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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	270712/AQU-039US/480541
First Named Inventor	Alexander Mark Schobel
Title	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 117] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 21]
6. **Inventor's Oath or Declaration** [*Total Pages* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
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ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s)) Name of Assignee ____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [ ] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] **Other:** ____

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(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

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ABSTRACT

Pharmaceutical compositions include a prodrug of epinephrine are described.

CLAIMS:

What is claimed is:

1. A method of treating a medical condition in a human subject comprising:

administering a composition including a prodrug and a permeation enhancer from a matrix;

the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

2. The method of claim 1, wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight.

3. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight.

4. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50 by weight.

5. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight.

6. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

7. The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

8. The method of claim 1, further including administering a pharmaceutically active ingredient with the prodrug.

9. A method of treating a medical condition in a human subject comprising:

administering a composition including a prodrug from a matrix;

delivering the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

10. The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by % weight.

11. The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by % weight.

12. The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.

13. The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight

14. The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.

15. The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.

16. The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.

17. The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

18. The method of claim 1, wherein prodrug has particle size of no more than 100 microns.

19. The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

20. The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.

21. The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

22. The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

23. The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

24. The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

25. The method of claim 1, wherein the prodrug includes an ester of epinephrine.

26. The method of claim 1, wherein at least half of the administered prodrug is converted inless than 240 minutes.

27. The method of claim 1, wherein at least half of the administered prodrug is converted inless than 120 minutes.

28. The method of claim 1, wherein at least half of the administered prodrug is converted inless than 60minutes.

29. The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of of 20 pg/ml to about 40 ng/ml of active compound in a period of less than 120 minutes.

30. The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

31. The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.

32. The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

33. The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.

34. The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.

35. The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.

36. The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.

37. The method of claim 1, wherein the medical condition is in a spectrum of anaphylaxis.

38. The method of claim 1, wherein the medical condition is an allergic reaction.

39. The method of claim 1, wherein the medical condition is a cardiac abnormality.

40. The method of claim 1, wherein the medical condition is a pulmonary abnormality.

41. The method of claim 1, wherein the permeation enhancer includes a phenylpropanoid.

42. The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.

43. The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

44. The method of claim 1, wherein the phenylpropanoid is a chavicol.

45. The method of claim 1, wherein the phenylpropanoid is a safrole.

46. The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.

47. The method of claim 1, wherein the permeation enhancer is synthetic.

48. The method of claim 1, wherein the permeation enhancer is biosynthetic.

49. The method of claim 1, wherein the permeation enhancer is natural.

50. The method of claim 1, wherein the permeation enhancer includes 150-95% eugenol.

51. The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or a sesquiterpene.

52. The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.

53. The method of claim 1, wherein the permeation enhancer includes farnesol.

54. The method of claim 1, wherein the permeation enhancer includes a self-emulsifying excipient.

55. The method of claim 1, wherein the matrix includes a mucoadhesive water soluble polymer.

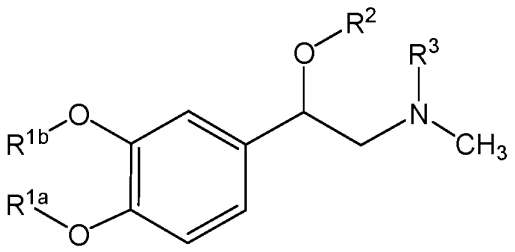
56. The method of claim 1, wherein the permeation enhancer includes linoleic acid.

57. The method of claim 1, wherein the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.

58. The method of claim 1, wherein one of the prodrugs is dipifevrin.

59. The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

60. The method of claim 1, wherein the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

61. The method of claim 60, wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

62. A method of treating a medical condition comprising

administering a prodrug from a matrix, the prodrug being converted to provide a concentration of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes.

63. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes.

64. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 100 minutes.

65. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 60 minutes.

66. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 45 minutes.

67. The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 ng/ml of active compound in less than 30 minutes.

68. The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml.

69. The method of claim 62, further including administering a pharmaceutically active ingredient with the prodrug.

70. The method of claim 62 in which less than 100% of the prodrug is converted.

71. The method of claim 62 in which 100% of the prodrug is converted.

72. A method of treating a medical condition comprising

administering a prodrug, the prodrug converting to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 240 minutes.

73. The method of claim 72 in which less than 100% of the prodrug is converted.

74. The method of claim 72 in which 100% of the prodrug is converted.

75. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 15 minutes.

76. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 30 minutes.

77. The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hours.

78. The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 4 hours.

5

PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

CLAIM OF PRIORITY

This application claims priority to U.S. Provisional Application No. 62/929,737, filed November 1, 2019, which is incorporated by reference in its entirety.

TECHNICAL FIELD

This invention relates to pharmaceutical compositions and methods of treatment.

BACKGROUND

Active ingredients, such as drugs or pharmaceuticals, are delivered to patients in deliberate fashion using a one or more prodrugs. Active ingredients can also be delivered to patients in combination with at least one other active or drug in the composition as part of a drug delivery system. In certain instances, the prodrugs themselves may have biological activity as well as the ability to convert or transform into one or more active drugs.

SUMMARY

Prodrug design is an important part of drug discovery and can offer many advantages over parent drugs such as increased solubility, enhanced stability, improved bioavailability, reduced side effects, and better selectivity. The selection and design of the prodrug can be affected by the site of drug delivery, the tissue type, enzymatic conversion, steric hindrance, and other molecular considerations.

Delivery of drugs or pharmaceuticals transdermally or transmucosally can require that the prodrug, drug, active or pharmaceutical alone or in combination permeate or otherwise cross at least one biological membrane partially or completely in an effective and efficient manner.

In general, a method of treating a medical condition in a human subject can include administering a composition including a prodrug and a permeation enhancer from a matrix and the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

In certain embodiments, the method of treating a medical condution can further including administering a pharmaceutically active ingredient with the prodrug.

In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight

In certain embodiments, the prodrug comprises 0.01-90% of the matrix by % weight. In certain embodiments, the prodrug comprises 0.1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 5-25% of the matrix by % weight.

In certain embodiments, the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes. In certain embodiments, the prodrug has a Tmax of less than 120 minutes. In certain embodiments, the prodrug has a Tmax of less than 60 minutes.

In certain embodiments, the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

In some embodiments, the prodrug has particle size of no more than 200 microns.

In certain embodiments, the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

In certain embodiments, the prodrug is an ester of a pharmaceutically active form of the prodrug.

In certain embodiments, the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

In certain embodiments, the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

In certain embodiments, the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

In certain embodiments, the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

In certain embodiments, the prodrug includes an ester of epinephrine.

In certain embodiments, the prodrug is converted to an active form of the prodrug compound. In certain embodiments, at least half of the administered prodrug is converted inless than 240 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 120 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 60 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 30 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 15 minutes.

In certain embodiments, at least half of the administered prodrug is converted in less than 10 minutes

In certain embodiments, at least half of the administered prodrug is converted in less than 1 minute.

In certain embodiments, the prodrug converts to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 120 minutes.

In certain embodiments, the matrix is applied as chewable or gelatin based dosage form, capsule, inhaled dosage form, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

In certain embodiments, the matrix is pharmaceutical film that has a residence time of less than 90 minutes in an oral cavity.

In certain embodiments, the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

In certain embodiments, the matrix is pharmaceutical film as a residence time of less than 15 minutes in an oral cavity.

In certain embodiments, administering the prodrug stimulates one or more adrenergic receptors. In certain embodiments, administering the prodrug may not activate the alpha 1 adrenergic receptor relative to epinephrine. In certain embodiments, administering the prodrug activates one or more adrenergic receptors in a ratio of 10:1 relative to epinephrine.

In certain embodiments, administering the prodrug minimizes a side effect of epigastric pain. The administering the prodrug can reduce or minimize a side effect of epigastric pain. In certain embodiments, administering the prodrug eliminates a side effect of epigastric pain.

In certain embodiments, the medical condition is in a spectrum of anaphylaxis. In certain embodiments, the medical condition is an allergic reaction. In certain embodiments, the medical condition is a cardiac abnormality. In certain embodiments, the medical condition is a pulmonary abnormality.

In certain embodiments, the permeation enhancer includes a phenylpropanoid. In certain embodiments, the phenylpropanoid is a eugenol or eugenol acetate.

In certain embodiments, the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid. In certain embodiments, the phenylpropanoid is a chavicol. In certain embodiments, the phenylpropanoid is a safrole.

In certain embodiments, the permeation enhancer includes an essential oil extract of a clove plant.

In certain embodiments, the permeation enhancer is synthetic. In certain embodiments, the permeation enhancer is biosynthetic. In certain embodiments, the permeation enhancer is natural.

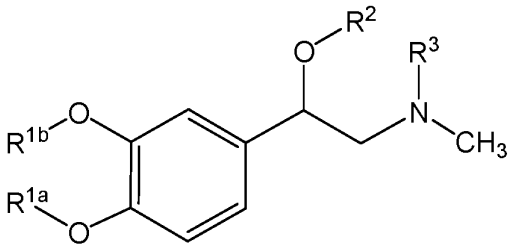
In certain embodiments, the permeation enhancer includes eugenol, for example, 15-95% eugenol. In certain embodiments, the permeation enhancer includes a terpenoid, terpene or a sesquiterpene. In certain embodiments, the permeation enhancer includes a benzyl alcohol. In certain embodiments, the permeation enhancer includes farnesol. In certain embodiments, the permeation enhancer includes a self-emulsifying excipient. In certain embodiments, the permeation enhancer includes linoleic acid. In certain embodiments, the permeation enhancer includes a surfactant such as a cationic surfactant, for example.

In certain embodiments, the matrix includes a mucoadhesive water soluble polymer.

In certain embodiments, the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient. In some of these embodiments, one of the prodrugs is dipivefrin.

In certain embodiments, the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

In certain embodiments, the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^{1a}, R^{1b}, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

In certain embodiments, R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, can be ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl. In some embodiments, both of R^{1a} and R^{1b} can be ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl. In some embodiments, one of R^{1a} and R^{1b} can be ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

In general, a method of treating a medical condition can include administering a prodrug from a matrix, the prodrug being converted at rate of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes.

The prodrug can be converted to 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes. In certain embodiments, prodrug is converted to 200 pg/ml to about 1200pg/ml of active compound in less than 100 minutes. The prodrug can also be converted to 200 pg/ml to about 600pg/ml of active compound in less than 60 minutes. In certain embodiments, the prodrug is converted to 200 pg/ml to about 600pg/ml of active compound in less than 45 minutes. In certain embodiments, the prodrug is converted to 200 pg/ml to about 600pg/ml of active compound in less than 30 minutes.

In certain embodiments, the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml of active compound.

In certain embodiments, less than 100% of the prodrug is converted. In other embodiments, 100% of the prodrug is converted.

In general, a method of treating a medical condition comprising administering a prodrug, the prodrug being converted to produce a concentration of active from 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes and in which 100% of prodrug is converted. In certain circumstances, a method of treating a medical condition comprising administering a prodrug from a matrix, the prodrug being converted to produce a concentration of active from 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes and in which less than 100% of prodrug is converted. The prodrug can be administered from a matrix.

In certain embodiments, the prodrug can produce therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hour. In certain embodiments, the prodrug can produce therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 2 hours. In certain embodiments, the prodrug produces therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 3 hours. In certain embodiments, the prodrug produces therapeutic levels over 100/ml pg of epinephrine for a duration of at least 4 hours.

In certain embodiments, the permeation enhancer can be a phytoextract. In certain embodiments, the permeation enhancer can include a phenylpropanoid. In certain embodiments, the pharmaceutical composition can include a fungal extract. In certain embodiments, the pharmaceutical composition can include a saturated or unsaturated alcohol. In certain embodiments, the alcohol can be an aromatic or aliphatic alcohol such as benzyl alcohol. In some cases, the flavonoid, phytoextract, phenylpropanoid, eugenol, or fungal extract can be used as a solubilizer. In certain embodiments, the phenylpropanoid can be eugenol, eugenol acetate, a cinnamic acid, a cinnamic acid ester, a cinnamic aldehyde, or a hydrocinnamic acid. In certain embodiments, the phenylpropanoid can be chavicol. In other embodiments, the phenylpropanoid can be safrole. In certain embodiments, the phytoextract can be an essential oil extract of a clove plant, such as from a flower bud, leaf or a stem of a clove plant.

In certain embodiments, the prodrug can be administered from a polymer matrix. The polymer matrix can include a polymer, which can include a water soluble polymer. The polymer can be a polyethylene oxide. The polymer can be a cellulosic polymer. The polymer can be a

polysaccharide. The cellulosic polymer can be hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethyl cellulose and/or sodium carboxymethylcellulose. The polymer can include polyethylene oxide and/or polyvinyl pyrrolidone. The polymeric matrix can include polyethylene oxide and/or a polysaccharide. The polymeric matrix can include polyethylene oxide, hydroxypropyl methylcellulose and/or a polysaccharide. The polymeric matrix can include polyethylene oxide, a cellulosic polymer, polysaccharide and/or polyvinylpyrrolidone.

The polymeric matrix can include at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide or propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

In certain embodiments, the pharmaceutical composition can further include a stabilizer. Stabilizers can include antioxidants, which can prevent unwanted oxidation of materials, sequestrants, which can form chelate complexes and inactivating traces of metal ions that would otherwise act as catalysts, emulsifiers and surfactants, which can stabilize emulsions, ultraviolet stabilizers, which can protect materials from harmful effects of ultraviolet radiation, UV absorbers, chemicals absorbing ultraviolet radiation and preventing it from penetrating the composition, quenchers, which can dissipate the radiation energy as heat instead of letting it break chemical bonds, or scavengers which can eliminate free radicals.

A prodrug can be structured to ensure its variable or customizable metabolic stability or protection, e.g., from enzymatic cleavage until a desired target is reached to alleviate certain side effects and/or enhance efficacy. Enzymatic cleavage can result from endogenous enzymes for example. In certain situations, enzymes can be intentionally added to a body to enhance metabolism for example.

In yet another aspect, the pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane

penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) a nitric oxide donor compound; (vi) a long chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced mucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

In general, a method of treating a medical condition can include administering an effective amount of a pharmaceutical composition including a prodrug of an active pharmaceutical component. An active pharmaceutical component can include epinephrine. Epinephrine can be administered as a prodrug, such as dipivefrin or other prodrug. The prodrug can include a natural or synthetic prodrug. The prodrug can be selected and designed based on the active pharmaceutical compound. It can be designed to have certain permeation parameters such that it can penetrate a transmucosal barrier, intercellular or intracellular space and a basement membrane such that it can reach the vascular system. The prodrug can also have sufficient hydrolysis parameters allowing it to be metabolized including by one or more enzymatic processes into one or more active compounds and absorbed in the tissue or biological fluid. This absorption can be in a range from a very rapid in uptake to very slow in uptake. In some embodiments, the uptake is controlled so that pharmacokinetic performance or profiles can be custom designed for unique or different pharmacodynamic effects.

Thus, a method of treating a medical condition can include administering an effective amount of a pharmaceutical composition including a polymeric matrix, in which the pharmaceutically active component may include one or more of a prodrug, a permeation

enhancer, or a combination of these in a specific ratio. In certain embodiments, the medical condition can include cardiac dysfunction, pulmonary dysfunction, dermatitis, type I-IV hypersensitivity reactions, hypotension, cardiac arrest, heart failure, anaphylaxis, mydriasis, asystole, pulseless electrical activity, ventricular fibrillation, pulseless ventricular tachycardia, bradycardia, arrhythmia, supraventricular tachycardia or asthma exacerbation.

In certain embodiments, a pharmaceutical film can include a polymeric matrix, a pharmaceutically active component including epinephrine or a prodrug or at least one prodrug alone or in combination with epinephrine contained in the polymeric matrix along with an adrenergic receptor interacter.

The active and/or the prodrug in the pharmaceutical film can have a Tmax of 1 seconds - 240 minutes, and a Cmax of 0.1 ng/ml - 2 ng/ml. In certain embodiments, the Tmax is 40 minutes or less and wherein the Cmax is 0.1 ng/ml or greater. In certain embodiments, the Tmax is 35 minutes or less and wherein the Cmax is 0.15 ng/ml or greater. In certain embodiments, Tmax is 30 minutes or less and wherein the Cmax is 0.2 ng/ml or greater.

The Cmax can be 0.1 ng/ml - 2 ng/ml, 0.15 ng/ml-2.5 ng/ml, 0.2 ng/ml - 1.0 ng/ml, 0.2 ng/ml - 1.2 ng/ml, and 0.2 ng/ml - 1.3 ng/ml. The Cmax can be greater than 0.1 ng/ml, greater than 0.15 ng/ml, greater than 0.2 ng/ml, greater than 0.4 ng/ml, greater than 0.5 ng/ml, greater than 1.0 ng/ml, greater than 1.2 ng/ml. The Cmax can be less than 3 ng/ml, less than 2 ng/ml and less than 1.5 ng/ml.

The Tmax can be 1 second-240 minutes, 10-60 minutes, 20-40 minutes, 12-15 minutes, and 5-10 minutes and 15 sec-5 min. The Tmax can be less than 120 minutes, 90 minutes, 60 minutes, 45 minutes, 35 minutes, 25 minutes, less than 20 minutes, 15 minutes, less than 12 minutes, and less than 10 minutes. It is understood that monophasic, biphasic and multiphasic pharmacokinetic curves can be produced with multiple and varying Tmax and Cmax and partial or complete AUC's (area under the curve or drug exposure) utilizing this invention.

Other aspects, embodiments, and features will be apparent from the following description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE FIGURES

Referring to Fig. 1A and Fig. 1B, plasma concentration is shown for EpiPen vs. dipivefrin soluble film (DSF).

Referring to Fig. 2A and 2B, plasma concentration vs. time is shown for dipivefrin in varying doses.

Referring to Fig. 3A and 3B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-10.

Referring to Fig. 4, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-04 and AQEP-05.

Referring to Fig. 5, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-03, AQEP-06 and AQPE-07.

Referring to Fig. 6A and Fig. 6B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-01, AQEP-02, AQEP-03 and AQEP-04.

Referring to Fig. 7A and 7B, epinephrine concentration in plasma is shown as converted from prodrugs dipivefrin and AQEP-03 and AQEP-05.

Referring to Fig. 8A-8C, epinephrine concentration in plasma for prodrug conversion was measured in. intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin to compare the pharmacokinetic profile of L-dipivefrin administered through intramuscular (IM) and subcutaneous (SC) routes to epinephrine (Epipen, 0.3 mg).

Referring to Fig. 9A, 9B and 9C, intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin was compared with the pharmacokinetic profile of L-dipivefrin.

Referring to Fig. 10, average dipivefrin plasma concentration over time is indicated as measured in IM and SC administration.

Referring to Fig. 11A conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using IM administration.

Referring to Fig.11B, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using SC administration.

Referring to Fig. 12A, the graph shows a comparison was performed for IM and SC administration of dipivefrin as compared to the Epipen.

Referring to Fig. 12B, the graph shows the dose response (epinephrine plasma levels) was obtained as a function of route of administration.

Referring to Fig. 12C, the graph shows dose response (epinephrine plasma levels) as a function of route of administration.

Referring to Fig. 13A, the graph shows prodrugs AQEP-08, AQEP-09 and AQEP-10 tested against L-dipivefrin for their resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 13B, the graph indicates prodrugs AQEP-11, AQEP-12 and AQEP-13 tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 13C, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 14A, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min).

Referring to Fig. 14B, the graph shows the ex vivo permeation data for AQEP-09 compared to L-dipivefrin.

Referring to Fig. 14C and Fig. 14D, the graphs show the ex vivo permeation data for AQEP-09 compared to L-dipivefrin with film compositions with varying polysaccharide and starch content.

Referring to Fig, 15, the graph indicates a study comparing in vitro human whole blood hydrolysis data for those prodrugs having acceptable levels of permeation.

Referring to Fig. 16, the graph indicates the results from a study of flux vs. carbon chain length.

Referring to Fig. 17, the graph indicates the effect of sodium fluoride on drug absorption.

Referring to Fig. 18A and 18B the graph show the results from the use of combination of two prodrugs in preclinical study.

DETAILED DESCRIPTION

Prodrugs can provide enhanced delivery of an active pharmaceutical ingredient such as epinephrine for example. Mucosal surfaces, such as the oral mucosa, are a convenient route for delivering drugs to the body due to the fact that they are highly vascularized and permeable, providing increased bioavailability and rapid onset of action because it does not pass through the digestive system and thereby avoids first pass metabolism. In particular, the buccal and

sublingual tissues offer advantageous sites for drug delivery because they are highly permeable regions of the oral mucosa, allowing drugs diffusing from the oral mucosa to have direct access to systemic circulation. This also offers increased convenience and therefore increased compliance in patients. The permeation may be 100% for some mucosal surfaces but may also be absorbed fractionally from one or more mucosal sites such as buccal, gingival, sublingual, esophageal, gastric, intestinal tract, dermal, epidermal, nasal, aural, bronchial, and colon. For certain drugs, or pharmaceutically active components, a permeation enhancer can help to overcome the mucosal barrier and improve permeability. Permeation enhancers reversibly modulate the penetrability of the barrier layer in favor of drug absorption. Permeation enhancers facilitate transport of molecules through the tissue. Absorption profiles and their rates can be controlled and modulated by a variety of parameters, such as but not limited to film size, drug loading, enhancer type/loading, polymer matrix release rate, mucosal residence time and by the use of at least one pharmaceutical active alone or in combination with one or more prodrugs.

A pharmaceutical composition can be designed to deliver a prodrug for a pharmaceutically active component in a deliberate and tailored way. U.S. Patent Applications 15/717,859 and 15/791,249, and PCT Application PCT/US2018/053042, published as WO 2019/067670 are each incorporated by reference herein.

Prodrug Design

Delivery of certain active compounds, such as epinephrine, is characterized by certain unique challenges. The compound is hydrophilic, endogenous, highly variable, requires rapid delivery, and promotes vasoconstriction. Thus, the concentration and timing of its delivery is often critical to manage and not easily accomplished. An effective approach to delivering epinephrine can be with a system that allows the compound to penetrate a transmucosal barrier. Transmucosal barriers include surface epithelial cells, intercellular space, and a basement membrane. The epithelial cells which can be overcome with a penetration enhancer or permeation enhancer. The intercellular space can be overcome with a cosolvent or fatty acid. Finally, the basement membrane delays, but does not prevent absorption of the compound, which can be delivered with a permeation enhancer and cosolvent or fatty acid, or a combination of these. While transmucosal delivery of epinephrine can be effective, often times, it may not be rapid enough, vasoconstriction can result in an undulating pharmacokinetic (PK) profile, and swallowed epinephrine that is not absorbed can result in epigastric pain (e.g., 7.5 mg - 30 mg).

A prodrug design can provide an alternative for the delivery of epinephrine, and indeed, for other active pharmaceutical ingredients. A prodrug can present improved hydrophobicity, better permeation, dose reduction, and enhanced speed of absorption. It can also provide alternative compositions with unique stability profiles. For example, while epinephrine is stabilized by sodium metabisulfite, the prodrug dipivefrin was found to be unstable in sodium metabisulfite. Other prodrugs could have similar stability and/or be designed based on the desired stability profile exhibited with certain additives. A prodrug that is not absorbed in the stomach can also avoid, minimize or eliminate the side effect of epigastric pain. Moreover, a prodrug can result in reduced adrenergic receptor binding, resulting in reduced variability of vasoconstriction and more stability. An expected disadvantage for the epinephrine prodrug approach is that it often requires conversion in the blood, can cause delay in epinephrine exposure as a function of its conversion rate, and since the molecular weight is often higher than that of the active pharmaceutical ingredient, it can also require a higher drug loading (e.g. if the prodrug is twice the molecular weight of the active pharmaceutical ingredient, it can require twice the drug loading).

A prodrug can be metabolized, for example by hydrolysis. Metabolism can occur through enzymatic conversion, for example through hydrolytic enzymes, which convert a prodrug into an active compound. A prodrug can be converted at various times and in various ways in the body. A prodrug can be designed based on a targeted approach for in any suitable manner based on where and when conversion is desired. In some instances, prodrug conversion can occur systemically (e.g. in circulation). In some situations, prodrug conversion occurs intracellularly (e.g., antiviral nucleoside analogs, lipid-lowering statins). In some situations, prodrug conversion can occur extracellularly, for examples in digestive fluids or other extracellular body fluids).

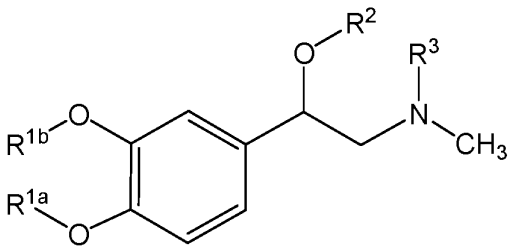
A prodrug can be administered orally. It can be administered in sublingual or buccal dosage forms, or a combination of the two. In certain embodiments, it can be administered as a chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

In certain embodiments, at least half of the administered prodrug is converted in less than 240 minutes. In certain embodiments, at least half of the administered prodrug is converted in less than 120 minutes. In other embodiments, at least half of the administered prodrug is

converted in less than 60 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 30 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 15 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 10 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 5 minutes. In other embodiments, at least half of the administered prodrug is converted in less than 1 minute.

In certain embodiments, a prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 120 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 60 minutes. A prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 30 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 15 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 10 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 5 minutes. The prodrug can be designed to convert to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 1 minute.

Other prodrugs for the delivery of an active pharmaceutical compound have been explored and are described herein. For example, the prodrug can be a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

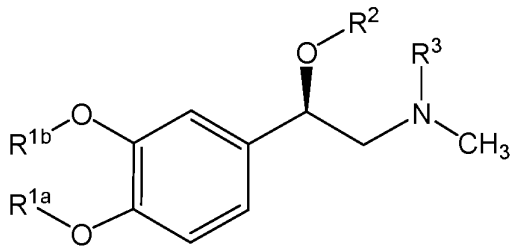
In formula I, each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3

together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^{1a}, R^{1b}, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof. In preferred circumstances, R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, can be C1-C16 acyl, for example, ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl. In certain circumstances, each of R^{1a} and R^{1b} is the same and is not H and R^2 and R^3 are H. In certain circumstances, both of R^{1a} and R^{1b} are not not pivaloyl.

