back of a subject (20cm x 20 cm). Plasma level of caffeine were tested at 1 hour, 2 hours, 4 hours, and 8 hours, respectively after the administration. Results are shown in Figs 1A~1H, and Table 19.

[0081] I) Transdermal delivery of caffeine using caffeine-helper compositions comprising tryptophan esters.HCl (0.35 mL, +6% caffeine in water, Fig. 1A, Table 19).

[0082] Compared to control composition (A), caffeine-helper compositions (B: tryptophan isopropyl ester.HCl; C: tryptophan ethyl ester.HCl; and D: tryptophan butyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0083] II) Transdermal delivery of caffeine using caffeine-helper compositions comprising leucine esters.HCl (0.70 mL, + 3% caffeine in water, Fig. 1B, Table 19).

[0084] Compared to control composition (A), caffeine-helper compositions (B: leucine isopropyl ester.HCl; C: leucine methyl ester.HCl; and D: leucine hexyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0085] III) Transdermal delivery of caffeine using caffeine-helper compositions comprising isoleucine esters.HCl (0.70 mL, +3% caffeine in water, Fig. 1C, Table 19).

[0086] Compared to control composition (A), caffeine-helper compositions (B: isoleucine isopropyl ester.HCl; C: isoleucine methyl ester.HCl; and D: isoleucine

hexyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0087] IV) Transdermal delivery of caffeine using caffeine-helper compositions comprising tyrosine esters.HCl (0.35 mL, +6% caffeine in water, Fig. 1D, Table 19).

[0088] Compared to control composition (A), caffeine-helper compositions (B: tyrosine isopropyl ester.HCl; C: tyrosine propyl ester.HCl; and D: tyrosine pentyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0089] V) Transdermal delivery of caffeine using caffeine-helper compositions comprising phenylalanine esters.HCl (0.70 mL, +3% caffeine in water, Fig. 1E, Table 19).

[0090] Compared to control composition (A), caffeine-helper compositions (B: phenylalanine isopropyl ester.HCl; C: phenylalanine methyl ester.HCl; and D: phenylalanine octyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0091] VI) Transdermal delivery of caffeine using caffeine-helper compositions comprising proline esters.HCl (0.70 mL, +3% caffeine in water, Fig. 1F, Table 19).

[0092] Compared to control composition (A), caffeine-helper compositions (B: proline isopropyl ester.HCl; C: proline methyl ester.HCl; and D: proline hexyl ester.HCl) provided more efficient and effective transdermal delivery of caffeine.

[0093] VII) Transdermal delivery of caffeine using caffeine-helper compositions comprising (dialkylamino)alkyl 2-acetoxybenzoate hydrochloride (0.35 mL, +6% caffeine in water, Fig. 1G, Table 19).

[0094] Compared to control composition (A), caffeine-helper compositions (B: 2-(diethylamino)ethyl 2-acetoxybenzoate hydrochloride; C: 3-(diethylamino)propyl 2-acetoxybenzoate hydrochloride; D: 6-(dimethylamino)hexyl 2-acetoxybenzoate hydrochloride; and E: 2-(dibutylamino)ethyl 2-acetoxybenzoate hydrochloride) provided more efficient and effective transdermal delivery of caffeine.

[0095] VIII) Transdermal delivery of caffeine using caffeine-helper compositions comprising (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate hydrochloride (0.70mL, +3% caffeine in water, Fig. 1H, Table 19).

[0096] Compared to control composition (A), caffeine-helper compositions (B: 5-(diethylamino)pentyl 2-(4-isobutylphenyl)propionate hydrochloride; C: 2-

(dimethylamino)ethyl 2-(4-isobutylphenyl)propionate hydrochloride; and D: 4-(diethylamino)butyl 2-(4-isobutylphenyl)propionate hydrochloride) provided more efficient and effective transdermal delivery of caffeine.

Table 19. Transdermal delivery of caffeine (108.14 moles of caffeine applied to the skin of the subject) using caffeine-helper compositions (Figs. 1A-1H)

Compound before Esterification	Helper esters	Total volume applied (mL)	Concentration of helper esters (mM)	Time after transdermal administration (hr)	Plasma level of caffeine (ng/mL)
TRYPTOPHAN	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	Tryptophan isopropyl ester hydrochloride	0.35	247.52	0	0
				1	578
				2	970
				4	1020
				8	958
	Tryptophan ethyl ester hydrochloride	0.35	260.47	0	0
				1	638
				2	875
				4	973
				8	786
	Tryptophan butyl ester hydrochloride	0.35	235.90	0	0
				1	610
				2	859
				4	935
				8	886
	None	1.05	0	0	0
				1	110

LEUCINE				2	128
				4	102
				8	89
	Leucine isopropyl ester hydrochloride	0.70	333.76	0	0
				1	580
				2	970
				4	910
				8	958
	Leucine methyl ester hydrochloride	0.70	385.28	0	0
				1	612
				2	875
				4	873
				8	798
	Leucine hexyl ester hydrochloride	0.70	278.04	0	0
				1	550
				2	689
				4	781
				8	816
ISOLEUCINE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	Isoleucine isopropyl ester	0.70	333.76	0	0
				1	590
				2	910
				4	980
				8	908
	Isoleucine methyl ester	0.70	385.28	0	0
				1	612
				2	951
				4	863
				8	788
	Isoleucine hexyl ester	0.70	278.04	0	0
				1	550
				2	629
				4	788
				8	830
TYROSINE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	Tyrosine isopropyl ester	0.35	269.50	0	0
				1	580
				2	1010
				4	970
				8	928

	Tyrosine propyl ester	0.35	269.5	0	0
				1	610
				2	961
				4	830
				8	888
	Tyrosine pentyl ester	0.35	243.25	0	0
				1	555
				2	713
				4	988
				8	850
PHENYLALANINE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	Phenylalanine isopropyl ester hydrochloride	0.70	287.21	0	0
				1	580
				2	810
				4	970
				8	828
	Phenylalanine methyl ester hydrochloride	0.70	324.52	0	0
				1	620
				2	861
				4	830
				8	788
	Phenylalanine octyl ester hydrochloride	0.70	223.02	0	0
				1	505
				2	613
				4	588
				8	450
PROLINE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	Proline isopropyl ester hydrochloride	0.70	361.41	0	0
				1	590
				2	810
				4	870
				8	728
	Proline methyl ester hydrochloride	0.70	422.66	0	0
				1	610
				2	761
				4	730
				8	688
	Proline hexyl ester hydrochloride	0.70	296.94	0	0
				1	565
				2	713