The compound of formula I can be a pharmaceutically acceptable salt. The pharmaceutically acceptable salt can be an acid addition salt or a base addition salt. Acid addition salts can be prepared by reacting the purified compound in its free-based form with a suitable organic or inorganic acid and isolating the salt thus formed. Examples of pharmaceutically acceptable acid addition salts include, without limitations, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid, or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid. Base addition salts can be prepared by reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Such salts include, without limitations, alkali metal (e.g., sodium, lithium, and potassium), alkaline earth metal (e.g., magnesium and calcium), ammonium, alkylammonium, substituted alkylammonium and $N^+(C_{1\text{-}4}alkyl)_4$ salts. The alkyl can be a hydroxyalkyl. Other pharmaceutically acceptable salts of the compound can include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts.

To deliver epinephrine, a class of prodrug compounds was tested having modifications made to the R^{1a}, R^{1b}, R^2 and R^3 groups of epinephrine as shown below. The R^{1a} and R^{1b} groups

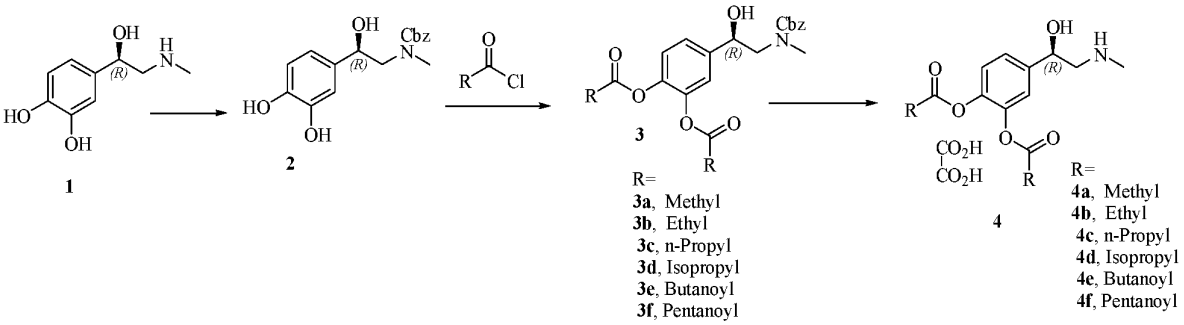
can include esters, amides, carbonates and carbamates, orthoesters or acetals. The groups can include for example, alkyl esters, chloroalkyl esters, amides, alkyl amides, chloroalkyl amides. The R^2 groups can include benzylic alcohol modification. The R^3 group can include amine modification or oxazolidines. An ideal prodrug would have one or more of the following attributes, is biologically acceptable, penetrates one or more mucosal membranes, is stable and converts in the body, tissue or blood. In some cases, the prodrug may not need any permeation enhancers at all but rather permeate sufficiently by itself. The conversion of the prodrug to active is not predictable based on chain length of the R^{1a}, R^{1b}, R^2 and R^3 groups. In particular, a tertiary group at the second atom of the R^{1a}, R^{1b}, R^2 or R^3 group. The permeation of the prodrug is also unpredictable based on the R^{1a}, R^{1b}, R^2 and R^3 groups.



The prodrug selection process for an active pharmaceutical ingredient was conducted by first synthesizing prodrugs with various substituents, conducting ex vivo permeation studies, and following those with in vitro hydrolysis assay using a biological fluid (e.g., human whole blood).

Synthesis

General synthetic procedures were used to synthesize epinephrine prodrugs as shown below.



Preparation of 2:

To a mixture of (-)-epinephrine (5 g) in water (50 ml) and THF (25 ml), was added $NaHCO_3$ (4.6 g, 2 equiv) and stirred for 5 min at 0-5 °C, then added a solution of N-(Benzyloxycarbonyloxy)succinimide (6.82 g, 1 equiv) in THF (25 ml) slowly and stirred at RT for 12 h. Solvent was removed in rotary evaporator, the slid residue was extracted with ethyl acetate (100 mL), washed with 2N HCl (50 mL), followed by brine (100 mL), dried over anhydrous sodium sulfate and the solvent was removed to obtain compound 2 (8.5 g) as a thick brown syrup.

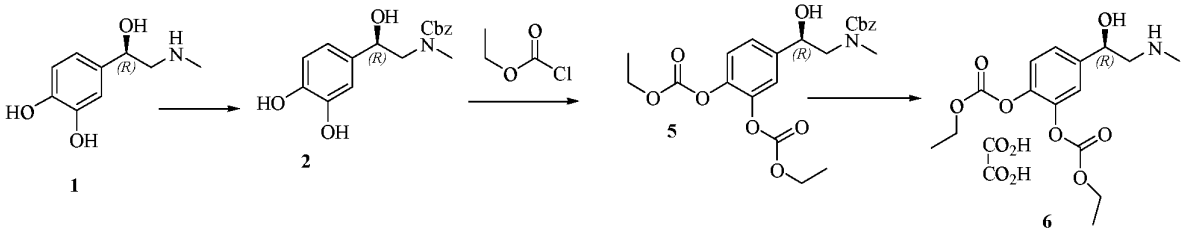
General procedure for preparation of esters 3a-3f.

To a solution of compound 2 (1 equiv), triethylamine (3 equiv) in dichloromethane (30 volumes to compound 2) was added the corresponding acid chloride (1.8 equiv) dropwise at 0-5 °C. Then, the mixture was gradually warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (30 volumes to compound 2). The organic phase was separated, dried over anhydrous sodium sulfate and concentrated to residue which was purified by column chromatography to isolate clean 3a-3f (~60% yield) as oils. Monosubstituted epinephrine prodrugs (not shown in the scheme above) were synthesised using lower equivalent of acid chloride.

General procedure for preparation of 4a-4f.

A mixture of 3a-3f in methanol (~20 vol), oxalic acid (1 equiv), 10% Pd/C (50% wet, 20% wt to the starting material) was stirred under hydrogen atmosphere (using a balloon) for 12 h; TLC was used to ensure completion of the reaction. The catalyst was filtered through celite bed and the filtrate was concentrated to dryness. The solids were suspended in Methyl tert-butyl ether (5 vol), stirred for 30 min; filtered the solids and dried. 4a-4F were isolated as white solids and confirmed by NMR and Mass spec.

Synthesis of biscarbonate 6:



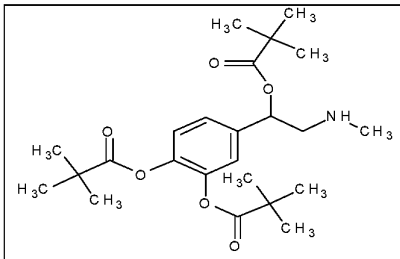
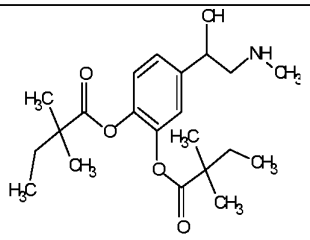
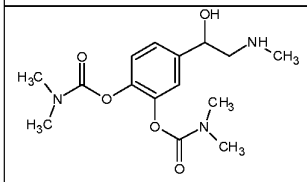
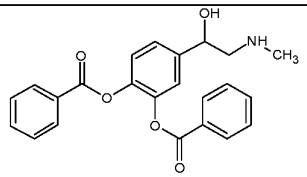
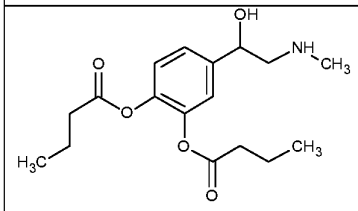
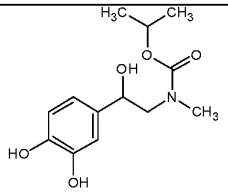
Compound 5:

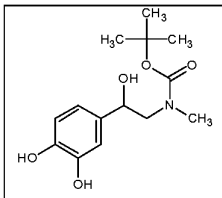
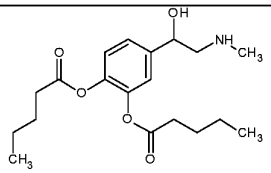
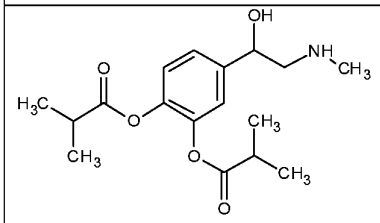
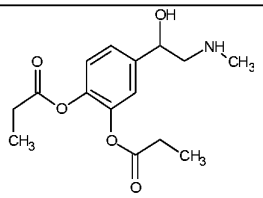
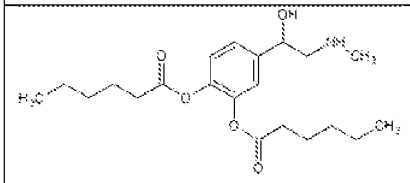
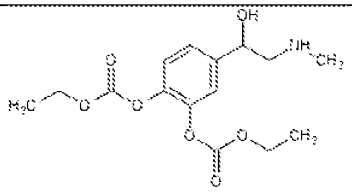
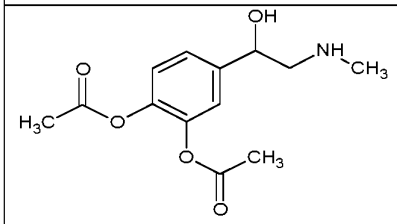
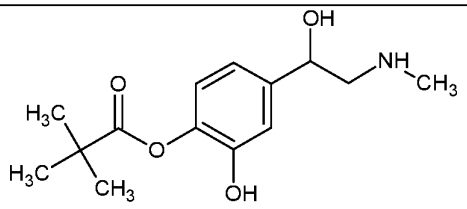
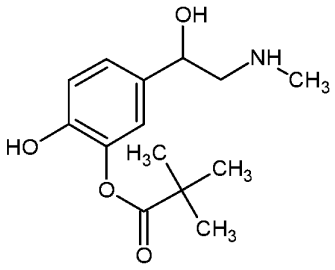
Same procedures as 3a-3f was followed.

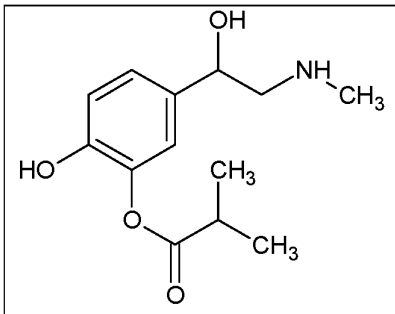
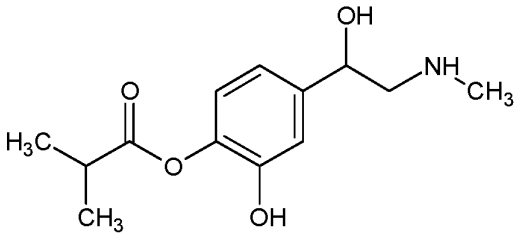
Compound 6:

Same procedures as 4a-4f was followed.

Exemplary prodrugs are provided in the table below.

	
AQEP-01	AQEP-02
	
AQEP-03	AQEP-04
	
AQEP-05	AQEP-06

	
AQEP-07	AQEP-08
	
AQEP-09	AQEP-10
	
AQEP-11	AQEP-12
	 4-Pivaloylepinephrine  3-Pivaloylepinephrine
AQEP-13	AQEP-14

 3-isobutyryl epinephrine  4-isobutyryl epinephrine	
AQEP-15	

The monoesters AQEP-14 and AQEP-15 are mixtures of the two regioisomers.

General Permeation Procedure – Ex vivo Permeation Study Protocol

A Franz diffusion cell is an apparatus used for ex vivo tissue permeation assay used in the formulation development to identify the most active permeation enhancer. The Franz diffusion cell apparatus consists of two chambers separated by a membrane. The permeation studies were conducted using porcine buccal mucosa obtained from a slaughterhouse. The tissues were dermatomed to typically 300-500 μm and mounted in vertical Franz diffusion cells maintained at 37 °C. The tissue membrane separates the donor compartment containing the drug mixed with the permeation enhancer solution and the receptor compartment containing the collection media whish was selected to provide sink conditions throughout the experiment. The permeation rate was observed over several hours by analysing drug concentration in the receptor medium.

In one example, a permeation procedure is conducted as follows. A temperature bath is set to 37° C, and receiver media is placed in a water bath to adjust the temperature and begin degassing. A Franz diffusion cell is obtained and prepared. The Franz diffusion cell includes a

donor compound, a donor chamber, a membrane, sampling port, receptor chamber, stir bar, and a heater/circulator. A stir bar is inserted into a Franz diffusion cell. Tissue is placed over the Franz diffusion cell, and it is ensured that the tissue covers the entire area with an overlap onto a glass joint. The top of a diffusion cell is placed over the tissue, and the top of the cell is clamped to the bottom. About 5 mL of receptor media is loaded into the receiver area to ensure that no air bubbles are trapped in the received portion of the cell. This ensures that all 5mL can fit into the receiver area. Stirring is begun, and temperature is allowed to equilibrate for about 20 minutes. Meanwhile, High Performance Liquid Chromatography (HPLC) vials are labelled by cell number and time point. One must then check again for air bubbles as the solution will degas during heating.

If testing films, one can perform the following next steps: (1) weigh films, punch to match diffusion area (or smaller), reweigh, record pre- and post-punching weight; (2) wet a donor area with approximately 100 µL of phosphate buffer; (3) place film on a donor surface, top with 400 µL of phosphate buffer, and start timers.

For solution studies, one can perform the following steps: (1) using a micropipette, dispense 500 µL of the solution into each donor cell, start the timers; (2) sample 200 µL at the following time points (time = 0 min, 20 min, 40 min, 60 min, 120 min, 180 min, 240 min, 300 min, 360 min), and place in labelled HPLC vials, ensure no air is trapped in the bottom of the vial by tapping the closed vials; (3) replace each sample time with 200 uL of receptor media (to maintain 5 mL); (4) When all time points completed, disassemble the cells and dispose of all materials properly.

Ex vivo Permeation Evaluation

An exemplary ex vivo permeation evaluation is as follows.

1. Tissue is freshly excised and shipped (e.g. overnight) at 4° C.
2. The tissue is processed and frozen at -20° C for up to three weeks prior to use.
3. The tissue is dermatomed to precise thickness.
4. Approximately 5 mL of receiving media is added to the receiving compartment. The media is selected to ensure sink conditions.
5. The tissue is placed in a Franz diffusion cell, which includes a donor compound, a donor chamber, a membrane, sampling port, receptor chamber, stir bar, and a heater/circulator.

6. Approximately 0.5 mL of donor solution is applied or 8 mm circular film and wetted with 500 µL PBS buffer.

7. Samples are taken from the receiving chamber at given intervals and replaced with fresh media.

Permeation Enhancers

Solubility and permeability of the pharmaceutically active component in vivo, in particular, in the mouth of a subject, can vary tremendously. A particular class of permeation enhancer can improve the uptake and bioavailability of the pharmaceutically active component in vivo. In particular, when delivered to the mouth via a film, the permeation enhancer can improve the permeability of the pharmaceutically active component through the mucosa and into the blood stream of the subject. The permeation enhancer can improve absorption rate and amount of the pharmaceutically active component by more than 5%, more than 10%, more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 100%, more than 150%, about 200% or more, or less than 200%, less than 150%, less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%, or a combination of these ranges, depending on the other components in the composition.

In certain embodiments, a pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis;

(x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced transmucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in blood plasma of a subject. Penetration enhancers have been described in J. Nicolazzo, et al., *J. of Controlled Disease*, 105 (2005) 1-15, which is incorporated by reference herein.

In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight. . In certain embodiments, the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

Oral Mucosa

There are many reasons why the oral mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation. Due to the direct drainage of blood from the buccal epithelium into the internal jugular vein first-pass metabolism in the liver and intestine may be avoided. First-pass effect can be a major reason for the poor bioavailability of some compounds when administered orally. Additionally, the mucosa lining the oral cavity is easily accessible, which ensures that a dosage form can be applied to the required site and can be removed easily in the case of an emergency. However, like the skin, the buccal mucosa acts as a barrier to the absorption of xenobiotics, which can hinder the permeation of compounds across this tissue. Consequently, the identification of safe and effective penetration enhancers has become a major goal in the quest to improve oral mucosal drug delivery and/or prodrug delivery.

Chemical penetration enhancers are substances that control the permeation rate of a coadministered drug through a biological membrane. While extensive research has focused on obtaining an improved understanding of how penetration enhancers might alter intestinal and

transdermal permeability, far less is known about the mechanisms involved in buccal and sublingual penetration enhancement.

The buccal mucosa delineates the inside lining of the cheek as well as the area between the gums and upper and lower lips and it has an average surface area of 100 cm^2. The surface of the buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by an undulating basement membrane (a continuous layer of extracellular material approximately 1–2 μm in thickness). This stratified squamous epithelium consists of differentiating layers of cells which change in size, shape, and content as they travel from the basal region to the superficial region, where the cells are shed. There are approximately 40–50 cell layers, resulting in a buccal mucosa which is 500–600 μm thick.

Structurally the sublingual mucosa is comparable to the buccal mucosa but the thickness of this epithelium is 100–200 μm. This membrane is also non-keratinised and being relatively thinner has been demonstrated to be more permeable than buccal mucosa. Blood flow to the sublingual mucosal is slower compared with the buccal mucosa and is of the order of 1.0 ml/ min^{-1}/cm^{-2}.

The permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. The differences in permeability are the result of structural differences between each of the tissues. The absence of organized lipid lamellae in the intercellular spaces of the buccal mucosa results in greater permeability of exogenous compounds, compared to keratinized epithelia of the skin; while the increased thickness and lack of tight junctions results in the buccal mucosa being less permeable than intestinal tissue.

The primary barrier properties of the buccal mucosa have been attributed to the upper one-third to one-quarter of the buccal epithelium. Researchers have learned that beyond the surface epithelium, the permeability barrier of nonkeratinized oral mucosa could also be attributed to contents extruded from the membrane-coating granules into the epithelial intercellular spaces.

The intercellular lipids of the nonkeratinized regions of the oral cavity are of a more polar nature than the lipids of the epidermis, palate, and gingiva, and this difference in the chemical nature of the lipids may contribute to the differences in permeability observed between these tissues. Consequently, it appears that it is not only the greater degree of intercellular lipid

packing in the stratum corneum of keratinized epithelia that creates a more effective barrier, but also the chemical nature of the lipids present within that barrier.

Paracellular and Transcellular Transport

The existence of hydrophilic and lipophilic regions in the oral mucosa has led researchers to postulate the existence of two routes of drug transport through the buccal mucosa paracellular (between the cells) and transcellular (across the cells).

Since drug delivery through the buccal mucosa is limited by the barrier nature of the epithelium and the area available for absorption, various enhancement strategies are required in order to deliver therapeutically relevant amounts of drug to the systemic circulation. Various methods, including the use of chemical penetration enhancers, prodrugs, and physical methods may be employed to overcome the barrier properties of the buccal mucosa.

A chemical penetration enhancer, or absorption promoter, is a substance added to a pharmaceutical formulation in order to increase the membrane permeation or absorption rate of the coadministered drug, without damaging the membrane and/or causing toxicity. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of compounds across the skin, nasal mucosa, and intestine. In recent years, more attention has been given to the effect of these agents on the permeability of the buccal mucosa. Since permeability across the buccal mucosa is considered to be a passive diffusion process the steady state flux (Jss) should increase with increasing donor chamber concentration (CD) according to Fick's first law of diffusion.

In certain embodiments, the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes. In certain embodiments, the prodrug has a Tmax of less than 120 minutes. In certain embodiments, the prodrug has a Tmax of less than 60 minutes.

In certain embodiments, the prodrug has a Cmax of greater than 0.1 pg/ml. The prodrug can have a Cmax of greater than 1 pg/ml. The prodrug can have a Cmax of greater than 10 pg/ml. The prodrug can have a Cmax of greater than 100 pg/ml. The prodrug can have a Cmax of greater than 1000 pg/ml. The prodrug can have a Cmax of greater than 10,000 pg/ml. The prodrug can have a Cmax of greater than 20,000 pg/ml. The prodrug can have a Cmax of greater than 30,000 pg/ml. The prodrug can have a Cmax of greater than 40,000 pg/ml. The prodrug can have a Cmax of less than 50,000 pg/ml.

The prodrug can be designed to be any particle size that enables it to be delivered effectively. In some embodiments, the prodrug has particle size of no more than 200 microns. In some embodiments, the prodrug has particle size of no more than 300 microns, the prodrug has particle size of no more than 400 microns. In some cases, the prodrug can be fully solubilized or partially solubilized, fully or partially suspended or fully or partially emulsified within a matrix.

The prodrug can be designed in a manner that permits effective metabolism or hydrolysis into an active compound. For example, in certain embodiments, the prodrug is an ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an isopropyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an ethyl ester of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes an amide of a pharmaceutically active form of the prodrug. In certain embodiments, the prodrug includes a carbonate of a pharmaceutically active form of the prodrug.

Surfactants, Bile Salts and Other Permeation Enhancers

Surfactants and bile salts have been shown to enhance the permeability of various compounds across the buccal mucosa, both in vitro and in vivo. The data obtained from these studies strongly suggest that the enhancement in permeability is due to an effect of the surfactants on the mucosal intercellular lipids. A permeation enhancer can be a synthetic compound. In certain embodiments, a permeation enhancer can be a biosynthetic compound. In certain embodiments, a permeation enhancer can be a natural compound. In other embodiments, a permeation enhancer can include a combination of compounds from one or more of these categories of compounds.

Fatty acids have been shown to enhance the permeation of a number of drugs through the skin, and this has been shown by differential scanning calorimetry and Fourier transform infrared spectroscopy to be related to an increase in the fluidity of intercellular lipids.

Additionally, pretreatment with ethanol has been shown to enhance the permeability of tritiated water and albumin across ventral tongue mucosa, and to enhance caffeine permeability across porcine buccal mucosa. There are also several reports of the enhancing effect of Azone®

on the permeability of compounds through oral mucosa. Further, chitosan, a biocompatible and biodegradable polymer, has been shown to enhance drug delivery through various tissues, including the intestine and nasal mucosa.

Oral transmucosal drug delivery (OTDD) is the administration of pharmaceutically active agents through the oral mucosa to achieve systemic effects. Permeation pathways and predictive models for OTDD are described, e.g. in M. Sattar, Oral transmucosal drug delivery – Current status and future prospects, *Int'l. Journal of Pharmaceutics*, 47(2014) 498-506, which is incorporated by reference herein. OTDD continues to attract the attention of academic and industrial scientists. Despite limited characterization of the permeation pathways in the oral cavity compared with skin and nasal routes of delivery, recent advances in our understanding of the extent to which ionized molecules permeate the buccal epithelium, as well as the emergence of new analytical techniques to study the oral cavity, and the progressing development of in silico models predictive of buccal and sublingual permeation, prospects are encouraging.

In certain embodiments, the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight. In certain embodiments, the enhancer to prodrug ratio is 50:1 to 1:50 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight. In certain embodiments, the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

In certain embodiments, the prodrug comprises 0.01-90% of the matrix by % weight. In certain embodiments, the prodrug comprises 0.1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 1-50% of the matrix by % weight. In certain embodiments, the permeation enhancer comprises 5-25% of the matrix by % weight.

In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue should be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. It has been shown that buccal penetration can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and their derivatives, chelators, cyclodextrins and chitosan. Among these chemicals used for the drug permeation enhancement, bile salts are the most common.

In vitro studies on enhancing effect of bile salts on the buccal permeation of compounds is discussed in Sevda Senel, Drug permeation enhancement via buccal route: possibilities and limitations, *Journal of Controlled Release* 72 (2001) 133–144, which is incorporated by reference herein. That article also discusses recent studies on the effects of buccal epithelial permeability of dihydroxy bile salts, sodium glycodeoxycholate (SGDC) and sodium taurodeoxycholate (TDC) and tri-hydroxy bile salts, sodium glycocholate(GC) and sodium taurocholate (TC) at 100 mM concentration including permeability changes correlated with the histological effects. Fluorescein isothiocyanate (FITC), morphine sulfate were each used as the model compound. Chitosan has also been shown to promote absorption of small polar molecules and peptide / protein drugs through nasal mucosa in animal models and human volunteers. Other studies have shown an enhancing effect on penetration of compounds across the intestinal mucosa and cultured Caco-2 cells.

The permeation enhancer can be a phytoextract. A phytoextract can be an essential oil or composition including essential oils extracted by distillation of the plant material. In certain circumstances, the phytoextract can include synthetic analogues of the compounds extracted from the plant material (i.e., compounds made by organic synthesis). The phytoextract can include a phenylpropanoid, for example, phenyl alanine, eugenol, eugenol acetate, a cinnamic acid, a cinnamic acid ester, a cinnamic aldehyde, a hydrocinnamic acid, chavicol, or safrole, or a combination thereof. The phytoextract can be an essential oil extract of a clove plant, for example, from the leaf, stem or flower bud of a clove plant. The clove plant can be *Syzygium aromaticum*. The phytoextract can include 20-95% eugenol, including 40-95% eugenol, including 60-95% eugenol, and for example, 80-95% eugenol. The extract can also include 5% to 15% eugenol acetate. The extract can also include caryophyllene. The extract can also include up to 2.1% α-humulen. Other volatile compounds included in lower concentrations in clove essential oil can be β-pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate. Other permeation enhancers may be added to the composition to improve absorption of the drug. Suitable permeation enhancers include natural or synthetic bile salts such as sodium fusidate; glycocholate or deoxycholate and their salts; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium lauryl sulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9,

polysorbates, sterols, or glycerides, such as caprylocaproyl polyoxylglycerides, e.g., Labrasol. The permeation enhancer can include phytoextract derivatives and/or monolignols. The permeation enhancer can also be a fungal extract.