				4	688
				8	550
2-(DIALKYLAMINO)ALKYL 2-ACETOXYBENZOATE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	2-(Diethylamino)ethyl 2-acetoxybenzoate hydrochloride	0.35	221.69	0	0
				1	630
				2	950
				4	910
				8	718
	3-(Diethylamino)propyl 2-acetoxybenzoate hydrochloride	0.35	212.24	0	0
				1	680
				2	910
				4	880
				8	758
	6-(Dimethylamino)hexyl 2-acetoxybenzoate hydrochloride	0.35	203.56	0	0
				1	595
				2	753
				4	818
				8	680
	2-(Dibutylamino)ethyl 2-acetoxybenzoate hydrochloride	0.35	188.23	0	0
				1	565
				2	743
				4	838
				8	710
2-(DIALKYLAMINO) ALKYL 2-(4-ISOBUTYLPHENYL) PROPIONATE	None	1.05	0	0	0
				1	110
				2	128
				4	102
				8	89
	5-(Diethylamino)pentyl 2-(4-isobutylphenyl)propionate hydrochloride	0.70	182.28	0	0
				1	680
				2	870
				4	910
				8	858
	2-(Dimethylamino)ethyl 2-(4-isobutylphenyl)p	0.70	222.60	0	0
				1	612
				2	895

	ropionate hydrochloride			4	863
				8	778
	4-(Diethylamino)butyl 2-(4-isobutylphenyl)propionate hydrochloride	0.70	189.21	0	0
				1	650
				2	889
				4	881
				8	816

[0097] Example 3. Transdermal delivery of caffeine using caffeine-helper compositions comprising various salts of tryptophan isopropyl ester as the helper esters.

[0098] In certain embodiments, caffeine-helper compositions comprising various salts of the helper esters disclosed herein formed with various acids showed similar improvements in transdermal delivery of caffeine (Figure 2, Table 20).

[0099] Control composition (1.05 ml of 2% caffeine in water) was applied to a skin on the neck of a subject (20cm x 20 cm). Various caffeine-helper compositions (3.5 mL, 7% helper esters and 6% caffeine in water) were applied to a skin on the back of a subject (20cm x 20 cm). Plasma level of caffeine were tested at 1 hour, 2 hours, 4 hours, and 8 hours, respectively after the administration. Results are shown in Fig. 2, and Table 20.

[00100] Compared to control composition (A), caffeine-helper compositions (B: hydrochloride salt; C: hydrofluoride salt; D: HBr salt; E: HI salt; F: citratre salt; G: acetate salt; H: benzoate salt; and I: lactate salt) provided more efficient and effective transdermal delivery of caffeine.

Table 20. Transdermal delivery of caffeine (108.14 moles of caffeine applied to the skin of the subject) using caffeine-helper compositions comprising various salts of tryptophan isopropyl ester (Fig. 2)

A-	Total volume applied (mL)	Concentration of helper esters (mM)	Time after transdermal administration (hr)	Plasma level of caffeine (ng/mL)	Total volume applied (mL)
N/A	1.05	0	102.99	0	0
				1	110
				2	128
				4	102

				8	89
Cl^-	0.35	247.52	308.98	0	0
				1	578
				2	970
				4	1020
				8	958
F^-	0.35	262.85	308.98	0	0
				1	618
				2	975
				4	993
				8	986
Br^-	0.35	220.92	308.98	0	0
				1	610
				2	899
				4	955
				8	986
I^-	0.35	187.04	308.98	0	0
				1	588
				2	950
				4	1120
				8	968
Citrate ion	0.35	159.67	308.98	0	0
				1	638
				2	875
				4	973
				8	786
AcO^-	0.35	228.48	308.98	0	0
				1	578
				2	859
				4	935
				8	855
Benzoate ion	0.35	189.98	308.98	0	0
				1	565
				2	895
				4	973
				8	796
Lactate ion	0.35	208.11	308.98	0	0
				1	570
				2	910
				4	935
				8	866

[00101] Thus, caffeine-helper compositions comprising salts of the helper esters disclosed herein formed with any acid that is non-toxic for humans and animals (e.g. pharmaceutically acceptable acids, as described supra) should also improve the transdermal delivery of caffeine .

Example 4. Preparations of helper esters

[00102] Other helper esters (e.g. esters of amino acids or other acids (e.g. (dialkylamino)ethyl 2-(4-isobutylphenyl)propionate and 2-(dialkylamino)alkyl 2-acetoxybenzoate), and pharmaceutically acceptable salts thereof (e.g. hydrochlorides thereof)) may be prepared by similar methods as described below.

I) Preparation of tryptophan isopropyl ester.HCl

[00103] Tryptophan (1 kg) was suspended in isopropanol (5 L) in a 10 L flask. HCl gas (350 g) was bubbled into the reaction mixture. The mixture was stirred for 2 days at 50°C. The solvent was evaporated off at below 40°C, and fresh isopropanol (4 L) was added into the residue. The mixture was stirred for 1 day at 50°C. The solvent was evaporated off at below 40°C, and isopropyl acetate (3 L) was added into the residue. The solid was collected by filtration and washed with isopropyl acetate (3 x 1 L). The solid was dried in a vacuum oven at 50°C.

II) Preparation of D-tryptophan isopropyl ester.HCl

[00104] D-Tryptophan (1 kg) was suspended in isopropanol (5 L) in a 10 L flask. HCl gas (350g) was bubbled into the reaction mixture. The mixture was stirred for 2 days at 50°C. The solvent was evaporated off at below 40°C, and fresh isopropanol (4 L) was added into the residue. The mixture was stirred for 1 day at 50°C. The solvent was evaporated off at below 40°C, and isopropyl acetate (3 L) was added into the residue. The solid was collected by filtration and washed with isopropyl acetate (3 x 1 L). The solid was dried in a vacuum oven at 50°C.

III) Preparation of 2-(diethylamino)ethyl 2-(4-isobutylphenyl)propionate hydrochloride

[00105] 2-(4-isobutylphenyl)propionoic acid (4120 g) was dissolved in ethyl acetate (R0061, 4 L) and thionyl chloride (1750 ml). The mixture was refluxed for 3 h. The mixture was evaporated to dryness completely. Isopropyl acetate (3 L) was added into the residue and the mixture was evaporated to dryness. Isopropyl acetate (3 L) was added into the residue and evaporated off. Isopropyl acetate (20 L) was added into the reaction mixture. The mixture was cooled to 5°C in an ice-water bath. N,N-diethylaminoethanol (2340 g) was added into the reaction mixture drop by drop. K_2CO_3 (2800 g) was added into the reaction mixture slowly. The mixture was stirred overnight at room temperature. Water (10 L) was added into the mixture. The ethyl acetate mixture was collected and washed with 5% $NaHCO_3$ (1 x 7 L) and water (3 x

6 L) and dried over Na_2SO_4. Sodium sulfate was removed by filtration and washed with isopropyl acetate (3 x 1 L). HCl gas (700 g) was added into the mixture and stirred. The solid was collected and washed with isopropyl acetate (3 x 2 L). The product was dried in a vacuum oven at 45°C.

Example 5. Preparation of caffeine-helper compositions

Preparation of composition 1.

[00106] Tryptophan ethyl ester.HCl (120 g) was dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 2.

[00107] D-Tryptophan ethyl ester.HCl (120 g) was dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 3.

[00108] Tryptophan isopropyl ester.HBr (120 g) was dissolved in water (1 L). Caffeine (100 g) and menthol (10 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 4.

[00109] Tryptophan isopropyl ester.lactic acid (120 g) was dissolved in water (1 L). Caffeine (100 g), menthol (20g) and ethanol (100 ml) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 5.

[00110] Tryptophan isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (60 g) and menthol (20 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 6.

[00111] Leucine isopropyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) and menthol (5g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 7.

[00112] Isoleucine isopropyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) and menthol (8 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 8.

[00113] Tyrosine isopropyl ester.HCl (120 g) was dissolved in water (1 L). Caffeine (100 g) and menthol (20 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 9.

[00114] Tyrosine isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (60 g) and menthol (10 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 10.

[00115] Tyrosine isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (50 g), ethanol (100 ml) and menthol (20 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 11.

[00116] Proline ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) and menthol (5 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 12.

[00117] Tyrosine isopropyl ester.HCl (70 g) and tyrosine (7g) were dissolved in water (1 L). Caffeine (50 g), ethanol (100 ml) and menthol (20 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 13.

[00118] Tyrosine isopropyl ester.HCl (70 g) and tyrosine (7g) were dissolved in water (1 L). Caffeine (50 g) and menthol (10 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 14.

[00119] Tryptophan isopropyl ester.HBr (120 g) and tryptophan (5g) were dissolved in water (1 L). Caffeine (100 g) and menthol (10 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 15.

[00120] Valine ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g), DMSO (200 ml), and menthol (30 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 16.

[00121] Valine ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g), DMSO (200 ml), and menthol (30 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 17.

[00122] Phenylalanine butyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g), glycerin (200 ml), and menthol (30 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 18.

[00123] Phenylalanine butyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g), sodium benzoate (50 g), and menthol (30 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 19.

[00124] 3-(diethylamino)propyl 2-acetoxybenzoate hydrochloride (100 g) was dissolved in water (1 L). Caffeine (80 g), glycerin (200 ml), and menthol (30 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 20.

[00125] 3-(diethylamino)propyl 2-acetoxybenzoate hydrochloride (70 g) was dissolved in water (1 L). Caffeine (60 g), and menthol (10 g) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled either into spray bottles or roll-on bottles.

Preparation of composition 21.

[00126] Tryptophan isopropyl ester.HBr (120 g) was dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 22.

[00127] Tryptophan isopropyl ester.lactic acid (120 g) was dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 23.

[00128] Tryptophan isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (60 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 24.

[00129] Leucine isopropyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 25.

[00130] Isoleucine isopropyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 26.

[00131] Tyrosine isopropyl ester.HCl (120 g) was dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 27.

[00132] Tyrosine isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (60 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 28.

[00133] Tyrosine isopropyl ester.HCl (70 g) was dissolved in water (1 L). Caffeine (50 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 29.

[00134] Proline ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 30.

[00135] Tyrosine isopropyl ester.HCl (70 g) and tyrosine (7g) were dissolved in water (1 L). Caffeine (50 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 31.

Tyrosine isopropyl ester.HCl (70 g) and tyrosine (7g) were dissolved in water (1 L). Caffeine (50 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 32.

[00136] Tryptophan isopropyl ester.HBr (120 g) and tryptophan (5g) were dissolved in water (1 L). Caffeine (100 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 33.

[00137] Valine ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 34.

[00138] Valine ethyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) was added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 35.

[00139] Phenylalanine butyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) and glycerin (200 ml) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 36.

[00140] Phenylalanine butyl ester.HCl (100 g) was dissolved in water (1 L). Caffeine (30 g) and sodium benzoate (50 g) were added into the mixture and the

mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

Preparation of composition 37.

[00141] 3-(diethylamino)propyl 2-acetoxybenzoate hydrochloride (100 g) was dissolved in water (1 L). Caffeine (80 g) and glycerin (200 ml) were added into the mixture and the mixture was stirred for a few minutes. The mixture was filled into either spray bottles or roll-on bottles.

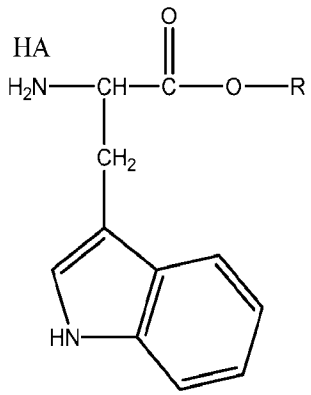
WHAT IS CLAIMED IS:

1. A caffeine-helper composition comprising caffeine, one or more helper esters, pharmaceutically acceptable solvates thereof, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable stereoisomers thereof, and mixtures thereof in any ratios.

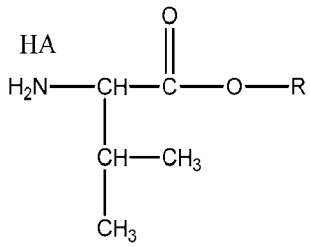
2. The caffeine-helper composition according to claim 1, wherein the helper esters comprise a lipophilic portion and a primary, secondary or tertiary amine group.

3. The caffeine-helper composition according to claim 2, wherein the primary, secondary or tertiary amine group forms a salt with a pharmaceutically acceptable acid selected from the group consisting of HF, HCl, HBr, HI, nitric acid, sulfuric acid, bisulfuricacid, phosphoric acid, phosphorous acid, phosphonic acid, isonicotinic acid, acetic acid, lactic acid, salicylic acid, citric acid, tartaric acid, pantothenic acid, bitartaric acid, ascorbic acid, succinic acid, maleic acid, gentisinic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzensulfonic acid, p-toluenesulfonic acid, and pamoic acid.

4. The caffeine-helper composition according to any of claims 1 to 3, wherein the one or more helper esters are selected from the group consisting of Structure 1, Structure 2, Structure 3, Structure 4, Structure 5, Structure 6, Structure 7, Structure 8, Structure 9, Structure 10, Structure 11, Structure 12, Structure 13, Structure 14, Structure 15, Structure 16, and Structure 17:



Structure 1



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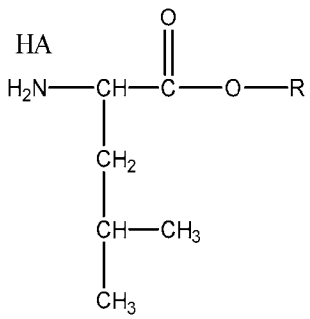

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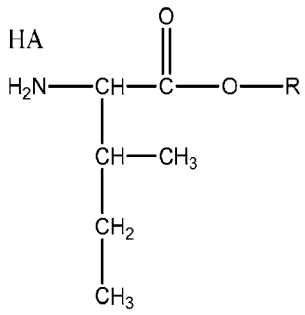

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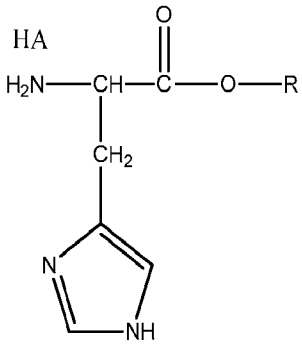