Some natural products of plant origin have been known to have a vasodilatory effect. There are several mechanisms or modes by which plant-based products can evoke vasodilation. For review, see McNeill J.R. and Jurgens, T.M., Can. J. Physiol. Pharmacol. 84:803-821 (2006), which is incorporated by reference herein. Specifically, vasorelaxant effects of eugenol have been reported in a number of animal studies. See, e.g., Lahlou, S., et al., J. Cardiovasc. Pharmacol. 43:250-57 (2004), Damiani, C.E.N., et al., Vascular Pharmacol. 40:59-66 (2003), Nishijima, H., et al., Japanese J. Pharmacol. 79:327-334 (1998), and Hume W.R., J. Dent Res. 62(9):1013-15 (1983), each of which is incorporated by reference herein. Calcium channel blockade was suggested to be responsible for vascular relaxation induced by a plant essential oil, or its main constituent, eugenol. See, Interaminense L.R.L. et al., Fundamental & Clin. Pharmacol. 21: 497-506 (2007), which is incorporated by reference herein.

Fatty acids can be used as inactive ingredients in drug preparations or drug vehicles. Fatty acids can also be used as formulation ingredients due to their certain functional effects and their biocompatible nature. Fatty acid, both free and as part of complex lipids, are major metabolic fuel (storage and transport energy), essential components of all membranes and gene regulators. For review, see Rustan A.C. and Drevon, C.A., Fatty Acids: Structures and Properties, Encyclopedia of Life Sciences (2005), which is incorporated by reference herein. There are two families of essential fatty acids that are metabolized in the human body: ω-3 and ω-6 polyunsaturated fatty acids (PUFAs). If the first double bond is found between the third and the fourth carbon atom from the ω carbon, they are called ω-3 fatty acids. If the first double bond is between the sixth and seventh carbon atom, they are called ω-6 fatty acids. PUFAs are further metabolized in the body by the addition of carbon atoms and by desaturation (extraction of hydrogen). Linoleic acid, which is a ω-6 fatty acid, is metabolized to γ-linolenic acid, dihomo-γ-linolinic acid, arachidonic acid, adrenic acid, tetracosatetraenoic acid, tetracosapentaenoic acid, docosapentaenoic acid, α-linolenic acid, which is a ω-3 fatty acid is metabolized to octadecatetraenoic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid and docosahexaenoic acid (DHA).

It has been reported that fatty acids, such as palmitic acid, oleic acid, linoleic acid and eicosapentaenoic acid, induced relaxation and hyperpolarization of porcine coronary artery smooth muscle cells via a mechanism involving activation of the Na^+K^+-APTase pump and the fatty acids with increasing degrees of *cis*-unsaturation had higher potencies. See, Pomposiello, S.I. et al., Hypertension 31:615-20 (1998), which is incorporated by reference herein. Interestingly, the pulmonary vascular response to arachidonic acid, a metabolite of linoleic acid, can be either vasoconstrictive or vasodilative, depending on the dose, animal species, the mode of arachidonic acid administration, and the tones of the pulmonary circulation. For example, arachidonic acid has been reported to cause cyclooxygenase-dependent and –independent pulmonary vasodilation. See, Feddersen, C.O. et al., J. Appl. Physiol. 68(5):1799-808 (1990); and see, Spannhake, E.W., et al., J. Appl. Physiol. 44:397-495 (1978) and Wicks, T.C. et al., Circ. Res. 38:167-71 (1976), each of which is incorporated by reference herein.

Many studies have reported effects of EPA and DHA on vascular reactivity after being administered as ingestible forms. Some studies found that EPA-DHA or EPA alone suppressed the vasoconstrictive effect of norepinephrine or increased vasodilatory responses to acetylcholine in the forearm microcirculation. See, Chin, J.P.F, et al., Hypertension 21:22-8 (1993), and Tagawa, H. et al., J Cardiovasc Pharmacol 33:633-40 (1999), each of which is incorporated by reference herein. Another study found that both EPA and DHA increased systemic arterial compliance and tended to reduce pulse pressure and total vascular resistance. See, Nestel, P. et al., Am J. Clin. Nutr. 76:326-30 (2002), which is incorporated by reference herein. Meanwhile, a study found that DHA, but not EPA, enhanced vasodilator mechanisms and attenuates constrictor responses in forearm microcirculation in hyperlipidemic overweight men. See, Mori, T.A., et al., Circulation 102:1264-69 (2000), which is incorporated by reference herein. Another study found vasodilator effects of DHA on the rhythmic contractions of isolated human coronary arteries *in vitro*. See Wu, K.-T. et al., Chinese J. Physiol. 50(4):164-70 (2007), which is incorporated by reference herein.

Adrenergic Receptors

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are a target of catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). Epinephrine (adrenaline) interacts with both α- and β-adrenoceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to

epinephrine, when activated, they override the vasodilation mediated by β-adrenoceptors because there are more peripheral α1 receptors than β-adrenoceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. At lower levels of circulating epinephrine, β-adrenoceptor stimulation dominates, producing vasodilation followed by decrease of peripheral vascular resistance. The α1-adrenoreceptor is known for smooth muscle contraction, mydriasis, vasoconstriction in the skin, mucosa and abdominal viscera and sphincter contraction of the gastrointestinal (GI) tract and urinary bladder. The α1-adrenergic receptors are member of the G_q protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, G_q, activates phospholipase C (PLC). The mechanism of action involves interaction with calcium channels and changing the calcium content in a cell. For review, see Smith R. S. et al., Journal of Neurophysiology 102(2): 1103-14 (2009), which is incorporated by reference herein. Many cells possess these receptors.

α1-Adrenergic receptors can be a main receptor for fatty acids. For example, saw palmetto extract (SPE), widely used for the treatment of benign prostatic hyperplasia (BPH), has been reported to bind α1-adrenergic, muscarinic and 1,4-dihydropyridine (1,4-DHP) calcium channel antagonist receptors. See, Abe M., et al., Biol. Pharm. Bull. 32(4) 646-650 (2009), and Suzuki M. et al., Acta Pharmacologica Sinica 30:271-81 (2009), each of which is incorporated by reference herein. SPE includes a variety of fatty acids including lauric acid, oleic acid, myristic acid, palmitic acid and linoleic acid. Lauric acid and oleic acid can bind noncompetitively to α1-adrenergic, muscarinic and 1,4-DHP calcium channel antagonist receptors.

In certain embodiments, a permeation enhancer can be an adrenergic receptor interacter. An adrenergic receptor interacter refers to a compound or substance that modifies and/or otherwise alters the action of an adrenergic receptor. For example, an adrenergic receptor interacter can prevent stimulation of the receptor by increasing, or decreasing their ability to bind. Such interacters can be provided in either short-acting or long-acting forms. Certain short-acting interacters can work quickly, but their effects last only a few hours. Certain long-acting interacters can take longer to work, but their effects can last longer. The interacter can be selected and/or designed based on, e.g., on one or more of the desired delivery and dose, active pharmaceutical ingredient, permeation modifier, permeation enhancer, matrix, and the condition being treated. An adrenergic receptor interacter can be an adrenergic receptor blocker. The

adrenergic receptor interacter can be a terpenoid, terpene (e.g. volatile unsaturated hydrocarbons found in the essential oils of plants, derived from units of isoprenes) or a C3-C22 alcohol or acid, preferably a C7-C18 alcohol or acid, or an aromatic or aliphatic alcohol. In certain embodiments, the adrenergic receptor interacter can include farnesol, linoleic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, and/or docosapentanoic acid. The acid can be a carboxylic acid, phosphoric acid, sulfuric acid, hydroxamic acid, or derivatives thereof. The derivative can be an ester, amide or carbonate. For example, the adrenergic receptor interacter can be a fatty acid or fatty alcohol.

The C3-C22 alcohol or acid can be an alcohol or acid having a straight C3-C22 hydrocarbon chain, for example a C3-C22 hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl, halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, -N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, or -O-C(O)-O-. Each of R^a and R^b, independently, is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl.

Fatty acids with a higher degree of unsaturation are effective candidates to enhance the permeation of drugs. Unsaturated fatty acids showed higher enhancement than saturated fatty acids, and the enhancement increased with the number of double bonds. See, A. Mittal, et al. Status of Fatty Acids as Skin Penetration Enhancers – A Review, *Current Drug Delivery*, 2009, 6, pp. 274-279, which is incorporated by reference herein. Position of double bond also affects the enhancing activity of fatty acids. Differences in the physicochemical properties of fatty acid which originate from differences in the double bond position most likely determine the efficacy of these compounds as skin penetration enhancers. Skin distribution increases as the position of the double bond is shifted towards the hydrophilic end. It has also been reported that fatty acid which has a double bond at an even number position more rapidly effects the perturbation of the structure of both the stratum corneum and the dermis than a fatty acid which has double bond at an odd number position. Cis-unsaturation in the chain can tend to increase activity.

An adrenergic receptor interacter can be a terpene. Hypotensive activity of terpenes in essential oils has been reported. See, Menezes I.A. et al., Z. Naturforsch. 65c:652-66 (2010),

which is incorporated by reference herein. In certain embodiments, the permeation enhancer can be a sesquiterpene. Sesquiterpenes are a class of terpenes that consist of three isoprene units and have the empirical formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids.

An adrenergic receptor interacter can be an unsaturated fatty acid such as linoleic acid. In certain embodiments, the permeation enhancer can be farnesol. Farnesol is a 15-carbon organic compound which is an acyclic sesquiterpene alcohol, which is a natural dephosphorylated form of farnesyl pyrophosphate. Under standard conditions, it is a colorless liquid. It is hydrophobic, and thus insoluble in water, but miscible with oils. Farnesol can be extracted from oils of plants such as citronella, neroli, cyclamen, and tuberose. It is an intermediate step in the biological synthesis of cholesterol from mevalonic acid in vertebrates. It has a delicate floral or weak citrus-lime odor and is used in perfumes and flavors. It has been reported that farnesol selectively kills acute myeloid leukemia blasts and leukemic cell lines in preference to primary hemopoietic cells. See, Rioja A. et al., FEBS Lett 467 (2-3): 291-5 (2000), which is incorporated by reference herein. Vasoactive properties of farnesyl analogues have been reported. See, Roullet, J.-B., et al., J. Clin. Invest., 1996, 97:2384-2390, which is incorporated by reference herein. Both Farnesol and N-acetyl-S-trans, trans-farnesyl-L-cysteine (AFC), a synthetic mimic of the carboxyl terminus of farnesylated proteins inhibited vasoconstriction in rat aortic rings. In certain embodiments, an interacter can be an aporphine alkaloid. For example, an interacter can be a dicentrine.

In general, an interacter can also be a vasodilator or a therapeutic vasodilator. Vasodilators are drugs that open or widen blood vessels. They are typically used to treat hypertension, heart failure and angina, but can be used to treat other conditions as well, including glaucoma for example. Some vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension, and heart failure, and angina; however, reflex cardiac stimulation makes some arterial dilators unsuitable for angina. Venous dilators are very effective for angina, and sometimes used for heart failure, but are not used as primary therapy for hypertension. Vasodilator drugs can be mixed (or balanced) vasodilators in that they dilate both arteries and veins and therefore can have wide application in hypertension, heart failure and angina. Some vasodilators, because of their mechanism of action, also have other important

actions that can in some cases enhance their therapeutic utility or provide some additional therapeutic benefit. For example, some calcium channel blockers not only dilate blood vessels, but also depress cardiac mechanical and electrical function, which can enhance their antihypertensive actions and confer additional therapeutic benefit such as blocking arrhythmias.

Vasodilator drugs can be classified based on their site of action (arterial versus venous) or by mechanism of action. Some drugs primarily dilate resistance vessels (arterial dilators; e.g., hydralazine), while others primarily affect venous capacitance vessels (venous dilators; e.g., nitroglycerine). Many vasodilator drugs have mixed arterial and venous dilator properties (mixed dilators; e.g., alpha-adrenoceptor antagonists, angiotensin converting enzyme inhibitors), such as phentolamine.

It is more common, however, to classify vasodilator drugs based on their primary mechanism of action. The figure to the right depicts important mechanistic classes of vasodilator drugs. These classes of drugs, as well as other classes that produce vasodilation, include: alpha-adrenoceptor antagonists (alpha-blockers); Angiotensin converting enzyme (ACE) inhibitors; Angiotensin receptor blockers (ARBs); beta$_2$-adrenoceptor agonists (β_2-agonists); calcium-channel blockers (CCBs); centrally acting sympatholytics; direct acting vasodilators; endothelin receptor antagonists; ganglionic blockers; nitrodilators; phosphodiesterase inhibitors; potassium-channel openers; or renin inhibitors.

In general, the active or inactive components or ingredients can be substances or compounds that create an increased blood flow or flushing of the tissue to enable a modification or difference (increase or decrease) in transmucosal uptake of the API(s), and/or have a positive or negative heat of solution which are used as aids to modify (increase or decrease) transmucosal uptake.

Sequence of Permeation Enhancer(s) and Active Pharmaceutical Ingredient(s)

The arrangement, order, or sequence of penetration enhancer(s) and active pharmaceutical ingredient(s)(API(s)) delivered to the desired mucosal surface can vary in order to deliver a desired pharmacokinetic profile. For example, one can apply the permeation enhancer(s) first by a film, by swab, spray, gel, rinse or by a first layer of a film then apply the API(s) by single film, by swab, or by a second layer of a film. The sequence can be reversed or modified, for example, by applying the API(s) first by film, by swab, or by a first layer of a film, and then applying the permeation enhancer(s) by a film, by swab, spray, gel, rinse or by a second

layer of a film. In another embodiment, one may apply a permeation enhancer(s) by a film, and a drug by a different film. For example, the permeation enhancer(s) film positioned under a film containing the API(s), or the film containing the API(s) positioned under a film containing the permeation enhancer(s), depending on the desired pharmacokinetic profile.

The arrangement, order, or sequence of prodrug(s) delivered to the desired mucosal surface can vary in order to deliver a desired pharmacokinetic profile. For example, one can apply a prodrug or combination of prodrugs by a film, by swab, spray, gel, rinse or by a layer of a film. In another example, one can apply a first prodrug by a film, by swab, spray, gel, rinse or by a layer of a film, followed by another application of a prodrug by a film, by swab, spray, gel, rinse or by a layer of a film. A subsequent prodrug can be a different prodrug from the first prodrug. In another example, the first prodrug and subsequent prodrug(s) can be the same compound. In another example, one can apply permeation enhancer(s) first by a film, by swab, spray, gel, rinse or by a first layer of a film then apply the prodrug(s) by single film, by swab, or by a second layer of a film. The sequence can be reversed or modified, for example, by applying the prodrug(s) first by film, by swab, or by a first layer of a film, and then applying the permeation enhancer(s) by a film, by swab, spray, gel, rinse or by a second layer of a film. In another embodiment, one may apply a permeation enhancer(s) by a film, and a drug by a different film. For example, the permeation enhancer(s) film positioned under a film containing the prodrug(s), or the film containing the prodrug(s) positioned under a film containing the permeation enhancer(s), depending on the desired pharmacokinetic profile.

For example, the penetration enhancer(s) can be used as a pretreatment alone or in combination with at least one API or prodrug to precondition the mucosa for further absorption of the API(s). The treatment can be followed by another treatment with neat penetration enhancer(s) to follow the at least one API mucosal application. The pretreatment can be applied as a separate treatment (film, gel, solution, swab etc.) or as a layer within a multilayered film construction of one or more layers. Similarly, the pretreatment may be contained within a distinct domain of a single film, designed to dissolve and release to the mucosa prior to release of the secondary domains with or without penetration enhancer(s) or API(s). The active ingredient may then be delivered from a second treatment, alone or in combination with additional penetration enhancer(s). There may also be a tertiary treatment or domain that delivers additional penetration enhancer(s) and/or at least one API(s) or prodrug(s), either at a different

ratio relative to each other or relative to the overall loading of the other treatments. This allows a custom pharmacokinetic profile to be obtained. In this way, the product may have single or multiple domains, with penetration enhancer(s) and API(s) that can vary in mucosal application order, composition, concentration, or overall loading that leads to the desired absorption amounts and/or rates that achieve the intended pharmacokinetic profile and/or pharmacodynamic effect.

The film format can be oriented such that no distinct sides, or such that the film has at least one side of a multiple layer film where the edges are co-terminus (having or meeting at a shared border or limit).

The pharmaceutical composition can be a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film. The composition can include textures, for example, at the surface, such as microneedles or micro-protrusions. Recently, the use of micron-scale needles in increasing skin permeability has been shown to significantly increase transdermal delivery, including and especially for macromolecules. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For such studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Microneedles can be, for example, polymeric, microscopic needles that deliver encapsulated drugs in a minimally invasive manner, but other suitable materials can be used.

Microneedles can be used to enhance the delivery of drugs through the oral mucosa, particularly with the claimed compositions. The microneedles create micron sized pores in the oral mucosa which can enhance the delivery of drugs across the mucosa. Solid, hollow or

dissolving microneedles can be fabricated out of suitable materials including, but not limited to, metal, polymer, glass and ceramics. The microfabrication process can include photolithography, silicon etching, laser cutting, metal electroplating, metal electro polishing and molding. Microneedles could be solid which is used to pretreat the tissue and are removed before applying the film. The drug loaded polymer film described in this application can be used as the matrix material of the microneedles itself. These films can have microneedles or micro protrusions fabricated on their surface which will dissolve after forming microchannels in the mucosa through which drugs can permeate.

The term "film" can include films and sheets, in any shape, including rectangular, square, or other desired shape. A film can be any desired thickness and size. In preferred embodiments, a film can have a thickness and size such that it can be administered to a user, for example, placed into the oral cavity of the user. A film can have a relatively thin thickness of from about 0.0025mm to about 0.250mm, or a film can have a somewhat thicker thickness of from about 0.250mm to about1.0mm. For some films, the thickness may be even larger, i.e., greater than about 1.0mm or thinner, i.e., less than about 0.0025mm. A film can be a single layer or a film can be multi-layered, including laminated or multiple cast films. A permeation enhancer and pharmaceutically active component can be combined in a single layer, each contained in separate layers, or can each be otherwise contained in discrete regions of the same dosage form. In certain embodiments, the pharmaceutically active component contained in the polymeric matrix can be dispersed in the matrix. In certain embodiments, the permeation enhancer being contained in the polymeric matrix can be dispersed in the matrix.

Oral dissolving films can fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Oral dissolving films can also include a combination of any of the above categories. Fast dissolving films can dissolve in about 1 second to about 30 seconds in the mouth, including more than 1 second, more than 5 seconds, more than 10 seconds, more than 20 seconds, or less than 30 seconds. Moderate dissolving films can dissolve in about 1 to about 30 minutes in the mouth including more than 1 minute, more than 5 minutes, more than 10 minutes, more than 20 minutes or less than 30 minutes, and slow dissolving films can dissolve in more than 30 minutes in the mouth. As a general trend, fast dissolving films can include (or consist of) low molecular weight hydrophilic polymers (e.g., polymers having a molecular weight between about 1,000 to 9,000 daltons, or polymers having a molecular weight up to 200,000

daltons). In contrast, slow dissolving films generally include high molecular weight polymers (e.g., having a molecular weight in millions). Moderate dissolving films can tend to fall in between the fast and slow dissolving films.

It can be preferable to use films that are moderate dissolving films. Moderate dissolving films can dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films can also be flexible, quickly wettable, and are typically non-irritating to the user. Such moderate dissolving films can provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user. This can ensure delivery of a pharmaceutically active component to a user.

A pharmaceutical composition can include one or more pharmaceutically active components. The pharmaceutically active component can be a single pharmaceutical component or a combination of pharmaceutical components. The pharmaceutically active component can be an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral drug, an antirheumatic, an antihypertensive, a bronchodilator, an anticholinergic, an anti-anxiety drug, an antiemetic compound, a hormone, a peptide, a protein or a vaccine. The pharmaceutically active component can be a pharmaceutically acceptable salt of a drug, a prodrug, a derivative, a drug complex or analog of a drug.

The term "prodrug" refers to a biologically inactive compound that can be metabolized in the body to produce a biologically active drug or the "prodrug" can be a biologically active compound where in addition to its inherent biological activity can be metabolized to another or even preferred biologically active drug. In certain embodiments, the prodrug can have its own biological activity that can be similar to or different from the active drug. For example, the prodrug can be an ester of epinephrine, for example, dipivefrin which is hydrolysed into epinephrine. *See, e.g.*, J. Anderson, et al., Site of ocular hydrolysis of a prodrug, dipivefrin, and a comparison of its ocular metabolism with that of the parent compounds, epinephrine, *Invest., Ophthalmol. Vis. Sci*. July 1980.

In some embodiments, more than one pharmaceutically active component may be included in the film. The pharmaceutically active components can be ace-inhibitors, anti-anginal

drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, amphetamines, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, diagnostic agents, imaging agents, dyes, or tracers, and combinations thereof. Suitable actives for use in the films herein include, but are not limited to, the following therapeutic classes: ace-inhibitor; adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; alkaloid; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-anxiety; anti-arthritic; anti-arrythmia; anti-asthmatic; anti-atherosclerotic; anti-cholesterolemic; antibacterial; antibiotic; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; antidote;

anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective (both systemic and non-systemic); anti-inflammatory; anti-lipid; anti-manic; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant; antineoplastic; antineutropenic; anti-obesity; antiparasitic; anti-parkinson; antiproliferative; antipsychotic; anti-pyretic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; anti-stroke; antithrombotic; anti-thyroid; anti-tumor; anti-tussive; anti-ulcerative; anti-uricemic; antiviral; appetite suppressant; appetite stimulant; biological response modifier; blood glucose regulator; blood modifier; blood metabolism regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; central nervous system stimulant; cerebral dilator; contraceptive; coronary dilator; cholinergic; cough suppressant; decongestant; depressant; diagnostic aid; dietary supplement; diuretic; dopaminergic agent; enzymes; estrogen receptor agonist; endometriosis management agent; expectorant; erectile dysfunction therapy; erythropoietic; ibrinolytic; fertility agent; fluorescent agent; free oxygen radical scavenger; gastric acid suppressant; gastrointestinal motility effector; genetic modifier; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; homeopathic remedy; hormone; hypercalcemia management agent; hypocalcemia management agent; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; ion exchange resin; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; laxative; LHRH agonist; mood regulator; motion sickness preparation; mucolytic; muscle relaxant; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; osteoporosis therapy; oxytocic; parasympatholytic; parasympathomimetic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; prostaglandin; psychotherapeutic; psychotropic; radioactive agent; respiratory agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; smoking cessation therapy; steroid; stimulant; sympatholytic; terine relaxant; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; tremor therapy; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; weight management; wound healing agent; xanthine oxidase inhibitor; and combinations thereof.

Examples of actives suitable for use herein include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (commercially available as Oxycontin®); ibuprofen (commercially available as Motrin®, Advil®, Motrin Children's®, Motrin IB®, Advil Children's®, Motrin Infants'®, Motrin Junior®, Ibu-2®, Proprinal®, Ibu-200®, Midol Cramp Formula®, Bufen®, Motrin Migraine Pain®, Addaprin® and Haltran®), aspirin (commercially available as Empirin®, Ecotrin®, Genuine Bayer®, and Halfprin®), acetaminophen (commercially available as Silapap Infant's®, Silapap Children's®, Tylenol®, Tylenol Children's®, Tylenol Extra Strength®, Tylenol Infants' Original®, Tylenol Infants'®, Tylenol Arthritis®, T-Painol®, Q-Pap®, Cetafen®, Dolono®, Tycolene®, APAP® and Aminofen®), and combinations thereof that may optionally include caffeine. Other pain relieving agents may be used in the present invention, including meperidine hydrochloride (commercially available as Demerol®), capsaicin (commercially available as Qutenza®), morphine sulfate and naltrexone hydrochloride (commercially available as Embeda®), hydromorphone hydrochloride (commercially available as Dilaudid®), propoxyphene napsylate and acetaminophen (commercially available as Darvocet-N®), Fentanyl (commercially available as Duragesic®, Onsolis®, and Fentora®), sodium hyaluronate (commercially available as Euflexxa®), adalimumab (commercially available as Humira®), sumatriptan succinate (commercially available as Imitrex®), fentanyl iontophoretic (commercially available as Ionsys®), orphenadrine citrate (commercially available as Norgesic®), magnesium salicylate tetrahydrate (commercially available as Novasal®), oxymorphone hydrochloride (commercially available as Opana ER®), methocarbamol (commercially available as Robaxin®), carisoprodol (commercially available as Soma®), tramadol hydrochloride (commercially available as Ultracet® and Ultram®), morphine sulfate (commercially available as MS Contin®), metaxalone (commercially available as Skelaxin®), oxycodone hydrochloride (commercially available as OxyContin®), acetaminophen/oxycodone hydrochloride (commercially available as Percocet®), oxycodone/aspirin (commercially available as Percodan®), hydrocodone bitartrate/acetaminophen (commercially available as Vicodin®), hydrocodone

bitartrate/ibuprofen (commercially available as Vicoprofen®), nepafenac (commercially available as Nevanac®), and pregabalin (commercially available as Lyrica®).

The films disclosed herein may further include agents such as NSAIDs, including etodolac (commercially available as Lodine®), ketorolac tromethamine (commercially available as Acular® or Acuvail®), naproxen sodium (commercially available as Anaprox®, Naprosyn®), flurbiprofen (commercially available as Ansaid®), diclofenac sodium/misoprostol (commercially available as Arthrotec®), celecoxib (commercially available as Celebrex®), sulindac (commercially available as Clinoril®), oxaprozin (commercially available as Daypro®), piroxicam (commercially available as Feldene®), indomethacin (commercially available as Indocin®), meloxicam (commercially available as Mobic®), mefenamic acid (commercially available as Ponstel®), tolmetin sodium (commercially available as Tolectin®), choline magnesium trisalicylate (commercially available as Trilisate®), diclofenac sodium (commercially available as Voltaren®), diclofenac potassium (commercially available as Cambia® or Zipsor®), and misoprostol (commercially available as Cytotec®). Opiate agonists and antagonists, such as buprenorphine and naloxone are further examples of drugs for use in the present invention.