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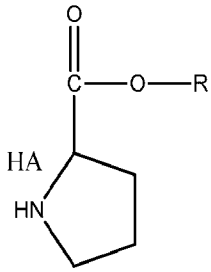

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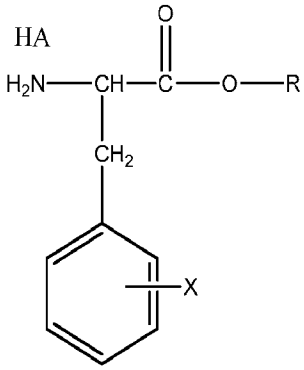
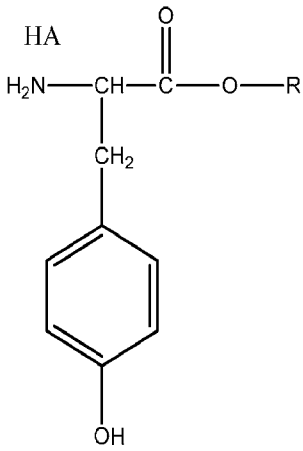
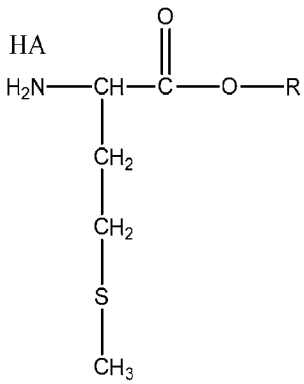


Structure 7



Structure 8



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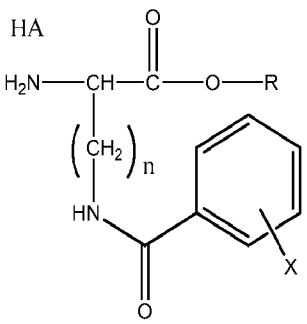
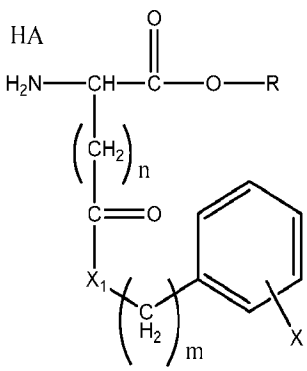
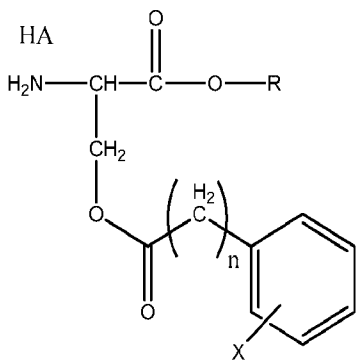


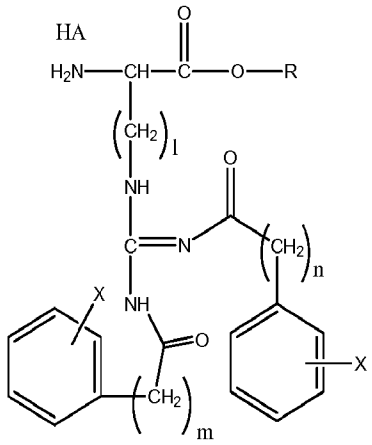
Structure 10



Structure 11



Structure 12



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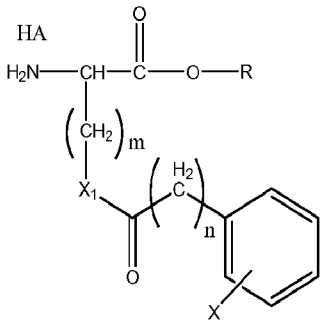
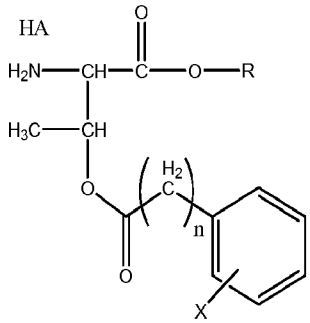
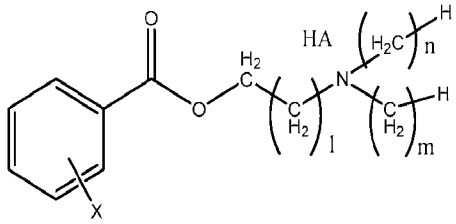


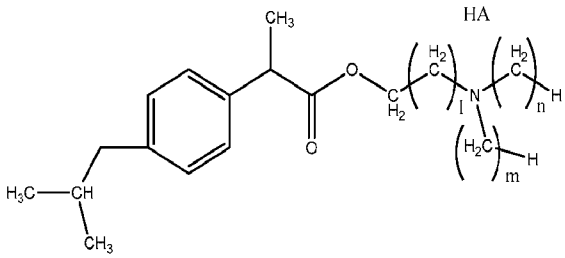
Structure 14



Structure 15



Structure 16



Structure 17, wherein:

each X is independently selected from the group consisting of H, NH_2, NHR_5, OH, $OCOR_5$, Cl, Br, I, CN, R_5COS, R_5O, R_5OCONH, CH_2NHR_5, R_5SO_2, R_5SO, NH_2SO_2, and NO_2;

each X_1 is independently selected from the group consisting of O, S, NH_2, and NHR_5;

each R_1, R_5 and R is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide, wherein any carbon or hydrogen may be further independently replaced with O, S, P, NRz, or any other pharmaceutically acceptable groups;

Rz is selected from the group consisting of H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, alkylthio, alkylamino, perfluoroalkyl, alkyl halide, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkoxyl, substituted alkylthio, substituted alkylamino, substituted perfluoroalkyl, and substituted alkyl halide;

each HA is independently selected from the group consisting of pharmaceutically acceptable acids; and

each l, m, and n is independently selected from the group consisting of 0,1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

5. The caffeine-helper composition according to claim 4, wherein the pharmaceutically acceptable acid is selected from the group consisting of HF, HCl, HBr, HI, acetic acid, citric acid, benzoic acid, lactic acid, nitric acid, sulfuric acid, bisulfuric acid, phosphoric acid, phosphorous acid, phosphonic acid, isonicotinic acid, acetic acid, lactic acid, salicylic acid, citric acid, tartaric acid, pantothenic acid, bitartaric acid, ascorbic acid, succinic acid, maleic acid, gentisinic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzensulfonic acid, p-toluenesulfonic acid, and pamoic acid.

6. The caffeine-helper composition according to any of claims 1 to 5, wherein the helper esters are esters of amino acids, (dialkylamino)alkyl 2-(4-isobutylphenyl)propionate, or (dialkylamino)alkyl 2-acetoxybenzoate.

7. The caffeine-helper composition according to claim 6, wherein the esters of amino acids are selected from the group consisting of L-tryptophan esters, L-leucine esters, L-isoleucine esters, L-proline esters, L-tyrosine esters, L-phenylalanine esters, L-arginine esters, L-alanine esters, L-asparagine esters, L-aspartic acid esters, L-cysteine esters, L-glutamine esters, L-histidine esters, L-lysine esters, L-methionine esters, L-serine esters, L-threonine esters, L-valine esters, D-tryptophan esters, D-leucine esters, D-isoleucine esters, D-proline esters, D-tyrosine esters, D-phenylalanine esters, D-arginine esters, D-alanine esters, D-asparagine esters, D-aspartic acid esters, D-cysteine esters, D-glutamine esters, D-histidine esters, D-lysine esters, D-methionine esters, D-serine esters, D-threonine esters, D-valine esters, and glycine esters.

8. The caffeine-helper composition according to any of claims 1 to 7, wherein the amount of caffeine ranges from about 1 percent to about 20 percent, from about 2 percent to about 12 percent, from about 3 percent to about 10 percent, or from about 4 percent to about 7 percent of the caffeine-helper composition by weight.

9. The caffeine-helper composition according to any of claims 1 to 8, wherein the amount of the helper esters ranges from about 1 percent to about 50 percent, from about 2 percent to about 25 percent, from about 3 percent to about 10 percent, or from about 4 percent to about 7 percent of the caffeine-helper composition by weight.

10. The caffeine-helper composition according to any of claims 1 to 9, further comprising one or more amino acids selected from the group consisting of, without limitation, L-tryptophan, L-leucine, L-isoleucine, L-proline, L-tyrosine, L-phenylalanine, L-arginine, L-alanine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamine, L-histidine, L-lysine, L-methionine, L-serine, L-threonine, L-valine, D-tryptophan, D-leucine, D-isoleucine, D-proline, D-tyrosine, D-phenylalanine, D-arginine, D-alanine, D-asparagine, D-aspartic acid, D-cysteine, D-glutamine, D-histidine, D-lysine, D-methionine, D-serine, D-threonine, D-valine, and glycine.

11. The caffeine-helper composition according to claim 10, wherein the amount of amino acids ranges from about 0.001 percent to about 50 percent, from about 0.01 percent to about 20 percent, from about 0.1 percent to about 10 percent, or from about 0.1 percent to about 2 percent of the caffeine-helper composition by weight.

12. The caffeine-helper composition according to any of claims 1 to 11, further comprising menthol, and the amount of menthol ranges from about 0.01 percent to about 20 percent, from about 0.1 percent to about 10 percent, from about 1 percent to about 5 percent, or from about 1 percent to about 3 percent of the caffeine-helper composition by weight.

13. The caffeine-helper composition according to any of claims 1 to 12, further comprising a solvent.

14. The caffeine-helper composition according to claim 13, wherein the solvent comprises water, and the amount of water ranges from about 1 percent to about 99 percent, from about 50 percent to about 95 percent, from about 70 percent to about 90 percent, or from about 75 percent to about 88 percent of the caffeine-helper composition by weight.

15. The caffeine-helper composition according to claim 13 or 14, wherein the solvent comprises one or more alcohols, and the amount of the one or more alcohols ranges from about 1 percent to about 99 percent, from about 5 percent to about 75 percent, from about 10 percent to about 50 percent, or from about 10 percent to about 25 percent of the caffeine-helper composition by weight.

16. The caffeine-helper composition according to claim 15, wherein the one or more alcohols are selected from the group consisting of ethanol, propanol, isopropanol, and butanol.

17. The caffeine-helper composition according to any of claims 13-16, wherein the solvent comprises glycerin, and the amount of glycerin ranges from about 1 percent to about 50 percent, from about 1 percent to about 25 percent, from about 5 percent to about 20 percent, or from about 5 percent to about 10 percent of the caffeine-helper compositions by weight.

18. The caffeine-helper composition according to any of claims 13-17, wherein the solvent comprises dimethyl sulfoxide (DMSO), and the amount of DMSO ranges from about 1 percent to about 80 percent, from about 5 percent to about 70 percent, from about 10 percent to about 50 percent, or from about 20 percent to about 30 percent of the caffeine-helper compositions by weight.

19. The caffeine-helper composition according to any of claims 1 to 18, further comprising one or more adjuvants selected from the group consisting of preservatives, wetting agents, emulsifying agents, dispersing agents, antibacterial agents, and antifungal agents.

The caffeine-helper composition according to claim 19, wherein the antibacterial agents and antifungal agents are selected from the group consisting of paraben, chlorobutanol, and phenol sorbic acid.

20. A method for delivering caffeine to a subject comprising applying the caffeine-helper composition according to any of claims 1-19 by an administration route selected from the group consisting of transdermal, transmucosal, trans-nasal, topical, and any combinations thereof.

21. The method according to claim 20, wherein the caffeine-helper composition is applied by spraying or rolling-on to the subject.