Other drugs for other actives for use herein include anti-diarrheals such as loperamide (commercially available as Imodium AD®, Imotil®, Kaodene®, Imperim®, Diamode®, QC Anti-Diarrheal®, Health Care America Anti-Diarrheal®, Leader A-D®, and Imogen®), nitazoxanide (commercially available as Alinia®) and diphenoxylate hydrochloride/atropine sulfate (commercially available as Lomotil®), anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, ibuprofen, chlorpheniramine maleate, dextromethorphan, dextromethorphan HBr, phenylephrine HCl, pseudoephedrine HCl, diphenhydramine and combinations thereof, such as dextromethophan HBr and phenylephrine HCl (available as Triaminic®) may be included in the film compositions of the present invention.

Other actives useful herein include, but are not limited to, alcohol dependence treatment, such as acamprosate calcium (commercially available as Campral®); Allergy treatment medications, such as promethazine hydrochloride (commercially available as Phenergan®), bepotastine besilate (commercially available as Bepreve®), hydrocodone

polistirex/chlorpheniramine polistirex (commercially available as Tussionex®), cetirizine hydrochloride (commercially available as Zyrtec®), cetirizine hydrochloride/pseudoephedrine hydrochloride (commercially available as Zyrtec-D®), promethazine hydrochloride/codeine phosphate (commercially available as Phenergan® with Codeine), pemirolast (commercially available as Alamast®), fexofenadine hydrochloride (commercially available as Allegra®), meclizine hydrochloride (commercially available as Antivert®), azelastine hydrochloride (commercially available as Astelin®), nizatidine (commercially available as Axid®), desloratadine (commercially available as Clarinex®), cromolyn sodium (commercially available as Crolom®), epinastine hydrochloride (commercially available as Elestat®), azelastine hydrochloride (commercially available as Optivar®), prednisolone sodium phosphate (commercially available as Orapred ODT®), olopatadine hydrochloride (commercially available as Patanol®), ketotifen fumarate (commercially available as Zaditor®), and montelukast sodium (commercially available as Singulair®); and anti-histamines such as diphenhydramine HCl (available as Benadryl®), loratadine (available as Claritin®), astemizole (available as Hismanal®), nabumetone (available as Relafen®), diphenydramine HCL (available as TheraFlu®) and clemastine (available as Tavist®).

Films of the present disclosure may further include Alzheimer's treatment medications, such as tacrine hydrochloride (commercially available as Cognex®), galantamine (commercially available as Razadyne®), donepezil hydrochloride (commercially available as Aricept®), rivastigmine tartrate (commercially available as Exelon®), caprylidene (commercially available as Axona®), and memantine (commercially available as Namenda®); anemia medication, such as cyanocobalamin (commercially available as Nascobal®) and ferumoxytol (commercially available as Feraheme®); anesthetics, such as antipyrine with benzocaine (commercially available as Auralgan®, Aurodex® and Auroto®); angina medication, such as amlodipine besylate (commercially available as Norvasc®), nitroglycerin (commercially available as Nitro-Bid®, Nitro-Dur®, Nitrolingual®, Nitrostat®, Transderm-Nitro®), isosorbide mononitrate (commercially available as Imdur®), and isosorbide dinitrate (commercially available as Isordil®); anti-tussives such as guaifensin; anti-Alzheimer's agents, such as nicergoline; and Ca^{H}-antagonists such as nifedipine (commercially available as Procardia® and Adalat®).

Actives useful in the present disclosure may also include anti-asthmatics, such as albuterol sulfate (commercially available as Proventil®), ipratropium bromide (commercially

available as Atrovent®), salmeterol xinafoate (commercially available as Serevent®), zafirlukast (commercially available as Accolate®), flunisolide (commercially available as AeroBid®), metaproterenol sulfate (commercially available as Alupent®), albuterol inhalation (commercially available as Ventolin®), terbutaline sulfate (commercially available as Brethine®), formoterol (commercially available as Foradil®), cromolyn sodium (commercially available as Intal®), levalbuterol hydrochloride (commercially available as Xopenex®), zileuton (commercially available as Zyflo®), fluticasone propionate/salmeterol (commercially available as Advair®), albuterol sulfate/triamcinolone acetonide (commercially available as Azmacort®), dimethylxanthine (commercially available as Theophylline®), and beclomethasone (commercially available as Beclovent®, Beconase®, Qvar®, Vancenase®, Vanceril®); angioedema medication, such as C1 esterase Inhibitor (human) (commercially available as Berinert®) and ecallantide (commercially available as Kalbitor®); and antibacterial medications, such as trimethoprim/sulfamethoxazole (commercially available as Bactrim®), mupirocin (commercially available as Bactroban®), metronidazole (commercially available as Flagyl®), sulfisoxazole acetyl (commercially available as Gantrisin®), bismuth subsalicylate and metronidazole/tetracycline hydrochloride (commercially available as Helidac Therapy®), nitrofurantoin (commercially available as Macrodantin®), norfloxacin (commercially available as Noroxin®), erythromycin ethylsuccinate/Sulfisoxazole acetyl (commercially available as Pediazole®), and levofloxacin (commercially available as Levaquin®).

The films of the present disclosure may further include one or more antibiotics, including amoxicillin (commercially available as Amoxil®), ampicillin (commercially available as Omnipen®, Polycillin® and Principen®), amoxicillin/clavulanate potassium (commercially available as Augmentin®), moxifloxacin hydrochloride (commercially available as Avelox®), besifloxacin (commercially available as Besivance®), clarithromycin (commercially available as Biaxin®), ceftibuten (commercially available as Cedax®), cefuroxime axetil (commercially available as Ceftin®), cefprozil (commercially available as Cefzil®), ciprofloxacin hydrochloride (commercially available as Ciloxan® and Cipro®), clindamycin phosphate (commercially available as Cleocin T®), doxycycline hyclate (commercially available as Doryx®), dirithromycin (commercially available as Dynabac®), erythromycin (commercially available as E.E.S. ®, E-Mycin®, Eryc®, Ery-Tab®, Erythrocin®, and PCE®), erythromycin topical (commercially available as A/T/S®, Erycette®, T-Stat®), gemifloxacin (commercially

available as Factive®), ofloxacin (commercially known as Ocuflox®, Floxin®), telithromycin (commercially available as Ketek®), lomefloxacin hydrochloride (commercially available as Maxaquin®), minocycline hydrochloride (commercially available as Minocin®), fosfomycin tromethamine (commercially available as Monurol®), penicillin with potassium (commercially available as Penicillin VK®, Veetids®), trimethoprim (commercially available as Primsol®), ciprofloxacin hydrochloride (commercially available as Proquin XR®), rifampin, isoniazid and pyrazinamide (commercially available as Rifater®), cefditoren (commercially available as Spectracef®), cefixime (commercially available as Suprax®), tetracycline (commercially available as Achromycin V® and Sumycin®), tobramycin (commercially available as Tobrex®), rifaximin (commercially available as Xifaxan®), azithromycin (commercially available as Zithromax®), azithromycin suspension (commercially available as Zmax®), linezolid (commercially available as Zyvox®), benzoyl peroxide and clindamycin (commercially available as BenzaClin®), erythromycin and benzoyl peroxide (commercially available as Benzamycin®), dexamethasone (commercially available as Ozurdex®), ciprofloxacin and dexamethasone (commercially available as Ciprodex®), polymyxin B sulfate/neomycin sulfate/hydrocortisone (commercially available as Cortisporin®), colistin sulfate/neomycin sulfate/hydrocortisone acetate/thonzonium bromide (commercially available as Cortisporin-TC Otic®), cephalexin hydrochloride (commercially available as Keflex®), cefdinir (commercially available as Omnicef®), and gatifloxacin (commercially available as Zymar®).

Other useful actives include cancer treatment medications, including cyclophosphamide (commercially available as Cytoxan®), methotrexate (commercially available as Rheumatrex® and Trexal®), tamoxifen citrate (commercially available as Nolvadex®), bevacizumab (commercially available as Avastin®), everolimus (commercially available as Afinitor®), pazopanib (commercially available as Votrient®), and anastrozole (commercially available as Arimidex®); leukemia treatment, such as ofatumumab (commercially available as Arzerra®); anti-thrombotic drugs, such as antithrombin recombinant lyophilized powder (commercially available as Atryn®), prasugrel (commercially available as Efient®); anti-coagulants, such as aspirin with extended-release dipyridamole (commercially available as Aggrenox®), warfarin sodium (commercially available as Coumadin®), dipyridamole (commercially available as Persantine®), dalteparin (commercially available as Fragmin®), danaparoid (commercially available as Orgaran®), enoxaparin (commercially available as Lovenox®), heparin

(commercially available as Hep-Lock, Hep-Pak, Hep-Pak CVC, Heparin Lock Flush), tinzaparin (commercially available as Innohep®), and clopidogrel bisulfate (commercially available as Plavix®); antiemetics, such as granisetron hydrochloride (commercially available as Kytril®) and nabilone (commercially available as Cesamet®), trimethobenzamide hydrochloride (commercially available as Tigan®), and ondansetron hydrochloride (commercially available as Zofran®); anti-fungal treatment, such as ketoconazole (commercially available as Nizoral®), posaconazole (commercially available as Noxafil®), ciclopirox (commercially available as Penlac®), griseofulvin (commercially available as Gris-PEG®), oxiconazole nitrate (commercially available as Oxistat®), fluconazole (commercially available as Diflucan®), sertaconazole nitrate (commercially available as Ertaczo®), terbinafine hydrochloride (commercially available as Lamisil®), ciclopirox (commercially available as Loprox®), nystatin/triamcinolone acetonide (commercially available as Mycolog-II®), econazole nitrate (commercially available as Spectazole®), itraconazole (commercially available as Sporanox®), and terconazole (commercially available as Terazol®).

Actives may further include anti-inflammatory medications, such as hydroxychloroquine sulfate (commercially available as Plaquenil®), fluticasone propionate (commercially available as Cutivate®), canakinumab (commercially available as Llaris®), amcinonide (commercially available as Cyclocort®), methylprednisolone (commercially available as Medrol®), budesonide (commercially available as Entocort EC®), anakinra (commercially available as Kineret®), diflorasone diacetate (commercially available as Psorcon®), and etanercept (commercially available as Enbrel®); antispasmodic medication, such as phenobarbital/hyoscyamine sulfate/atropine sulfate/scopolamine hydrobromide (commercially available as Donnatal®); antiviral treatment, such as oseltamivir phosphate (commercially available as Tamiflu®); anti-parasites medication, including tinidazole (commercially available as Tindamax®); appetite treatment mediations, such as megestrol acetate (commercially available as Megace ES®), phentermine hydrochloride (commercially available as Adipex-P®), and diethylpropion hydrochloride (commercially available as Tenuate®); arthritis medications, including leflunomide (commercially available as Arava®), certolizumab pegol (commercially available as Cimzia®), diclofenac sodium (commercially available as Pennsaid®), golimumab (commercially available as Simponi®), and tocilizumab (commercially available as Actemra®); bladder control medication, such as trospium chloride (commercially available as Sanctura®), desmopressin

acetate (commercially available as DDAVP®), tolterodine tartrate (commercially available as Detrol®), oxybutynin chloride (commercially available as Ditropan® or Gelnique®), darifenacin (commercially available as Enablex®), and solifenacin succinate (commercially available as VESIcare®); blood vessel constrictors, such as methylergonovine maleate (commercially available as Methergine®); plasma uric managers, such as rasburicase (commercially available as Elitek®); iron deficiency anemia medications, such as ferumoxytol (commercially available as Feraheme®); lymphoma medications, such as pralatrexate (commercially available as Folotyn®), romidepsin (commercially available as Isodax®); malaria medication, such as artemether/lumefantrine (commercially available as Coartem®); hyponatremia medication, such as tolvatpan (commercially available as Samsca®); medication for treatment of von Willebrand disease (commercially available as Wilate®); anti-hypertension medications, such as treprostinil (commercially available as Tyvaso®), tadalafil (commercially available as Adcirca®); cholesterol lowering medication, including paricalcitol (commercially available as Altocor®), pitavastatin (commercially available as Livalo®), lovastatin, niacin (commercially available as Advicor®), colestipol hydrochloride (commercially available as Colestid®), rosuvastatin calcium (commercially available as Crestor®), fluvastatin sodium (commercially available as Lescol®), atorvastatin calcium (commercially available as Lipitor®), lovastatin (commercially available as Mevacor®), niacin (commercially available as Niaspan®), pravastatin sodium (commercially available as Pravachol®), pavastatin sodium with buffered aspirin (commercially available as Pravigard PAC®), cholestyramine (commercially available as Questran®), simvastatin and niacin (commercially available as Simcor®), atenolol, chlorthalidone (commercially available as Tenoretic®), atenolol (commercially available as Tenormin®), fenofibrate (commercially available as Tricor®), fenofibrate (commercially available as Triglide®), ezetimibe/simvastatin (commercially available as Vytorin®), colesevelam (commercially available as WelChol®), bisoprolol fumarate (commercially available as Zebeta®), ezetimibe (commercially available as Zetia®), bisoprolol fumarate/hydrochlorothiazide (commercially available as Ziac®), and simvastatin (commercially available as Zocor®).

The actives included herein may also include chronic kidney disease medication, such as paricalcitol (commercially available as Zemplar®); contraceptive agents, including etonogestrel (commercially available as Implanon®), norethindrone acetate, ethinyl estradiol (commercially

available as Loestrin 24 FE®), ethinyl estradiol, norelgestromin (commercially available as Ortho Evra®), levonorgestrel (commercially available as Plan B®), levonorgestrel and ethinyl estradiol (commercially available as Preven®), levonorgestrel, ethinyl estradiol (commercially available as Seasonique®), and medroxyprogesterone acetate (commercially available as Depo-Provera®); COPD medication, such as arformoterol tartrate (commercially available as Brovana®) and ipratropium bromide, albuterol sulfate (commercially available as Combivent®); cough suppressants, including benzonatate (commercially available as Tessalon®), guaifenesin, codeine phosphate (commercially available as Tussi-Organidin NR®), and acetaminophen, codeine phosphate (commercially available as Tylenol with Codeine®); medication for the treatment of diabetes, including pioglitazone hydrochloride, metformin hydrochloride (commercially available as ACTOplus met®), bromocriptine mesylate (commercially available as Cycloset®), liraglutide (commercially available as Victoza®), saxagliptin (commercially available as Onglyza®), pioglitazone hydrochloride (commercially available as Actos®), glimepiride (commercially available as Amaryl®), rosiglitazone maleate, metformin hydrochloride (commercially available as Avandamet®), rosiglitazone maleate (commercially available as Avandaryl®), rosiglitazone maleate (commercially available as Avandia®), exenatide (commercially available as Byetta®), exenatide (commercially available as Bydureon®), chlorpropamide (commercially available as Diabinese®), pioglitazone hydrochloride, glimepiride (commercially available as Duetact®), metformin hydrochloride (commercially available as Glucophage®), glipizide (commercially available as Glucotrol®), glyburide, metformin (commercially available as Glucovance® and Fortamet®), metformin hydrochloride (commercially available as Glumetza®), sitagliptin (commercially available as Januvia®), detemir (commercially available as Levemir®), glipizide, metformin hydrochloride (commercially available as Metaglip®), glyburide (commercially available as Micronase®), repaglinide (commercially available as Prandin®), acarbose (commercially available as Precose®), nateglinide (commercially available as Starlix®), pramlintide acetate (commercially available as Symlin®), canagliflozin (commercially available as Invokana®), linagliptin (commercially available as Tradjenta®), dapagliflozin (commercially available as Farxiga®), insulin glargine (commercially available as Lantus® or Toujeo®), insulin aspart (commercially available as Novolog®), insulin lispro, empagliflozin (commercially available as Jardiance®), and tolazamide (commercially available as Tolinase®).

Other useful actives may include digestive agents, such as sulfasalazine (commercially available as Azulfidine®), rabeprazole sodium (commercially available as AcipHex®), lubiprostone (commercially available as Amitiza®), dicyclomine hydrochloride (commercially available as Bentyl®), sucralfate (commercially available as Carafate®), lactulose (commercially available as Chronulac®), docusate (commercially available as Colace®), balsalazide disodium (commercially available as Colazal®), losartan potassium (commercially available as Cozaar®), olsalazine sodium (commercially available as Dipentum®), chlordiazepoxide hydrochloride, clidinium bromide (commercially available as Librax®), esomeprazole magnesium (commercially available as Nexium®), famotidine (commercially available as Pepcid®), lansoprazole (commercially available as Prevacid®), lansoprazole and naproxen (commercially available as Prevacid NapraPAC®), amoxicillin/clarithromycin/lansoprazole (commercially available as Prevpac®), omeprazole (commercially available as Prilosec®), pantoprazole sodium (commercially available as Protonix®), metoclopramide hydrochloride (commercially available as Reglan® or Metozolv®), cimetidine (commercially available as Tagamet®), ranitidine hydrochloride (commercially available as Zantac®), and omeprazole, sodium bicarbonate (commercially available as Zegerid®); diuretics, including spironolactone, hydrochlorothiazide (commercially available as Aldactazide®), spironolactone (commercially available as Aldactone®), bumetanide (commercially available as Bumex®), torsemide (commercially available as Demadex®), chlorothiazide (commercially available as Diuril®), furosemide (commercially available as Lasix®), metolazone (commercially available as Zaroxolyn®), and hydrochlorothiazide, triamterene (commercially available as Dyazide®).

Actives useful herein may also include treatment for emphysema, such as tiotropium bromide (commercially available as Spiriva®); fibromyalgia medication, such as milnacipran hydrochloride (commercially available as Savella®); medication for the treatment of gout, such as colchicine (commercially available as Colcrys®), and febuxostat (commercially available as Uloric®); enema treatments, including aminosalicylic acid (commercially available as Mesalamine® and Rowasa®); epilepsy medications, including valproic acid (commercially available as Depakene®), felbamate (commercially available as Felbatol®), lamotrigine (commercially available as Lamictal®), primidone (commercially available as Mysoline®), oxcarbazepine (commercially available as Trileptal®), zonisamide(commercially available as

Zonegran®), levetiracetam (commercially available as Keppra®), and phenytoin sodium (commercially available as Dilantin®).

Actives useful herein may further include eye medications and treatment, such as dipivefrin hydrochloride (commercially available as Propine®), valganciclovir (commercially available as Valcyte®), ganciclovir ophthalmic gel (commercially available as Zirgan®); bepotastine besilate (commercially available as Bepreve®), besifloxacin (commercially available as Besivance®), bromfenac (commercially available as Xibrom®), fluorometholone (commercially available as FML®), pilocarpine hydrochloride (commercially available as Pilocar®), cyclosporine (commercially available as Restasis®), brimonidine tartrate (commercially available as Alphagan P®), dorzolamide hydrochloride/timolol maleate (commercially available as Cosopt®), bimatoprost (commercially available as Lumigan®), timolol maleate (available as Timoptic®), travoprost (commercially available as Travatan®), latanoprost (commercially available as Xalatan®), echothiophate iodide (commercially available as Phospholine Iodide®), and ranibizumab (commercially available as Lucentis®); fluid controllers, such as acetazolamide (commercially available as Diamox®); gallstone medications, including ursodiol (commercially available as Actigall®); medication for the treatment of gingivitis, including chlorhexidine gluconate (commercially available as Peridex®); headache medications, including butalbital/codeine phosphate/aspirin/caffeine (commercially available as Fiornal® with Codeine), naratriptan hydrochloride (commercially available as Amerge®), almotriptan (commercially available as Axert®), ergotamine tartrate/caffeine (commercially available as Cafergot®), butalbital/acetaminophen/caffeine (commercially available as Fioricet®), butalbital/aspirin/caffeine (commercially available as Fiorinal®), frovatriptan succinate (commercially available as Frova®), rizatriptan benzoate (commercially available as Maxalt®), isometheptene mucate/dichloralphenazone/acetaminophen (commercially available as Midrin®), dihydroergotamine mesylate (commercially available as Migranal®), eletriptan hydrobromide (commercially available as Relpax®), and zolmitriptan (commercially available as Zomig®); influenza medication, such as haemophilus b conjugate vaccine; tetanus toxoid conjugate (commercially available as Hiberix®); and heart treatments, including quinidine sulfate, isosorbide dinitrate/hydralazine hydrochloride (commercially available as BiDil®), digoxin (commercially available as Lanoxin®), flecainide acetate (commercially available as Tambocor®), mexiletine hydrochloride (commercially available as Mexitil®), disopyramide

phosphate (commercially available as Norpace®), procainamide hydrochloride (commercially available as Procanbid®), and propafenone (commercially available as Rythmol®).

Other useful actives include hepatitis treatments, including entecavir (commercially available as Baraclude®), hepatitis B immune globulin (commercially available as HepaGam B®), and copegus/rebetol/ribasphere/vilona/virazole (commercially available as Ribavirin®); herpes treatments, including valacyclovir hydrochloride (commercially available as Valtrex®), penciclovir (commercially available as Denavir®), acyclovir (commercially available as Zovirax®), and famciclovir (commercially available as Famvir®); treatment for high blood pressure, including enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®), verapamil hydrochloride (available as Calan®), ramipril (commercially available as Altace®), olmesartan medoxomil (commercially available as Benicar®), amlodipine/atorvastatin (commercially available as Caduet®), nicardipine hydrochloride (commercially available as Cardene®), diltiazem hydrochloride (commercially available as Cardizem®), quinapril hydrochloride (commercially available as Accupril®), quinapril hydrochloride/hydrochlorothiazide (commercially available as Accuretic®), perindopril erbumine (commercially available as Aceon®), candesartan cilexetil (commercially available as Atacand®), candesartan cilexetil/hydrochlorothiazide (commercially available as Atacand HCT®), irbesartan/hydrochlorothiazide (commercially available as Avalide®), irbesartan (commercially available as Avapro®), amlodipine besylate/olmesartan medoxomil (commercially available as Azor®), levobunolol hydrochloride (commercially available as Betagan®), betaxolol hydrochloride (commercially available as Betoptic®), nebivolol (commercially available as Bystolic®), captopril/hydrochlorothiazide (commercially available as Capozide®), doxazosin mesylate (commercially available as Cardura®), clonidine hydrochloride (commercially available as Catapres®), carvedilol (commercially available as Coreg®), nadolol (commercially available as Corgard®), nadolol/bendroflumethiazide (commercially available as Corzide®), valsartan (commercially available as Diovan®), isradipine (commercially available as DynaCirc®), Guanabenz acetate. (commercially available as Wytensin ®), Guanfacine hydrochloride (commercially available as Tenex ® or Intuniv®), losartan potassium/hydrochlorothiazide (commercially available as Hyzaar®), propranolol hydrochloride (commercially available as Indera®), propranolol hydrochloride/hydrochlorothiazide (commercially available as Inderide®), eplerenone (commercially available as Inspra®),

ambrisentan (commercially available as Letairis®), enalapril maleate/felodipine (commercially available as Lexxel®), metoprolol tartrate (commercially available as Lopressor®), benazepril hydrochloride (commercially available as Lotensin®), benazepril hydrochloride/hydrochlorothiazide (commercially available as Lotensin HCT®), amlodipine/benazepril hydrochloride (commercially available as Lotrel®), indapamide (commercially available as Lozol®), trandolapril (commercially available as Mavik®), telmisartan (commercially available as Micardis®), telmisartan/hydrochlorothiazide (commercially available as Micardis HCT®), prazosin hydrochloride (commercially available as Minipress®), amiloride, hydrochlorothiazide (commercially available as Moduretic®), fosinopril sodium (commercially available as ZZXT Monopril®), fosinopril sodium/hydrochlorothiazide (commercially available as Monopril-HCT®), pindolol (commercially available as Visken®), felodipine (commercially available as Plendil®), sildenafil citrate (commercially available as Revatio®), Nisoldipine (commercially available as Sular®), trandolapril/verapamil hydrochloride (commercially available as Tarka®), aliskiren (commercially available as Tekturna®), eprosartan mesylate (commercially available as Teveten®), eprosartan mesylate/hydrochlorothiazide (commercially available as Teveten HCT®), moexipril hydrochloride/hydrochlorothiazide (commercially available as Uniretic®), moexipril hydrochloride (commercially available as Univasc®), enalapril maleate/hydrochlorothiazide (commercially available as Vaseretic®), and lisinopril/hydrochlorothiazide (commercially available as Zestoretic®).

The films of the present disclosure may include actives useful in the medication for the treatment of HIV/AIDS, such as amprenavir (commercially available as Agenerase®), tipranavir (commercially available as Aptivus®), efavirenz/emtricitabine/tenofovir (commercially available as Atripla®), lamivudine/zidovudine (commercially available as Combivir®), indinavir sulfate (commercially available as Crixivan®), lamivudine (commercially available as Epivir®), saquinavir (commercially available as Fortovase®), zalcitabine (commercially available as Hivid®), lopinavir/ritonavir (commercially available as Kaletra®), fosamprenavir calcium (commercially available as Lexiva®), ritonavir (commercially available as Norvir®), zidovudine (commercially available as Retrovir®), atazanavir sulfate (commercially available as Reyataz®), efavirenz (commercially available as Sustiva®), abacavir/lamivudine/zidovudine (commercially available as Trizivir®), didanosine (commercially available as Videx®), nelfinavir mesylate

(commercially available as Viracept®), nevirapine (commercially available as Viramune®), tenofovir disoproxil fumarate (commercially available as Viread®), stavudine (commercially available as Zerit®), and abacavir sulfate (commercially available as Ziagen®); homocysteiene removers, including betaine anhydrous (commercially available as Cystadane®); medications, such as insulin (commercially available as Apidra®, Humalog®, Humulin®, Iletin®, Tresiba®, and Novolin®); and HPV treatment, such as Human papillomavirus vaccine (commercially available as Gardasil®) or human papillomavirus bivalent (commercially available as Cervarix®); immunosuppressants, including cyclosporine (commercially available as Gengraf®, Neoral®, Sandimmune®, and Apo-Cyclosporine®).