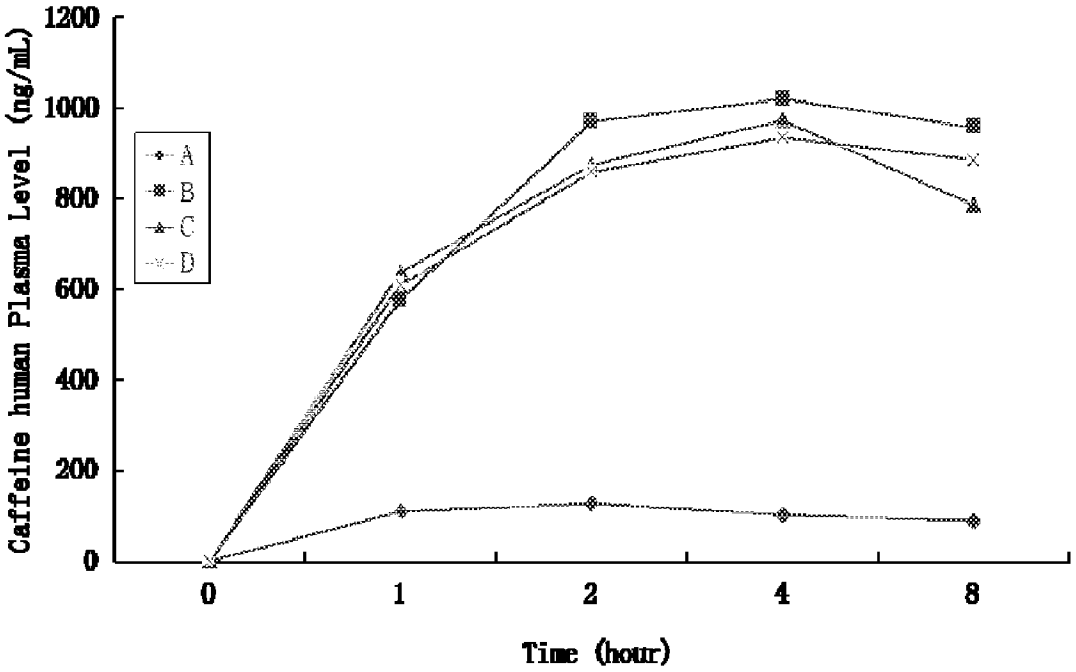

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1A

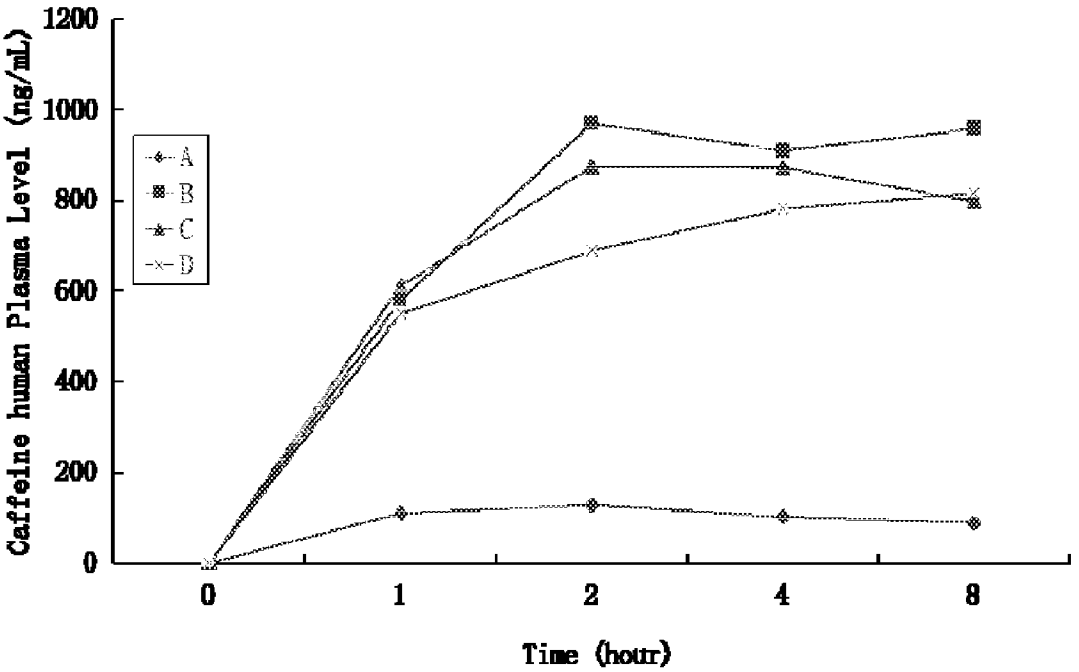

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1B

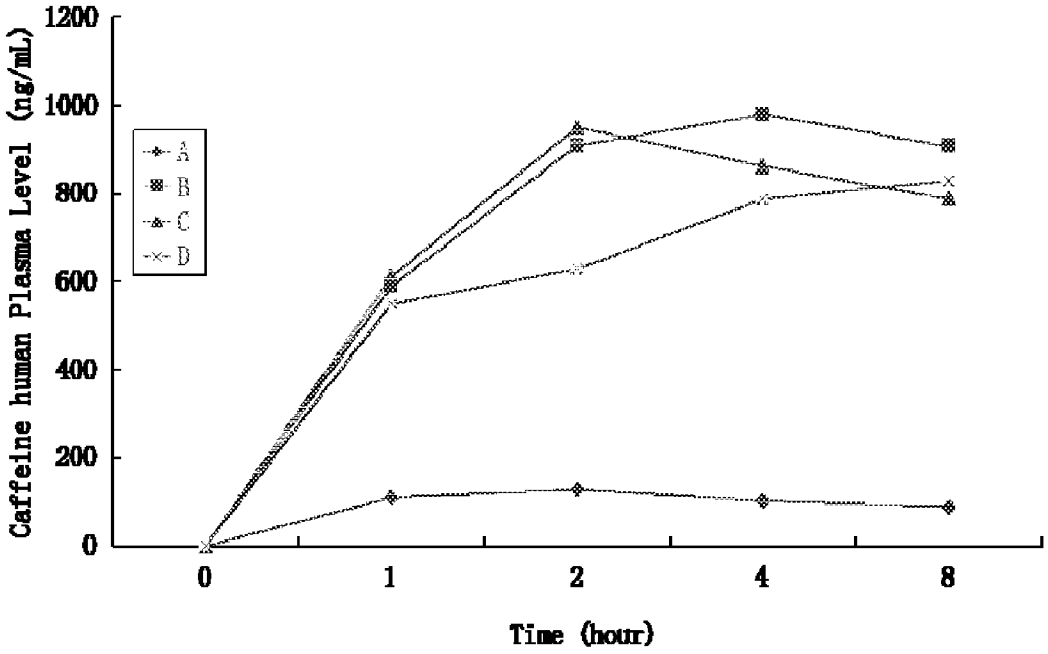

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1C

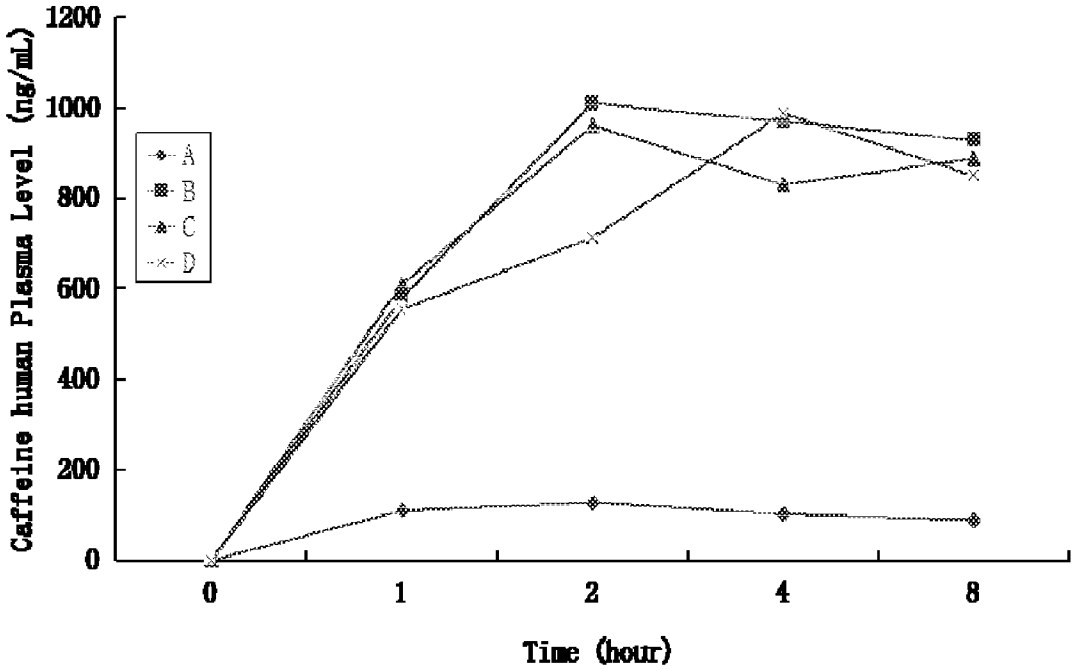

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1D

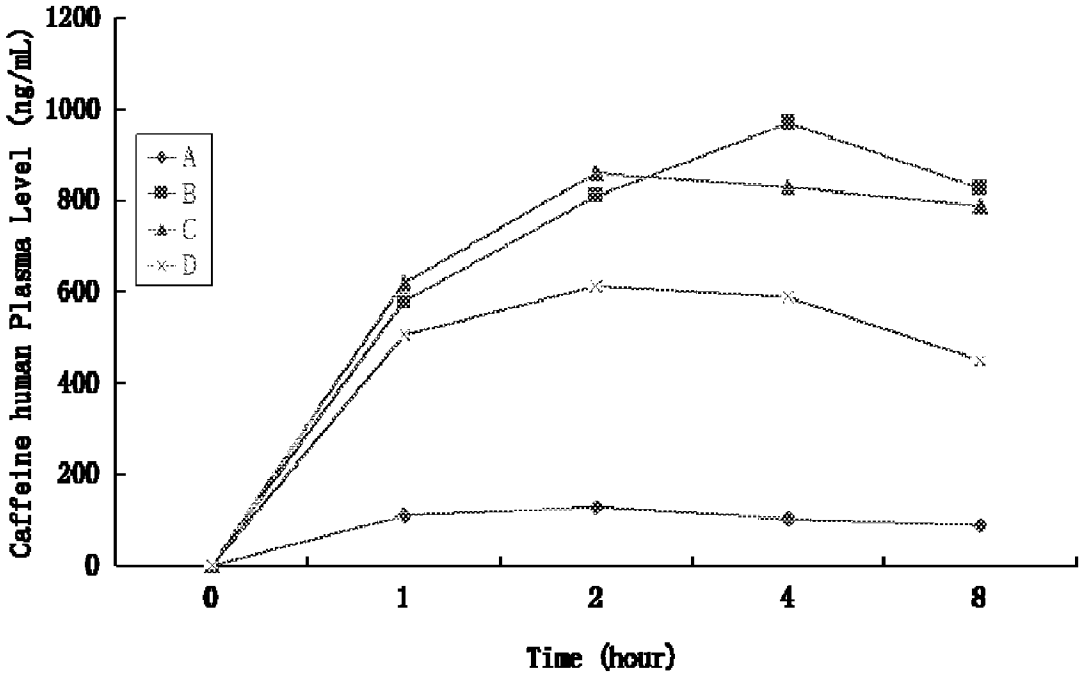

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1E

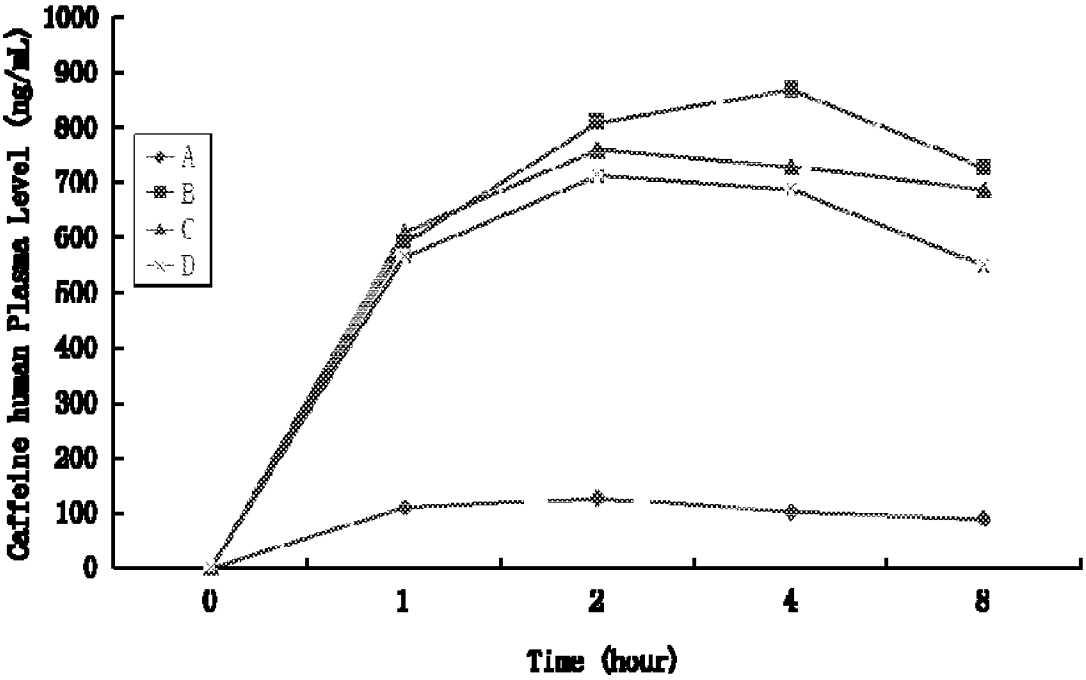

Caffeine human Plasma Level (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1F

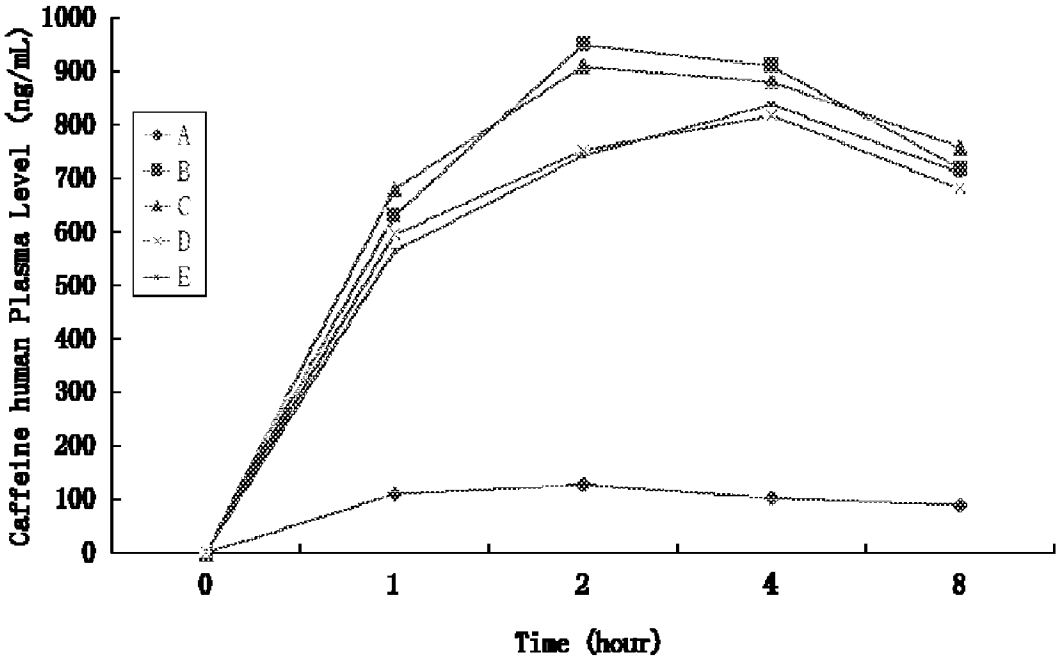

Caffeine human Plasma Level (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
A
B
C
D
E
0
1
2
4
8
Time (hour)