Actives useful in the present disclosure may further include prolactin inhibitors, such as bromocriptine mesylate (commercially available as Parlodel®); medications for aiding in stress tests, such as regadenoson (commercially available as Lexiscan®); baldness medication, including finasteride (commercially available as Propecia® and Proscar®); pancreatitis treatment, such as gemfibrozil (commercially available as Lopid®); hormone medications, such as norethindrone acetate/ethinyl estradiol (commercially available as femHRT®), goserelin acetate (commercially available as Zoladex®), progesterone gel (commercially available as Prochieve®), progesterone (commercially available as Prometrium®), calcitonin-salmon (commercially available as Miacalcin®), calcitriol (commercially available as Rocaltrol®), synthroid (commercially available as Levothroid®, Levoxyl®, Unithroid®), testosterone (commercially available as Testopel®, Androderm®, Testoderm®, and AndroGel®); menopause medication, such as estradiol/norethindrone acetate (commercially available as Activella®), drospirenone/estradiol (commercially available as Angeliq®), estradiol/levonorgestrel (commercially available as Climara Pro®), estradiol/norethindrone acetate (commercially available as CombiPatch®), estradiol (commercially available as Estrasorb®, Vagifem® and EstroGel®), esterified estrogens and methyltestosterone (commercially available as Estratest®), estrogen (commercially available as Alora®, Climara®, Esclim®, Estraderm®, Vivelle®, Vivelle-Dot®), estropipate (commercially available as Ogen®), conjugated estrogens (commercially available as Premarin®), and medroxyprogesterone acetate (commercially available as Provera®); menstrual medications, including leuprolide acetate (commercially available as Lupron Depot), tranexamic acid (commercially available as Lysteda®), and norethindrone acetate (commercially available as Aygestin®); and muscle relaxants, including

cyclobenzaprine hydrochloride (commercially available as Flexeril®), tizanidine (commercially available as Zanaflex®), and hyoscyamine sulfate (commercially available as Levsin®).

Actives useful herein may also include osteoporosis medications, including ibrandronate sodium (commercially available as Boniva®), risedronate (commercially available as Actonel®), raloxifene hydrochloride (commercially available as Evista®, Fortical®), and alendronate sodium (commercially available as Fosamax®); ovulation enhancers, including clomiphene citrate (commercially available as Serophene®, Clomid®, Serophene®); Paget's disease treatment, such as etidronate disodium (commercially available as Didronel®); pancreatic enzyme deficiency medications, such as pancrelipase (commercially available as Pancrease® or Zenpep®); medication for the treatment of Parkinson's disease, such as pramipexole dihydrochloride (commercially available as Mirapex®), ropinirole hydrochloride (commercially available as Requip®), carbidopa/levodopa (commercially available as Sinemet CR®), carbidopa/levodopa/entacapone (commercially available as Stalevo®), selegiline hydrochloride (commercially available as Zelapar®), rasagiline (commercially available as Azilect®), entacapone (commercially available as Comtan®), and selegiline hydrochloride (commercially available as Eldepryl®); multiple sclerosis medication, such as dalfampridine (commercially available as Ampyra®) and interferon beta-I b (commercially available as Extavia®); prostate medication, including flutamide (commercially available as Eulexin®), nilutamide (commercially available as Nilandron®), dutasteride (commercially available as Avodart®), tamsulosin hydrochloride (commercially available as Flomax®), terazosin hydrochloride (commercially available as Hytrin®), and alfuzosin hydrochloride (commercially available as UroXatral®).

Films of the present disclosure may further include psychiatric medications, including alprazolam (available as Niravam®, Xanax®), clozopin (available as Clozaril®), haloperidol (available as Haldol®), fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), asenapine (commercially available as Saphris®), iloperidone (commercially available as Fanapt®), paroxtine hydrochloride (available as Paxil®), aripiprazole (commercially available as Abilify®), guanfacine (commercially available as Intuniv®), Amphetamines and methamphetamines (commercially available as Adderall® and Desoxyn®), clomipramine hydrochloride (commercially available as Anafranil®), Buspirone hydrochloride (commercially available as BuSpar®), citalopram hydrobromide (commercially available as

Celexa®), duloxetine hydrochloride (commercially available as Cymbalta®), methylphenidate (commercially available as Ritalin, Daytrana®), divalproex sodium (Valproic acid) (commercially available as Depakote®), dextroamphetamine sulfate (commercially available as Dexedrine®), venlafaxine hydrochloride (commercially available as Effexor®), selegiline (commercially available as Emsam®), carbamazepine (commercially available as Equetro®), lithium carbonate (commercially available as Eskalith®), fluvoxamine maleate/dexmethylphenidate hydrochloride (commercially available as Focalin®), ziprasidone hydrochloride (commercially available as Geodon®), ergoloid mesylates (commercially available as Hydergine®), escitalopram oxalate (commercially available as Lexapro®), chlordiazepoxide (commercially available as Librium®), molindone hydrochloride (commercially available as Moban®), phenelzine sulfate (commercially available as Nardil®), thiothixene (commercially available as Navane®), desipramine hydrochloride (commercially available as Norpramin®), benzodiazepines (such as those available as Oxazepam®), nortriptyline hydrochloride (commercially available as Pamelor®), tranylcypromine sulfate (commercially available as Parnate®), prochlorperazine, mirtazapine (commercially available as Remeron®), risperidone (commercially available as Risperdal®), quetiapine fumarate (commercially available as Seroquel®), doxepin hydrochloride (commercially available as Sinequan®), atomoxetine hydrochloride (commercially available as Strattera®), trimipramine maleate (commercially available as Surmontil®), olanzapine/fluoxetine hydrochloride (commercially available as Symbyax®), imipramine hydrochloride (commercially available as Tofranil®), protriptyline hydrochloride (commercially available as Vivactil®), bupropion hydrochloride (commercially available as Wellbutrin®, Wellbutrin SR®, and Wellbutrin XR®), and olanzapine (commercially available as Zyprexa®).

Actives useful herein may also include uric acid reduction treatment, including allopurinol (commercially available as Zyloprim®); seizure medications, including gabapentin (commercially available as Neurontin®), ethotoin (commercially available as Peganone®), vigabatrin (commercially available as Sabril®), and topiramate (commercially available as Topamax®); treatment for shingles, such as zoster vaccine live (commercially available as Zostavax®); skin care medications, including calcipotriene (commercially available as Dovonex®), ustekinumab (commercially available as Stelara®), televancin (commercially available as Vibativ®), isotretinoin (commercially available as Accutane®),

hydrocortisone/iodoquinol (commercially available as Alcortin ®), sulfacetamide sodium/sulfur (commercially available as Avar®), azelaic acid (commercially available as Azelex®, Finacea®), benzoyl peroxide (commercially available as Desquam-E®), adapalene (commercially available as Differin®), fluorouracil (commercially available as Efudex®), pimecrolimus (commercially available as Elidel®), topical erythromycin (commercially available as A/T/S®, Erycette®, T-Stat®), hydrocortisone (commercially available as Cetacort®, Hytone®, Nutracort®), metronidazole (commercially available as MetroGel®), doxycycline (commercially available as Oracea®), tretinoin (commercially available as Retin-A® and Renova®), mequinol/tretinoin (commercially available as Solagé®), acitretin (commercially available as Soriatane®), calcipotriene hydrate/betamethasone dipropionate (commercially available as Taclonex®), tazarotene (commercially available as Tazorac®), fluocinonide (commercially available as Vanos®), desonide (commercially available as Verdeso®), miconazole nitrate/Zinc oxide (commercially available as Vusion®), ketoconazole (commercially available as Xolegel®), and efalizumab (commercially available as Raptiva®).

Other actives useful herein may include Sleep disorder medications, including zaleplon (available as Sonata®), eszopiclone (available as Lunesta®), zolpidem tartrate (commercially available as Ambien®, Ambien CR®, Edluar®), lorazepam (commercially available as Ativan®), flurazepam hydrochloride (commercially available as Dalmane®), triazolam (commercially available as Halcion®), clonazepam (commercially available as Klonopin®), barbituates, such as Phenobarbital®), Modafinil (commercially available as Provigil®), temazepam (commercially available as Restoril®), ramelteon (commercially available as Rozerem®), clorazepate dipotassium (commercially available as Tranxene®), diazepam (commercially available as Valium®), quazepam (commercially available as Doral®), and estazolam (commercially available as ProSom®); smoking cessation medications, such as varenicline (commercially available as Chantix®), nicotine, such as Nicotrol®, and bupropion hydrochloride (commercially available as Zyban®); and steroids, including alclometasone dipropionate (commercially available as Aclovate®), betamethasone dipropionate (commercially available as Diprolene®), mometasone furoate (commercially available as Elocon®), fluticasone (commercially available as Flonase®, Flovent®, Flovent Diskus®, Flovent Rotadisk®), fluocinonide (commercially available as Lidex®), mometasone furoate monohydrate (commercially available as Nasonex®), desoximetasone (commercially available as Topicort®),

clotrimazole/betamethasone dipropionate (commercially available as Lotrisone®), prednisolone acetate (commercially available as Pred Forte®, Prednisone®, Budesonide Pulmicort®, Rhinocort Aqua®), prednisolone sodium phosphate (commercially available as Pediapred®), desonide (commercially available as Tridesilon®), and halobetasol propionate (commercially available as Ultravate®).

Films of the present invention may further include actives useful for thyroid disease treatment, such as hormones TC and TD (commercially available as Armour Thyroid®); potassium deficiency treatment, including potassium chloride (commercially available as Micro-K®); triglycerides regulators, including omega-3-acid ethyl esters (commercially available as Omacor®); urinary medication, such as phenazopyridine hydrochloride (commercially available as Pyridium®) and methenamine, methylene blue/phenyl salicylate/benzoic acid/atropine sulfate/hyoscyamine (commercially available as Urised®); prenatal vitamins (commercially available as Advanced Natalcare®, Materna®, Natalins®, Prenate Advance®); weight control medication, including orlistat (commercially available as Xenical®) and sibutramine hydrochloride (commercially available as Meridia®).

The popular H_2-antagonists which are contemplated for use herein include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

Examples of specific actives include but are not limited to 16-alpha fluorocstradiol, 16-alpha-gitoxin, 16-epiestriol, 17 alpha dihydroequilenin, 17 alpha estradiol, 17 beta estradiol, 17 hydroxy progesterone, lalpha-hydroxyvitamin D2,1-dodecpyrrolidinone, 20-epi-1,25 dihydroxyvitamin D3, 22-oxacalcitriol, 2CVV, 2′-nor-cGMP, 3-isobutyl GABA, 5-ethynyluracil, 6-FUDCA, 7-methoxytacrine, Abamectin, abanoquil, abecarnil, abiraterone, Ablukast, Ablukast Sodium, Acadesine, acamprosate, Acarbose, Acebutolol, Acecainide Hydrochloride, Aceclidine, aceclofenae, Acedapsone, Aceglutamide Aluminum, Acemannan, Acetaminophen, Acetazolamide, Acetohexamide, Acetohydroxamic Acid, acetomepregenol, Acetophenazine Maleate, Acetosulfone Sodium, Acetylcholine Chloride, Acetylcysteine, acetyl-L-carnitine, acetylmethadol, Acifran, acipimox, acitemate, Acitretin, Acivicin, Aclarubicin, aclatonium, Acodazole Hydrochloride, aconiazide, Acrisorcin, Acrivastine, Acronine, Actisomide, Actodigin, Acyclovir, acylfulvene, adafenoxate, adapalene, Adapalene, adatanserin, Adatanserin Hydrochloride, adecypenol, adecypenol, Adefovir, adelmidrol, ademetionine, Adenosine, Adinazolam, Adipheinine Hydrochloride, adiposin, Adozelesin, adrafinil, Adrenalone, airbutamine, alacepril, Alamecin, Alanine, Alaproclate, alaptide, Albendazole, albolabrin, Albuterol, Albutoin, Alclofenae, Alclometasone Dipropionate, Alcloxa, aldecalmycin, Aldesleukin, Aldioxa, Alendronate Sodium, alendronic acid, alentemol, Alentemol Hydrobromide, Aletamine Hydrochloride, Aleuronium Chloride, Alexidine, alfacalcidol, Alfentanil Hydrochloride, alfuzosin, Algestone Acetonide, alglucerase, Aliflurane, alinastine, Alipamide, Allantoin, Allobarbital, Allopurinol, ALL-TK antagonists, Alogliptin, Alonimid, alosetron, Alosetron Hydrochloride, Alovudine, Alpertine, Alpha Amylase, alpha idosone, Alpidem, Alprazolam, Alprenolol Hydrochloride, Alprenoxime Hydrochloride, Alprostadil, Alrestatin Sodium, Altanserin Tartrate, Alteplase, Althiazide, Altretamine, altromycin B, Alverinc Citrate, Alvircept Sudotox, Amadinone Acetate, Amantadine Hydrochloride, ambamustine, Ambomycin, Ambruticin, Ambuphylline, Ambuside, Amcinafal, Amcinonide, Amdinocillin, Amdinocillin Pivoxil, Amedalin Hydrochloride, amelometasone, Ameltolide, Amesergide, Ametantrone Acetate, amezinium metilsulfate, amfebutamone, Amfenac Sodium, Amflutizole, Amicycline, Amidephrine Mesylate, amidox, Amifloxacin, amifostine, Amikacin, Amiloride Hydrochloride, Aminacrine Hydrochloride, Aminobenzoate Potassium, Aminobenzoate Sodium, Aminocaproic Acid, Aminoglutethimide, Aminohippurate Sodium, aminolevulinic acid, Aminophylline, A minorex, Aminosalicylate sodium, Aminosalicylic acid,

Amiodarone, Amiprilose Hydrochloride, Amiquinsin Hydrochloride, amisulpride, Amitraz, Amitriptyline Hydrochloride, Amlexanox, amlodipine, Amobarbital Sodium, Amodiaquine, Amodiaquine Hydrochloride, Amorolfine, Amoxapine, Amoxicillin, Amphecloral, Amphetamine Sulfate, Amphomycin, Amphotericin B, Ampicillin, ampiroxicam, Ampyzine Sulfate, Amquinate, Amrinone, amrinone, amrubicin, Amsacrine, amylin, amythiamicin, Anagestone Acetate, anagrelide, Anakinra, ananain, anaritide, Anaritide Acetate, Anastrozole, Anazolene Sodium, Ancrod, andrographolide, Androstenedione, angiogenesis inhibitors, Angiotensin Amide, Anidoxime, Anileridine, Anilopam Hydrochloride, Aniracetam, Anirolac, Anisotropine Methylbromide, Anistreplase, Anitrazafen, anordrin, antagonist D, antagonist G, antarelix, Antazoline Phosphate, Anthelmycin, Anthralin, Anthramycin, antiandrogen, Acedapsone, Felbamate, antiestrogen, antineoplaston, Antipyrine, antisense oligonucleotides, apadoline, apafant, Apalcillin Sodium, apaxifylline, Apazone, aphidicolin glycinate, Apixifylline, Apomorphine Hydrochloride, apraclonidine, Apraclonidine Hydrochloride, Apramycin, Aprindine, Aprindine Hydrochloride, aprosulate sodium, Aprotinin, Aptazapine Maleate, aptiganel, apurinic acid, apurinic acid, aranidipine, Aranotin, Arbaprostil, arbekicin, arbidol, Arbutamine Hydrochloride, Arclofenin, Ardeparin Sodium, argatroban, Arginine, Argipressin Tannate, Arildone, aripiprazol, arotinolol, Arpinocid, Arteflene, Artilide Fumarate, asimadoline, aspalatone, Asparaginase, Asparic Acid, Aspartocin, asperfuran, Aspirin, aspoxicillin, Asprelin, Astemizole, Astromicin Sulfate, asulacrine, atamestane, Atenolol, atevirdine, Atipamezole, Atiprosin Maleate, Atolide, Atorvastatin Calcium, Atosiban, Atovaquone, atpenin B, Atracurium Besylate, atrimustine, atrinositol, Atropine, Auranofin, aureobasidin A, Aurothioglucose, Avilamycin, Avoparcin, Avridine, Axid, axinastatin 1, axinastatin 2, axinastatin 3, Azabon, Azacitidinie, Azaclorzine Hydrochloride, Azaconazole, azadirachtine, Azalanstat Dihydrochloride, Azaloxan Fumarate, Azanator Maleate, Azanidazole, Azaperone, Azaribine, Azaserine, azasetron, Azatadine Maleate, Azathioprine, Azathioprine Sodium, azatoxin, azatyrosine, azelaic acid, azelastine, azelnidipine, Azepindole, Azetepa, azimilide, Azithromycin, Azlocillin, Azolimine, Azosemide, Azotomycin, Aztreonam, Azumolene Sodium, Bacampicillin Hydrochloride, baccatin III, Bacitracin, Baclofen, bacoside A, bacoside B, bactobolamine, balanol, balazipone, balhimycin, balofloxacin, balsalazide, Bambermycins, bambuterol, Bamethan Sulfate, Bamifylline Hydrochloride, Bamidazole, baohuoside 1, Barmastine, barnidipine, Basifungin, Batanopride Hydrochloride, batebulast,

Batelapine Maleate, Batimastat, beauvericin, Becanthone Hydrochloride, becaplermin, becliconazole, Beclomethasone Dipropionate, befloxatone, Beinserazide, Belfosdil, Belladonna, Beloxamide, Bemesetron, Bemitradine, Bemoradan, Benapryzine Hydrochloride, Benazepril Hydrochloride, Benazeprilat, Bendacalol Mesylate, Bendazac, Bendroflumethiazide, benflumetol, benidipine, Benorterone, Benoxaprofen, Benoxaprofen, Benoxinate Hydrochloride, Benperidol, Bentazepam, Bentiromide, Benurestat, Benzbromarone, Benzethonium Chloride, Benzetimide Hydrochloride, Benzilonium Bromide, Benzindopyrine Hydrochloride, benzisoxazole, Benzocaine, benzochlorins, Benzoctamine Hydrochloride, Benzodepa, benzoidazoxan, Benzonatate, Benzoyl Peroxide, Benzoylpas Calcium, benzoylstaurosporine, Benzquinamide, Benzthiazide, benztropine, Benztropine Mesylate, Benzydamine Hydrochloride, Benzylpenicilloyl Polylysine, bepridil, Bepridil Hydrochloride, Beractant, Beraprost, Berefrine, berlafenone, bertosamil, Berythromycin, besipirdine, beta-alethine, betaclamycin B, Betamethasone, betamipron, betaxolol, Betaxolol Hydrochloride, Bethanechol Chloride, Bethanidine Sulfate, betulinic acid, bevantolol, Bevantolol Hydrochloride, Bezafibrate, bFGF inhibitor, Bialamicol Hydrochloride, Biapenem, Bicalutamide, Bicifadine Hydrochloride, Biclodil Hydrochloride, Bidisomide, bifemelane, Bifonazole, bimakalim, bimithil, Bindarit, Biniramycin, binospirone, bioxalomycin alpha2, Bipenamol Hydrochloride, Biperiden, Biphenamine Hydrochloride, biriperone, bisantrene, bisaramil, bisaziridinylspermine, bis-benzimidazole A, bis-benzimidazole B, bisnafide, Bisobrin Lactate, Bisoprolol, Bispyrithione Magsulfex, bistramide D, bistramide K, bistratene A, Bithionolate Sodium, Bitolterol Mesylate, Bivalirudin, Bizelesin, Bleomycin Sulfate, Bolandiol Dipropionate, Bolasterone, Boldenone Undecylenate, boldine, Bolenol, Bolmantalate, bopindolol, Bosentan, Boxidine, brefeldin, breflate, Brequinar Sodium, Bretazenil, Bretylium Tosylate, Brifentanil Hydrochloride, brimonidine, Brinolase, Brocresine, Brocrinat, Brofoxine, Bromadoline Maleate, Bromazepam, Bromchlorenone, Bromelains, bromfenac, Brominidione, Bromocriptine, Bromodiphenhydramine Hydrochloride, Bromoxamide, Bromperidol, Bromperidol Decanoate, Brompheniramine Maleate, Broperamole, Bropirimine, Brotizolam, Bucainide Maleate, bucindolol, Buclizine Hydrochloride, Bucromarone, Budesonide, budipine, budotitane, Buformin, Bumetamide, Bunaprolast, bunazosin, Bunolol Hydrochloride, Bupicomide, Bupivacaine Hydrochloride, Buprenorphine Hydrochloride, Bupropion Hydrochloride, Buramate, Buserelin Acetate, Buspirone Hydrochloride, Busulfan, Butabarbital, Butacetin,

Butaclamol Hydrochloride, Butalbital, Butamben, Butamirate Citrate, Butaperazine, Butaprost, Butedronate Tetrasodium, butenafine, Buterizine, buthionine sulfoximine, Butikacin, Butilfenin, Butirosin Sulfate, Butixirate, butixocort propionate, Butoconazole Nitrate, Butonate, Butopamine, Butoprozine Hydrochloride, Butorphanol, Butoxamine Hydrochloride, Butriptyline Hydrochloride, Cactinomycin, Cadexomer Iodine, Caffeine, calanolide A, Calcifediol, Calcipotriene, calcipotriol, Calcitonin, Calcitriol, Calcium Undecylenate, calphostin C, Calusterone, Cambendazole, camonagrel, camptothecin derivatives, canagliflozin, canarypox IL-2, candesartan, Candicidin, candoxatril, candoxatrilat, Caniglibose, Canrenoate Potassium, Canrenone, capecitabine, Capobenate Sodium, Capobenic Acid, Capreomycin Sulfate, capromab, capsaicin, Captopril, Capuride, Caracemide, Carbachol, Carbadox, Carbamazepine, Carbamide Peroxide, Carbantel Lauryl Sulfate, Carbaspirin Calcium, Carbazeran, carbazomycin C, Carbenicillin Potassium, Carbenoxolone Sodium, Carbetimer, carbetocin, Carbidopa, Carbidopa-Levodopa, Carbinoxamine Maleate, Carbiphene Hydrochloride, Carbocloral, Carbocysteine, Carbol-Fuchsin, Carboplatin, Carboprost, carbovir, carboxamide-amino-triazo-le, carboxyamidotriazole, carboxymethylated beta-1,3-glucan, Carbuterol Hydrochloride, CaRest M3, Carfentanil Citrate, Carisoprodol, Carmantadine, Carmustine, CARN 700, Camidazole, Caroxazone, carperitide, Carphenazine Maleate, Carprofen, Carsatrin Succinate, Cartazolate, carteolol, Carteolol Hydrochloride, cartilage derived inhibitor, Carubicin Hydrochloride, Carumonam Sodium, carvedilol, carvotroline, Carvotroline Hydrochloride, carzelesin, casein kinase inhibitors (ICOS), castanospermine, caurumonam, cebaracetam, cecropin B, Cedefingol, Cefaclor, Cefadroxil, Cefamandole, Cefaparole, Cefatrizine, Cefazaflur Sodium, Cefazolin, Cefbuperazone, cefcapene pivoxil, cefdaloxime pentexil tosilate, Cefdinir, cefditoren pivoxil, Cefepime, cefetamet, Cefetecol, cefixime, cefluprenam, Cefinenoxime Hydrochloride, Cefinetazole, cefminlox, cefodizime, Cefonicid Sodium, Cefoperazone Sodium, Ceforamide, cefoselis, Cefotaxime Sodium, Cefotetan, cefotiam, Cefoxitin, cefozopran, cefpimizole, Cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, Cefroxadine, cefsulodin, Ceftazidime, cefteram, ceftibuten, Ceftizoxime Sodium, ceftriaxone, Cefuroxime, celastrol, celikalim, celiprolol, cepacidiine A, Cephacetrile Sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalothin Sodium, Cephapirin Sodium, Cephradine, cericlamine, cerivastatin, Ceronapril, certoparin sodium, Ceruletide, Cetaben Sodium, Cetalkonium Chloride, Cetamolol Hydrochloride, cetiedil, cetirizine, Cetophenicol, Cetraxate Hydrochloride, cetrorelix,