FIG. 1G

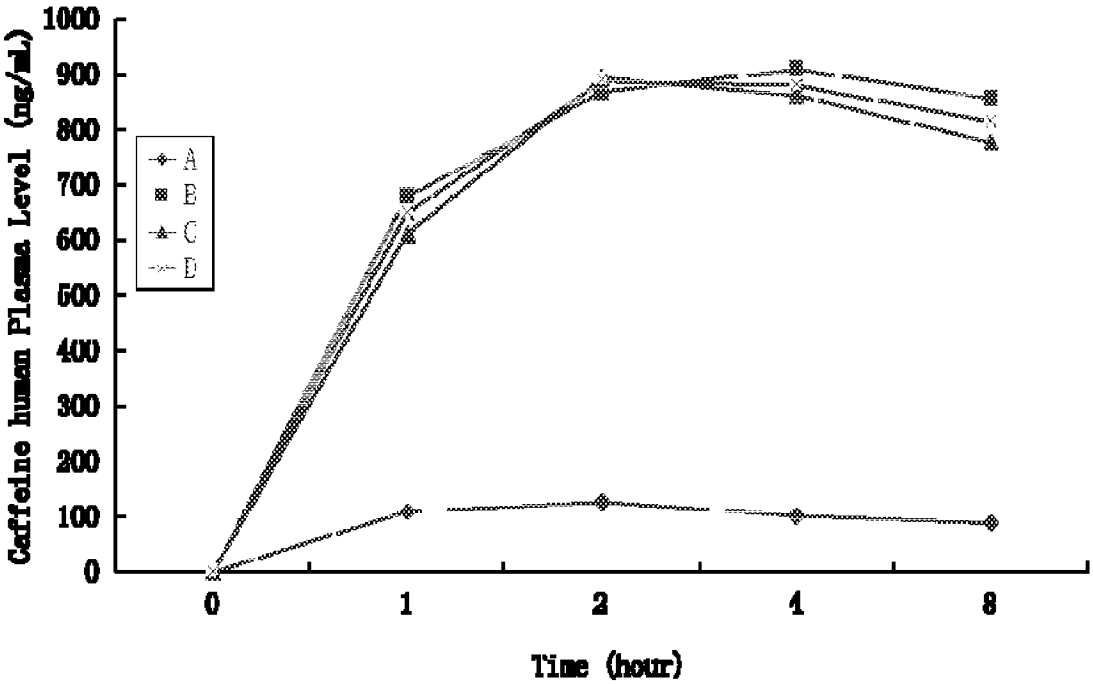

Caffeine human Plasma Level (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
A
B
C
D
0
1
2
4
8
Time (hour)

FIG. 1H

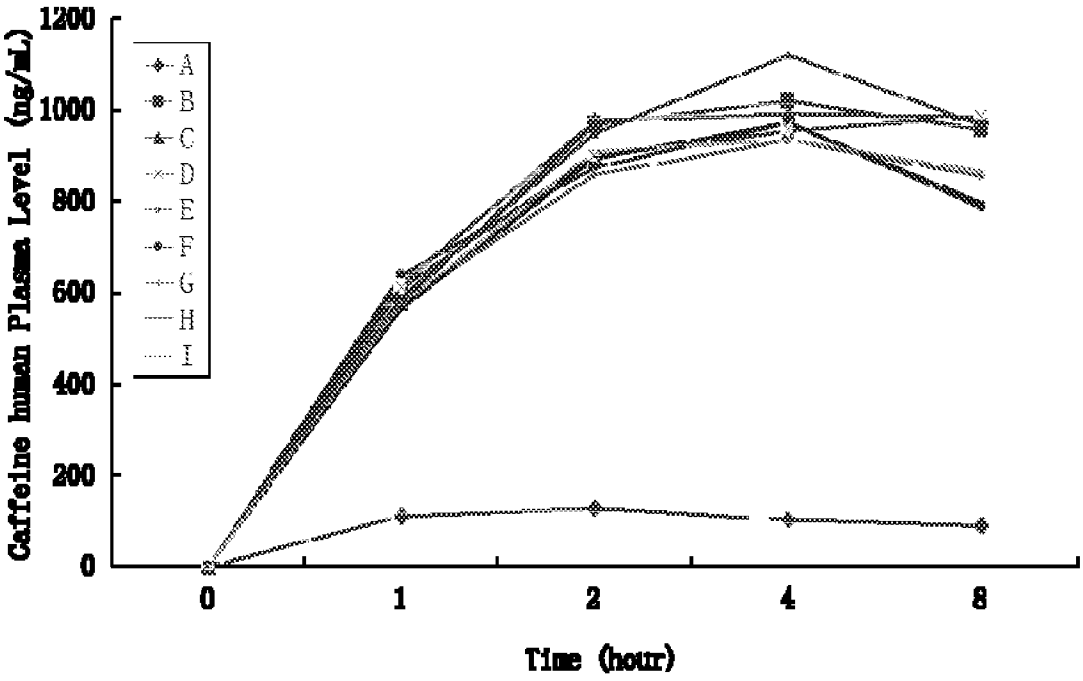

Caffeine human Plasma Level (ng/mL)
1200
1000
800
600
400
200
0
A
B
C
D
E
F
G
H
I
0
1
2
4
8
Time (hour)

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/22157

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/522 (2014.01)
USPC - 514/263.31
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/522 (2014.01)
USPC - 514/263.31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/263.3; 514/785; 514/788; 560/19; 424/400 (search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase (AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO), PubWest, Google Web
search terms: caffeine amino acid ester tryptophan valine leucine isoleucine histidine proline phenylalanine tyrosine methionine arginine alanine asparagine cysteine glutamine lysine serine threonine glycine acid pharmaceutically acceptable transdermal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,961,060 A (Fuxe) 01 June 1976 (01.06.1976), col 1, ln 39-52; col 3, ln 23-33; col 12, ln 36-50	1-5
X ----- Y	US 2003/0165585 A1 (Mann) 04 September 2003 (04. 09.2003), para [0014], [0019], [0020], [0025], [0040]	1, 2, 4 --------- 3, 5
Y	US 4,945,094 A (Salim) 31 July 1990 (31.07.1990), col 1, ln 20-34; col 2, ln 10-16	3, 5
X, P	US 2014/0057873 A1 (Farber) 27 February 2014 (27.02.2014), para [0163], [0168]-[0169], [0173], [0241], [0245], [0261], [0277]	1-5

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2014 (22.05.2014)	23 JUN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/22157

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

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

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

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

3. ☒ Claims Nos.: 6-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.