Cetylpyridinium Chloride, Chenodiol, Chlophedianol Hydrochloride, Chloral Betaine, Chlorambucil, Chloramphenicol, Chlordantoin, Chlordiazepoxide, Chlorhexidine Gluconate, chlorins, Chlormadinone Acetate, chloroorienticin A, Chloroprocaine Hydrochloride, Chloropropamide, Chloroquine, chloroquinoxaline sulfonamide, Chlorothiazide, Chlorotrianisene, Chloroxine, Chloroxylenol, Chlorphenesin Carbamate, Chlorpheniramine Maleate, Chlorpromazine, Chlorpropamide, Chlorprothixene, Chlortetracycline Bisulfate, Chlorthalidone, Chlorzoxazone, Cholestyramine Resin, Chromonar Hydrochloride, cibenzoline, cicaprost, Ciclafrine Hydrochloride, Ciclazindol, ciclesonide, cicletanine, Ciclopirox, Cicloprofen, cicloprolol, Cidofovir, Cidoxepin Hydrochloride, Cifenline, Ciglitazone, Ciladopa Hydrochloride, cilansetron, Cilastatin Sodium, Cilazapril, cilnidipine, Cilobamine Mesylate, cilobradine, Cilofungin, cilostazol, Cimaterol, Cimetidine, cimetropium bromide, Cinalukast, Cinanserin Hydrochloride, Cinepazet Maleate, Cinflumide, Cingestol, cinitapride, Cinnamedrine, Cinnarizine, cinolazepam, Cinoxacin, Cinperene, Cinromide, Cintazone, Cintriamide, Cioteronel, Cipamfylline, Ciprefadol Succinate, Ciprocinonide, Ciprofibrate, Ciprofloxacin, ciprostene, Ciramadol, Cirolemycin, cisapride, cisatracurium besilate, Cisconazole, Cisplatin, cis-porphyrin, cistinexine, citalopram, Citenamide, citicoline, citreamicin alpha, cladribine, Clamoxyquin Hydrochloride, Clarithromycin, clausenamide, Clavulanate Potassium, Clazolam, Clazolimine, clebopride, Clemastine, Clentiazem Maleate, Clidinium Bromide, clinafloxacin, Clindamycin, Clioquinol, Clioxamide, Cliprofen, clobazam, Clobetasol Propionate, Clobetasone Butyrate, Clocortolone Acetate, Clodanolene, Clodazon Hydrochloride, clodronic acid, Clofazimine, Clofibrate, Clofilium Phosphate, Clogestone Acetate, Clomacran Phosphate, Clomegestone Acetate, Clometherone, clomethiazole, clomifene analogues, Clominorex, Clomiphene, Clomipramine Hydrochloride, Clonazepam, Clonidine, Clonitrate, Clonixeril, Clonixin, Clopamide, Clopenthixol, Cloperidone Hydrochloride, clopidogrel, Clopimozide, Clopipazan Mesylate, Clopirac, Cloprednol, Cloprostenol Sodium, Clorazepate Dipotassium, Clorethate, Clorexolone, Cloroperone Hydrochloride, Clorprenaline Hydrochloride, Clorsulon, Clortermine Hydrochloride, Closantel, Closiramine Aceturate, Clothiapine, Clothixamide Maleate Cloticasone Propionate, Clotrimazole, Cloxacillin Benzathine, Cloxyquin, Clozapine, Cocaine, Coccidioidin, Codeine, Codoxime, Colchicine, colestimide, Colestipol Hydrochloride, Colestolone, Colforsin, Colfosceril Palmitate, Colistimethate Sodium, Colistin Sulfate, collismycin A, collismycin B, Colterol Mesylate, combretastatin A4, combretastatin analogue,

complestatin, conagenin, Conorphone Hydrochloride, contignasterol, contortrostatin, Cormethasone Acetate, Corticorelin Ovine Triflutate, Corticotropin, Cortisone Acetate, Cortivazol, Cortodoxone, cosalane, costatolide, Cosyntropin, cotinine, Coumadin, Coumermycin, crambescidin 816, Crilvastatin, crisnatol, Cromitrile Sodium, Cromolyn Sodium, Crotamiton, cryptophycin 8, cucumariosid, Cuprimyxin, curacin A, curdlan sulfate, curiosin, Cyclacillin, Cyclazocine, cyclazosin, cyclic HPMPC, Cyclindole, Cycliramine Maleate, Cyclizine, Cyclobendazole, cyclobenzaprine, cyclobut A, cyclobut G, cyclocapron, Cycloguanil Pamoate, Cycloheximide, cyclopentanthraquinones, Cyclopenthiazide, Cyclopentolate Hydrochloride, Cyclophenazine Hydrochloride, Cyclophosphamide, cycloplatam, Cyclopropane, Cycloserine, cyclosin, Cyclosporine, cyclothialidine, Cyclothiazide, cyclothiazomycin, Cyheptamide, cypemycin, Cypenamine Hydrochloride, Cyprazepam, Cyproheptadine Hydrochloride, Cyprolidol Hydrochloride, cyproterone, Cyproximide, Cysteamine, Cysteine Hydrochloride, Cystine, Cytarabine, Cytarabine Hydrochloride, cytarabine ocfosfate, cytochalasin B, cytolytic factor, cytostatin, Dacarbazine, dacliximab, dactimicin, Dactinomycin, daidzein, Daledalin Tosylate, dalfopristin, Dalteparin Sodium, Daltroban, Dalvastatin, danaparoid, Danazol, Dantrolene, dapagliflozin, daphlnodorin A, dapiprazole, dapitant, Dapoxetine Hydrochloride, Dapsone, Daptomycin, Darglitazone Sodium, darifenacin, darlucin A, Darodipine, darsidomine, Daunorubicin Hydrochloride, Dazadrol Maleate, Dazepinil Hydrochloride, Dazmegrel, Dazopride Fumarate, Dazoxiben Hydrochloride, Debrisoquin Sulfate, Decitabine, deferiprone, deflazacort, Dehydrocholic Acid, dehydrodidemnin B, Dehydroepiandrosterone, delapril, Delapril Hydrochloride, Delavirdine Mesylate, delequamine, delfaprazine, Delmadinone Acetate, delmopinol, delphinidin, Demecarium Bromide, Demeclocycline, Demecycline, Demoxepam, Denofungin, deoxypyridinoline, Depakote, deprodone, Deprostil, depsidomycin, deramciclane, dermatan sulfate, Desciclovir, Descinolone Acetonide, Desflurane, Desipramine Hydrochloride, desirudin, Deslanoside, deslorelin, desmopressin, desogestrel, Desonide, Desoximetasone, desoxoamiodarone, Desoxycorticosterone Acetate, detajmium bitartrate, Deterenol Hydrochloride, Detirelix Acetate, Devazepide, Dexamethasone, Dexamisole, Dexbrompheniramine Maleate, Dexchlorpheniramine Maleate, Dexclamol Hydrochloride, Dexetimide, Dexfenfluramine Hydrochloride, dexifosfamide, Deximafen, Dexivacaine, dexketoprofen, dexloxiglumide, Dexmedetomidine, Dexormaplatin, Dexoxadrol Hydrochloride, Dexpanthenol, Dexpemedolac, Dexpropranolol

Hydrochloride, Dexrazoxane, dexsotalol, dextrin 2-sulphate, Dextroamphetamine, Dextromethorphan, Dextrorphan Hydrochloride, Dextrothyroxine Sodium, dexverapamil, Dezaguanine, dezinamide, dezocine, Diacetolol Hydrochloride, Diamocaine Cyclamate, Diapamide, Diatrizoate Meglumine, Diatrizoic Acid, Diaveridine, Diazepam, Diaziquone, Diazoxide, Dibenzepin Hydrochloride, Dibenzothiophene, Dibucaine, Dichliorvos, Dichloralphenazone, Dichlorphenamide, Dicirenone, Diclofenac Sodium, Dicloxacillin, dicranin, Dicumarol, Dicyclomine Hydrochloride, Didanosine, didemnin B, didox, Dienestrol, dienogest, Diethylcarbamazine Citrate, diethylhomospermine, diethylnorspermine, Diethylpropion Hydrochloride, Diethylstilbestrol, Difenoximide Hydrochloride, Difenoxin, Diflorasone Diacetate, Difloxacin Hydrochloride, Difluanine Hydrochloride, Diflucortolone, Diflumidone Sodium, Diflunisal, Difluprednate, Diftalone, Digitalis, Digitoxin, Digoxin, Dihexyverine Hydrochloride, dihydrexidine, dihydro-5-azacytidine, Dihydrocodeine Bitartrate, Dihydroergotamine Mesylate, Dihydroestosterone, Dihydrostreptomycin Sulfate, Dihydrotachysterol, dihydrotaxol, 9-, Dilantin, Dilevalol Hydrochloride, Diltiazem Hydrochloride, Dimefadane, Dimefline Hydrochloride, Dimenhydrinate, Dimercaprol, Dimethadione, Dimethindene Maleate, Dimethisterone, dimethyl prostaglandin Al, Dimethyl Sulfoxide, dimethylhomospermine, dimiracetam, Dimoxamine Hydrochloride, Dinoprost, Dinoprostone, Dioxadrol Hydrochloride, dioxamycin, Diphenhydramine Citrate, Diphenidol, Diphenoxylate Hydrochloride, diphenyl spiromustine, Dipivefin Hydrochloride, Dipivefrin, dipliencyprone, diprafenone, dipropylnorspermine, Dipyridamole, Dipyrithione, Dipyrone, dirithromycin, discodermolide, Disobutamide, Disofenin, Disopyramide, Disoxaril, disulfiram, Ditekiren, Divalproex Sodium, Dizocilpine Maleate, Dobutamine, docarpamine, Docebenone, Docetaxel, Doconazole, docosanol, dofetilide, dolasetron, Ebastine, ebiratide, ebrotidine, ebselen, ecabapide, ecabet, ecadotril, ecdisteron, echicetin, echistatin, Echothiophate Iodide, Eclanamine Maleate, Eclazolast, ecomustine, Econazole, ecteinascidin 722, edaravone, Edatrexate, edelfosine, Edifolone Acetate, edobacomab, Edoxudine, edrecolomab, Edrophonium Chloride, edroxyprogesteone Acetate, efegatran, eflornithine, efonidipine, egualcen, Elantrine, eleatonin, elemene, eletriptan, elgodipine, eliprodil, Elsamitrucin, eltenae, Elucaine, emalkalim, emedastine, Emetine Hydrochloride, emiglitate, Emilium Tosylate, emitefur, emoctakin, empagliflozin, Enadoline Hydrochloride, enalapril, Enalaprilat, Enalkiren, enazadrem, Encyprate, Endralazine Mesylate, Endrysone, Enflurane, englitazone, Enilconazole, Enisoprost,

Enlimomab, Enloplatin, Enofelast, Enolicam Sodium, Enoxacin, enoxacin, enoxaparin sodium, Enoxaparin Sodium, Enoximone, Enpiroline Phosphate, Enprofylline, Enpromate, entacapone, enterostatin, Enviradene, Enviroxime, Ephedrine, Epicillin, Epimestrol, Epinephrine, Epinephryl Borate, Epipropidine, Epirizole, epirubicin, Epitetracycline Hydrochloride, Epithiazide, Epoetin Alfa, Epoetin Beta, Epoprostenol, Epoprostenol Sodium, epoxymexrenone, epristeride, Eprosartan, eptastigmine, equilenin, Equilin, Erbulozole, erdosteine, Ergoloid Mesylates, Ergonovine Maleate, Ergotamine Tartrate, ersentilide, Ersofermin, erythritol, Erythrityl Tetranitrate, Erythromycin, Esmolol Hydrochloride, Esorubicin Hydrochloride, Esproquin Hydrochloride, Estazolam, Estradiol, Estramustine, estramustine analogue, Estrazinol Hydrobromide, Estriol, Estrofurate, estrogen agonists, estrogen antagonists, Estrogens, Conjugated Estrogens, Esterified Estrone, Estropipate, esuprone, Etafedrine Hydrochloride, Etanidazole, etanterol, Etarotene, Etazolate Hydrochloride, Eterobarb, ethacizin, Ethacrynate Sodium, Ethacrynic Acid, Ethambutol Hydrochloride, Ethamivan, Ethanolamine Oleate, Ethehlorvynol, Ether, Ethinyl estradiol, Ethiodized Oil, Ethionamide, Ethonam Nitrate, Ethopropazine Hydrochloride, Ethosuximide, Ethotoin, Ethoxazene Hydrochloride, Ethybenztropine, Ethyl Chloride, Ethyl Dibunate, Ethylestrenol, Ethyndiol, Ethynerone, Ethynodiol Diacetate, Etibendazole, Etidocaine, Etidronate Disodium, Etidronic Acid, Etifenin, Etintidine Hydrochloride, etizolam, Etodolac, Etofenamate, Etoformin Hydrochloride, Etomidate, Etonogestrel, Etoperidone Hydrochloride, Etoposide, Etoprine, Etoxadrol Hydrochloride, Etozolin, etrabamine, Etretinate, Etryptamine Acetate, Eucatropine Hydrochloride, Eugenol, Euprocin Hydrochloride, eveminomicin, Exametazime, examorelin, Exaprolol Hydrochloride, exemestane, fadrozole, faeriefungin, Famciclovir, Famotidine, Fampridine, fantofarone, Fantridone Hydrochloride, faropenem, fasidotril, fasudil, fazarabine, fedotozine, felbamate, Felbinac, Felodipine, Felypressin, Fenalamide, Fenamole, Fenbendazole, Fenbufen, Fencibutirol, Fenclofenac, Fenclonine, Fenclorac, Fendosal, Fenestrel, Fenethylline Hydrochloride, Fenfluramine Hydrochloride, Fengabine, Fenimide, Fenisorex, Fenmetozole Hydrochloride, Fenmetramide, Fenobam, Fenoctimine Sulfate, fenofibrate, fenoldopam, Fenoprofen, Fenoterol, Fenpipalone, Fenprinast Hydrochloride, Fenprostalene, Fenquizone, fenretinide, fenspiride, Fentanyl Citrate, Fentiazac, Fenticlor, fenticonazole, Fenyripol Hydrochloride, fepradinol, ferpifosate sodium, ferristene, ferrixan, Ferrous Sulfate, Dried, Ferumoxides, ferumoxsil, Fetoxylate Hydrochloride, fexofenadine, Fezolamine Fumarate,

Fiacitabine, Fialuridine, Fibrinogen 1 125, filgrastim, Filipin, finasteride, Flavodilol Maleate, flavopiridol, Flavoxate Hydrochloride, Flazalone, flecainide, flerobuterol, Fleroxacin, flesinoxan, Flestolol Sulfate, Fletazepam, flezelastine, flobufen, Floctafenine, flomoxef, Flordipine, florfenicol, florifenine, flosatidil, Flosequinan, Floxacillin, Floxuridine, fluasterone, Fluazacort, Flubanilate Hydrochloride, Flubendazole, Flucindole, Flucloronide, Fluconazole, Flucytosine, Fludalanine, Fludarabine Phosphate, Fludazonium Chloride, Fludeoxyglucose F 18, Fludorex, Fludrocortisone Acetate, Flufenamic Acid, Flufenisal, Flumazenil, flumecinol, Flumequine, Flumeridone, Flumethasone, Flumetramide, Flumezapine, Fluminorex, Flumizole, Flumoxonide, flunarizine, Flunidazole, Flunisolide, Flunitrazepam, Flunixin, fluocalcitriol, Fluocinolone Acetonide, Fluocinonide, Fluocortin Butyl, Fluocortolone, Fluorescein, fluorodaunorunicin hydrochloride, Fluorodopa F 18, Fluorometholone, Fluorouracil, Fluotracen Hydrochloride, Fluoxetine, Fluoxymesterone, fluparoxan, Fluperamide, Fluperolone Acetate, Fluphenazine Decanoate, flupirtine, Fluprednisolone, Fluproquazone, Fluprostenol Sodium, Fluquazone, Fluradoline Hydrochloride, Flurandrenolide, Flurazepam Hydrochloride, Flurbiprofen, Fluretofen, flurithromycin, Flurocitabine, Flurofamide, Flurogestone Acetate, Flurothyl, Fluroxene, Fluspiperone, Fluspirilene, Fluticasone Propionate, flutrimazole, Flutroline, fluvastatin, Fluvastatin Sodium, fluvoxamine, Fluzinamide, Folic Acid, Follicle regulatory protein, Folliculostatin, Fomepizole, Fonazine Mesylate, forasartan, forfenimex, forfenirmex, formestane, Formocortal, formoterol, Fosarilate, Fosazepam, Foscarnet Sodium, fosfomycin, Fosfonet Sodium, fosinopril, Fosinoprilat, fosphenyloin, Fosquidone, Fostedil, fostriecin, fotemustine, Fuchsin, Basic, Fumoxicillin, Fungimycin, Furaprofen, Furazolidone, Furazolium Chloride, Furegrelate Sodium, Furobufen, Furodazole, Furosemide, Fusidate Sodium, Fusidic Acid, gabapentin, Gadobenate Dimeglumine, gadobenic acid, gadobutrol, Gadodiamide, gadolinium texaphyrin, Gadopentetate Dimegiumine, gadoteric acid, Gadoteridol, Gadoversetamide, galantamine, galdansetron, Galdansetron Hydrochloride, Gallamine Triethiodide, gallium nitrate, gallopamil, galocitabine, Gamfexine, gamolenic acid, Ganciclovir, ganirelix, gelatinase inhibitors, Gemcadiol, Gemcitabine, Gemeprost, Gemfibrozil, Gentamicin Sulfate, Gentian Violet, gepirone, Gestaclone, Gestodene, Gestonorone Caproate, Gestrinone, Gevotroline Hydrochloride, girisopam, glaspimod, glaucocalyxin A, Glemanserin, Gliamilide, Glibornuride, Glicetanile Sodium, Gliflumide, Glimepiride, Glipizide, Gloximonam, Glucagon, glutapyrone, glutathione inhibitors, Glutethimide, Glyburide, glycopine, glycopril,

Glycopyrrolate, Glyhexamide, Glymidine Sodium, Glyoctamide, Glyparamide, Gold Au 198, Gonadoctrinins, Gonadorelin, Gonadotropins, Goserelin, Gramicidin, Granisetron, grepafloxacin, Griseofulvin, Guaiapate, Guaithylline, Guanabenz, Guanabenz Acetate, Guanadrel Sulfate, Guancydine, Guanethidine Monosulfate, Guanfacine Hydrochloride, Guanisoquin Sulfate, Guanoclor Sulfate, Guanoctine Hydrochloride, Guanoxabenz, Guanoxan Sulfate, Guanoxyfen Sulfate, Gusperimus Trihydrochloride, Halazepam, Halcinonide, halichondrin B, Halobetasol Propionate, halofantrine, Halofantrine Hydrochloride, Halofenate, Halofuginone Hydrobromide, halomon, Halopemide, Haloperidol, halopredone, Haloprogesterone, Haloprogin, Halothane, Halquinols, Hamycin, Han memopausal gonadotropins, hatomamicin, hatomarubigin A, hatomarubigin B, hatomarubigin C, hatomarubigin D, Heparin Sodium, hepsulfam, heregulin, Hetacillin, Heteronium Bromide, Hexachlorophene: Hydrogen Peroxide, Hexafluorenium Bromide, hexamethylene bisacetamide, Hexedine, Hexobendine, Hexoprenaline Sulfate, Hexylresorcinol, Histamine Phosphate, Histidine, Histoplasmin, Histrelin, Homatropine Hydrobromide, Hoquizil Hydrochloride, Human chorionic gonadotropin, Hycanthone, Hydralazine Hydrochloride, Hydralazine Polistirex, Hydrochlorothiazide, Hydrocodone Bitartrate, Hydrocortisone, Hydroflumethiazide, Hydromorphone Hydrochloride, Hydroxyamphetamine Hydrobromide, Hydroxychloroquine Sulfate, Hydroxyphenamate, Hydroxyprogesterone Caproate, Hydroxyurca, Hydroxyzine Hydrochloride, Hymecromone, Hyoscyamine, hypericin, Ibafloxacin, ibandronic acid, ibogaine, Ibopamine, ibudilast, Ibufenac, Ibuprofen, Ibutilide Fumarate, Icatibant Acetate, Ichthammol, Icotidine, idarubicin, idoxifene, Idoxuridine, idramantone, Iemefloxacin, Iesopitron, Ifetroban, Ifosfamide, Ilepeimide, illimaquinone, ilmofosine, ilomastat, Ilonidap, iloperidone, iloprost, Imafen Hydrochloride, Imazodan Hydrochloride, imidapril, imidazenil, imidazoacridones, Imidecyl Iodine, Imidocarb Hydrochloride, Imidoline Hydrochloride, Imidurea, Imiloxan Hydrochloride, Imipenem, Imipramine Hydrochloride, imiquimod, immunostimulant peptides, Impromidine Hydrochloride, Indacrinone, Indapamide, Indecainide Hydrochloride, Indeloxazine Hydrochloride, Indigotindisulfonate Sodium, indinavir, Indocyanine Green, Indolapril Hydrochloride, Indolidan, indometacin, Indomethacin Sodium, Indoprofen, indoramin, Indorenate Hydrochloride, Indoxole, Indriline Hydrochloride, inocoterone, inogatran, inolimomab, Inositol Niacinate, Insulin, interferons, interleukins, Intrazole, Intriptyline Hydrochloride, iobenguane, Iobenzamic Acid, iobitridol, Iocarmate Meglumine, Iocarmic Acid,

Iocetamic Acid, Iodamide, Iodine, Iodipamide Meglumine, Iodixanol, iodoamiloride, Iodoantipyrine I 131, Iodocholesterol I 131, iododoxorubicin, Iodohippurate Sodium I 131, Iodopyracet I 125, Iodoquinol, Iodoxamate Meglumine, Iodoxamie Acid, Ioglicic Acid, Iofetamine Hydrochloride I 123, iofratol, Ioglucol, Ioglucomide, Ioglycamic Acid, Iogulamide, Iohexol, iomeprol, Iomethin I 125, Iopamidol, Iopanoic Acid, iopentol, Iophendylate, Ioprocemic Acid, iopromide, Iopronic Acid, Iopydol, Iopydone, iopyrol, Iosefamic Acid, Ioseric Acid, Iosulamide Meglumine, Iosumetic Acid, Iotasul, Iotetric Acid, Iothalamate Sodium, Iothalamic Acid, iotriside, Iotrolan, Iotroxic Acid, Iotyrosine I 131, Ioversol, Ioxagiate Sodium, Ioxaglate Meglumine, Ioxaglic Acid, ioxilan, Ioxotrizoic Acid, ipazilide, ipenoxazone, ipidacrine, Ipodate Calcium, ipomeanol, 4-, Ipratropium Bromide, ipriflavone, Iprindole, Iprofenin, Ipronidazole, Iproplatin, Iproxamine Hydrochloride, ipsapirone, irbesartan, irinotecan, irloxacin, iroplact, irsogladine, Irtemazole, isalsteine, Isamoxole, isbogrel, Isepamicin, isobengazole, Isobutamben, Isocarboxazid, Isoconazole, Isoetharine, isofloxythepin, Isoflupredone Acetate, Isoflurane, Isoflurophate, isohomohalicondrin B, Isoleucine, Isomazole Hydrochloride, Isomylamine Hydrochloride, Isoniazid, Isopropamide Iodide, Isopropyl Alcohol, isopropyl unoprostone, Isoproterenol Hydrochloride, Isosorbide, Isosorbide Mononitrate, Isotiquimide, Isotretinoin, Isoxepac, Isoxicam, Isoxsuprine Hydrochloride, isradipine, itameline, itasetron, Itazigrel, itopride, Itraconazole, Ivermectin, jasplakinolide, Josamycin, kahalalide F, Kalafungin, Kanamycin Sulfate, Ketamine Hydrochloride, Ketanserin, Ketazocine, Ketazolam, Kethoxal, Ketipramine Fumarate, Ketoconazole, Ketoprofen, Ketorfanol, ketorolac, Ketotifen Fumarate, Kitasamycin, Labetalol Hydrochloride, Lacidipine, lacidipine, lactitol, lactivicin, lacosamide, laennec, lafutidine, lamellarin-N triacetate, lamifiban, Lamivudine, Lamotrigine, lanoconazole, Lanoxin, lanperisone, lanreotide, Lansoprazole, latanoprost, lateritin, laurocapram, Lauryl Isoquinolinium Bromide, Lavoltidine Succinate, lazabemide, Lecimibide, leinamycin, lemildipine, leminoprazole, lenercept, Leniquinsin, lenograstim, Lenperone, lentinan sulfate, leptin, leptolstatin, lercanidipine, Lergotrile, lerisetron, Letimide Hydrochloride, letrazuril, letrozole, Leucine, leucomyzin, Leuprolide Acetate, leuprolide+estrogen+progesterone, leuprorelin, Levamfetamine Succinate, levamisole, Levdobutamine Lactobionate, Leveromakalim, levetiracetam, Leveycloserine, levobetaxolol, levobunolol, levobupivacaine, levocabastine, levocarnitine, Levodopa, levodropropizine, levofloxacin, Levofuraltadone, Levoleucovorin Calcium, Levomethadyl Acetate, Levomethadyl Acetate Hydrochloride,

levomoprolol, Levonantradol Hydrochloride, Levonordefrin, Levonorgestrel, Levopropoxyphene Napsylate, Levopropylcillin Potassium, levormeloxifene, Levorphanol Tartrate, levosimendan, levosulpiride, Levothyroxine Sodium, Levoxadrol Hydrochloride, Lexipafant, Lexithromycin, liarozole, Libenzapril, Lidamidine Hydrochloride, Lidocaine, Lidofenin, Lidoflazine, Lifarizine, Lifibrate, Lifibrol, Linarotene, Lincomycin, linear polyamine analogue, Linogliride, Linopirdine, linotroban, linsidomine, lintitript, lintopride, Liothyronine I 125, liothyronine sodium, Liotrix, lirexapride, lisinopril, lissoclinamide 7, Lixazinone Sulfate, lobaplatin, Lobenzarit Sodium, Lobucavir, Lodelaben, Iodoxamide, Lofemizole Hydrochloride, Lofentanil Oxalate, Lofepramine Hydrochloride, Lofexidine Hydrochloride, lombricine, Lomefloxacin, lomerizine, Lometraline Hydrochloride, lometrexol, Lomofungin, Lomoxicam, Lomustine, Lonapalene, lonazolac, lonidamine, Loperamide Hydrochloride, loracarbef, Lorajmine Hydrochloride, loratadine, Lorazepam, Lorbamate, Lorcainide Hydrochloride, Loreclezole, Loreinadol, lorglumide, Lormetazepam, Lornoxicam, lornoxicam, Lortalamine, Lorzafone, losartan, losigamone, losoxantrone, Losulazine Hydrochloride, loteprednol, lovastatin, loviride, Loxapine, Loxoribine, lubeluzole, Lucanthone Hydrochloride, Lufironil, Lurosetron Mesylate, lurtotecan, luteinizing hormone, lurasidone, lutetium, Lutrelin Acetate, luzindole, Lyapolate Sodium, Lycetamine, lydicamycin, Lydimycin, Lynestrenol, Lypressin, Lysine, lysofylline, lysostaphin, lytic peptides, Maduramicin, Mafenide, magainin 2 amide, Magnesium Salicylate, Magnesium Sulfate, magnolol, maitansine, Malethamer, mallotochromene, mallotojaponin, Malotilate, malotilate, mangafodipir, manidipine, maniwamycin A, Mannitol, mannostatin A, manumycin E, manumycin F, mapinastine, Maprotiline, marimastat, Martek 8708, Martek 92211, Masoprocol, maspin, massetolide, matrilysin inhibitors, Maytansine, Mazapertine Succiniate, Mazindol, Mebendazole, Mebeverine Hydrochloride, Mebrofenin, Mebutamate, Mecamylamine Hydrochloride, Mechlorethamine Hydrochloride, Meclocycline, Meclofenamate Sodium, Mecloqualone, Meclorisone Dibutyrate, Medazepam Hydrochloride, Medorinone, Medrogestone, Medroxalol, Medroxyprogesterone, Medrysone, Meelizine Hydrochloride, Mefenamic Acid, Mefenidil, Mefenorex Hydrochloride, Mefexamide, Mefloquine Hydrochloride, Mefruside, Megalomicin Potassium Phosphate, Megestrol Acetate, Meglumine, Meglutol, Melengestrol Acetate, Melitracen Hydrochloride, Melphalan, Memotine Hydrochloride, Menabitan Hydrochloride, Menoctone, menogaril, Menotropins, Meobentine Sulfate, Mepartricin, Mepenzolate Bromide, Meperidine Hydrochloride, Mephentermine Sulfate,

Mephenyloin, Mephobarbital, Mepivacaine Hydrochloride, Meprobamate, Meptazinol Hydrochloride, Mequidox, Meralein Sodium, merbarone, Mercaptopurine, Mercufenol Chloride, Mercury, Ammoniated, Merisoprol Hg 197, Meropenem, Mesalamine, Meseclazone, Mesoridazine, Mesterolone, Mestranol, Mesuprine Hydrochloride, Metalol Hydrochloride, Metaproterenol Polistirex, Metaraminol Bitartrate, Metaxalone, Meteneprost, meterelin, Metformin, Methacholine Chloride, Methacycline, Methadone Hydrochloride, Methadyl Acetate, Methalthiazide, Methamphetamine Hydrochloride, Methaqualone, Methazolamide, Methdilazine, Methenamine, Methenolone Acetate, Methetoin, Methicillin Sodium, Methimazole, methioninase, Methionine, Methisazone, Methixene Hydrochloride, Methocarbamol, Methohexital Sodium, Methopholine, Methotrexate, Methotrimeprazine, methoxatone, Methoxyflurane, Methsuximide, Methyclothiazide, Methyl Palmoxirate, Methylatropine Nitrate, Methylbenzethonium Chloride, Methyldopa, Methyldopate Hydrochloride, Methylene Blue, Methylergonovine Maleate, methylhistamine, R-alpha, methylinosine monophosphate, Methylphenidate Hydrochloride, Methylprednisolone, Methyltestosterone, Methynodiol Diacelate, Methysergide, Methysergide Maleate, Metiamide, Metiapine, Metioprim, metipamide, Metipranolol, Metizoline Hydrochloride, Metkephamid Acetate, metoclopramide, Metocurine Iodide, Metogest, Metolazone, Metopimazine, Metoprine, Metoprolol, Metoquizine, metrifonate, Metrizamide, Metrizoate Sodium, Metronidazole, Meturedepa, Metyrapone, Metyrosine, Mexiletine Hydrochloride, Mexrenoate Potassium, Mezlocillin, mfonelic Acid, Mianserin Hydrochloride, mibefradil, Mibefradil Dihydrochloride, Mibolerone, michellamine B, Miconazole, microcolin A, Midaflur, Midazolam Hydrochloride, midodrine, mifepristone, Mifobate, miglitol, milacemide, milameline, mildronate, Milenperone, Milipertine, milnacipran, Milrinone, miltefosine, Mimbane Hydrochloride, minaprine, Minaxolone, Minocromil, Minocycline, Minoxidil, Mioflazine Hydrochloride, miokamycin, mipragoside, mirfentanil, mirimostim, Mirincamycin Hydrochloride, Mirisetron Maleate, Mirtazapine, mismatched double stranded RNA, Misonidazole, Misoprostol, Mitindomide, Mitocarcin, Mitocromin, Mitogillin, mitoguazone, mitolactol, Mitomalcin, Mitomycin, mitonafide, Mitosper, Mitotane, mitoxantrone, mivacurium chloride, mivazerol, mixanpril, Mixidine, mizolastine, mizoribine, Moclobemide, modafinil, Modaline Sulfate, Modecainide, moexipril, mofarotene, Mofegiline Hydrochloride, mofezolac, molgramostim, Molinazone, Molindone Hydrochloride, Molsidomine, mometasone, Monatepil Maleate, Monensin,

Monoctanoin, Montelukast Sodium, montirelin, mopidamol, moracizine, Morantel Tartrate, Moricizine, Morniflumate, Morphine Sulfate, Morrhuate Sodium, mosapramine, mosapride, motilide, Motretinide, Moxalactam Disodium, Moxazocine, moxiraprine, Moxnidazole, moxonidine, Mumps Skin Test Antigen, mustard anticancer agent, Muzolimine, mycaperoxide B, Mycophenolic Acid, myriaporone, Nabazenil, Nabilone, Nabitan Hydrochloride, Naboctate Hydrochloride, Nabumetone, N-acetyldinaline, Nadide, nadifloxacin, Nadolol, nadroparin calcium, nafadotride, nafamostat, nafarelin, Nafcillin Sodium, Nafenopin, Nafimidone Hydrochloride, Naflocort, Nafomine Malate, Nafoxidine Hydrochloride, Nafronyl Oxalate, Naftifine Hydrochloride, naftopidil, naglivan, nagrestip, Nalbuphine Hydrochloride, Naldemedine, Nalidixate Sodium, Nalidixic Acid, nalmefene, Nalmexone Hydrochloride, naloxone+pentazocine, Naltrexone, Namoxyrate, Nandrolone Phenpropionate, Nantradol Hydrochloride, Napactadine Hydrochloride, napadisilate, Napamezole Hydrochloride, napaviin, Naphazoline Hydrochloride, naphterpin, Naproxen, Naproxol, napsagatran, Naranol Hydrochloride, Narasin, naratriptan, nartograstim, nasaruplase, Natamycin, nateplase, Naxagolide Hydrochloride, Nebivolol, Nebramycin, nedaplatin, Nedocromil, Nefazodone Hydrochloride, Neflumozide Hydrochloride, Nefopam Hydrochloride, Nelezaprine Maleate, Nemazoline Hydrochloride, nemorubicin, Neomycin Palmitate, Neostigmine Bromide, neridronic acid, Netilmicin Sulfate, neutral endopeptidase, Neutramycin, Nevirapine, Nexeridine Hydrochloride, Niacin, Nibroxane, Nicardipine Hydrochloride, Nicergoline, Niclosamide, Nicorandil, Nicotinyl Alcohol, Nifedipine, Nifirmerone, Nifluridide, Nifuradene, Nifuraldezone, Nifuratel, Nifuratrone, Nifurdazil, Nifurimide, Nifurpirinol, Nifurquinazol, Nifurthiazole, nilutamide, Nilvadipine, Nimazone, Nimodipine, niperotidine, niravoline, Niridazole, nisamycin, Nisbuterol Mesylate, nisin, Nisobamate, Nisoldipine, Nisoxetine, Nisterime Acetate, Nitarsone, nitazoxamide, nitecapone, Nitrafudam Hydrochloride, Nitralamine Hydrochloride, Nitramisole Hydrochloride, Nitrazepam, Nitrendipine, Nitrocycline, Nitrodan, Nitrofurantoin, Nitrofurazone, Nitroglycerin, Nitromersol, Nitromide, Nitromifene Citrate, Nitrous Oxide, nitroxide antioxidant, nitrullyn, Nivazol, Nivimedone Sodium, Nizatidine, Noberastine, Nocodazole, Nogalamycin, Nolinium Bromide, Nomifensine Maleate, Noracymethadol Hydrochloride, Norbolethone, Norepinephrine Bitartrate, Norethindrone, Norethynodrel, Norfloxacin, Norflurane, Norgestimate, Norgestomet, Norgestrel, Nortriptyline Hydrochloride, Noscapine, Novobiocin Sodium, N-substituted benzaimides, Nufenoxole, Nylestriol, Nystatin, O6-benzylguanine,

Obidoxime Chloride, Ocaperidone, Ocfentanil Hydrochloride, Ocinaplon, Octanoic Acid, Octazamide, Octenidine Hydrochloride, Octodrine, Octreotide, Octriptyline Phosphate, Ofloxacin, Oformine, okicenone, Olanzapine, oligonucleotides, olopatadine, olprinone, olsalazine, Olsalazine Sodium, Olvanil, omeprazole, onapristone, ondansetron, Ontazolast, Oocyte maturation inhibitor, Opipramol Hydrochloride, oracin, Orconazole Nitrate, Orgotein, Orlislat, Ormaplatin, Ormetoprim, Ornidazole, Orpanoxin, Orphenadrine Citrate, osaterone, otenzepad, Oxacillin Sodium, Oxagrelate, oxaliplatin, Oxamarin Hydrochloride, oxamisole, Oxamniquine, oxandrolone, Oxantel Pamoate, Oxaprotiline Hydrochloride, Oxaprozin, Oxarbazole, Oxatomide, oxaunomycin, Oxazepam, oxcarbazepine, Oxendolone, Oxethazaine, Oxetorone Fumarate, Oxfendazole, Oxfenicine, Oxibendazole, oxiconazole, Oxidopamine, Oxidronic Acid, Oxifungin Hydrochloride, Oxilorphan, Oximonam, Oximonam Sodium, Oxiperomide, oxiracetam, Oxiramide, Oxisuran, Oxmetidine Hydrochloride, oxodipine, Oxogestone Phenpropionate, Oxolinic Acid, Oxprenolol Hydrochloride, Oxtriphylline, Oxybutynin Chloride, Oxychlorosene, Oxycodone, Oxymetazoline Hydrochloride, Oxymetholone, Oxymorphone Hydrochloride, Oxypertine, Oxyphenbutazone, Oxypurinol, Oxytetracycline, Oxytocin, ozagrel, Ozolinone, Paclitaxel, palauamine, Paldimycin, palinavir, palmitoylrhizoxin, Palmoxirate Sodium, pamaqueside, Pamatolol Sulfate, pamicogrel, Pamidronate Disodium, pamidronic acid, Panadiplon, panamesine, panaxytriol, Pancopride, Pancuronium Bromide, panipenem, pannorin, panomifene, pantethine, pantoprazole, Papaverine Hydrochloride, parabactin, Parachlorophenol, Paraldehyde, Paramethasone Acetate, Paranyline Hydrochloride, Parapenzolate Bromide, Pararosaniline Pamoate, Parbendazole, Parconazole Hydrochloride, Paregoric, Pareptide Sulfate, Pargyline Hydrochloride, parnaparin sodium, Paromomycin Sulfate, Paroxetine, parthenolide, Partricin, Paulomycin, pazelliptine, Pazinaclone, Pazoxide, pazufloxacin, pefloxacin, pegaspargase, Pegorgotein, Pelanserin Hydrochloride, peldesine, Peliomycin, Pelretin, Pelrinone Hydrochloride, Pemedolac, Pemerid Nitrate, pemirolast, Pemoline, Penamecillin, Penbutolol Sulfate, Penciclovir, Penfluridol, Penicillin G Benzathine, Penicillin G Potassium, Penicillin G Procaine, Penicillin G Sodium, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penicillin V Potassium, Pentabamate, Pentaerythritol Tetranitrate, pentafuside, pentamidine, pentamorphone, Pentamustine, Pentapiperium Methylsulfate, Pentazocine, Pentetic Acid, Pentiapine Maleate, pentigetide, Pentisomicin, Pentizidone Sodium, Pentobarbital, Pentomone, Pentopril, pentosan, pentostatin,

Pentoxifylline, Pentrinitrol, pentrozole, Peplomycin Sulfate, Pepstatin, perflubron, perfofamide, Perfosfamide, pergolide, Perhexiline Maleate, perillyl alcohol, Perindopril, perindoprilat, Perlapine, Permethrin, perospirone, Perphenazine, Phenacemide, phenaridine, phenazinomycin, Phenazopyridine Hydrochloride, Phenbutazone Sodium Glycerate, Phencarbamide, Phencyclidine Hydrochloride, Phendimetrazine Tartrate, Phenelzine Sulfate, Phenmetrazine Hydrochloride, Phenobarbital, Phenoxybenzamine Hydrochloride, Phenprocoumon, phenserine, phensuccinal, Phensuximide, Phentermine, Phentermine Hydrochloride, phentolamine mesilate, Phentoxifylline, Phenyl Aminosalicylate, phenylacetate, Phenylalanine, phenylalanyl ketoconazole, Phenylbutazone, Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, Phenylpropanolamine Polistirex, Phenyramidol Hydrochloride, Phenyloin, phosphatase inhibitors, Physostigmine, picenadol, picibanil, Picotrin Diolamine, picroliv, picumeterol, pidotimod, Pifamine, Pilocarpine, pilsicainide, pimagedine, Pimetine Hydrochloride, pimilprost, Pimobendan, Pimozide, Pinacidil, Pinadoline, Pindolol, pinnenol, pinocebrin, Pinoxepin Hydrochloride, pioglitazone, Pipamperone, Pipazethate, pipecuronium bromide, Piperacetazine, Piperacillin Sodium, Piperamide Maleate, piperazine, Pipobroman, Piposulfan, Pipotiazine Palmitate, Pipoxolan Hydrochloride, Piprozolin, Piquindone Hydrochloride, Piquizil Hydrochloride, Piracetam, Pirandamine Hydrochloride, pirarubicin, Pirazmonam Sodium, Pirazolac, Pirbenicillin Sodium, Pirbuterol Acetate, Pirenperone, Pirenzepine Hydrochloride, piretamide, Pirfenidone, Piridicillin Sodium, Piridronate Sodium, Piriprost, piritrexim, Pirlimycin Hydrochloride, pirlindole, pirmagrel, Pirmenol Hydrochloride, Pirnabine, Piroctone, Pirodavir, pirodomast, Pirogliride Tartrate, Pirolate, Pirolazamide, Piroxantrone Hydrochloride, Piroxicam, Piroximone, Pirprofen, Pirquinozol, Pirsidomine, Prenylamine, Pituitary, Posterior, Pivampicillin Hydrochloride, Pivopril, Pizotyline, placetin A, platinum compounds, platinum-triamine complex, Plicamycin, Plomestane, Pobilukast Edamine, Podofilox, Poisonoak Extract, Poldine Methylsulfate, Poliglusam, Polignate Sodium, Polymyxin B Sulfate, Polythiazide, Ponalrestat, Porfimer Sodium, Porfiromycin, Potassium Chloride, Potassium Iodide, Potassium Permanganate, Povidone-Iodine, Practolol, Pralidoxime Chloride, Pramiracetam Hydrochloride, Pramoxine Hydrochloride, Pranolium Chloride, Pravadoline Maleate, Pravastatin (Pravachol), Prazepam, Prazosin, Prazosin Hydrochloride, Prednazate, Prednicarbate, Prednimustine, Prednisolone, Prednisone, Prednival, Pregnenolone Succiniate, Prenalterol Hydrochloride, Pridefine Hydrochloride, Prifelone, Prilocalne Hydrochloride,

Prilosec, Primaquine Phosphate, Primidolol, Primidone, Prinivil, Prinomide Tromethamine, Prinoxodan, Prizidilol Hydrochloride, Proadifen Hydrochloride, Probenecid, Probicromil Calcium, Probucol, Procainamide Hydrochloride, Procaine Hydrochloride, Procarbazine Hydrochloride, Procaterol Hydrochloride, Prochlorperazine, Procinonide, Proclonol, Procyclidine Hydrochloride, Prodilidine Hydrochloride, Prodolic Acid, Profadol Hydrochloride, Progabide, Progesterone, Proglumide, Proinsulin Human, Proline, Prolintane Hydrochloride, Promazine Hydrochloride, Promethazine Hydrochloride, Propafenone Hydrochloride, propagermanium, Propanidid, Propantheline Bromide, Proparacaine Hydrochloride, Propatyl Nitrate, propentofylline, Propenzolate Hydrochloride, Propikacin, Propiomazine, Propionic Acid, propionylcarnitine, L-, propiram, propiram+paracetamol, propiverine, Propofol, Propoxycaine Hydrochloride, Propoxyphene Hydrochloride, Propranolol Hydrochloride, Propulsid, propyl bis-acridone, Propylhexedrine, Propyliodone, Propylthiouracil, Proquazone, Prorenoate Potassium, Proroxan Hydrochloride, Proscillaridin, Prostalene, prostratin, Protamine Sulfate, protegrin, Protirelin, protosufloxacin, Protriptyline Hydrochloride, Proxazole, Proxazole Citrate, Proxicromil, Proxorphan Tartrate, prulifloxacin, Pseudoephedrine Hydrochloride, Puromycin, purpurins, Pyrabrom, Pyrantel Pamoate, Pyrazinamide, Pyrazofurin, pyrazoloacridine, Pyridostigmine Bromide, Pyrilamine Maleate, Pyrimethamine, Pyrinoline, Pyrithione Sodium, Pyrithione Zinc, Pyrovalerone Hydrochloride, Pyroxamine Maleate, Pyrrocaine, Pyrroliphene Hydrochloride, Pyrrolnitrin, Pyrvinium Pamoate, Quadazocine Mesylate, Quazepam, Quazinone, Quazodine, Quazolast, quetiapine, quiflapon, quinagolide, Quinaldine Blue, quinapril, Quinaprilat, Quinazosin Hydrochloride, Quinbolone, Quinctolate, Quindecamine Acetate, Quindonium Bromide, Quinelorane Hydrochloride, Quinestrol, Quinfamide, Quingestanol Acetate, Quingestrone, Quinidine Gluconate, Quinielorane Hydrochloride, Quinine Sulfate, Quinpirole Hydrochloride, Quinterenol Sulfate, Quinuclium Bromide, Quinupristin, Quipazine Maleate, Rabeprazole Sodium, Racephenicol, Racepinephrine, raf antagonists, Rafoxamide, Ralitoline, raloxifene, raltitrexed, ramatroban, Ramipril, Ramoplanin, ramosetron, ranelic acid, Ranimycin, Ranitidine, ranolazine, Rauwolfia Serpentina, recainam, Recainam Hydrochloride, Reclazepam, regavirumab, Regramostim, Relaxin, Relomycin, Remacemide Hydrochloride, Remifentanil Hydrochloride, Remiprostol, Remoxipride, Repirinast, Repromicin, Reproterol Hydrochloride, Reserpine, resinferatoxin, Resorcinol, retelliptine demethylated, reticulon, reviparin sodium, revizinone, rhenium Re 186 etidronate, rhizoxin, Ribaminol, Ribavirin,

Riboprine, ribozymes, ricasetron, Ridogrel, Rifabutin, Rifametane, Rifamexil, Rifamide, Rifampin, Rifapentine, Rifaximin, RII retinamide, rilopirox, Riluzole, rimantadine, Rimcazole Hydrochloride, Rimexolone, Rimiterol Hydrobromide, rimoprogin, riodipine, Rioprostil, Ripazepam, ripisartan, Risedronate Sodium, risedronic acid, Risocaine, Risotilide Hydrochloride, rispenzepine, Risperdal, Risperidone, Ritanserin, ritipenem, Ritodrine, Ritolukast, ritonavir, rizatriptan benzoate, Rocastine Hydrochloride, Rocuronium Bromide, Rodocaine, Roflurane, Rogletimide, rohitukine, rokitamycin, Roletamicide, Rolgamidine, Rolicyprine, Rolipram, Rolitetracycline, Rolodine, Romazarit, romurtide, Ronidazole, ropinirole, Ropitoin Hydrochloride, ropivacaine, Ropizine, roquinimex, Rosaramicin, rosiglitazone, Rosoxacin, Rotoxamine, roxaitidine, Roxarsone, roxindole, roxithromycin, rubiginone B1, ruboxyl, rufloxacin, rupatidine, Rutamycin, ruzadolane, Sabeluzole, safingol, safironil, saintopin, salbutamol, R-Salcolex, Salethamide Maleate, Salicyl Alcohol, Salicylamide, Salicylate Meglumine, Salicylic Acid, Salmeterol, Salnacediin, Salsalate, sameridine, sampatrilat, Sancycline, sanfetrinem, Sanguinarium Chloride, Saperconazole, saprisartan, sapropterin, saquinavir, Sarafloxacin Hydrochloride, Saralasin Acetate, SarCNU, sarcophytol A, sargramostim, Sarmoxicillin, Sarpicillin, sarpogrelate, saruplase, saterinone, satigrel, satumomab pendetide, Schick Test Control, Scopafungin, Scopolamine Hydrobromide, Scrazaipine Hydrochloride, Sdi 1 mimetics, Secalciferol, Secobarbital, Seelzone, Seglitide Acetate, selegiline, Selegiline Hydrochloride, Selenium Sulfide, Selenomethionine Se 75, Selfotel, sematilide, semduramicin, semotiadil, semustine, sense oligonucleotides, Sepazonium Chloride, Seperidol Hydrochloride, Seprilose, Seproxetine Hydrochloride, Seractide Acetate, Sergolexole Maleate, Serine, Sermetacin, Sermorelin Acetate, sertaconazole, sertindole, sertraline, setiptiline, Setoperone, sevirumab, sevoflurane, sezolamide, Sibopirdine, Sibutramine Hydrochloride, signal transduction inhibitors, Silandrone, silipide, silteplase, Silver Nitrate, simendan, Simtrazene, Simvastatin, Sincalide, Sinefungin, sinitrodil, sinnabidol, sipatrigine, sirolimus, Sisomicin, Sitogluside, sizofiran, sobuzoxane, Sodium Amylosulfate, Sodium Iodide I 123, Sodium Nitroprusside, Sodium Oxybate, sodium phenylacetate, Sodium Salicylate, solverol, Solypertine Tartrate, Somalapor, Somantadine Hydrochloride, somatomedin B, somatomedin C, somatrem, somatropin, Somenopor, Somidobove, sonermin, Sorbinil, Sorivudine, sotalol, Soterenol Hydrochloride, Sparfloxacin, Sparfosate Sodium, sparfosic acid, Sparsomycin, Sparteine Sulfate, Spectinomycin Hydrochloride, spicamycin D, Spiperone, Spiradoline Mesylate, Spiramycin,

Spirapril Hydrochloride, Spiraprilat, Spirogermanium Hydrochloride, Spiromustine, Spironolactone, Spiroplatin, Spiroxasone, splenopentin, spongistatin 1, Sprodiamide, squalamine, Stallimycin Hydrochloride, Stannous Pyrophosphate, Stannous Sulfur Colloid, Stanozolol, Statolon, staurosporine, stavudine, Steffimycin, Stenbolone Acetate, stepronin, Stilbazium Iodide, Stilonium Iodide, stipiamide, Stiripentol, stobadine, Streptomycin Sulfate, Streptonicozid, Streptonigrin, Streptozocin, stromelysin inhibitors, Strontium Chloride Sr 89, succibun, Succimer, Succinylcholine Chloride, Sucralfate, Sucrosofate Potassium, Sudoxicam, Sufentanil, Sufotidine, Sulazepam, Sulbactam Pivoxil, Sulconazole Nitrate, Sulfabenz, Sulfabenzamide, Sulfacetamide, Sulfacytine, Sulfadiazine, Sulfadoxine, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizole, Sulfamethoxazole, Sulfamonomethoxine, Sulfamoxole, Sulfanilate Zinc, Sulfanitran, sulfasalazine, Sulfasomizole, Sulfazamet, Sulfinalol Hydrochloride, sulfinosine, Sulfinpyrazone, Sulfisoxazole, Sulfomyxin, Sulfonterol Hydrochloride, sulfoxamine, Sulinldac, Sulmarin, Sulnidazole, Suloctidil, Sulofenur, sulopenem, Suloxifen Oxalate, Sulpiride, Sulprostone, sultamicillin, Sulthiame, sultopride, sulukast, Sumarotene, sumatriptan, Suncillin Sodium, Suproclone, Suprofen, suradista, suramin, Surfomer, Suricainide Maleate, Suritozole, Suronacrine Maleate, Suxemerid Sulfate, swainsonine, symakalim, Symclosene, Symetine Hydrochloride, synthetic glycosaminoglycans, Taciamine Hydrochloride, Tacrine Hydrochloride, Tacrolimus, Talampicillin Hydrochloride, Taleranol, Talisomycin, tallimustine, Talmetacin, Talniflumate, Talopram Hydrochloride, Talosalate, Tametraline Hydrochloride, Tamoxifen, Tampramine Fumarate, Tamsulosin Hydrochloride, Tandamine Hydrochloride, tandospirone, tapgen, taprostene, Tasosartan, tauromustine, Taxane, Taxoid, Tazadolene Succinate, tazanolast, tazarotene, Tazifylline Hydrochloride, Tazobactam, Tazofelone, Tazolol Hydrochloride, Tebufelone, Tebuquine, Technetium Tc 99 m Bicisate, Teclozan, Tecogalan Sodium, Teecleukin, Teflurane, Tegafur, Tegretol, Teicoplanin, telenzepine, tellurapyrylium, telmesteine, telmisartan, telomerase inhibitors, Teloxantrone Hydrochloride, Teludipine Hydrochloride, Temafloxacin Hydrochloride, Tematropium Methyl sulfate, Temazepam, Temelastine, temocapril, Temocillin, temoporfin, temozolomide, Tenidap, Teniposide, tenosal, tenoxicam, tepirindole, Tepoxalin, Teprotide, terazosin, Terbinafine, Terbutaline Sulfate, Terconazole, terfenadine, terflavoxate, terguride, Teriparatide Acetate, terlakiren, terlipressin, terodiline, Teroxalene Hydrochloride, Teroxirone, tertatolol, Tesicam, Tesimide, Testolactone, Testosterone, Tetracaine,

tetrachlorodecaoxide, Tetracycline, Tetrahydrozoline Hydrochloride, Tetramisole Hydrochloride, Tetrazolast Meglumine, tetrazomine, Tetrofosmin, Tetroquinone, Tetroxoprim, Tetrydamine, thaliblastine, Thalidomide, Theofibrate, Theophylline, Thiabendazole, Thiamiprine, Thiamphenicol, Thiamylal, Thiazesim Hydrochloride, Thiazinamium Chloride, Thiethylperazine, Thimerfonate Sodium, Thimerosal, thiocoraline, thiofedrine, Thioguanine, thiomarinol, Thiopental Sodium, thioperamide, Thioridazine, Thiotepa, Thiothixene, Thiphenamil Hydrochloride, Thiphencillin Potassium, Thiram, Thozalinone, Threonine, Thrombin, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, Thyromedan Hydrochloride, Thyroxine 1 125, Thyroxine 1 131, Tiacrilast, Tiacrilast Sodium, tiagabine, Tiamenidine, tianeptine, tiapafant, Tiapamil Hydrochloride, Tiaramide Hydrochloride, Tiazofurin, Tibenelast Sodium, Tibolone, Tibric Acid, Ticabesone Propionate, Ticarbodine, Ticarcillin Cresyl Sodium, Ticlatone, ticlopidine, Ticrynafen, tienoxolol, Tifurac Sodium, Tigemonam Dicholine, Tigestol, Tiletamine Hydrochloride, Tilidine Hydrochloride, tilisolol, tilnoprofen arbamel, Tilorone Hydrochloride, Tiludronate Disodium, tiludronic acid, Timefurone, Timobesone Acetate, Timolol, tin ethyl etiopurpurin, Tinabinol, Timidazole, Tinzaparin Sodium, Tioconazole, Tiodazosin, Tiodonium Chloride, Tioperidone Hydrochloride, Tiopinac, Tiospirone Hydrochloride, Tiotidine, tiotropium bromide, Tioxidazole, Tipentosin Hydrochloride, Tipredane, Tiprenolol Hydrochloride, Tiprinast Meglumine, Tipropidil Hydrochloride, Tiqueside, Tiquinamide Hydrochloride, tirandalydigin, Tirapazamine, tirilazad, tirofiban, tiropramide, titanocene dichloride, Tixanox, Tixocortol Pivalate, Tizanidine Hydrochloride, Tobramycin, Tocainide, Tocamphyl, Tofenacin Hydrochloride, Tolamolol, Tolazamide, Tolazoline Hydrochloride, Tolbutamide, Tolcapone, Tolciclate, Tolfamide, Tolgabide, lamotrigine, Tolimidone, Tolindate, Tolmetin, Tolnaftate, Tolpovidone 1 131, Tolpyrramide, Tolrestat, Tomelukast, Tomoxetine Hydrochloride, Tonazocine Mesylate, Topiramate, topotecan, Topotecan Hydrochloride, topsentin, Topterone, Toquizine, torasemide, toremifene, Torsemide, Tosifen, Tosufloxacin, totipotent stem cell factor, Tracazolate, trafermin, Tralonide, Tramadol Hydrochloride, Tramazoline Hydrochloride, trandolapril, Tranexamic Acid, Tranilast, Transcainide, translation inhibitors, traxanox, Trazodone Hydrochloride, Trazodone-HCL, Trebenzomine Hydrochloride, Trefentanil Hydrochloride, Treloxinate, Trepipam Maleate, Trestolone Acetate, tretinoin, Triacetin, triacetyluridine, Triafungin, Triamcinolone, Triampyzine Sulfate, Triamterene, Triazolam, Tribenoside, tricaprilin, Tricetamide, Trichlormethiazide,

trichohyalin, triciribine, Tricitrates, Triclofenol piperazine, Triclofos Sodium, Triclonide, trientine, Trifenagrel, triflavin, Triflocin, Triflubazam, Triflumidate, Trifluoperazine Hydrochloride, Trifluperidol, Triflupromazine, Triflupromazine Hydrochloride, Trifluridine, Trihexyphenidyl Hydrochloride, Trilostane, Trimazosin Hydrochloride, trimegestone, Trimeprazine Tartrate, Trimethadione, Trimethaphan Camsylate, Trimethobenzamide Hydrochloride, Trimethoprim, Trimetozine, Trimetrexate, Trimipramine, Trimoprostil, Trimoxamine Hydrochloride, Triolein I 125, Triolein I 131, Trioxifene Mesylate, Tripamide, Tripelennamine Hydrochloride, Triprolidine Hydrochloride, Triptorelin, Trisulfapyrimidines, Troclosene Potassium, troglitazone, Trolamine, Troleandomycin, trombodipine, trometamol, Tropanserin Hydrochloride, Tropicamide, tropine ester, tropisetron, trospectomycin, trovafloxacin, trovirdine, Tryptophan, Tuberculin, Tubocurarine Chloride, Tubulozole Hydrochloride, tucarcsol, tulobuterol, turosteride, Tybamate, tylogenin, Tyropanoate Sodium, Tyrosine, Tyrothricin, tyrphostins, ubenimex, Uldazepam, Undecylenic Acid, Uracil Mustard, urapidil, Urea, Uredepa, uridine triphosphate, Urofollitropin, Urokinase, Ursodiol, valaciclovir, Valine, Valnoctamide, Valproate Sodium, Valproic Acid, valsartan, vamicamide, vanadeine, Vancomycin, vaninolol, Vapiprost Hydrochloride, Vapreotide, variolin B, Vasopressin, Vecuronium Bromide, velaresol, Velnacrine Maleate, venlafaxine, Veradoline Hydrochloride, veramine, Verapamil Hydrochloride, verdins, Verilopam Hydrochloride, Verlukast, Verofylline, veroxan, verteporfin, Vesnarinone, vexibinol, Vidarabine, vigabatrin, Viloxazine Hydrochloride, Vinblastine Sulfate, vinburnine citrate, Vincofos, vinconate, Vincristine Sulfate, Vindesine, Vindesine Sulfate, Vinepidine Sulfate, Vinglycinate Sulfate, Vinleurosine Sulfate, vinorelbine, vinpocetine, vintoperol, vinxaltine, Vinzolidine Sulfate, Viprostol, Virginiamycin, Viridofulvin, Viroxime, vitaxin, Volazocine, voriconazole, vorozole, voxergolide, Warfarin Sodium, Xamoterol, Xanomeline, Xanoxate Sodium, Xanthinol Niacinate, xemilofiban, Xenalipin, Xenbucin, Xilobam, ximoprofen, Xipamide, Xorphanol Mesylate, Xylamidine Tosylate, Xylazine Hydrochloride, Xylometazoline Hydrochloride, Xylose, yangambin, zabicipril, zacopride, zafirlukast, Zalcitabine, zaleplon, zalospirone, Zaltidine Hydrochloride, zaltoprofen, zanamivir, zankiren, zanoterone, Zantac, Zarirlukast, zatebradine, zatosetron, Zatosetron Maleate, zenarestat, Zenazocine Mesylate, Zeniplatin, Zeranol, Zidometacin, Zidovudine, zifrosilone, Zilantel, zilascorb, zileuton, Zimeldine Hydrochloride, Zinc Undecylenate, Zindotrine, Zinoconazole Hydrochloride, Zinostatin, Zinterol Hydrochloride, Zinviroxime,

ziprasidone, Zobolt, Zofenopril Calcium, Zofenoprilat, Zolamine Hydrochloride, Zolazepam Hydrochloride, zoledronie acid, Zolertine Hydrochloride, zolmitriptan, zolpidem, Zomepirac Sodium, Zometapine, Zoniclezole Hydrochloride, Zonisamide, zopiclone, Zopolrestat, Zorbamyciin, Zorubicin Hydrochloride, zotepine, Zucapsaicin.

Another pharmaceutical active acceptable for use herein is lumateperone, as disclosed in U.S. Patent Nos. 9745300, 9708322, 7183282, 7071186, 6552017, 8648077, 8598119, 9751883, 9371324, 9315504, 9428506, 8993572, 8309722, 6713471, 8779139, 9168258, RE039680E1, 9616061, 9586960, and in U.S. Patent Publication Nos. 2017114037, 2017183350, 2015072964, 2004034015, 2017189398, 2016310502, 2015080404, the aforementioned contents of which are incorporated by reference herein in their entirety.

Further examples of antidiabetic actives include but not limited to JTT-501 (PNU-182716) (Reglitazar), AR-H039242, MCC-555 (Netoglitazone), AR-H049020 Tesaglitazar), CS-011 (CI-1037), GW-409544×, KRP-297, RG-12525, BM-15.2054, CLX-0940, CLX-0921, DRF-2189, GW-1929, GW-9820, LR-90, LY-510929, NIP-221, NIP-223, JTP-20993, LY 29311 Na, FK 614, BMS 298585, R 483, TAK 559, DRF 2725 (Ragaglitazar), L-686398, L-168049, L-805645, L-054852, Demethyl asteriquinone B1 (L-783281), L-363586, KRP-297, P32/98, CRE-16336 and EML-16257.

Erectile dysfunction therapies useful herein include, but are not limited to, agents for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful actives for treatment of erectile dysfunction include, for example, but are not limited to, alprostadil, tadalafil, vardenafil, apomorphine, yohimbine hydrochloride, sildenafil citrate, and any combination thereof. In an embodiment, the active is tadalafil.

Actives or medications for the treatment of headaches and/or migraines may also be used herein. Examples of specific actives include, but are not limited to, triptans, such as eletriptan, naratriptan, rizatriptan (rizatriptan benzoate), sumatriptan, and zolmitriptan. In an embodiment, the active is rizatriptan, optionally in combination with an NSAID.

In certain embodiments, the pharmaceutically active component can be epinephrine, a prodrug, analog, derivative or salt of epinephrine.

Epinephrine/Dipivefrin Dosage Profiles

In one example, a composition including a prodrug, such as a prodrug for epinephrine, can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen.

Epinephrine or its prodrug can be present in an amount of from about 0.01 mg to about 100 mg per dosage, for example, at a 0.1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage, including greater than 0.1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof.

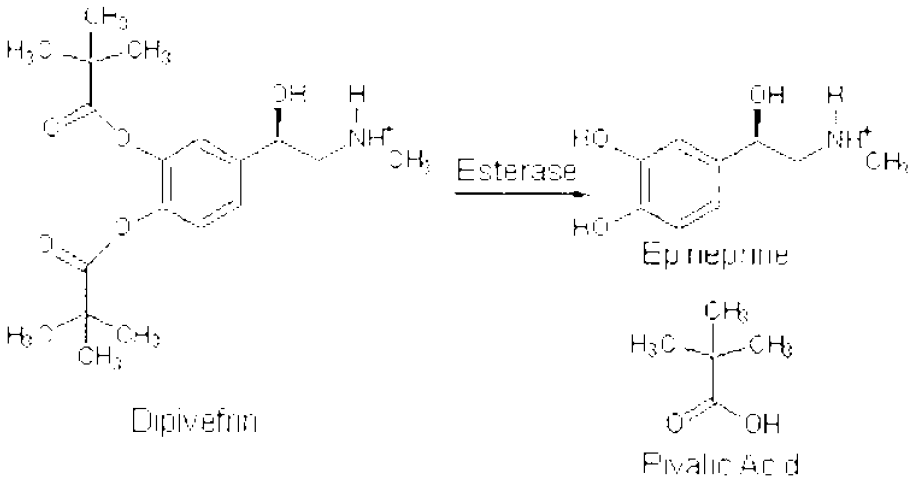
Dipivefrin can be present in an amount of from about 0.5 mg to about 100 mg per dosage, for example, at a 0.5mg, 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage including greater than 1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof.

Prodrug Composition

In another example, a composition (e.g., including epinephrine) can have a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long chain amphipathic molecule; (vii) a hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the

membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; or (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced mucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject. The formulation can include approximately the same active pharmaceutical ingredient (API): enhancer ratio as in the other examples for epinephrine.

Administering epinephrine as a prodrug such as dipivefrin, or prodrugs AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, AQEP-13, AQEP-14 or AQEP-15 confer certain advantages. For one, dipivefrin and prodrugs AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, AQEP-13, AQEP-14 and AQEP-15 are lipophilic and therefore has a higher permeation through a mucosa. Dipivefrin and prodrugs AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, AQEP-13, AQEP-14 and AQEP-15 each have a longer plasma half-life due to higher protein binding. Dipivefrin is capable of sustained blood levels, and has a reduced interaction with α-receptors, therefore minimizing or eliminating unwanted or harmful vasoconstriction. Prodrugs, for example, AQEP-09, can exhibit higher binding affinity for α- and β- receptors, with binding and activation profiles that are more similar to epinephrine than dipivefrin. Other prodrugs, and combinations of prodrugs, can exhibit binding affinities for α- and β- receptors that favor one or more receptor, similar to or different from epinephrine.



Dipivefrin or prodrugs AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, AQEP-13, AQEP-14 or AQEP-15, alone or in combination, can be delivered in sublingual film in a similar manner as with epinephrine delivered by other methods, including injection.

A film and/or its components can be water-soluble, water swellable, water dispersable or water-insoluble. The term "water-soluble" can refer to substances that are at least partially dissolvable in an aqueous solvent, including but not limited to water. The term "water-soluble" may not necessarily mean that the substance is 100% dissolvable in the aqueous solvent. The term "water-insoluble" refers to substances that are not dissolvable in an aqueous solvent, including but not limited to water. A solvent can include water, or alternatively can include other solvents (preferably, polar solvents) by themselves or in combination with water.

Polymeric Matrix

The composition can include a polymeric matrix. Any desired polymeric matrix may be used, provided that it is orally dissolvable or erodible. The dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. They can be moderate-dissolving in the oral cavity and particularly suitable for delivery of pharmaceutically active components, although both fast release, delayed release, controlled release and sustained release compositions are also among the various embodiments contemplated.

The pharmaceutical composition film can include dendritic polymers which can include highly branched macromolecules with various structural architectures. The dendritic polymers can include dendrimers, dendronised polymers (dendrigrafted polymers), linear dendritic hybrids, multi-arm star polymers, or hyperbranched polymers.

Hyperbranched polymers are highly branched polymers with imperfections in their structure. However, they can be synthesized in a single step reaction which can be an advantage over other dendritic structures and are therefore suitable for bulk volume applications. The properties of these polymers apart from their globular structure are the abundant functional groups, intramolecular cavities, low viscosity and high solubility. Dendritic polymers have been used in several drug delivery applications. See, e.g., Dendrimers as Drug Carriers: Applications in Different Routes of Drug Administration. J Pharm Sci, VOL. 97, 2008, 123-143, which is incorporated by reference herein.

The dendritic polymers can have internal cavities which can encapsulate drugs. The steric hindrance caused by the highly dense polymer chains might prevent the crystallization of the drugs. Thus, branched polymers can provide additional advantages in formulating crystallizable drugs in a polymer matrix.

Examples of suitable dendritic polymers include poly(ether) based dendrons, dendrimers and hyperbranched polymers, poly(ester) based dendrons, dendrimers and hyperbranched polymers, poly(thioether) based dendrons, dendrimers and hyperbranched polymers, poly(amino acid) based dendrons dendrimers and hyperbranched polymers, poly(arylalkylene ether) based dendrons, dendrimers and hyperbranched polymers, poly(alkyleneimine) based dendrons, dendrimers and hyperbranched polymers, poly(amidoamine) based dendrons, dendrimers or hyperbranched polymers.

Other examples of hyperbranched polymers include poly(amines)s, polycarbonates, poly(ether ketone)s, polyurethanes, polycarbosilanes, polysiloxanes, poly(ester amine)s, poly(sulfone amine)s, poly(urea urethane)s and polyether polyols such as polyglycerols.

A film can be produced by a combination of at least one polymer and a solvent, optionally including other components. The solvent may be water, a polar organic solvent including, but not limited to, methanol, ethanol, isopropanol, t-butyl alcohol, acetone, acetonitrile, 2-butanone, 1,2-dimethoxy ethane, or tetrahydrofuran, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene

chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through a controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. The controlled drying processes can include air alone, heat alone or heat and air together contacting the top of the film or bottom of the film or the substrate supporting the cast or deposited or extruded film or contacting more than one surface at the same time or at different times during the drying process. Some of such processes are described in more detail in U.S. Patent No. 8,765,167 and U.S. Patent No. 8,652,378, which are incorporated by reference herein. Alternatively, the films may be extruded as described in U.S. Patent Publication No. 2005/0037055 A1, which is incorporated by reference herein.

A polymer included in the films may be water-soluble, water-swellable, water-insoluble, or a combination of one or more either water-soluble, water-swellable or water-insoluble polymers. The polymer may include cellulose, cellulose derivatives or gums. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

As used herein the phrase "water-soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swellable polymers. The materials useful with the present invention may be water-soluble or water-swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swellable at pressures less than atmospheric pressure. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers or combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). The polymers incorporated in the films can also include a combination of biodegradable or bioerodable materials. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(alpha-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of alpha-amino acids, copolymers of alpha-amino acids and caproic acid, copolymers of alpha-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates or mixtures thereof. The polymer matrix can include one, two, three, four or more components.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of pharmaceutically active component contained in the composition. Some pharmaceutically active components may only require a few minutes for delivery through the mucosal tissue, whereas other pharmaceutically active components may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue

for longer periods of time, such as up to several hours, which may be desirable for delivery of certain pharmaceutically active components.

Film Properties

Desirably, an individual film dosage of the pharmaceutical film can have a suitable thickness, and small size, which is between about 0.0625-3 inch by about 0.0625-3 inch. The film size can also be greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, about 3 inches, and greater than 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in at least one aspect, or greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, or greater than 3 inches, about 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in another aspect. The aspect ratio, including thickness, length, and width can be optimized by a person of ordinary skill in the art based on the chemical and physical properties of the polymeric matrix, the active pharmaceutical ingredient, dosage, enhancer, and other additives involved as well as the dimensions of the desired dispensing unit. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments, the film dosage may be capable of dispersing and dissolving between about 1 to about 30 minutes, for example, about 1 to about 20 minutes, or more than 1 minute, more than 5 minutes, more than 7 minutes, more than 10 minutes, more than 12 minutes, more than 15 minutes, more than 20 minutes, more than 30 minutes, about 30 minutes, or less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 12 minutes, less than 10 minutes, less than 7 minutes, less than 5 minutes, or less than 1 minute. Sublingual dispersion times may be shorter than buccal dispersion times.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In some embodiments, one or more water-swellable, water-

insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight, including greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, and greater than 70%, about 70%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10% or less than 5% by weight.

Steric Hindrance

Steric hindrance is the slowing of chemical reactions due to steric bulk. It is usually manifested in intermolecular reactions such as enzymatic reactions. Steric hindrance is often exploited to control selectivity, such as slowing unwanted side-reactions. In pharmacology, steric effects determine how and at what rate a drug will interact with its target bio-molecules. The design of a prodrug needs to account for steric hindrance resulting from the prodrug substituents and its interactions with respective enzymes, including hydrolases, esterases and amidases for example. Additives, such as those described below, can also impact the activity and/or interaction with enzymes. In certain embodiments, one or more of these enzymes can be endogenous. In other embodiments, one or more of these enzymes can be exogenous. Stereospecific nucleophilic attack on substituted carbon atoms is a simple and versatile way to construct stereocenter next to heteroatoms with overall inversion of stereochemistry. A tertiary group adjacent to the ester unexpectedly impedes hydrolysis more when compared to non-tertiary groups.

Additives

Additives may be included in the films. Examples of classes of additives include preservatives, antimicrobials, excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, salts, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers,

elastomers, anti-tacking agents, anti-static agents and mixtures thereof. These additives may be added with the pharmaceutically active component(s). As used herein, the term "stabilizer" means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation, of the active pharmaceutical ingredient, another excipient, or the combination thereof.

Stabilizers may also be classified as antioxidants, sequestrants, pH modifiers, emulsifiers and/or surfactants, or UV stabilizers.

Antioxidants (i.e., pharmaceutically compatible compound(s) or composition(s) that decelerates, inhibits, interrupts and/or stops oxidation processes) include, in particular, the following substances: tocopherols and the esters thereof, sesamol of sesame oil, coniferyl benzoate of benzoin resin, nordihydroguaietic resin and nordihydroguaiaretic acid (NDGA), gallic acid, gallates (among others, methyl, ethyl, propyl, amyl, butyl, lauryl gallates), butylated hydroxyanisole (BHA/BHT, also butyl-p-cresol); ascorbic acid and salts and esters thereof (for example, acorbyl palmitate), erythorbinic acid (isoascorbinic acid) and salts and esters thereof, monothioglycerol, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium bisulfite, sodium sulfite, potassium metabisulfite, ethylenediamine tetra acetic acid (EDTA), ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA), butylated hydroxytoluene (BHT) (including t-butylhydroxytoluene), cysteine, ferulic acid, caffeic acid, tannic acid, uric acid, and propionic acid. Typical antioxidants are tocopherol such as, for example, α-tocopherol and the esters thereof, butylated hydroxytoluene and butylated hydroxyanisole. The terms "tocopherol" also includes esters of tocopherol. A known tocopherol is α-tocopherol. The term "α-tocopherol" includes esters of α-tocopherol (for example, α-tocopherol acetate).

Sequestrants (i.e., any compounds which can engage in host-guest complex formation with another compound, such as the active ingredient or another excipient; also referred to as a sequestering agent) include calcium chloride, calcium disodium ethylene diamine tetra-acetate, glucono delta-lactone, sodium gluconate, potassium gluconate, sodium tripolyphosphate, sodium hexametaphosphate, and combinations thereof. Sequestrants also include cyclic oligosaccharides, such as cyclodextrins, cyclomannins (5 or more α-D-mannopyranose units linked at the 1,4 positions by α linkages), cyclogalactins (5 or more β-D-galactopyranose units linked at the 1,4 positions by β linkages), cycloaltrins (5 or more α-D-altropyranose units linked at the 1,4 positions by α linkages), and combinations thereof.

pH modifiers or stabilizers include acids (e.g., hydrochloric acid, hydrofluoric acid, tartaric acid, citric acid, lactic acid, fumaric acid, phosphoric acid, ascorbic acid, acetic acid, succinic acid, propanoic acid, butyric acid, isobutyric acid, pivalic acid, malic acid, tartaric acid, adipic acid and maleic acid), acidic amino acids (e.g., glutamic acid, aspartic acid, etc.), inorganic salts (alkali metal salt, alkaline earth metal salt, ammonium salt, etc.) of such acidic substances, a salt of such acidic substance with an organic base (e.g., basic amino acid such as lysine, arginine and the like, meglumine and the like), and a solvate (e.g., hydrate) thereof. Other examples of pH modifiers include silicified microcrystalline cellulose, magnesium aluminometasilicate, calcium salts of phosphoric acid (e.g., calcium hydrogen phosphate anhydrous or hydrate, calcium, sodium or potassium carbonate or hydrogencarbonate and calcium lactate or mixtures thereof), sodium and/or calcium salts of carboxymethyl cellulose, cross-linked carboxymethylcellulose (e.g., croscarmellose sodium and/or calcium), polacrilin potassium, sodium and or/calcium alginate, docusate sodium, magnesium calcium, aluminium or zinc stearate, magnesium palmitate and magnesium oleate, sodium stearyl fumarate, and combinations thereof.

Examples of emulsifiers and/or surfactants include poloxamers or pluronics, polyethylene glycols, polyethylene glycol monostearate, polysorbates, sodium lauryl sulfate, polyethoxylated and hydrogenated castor oil, alkyl polyoside, a grafted water soluble protein on a hydrophobic backbone, lecithin, glyceryl monostearate, glyceryl monooleate, glyceryl monostearate/polyoxyethylene stearate, ketostearyl alcohol/sodium lauryl sulfate, carbomer, phospholipids, (C_{10}-C_{20})-alkyl and alkylene carboxylates, alkyl ether carboxylates, fatty alcohol sulfates, fatty alcohol ether sulfates, alkylamide sulfates and sulfonates, fatty acid alkylamide polyglycol ether sulfates, alkanesulfonates and hydroxyalkanesulfonates, olefinsulfonates, acyl esters of isethionates, α-sulfo fatty acid esters, alkylbenzenesulfonates, alkylphenol glycol ether sulfonates, sulfosuccinates, sulfosuccinic monoesters and diesters, fatty alcohol ether phosphates, protein/fatty acid condensation products, alkyl monoglyceride sulfates and sulfonates, alkylglyceride ether sulfonates, fatty acid methyltaurides, fatty acid sarcosinates, sulforicinoleates, and acylglutamates, quaternary ammonium salts (e.g., di-(C_{10}-C_{24})-alkyl-dimethylammonium chloride or bromide), (C_{10}-C_{24})-alkyl-dimethylethylammonium chloride or bromide, (C_{10}-C_{24})-alkyl-trimethylammonium chloride or bromide (e.g., cetyltrimethylammonium chloride or bromide), (C_{10}-C_{24})-alkyl-dimethylbenzylammonium chloride or bromide (e.g., (C_{12}—C_{18})-alkyl-dimethylbenzylammonium chloride), N—(C_{10}-C_{18})-alkyl-pyridinium chloride or bromide (e.g.,

N—(C_{12}-C_{16})-alkyl-pyridinium chloride or bromide), N—(C_{10}-C_{18})-alkyl-isoquinolinium chloride, bromide or monoalkyl sulfate, N—(C_{12}-C_{18})-alkyl-polyoylaminoformylmethylpyridinium chloride, N—(C_{12}-C_{18})-alkyl-N-methylmorpholinium chloride, bromide or monoalkyl sulfate, N—(C_{12}-C_{18})-alkyl-N-ethylmorpholinium chloride, bromide or monoalkyl sulfate, (C_{16}-C_{18})-alkyl-pentaoxethylammonium chloride, diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride, salts of N,N-di-ethylaminoethylstearylamide and -oleylamide with hydrochloric acid, acetic acid, lactic acid, citric acid, phosphoric acid, N-acylaminoethyl-N,N-diethyl-N-methylammonium chloride, bromide or monoalkyl sulfate, and N-acylaminoethyl-N,N-diethyl-N-benzylammonium chloride, bromide or monoalkyl sulfate (in the foregoing, "acyl" standing for, e.g., stearyl or oleyl), and combinations thereof.

Examples of UV stabilizers include UV absorbers (e.g., benzophenones), UV quenchers (i.e., any compound that dissipates UV energy as heat, rather than allowing the energy to have a degradation effect), scavengers (i.e., any compound that eliminates free radicals resulting from exposure to UV radiation), and combinations thereof.

In other embodiments, stabilizers include ascorbyl palmitate, ascorbic acid, alpha tocopherol, butylated hydroxytoluene, butylated hydroxyanisole, cysteine HC1, citric acid, ethylenediamine tetra acetic acid (EDTA), methionine, sodium citrate, sodium ascorbate, sodium thiosulfate, sodium metabisulfite, sodium bisulfite, propyl gallate, glutathione, thioglycerol, singlet oxygen quenchers, hydroxyl radical scavengers, hydroperoxide removing agents, reducing agents, metal chelators, detergents, chaotropes, and combinations thereof. "Singlet oxygen quenchers" include, but are not limited to, alkyl imidazoles (e.g., histidine, L-camosine, histamine, imidazole 4-acetic acid), indoles (e.g., tryptophan and derivatives thereof, such as N-acetyl-5-methoxytryptamine, N-acetylserotonin, 6-methoxy-1,2,3,4-tetrahydro-beta-carboline), sulfur-containing amino acids (e.g., methionine, ethionine, djenkolic acid, lanthionine, N-formyl methionine, felinine, S-allyl cysteine, S-aminoethyl-L-cysteine), phenolic compounds (e.g., tyrosine and derivatives thereof), aromatic acids (e.g., ascorbate, salicylic acid, and derivatives thereof), azide (e.g., sodium azide), tocopherol and related vitamin E derivatives, and carotene and related vitamin A derivatives. "Hydroxyl radical scavengers" include, but are not limited to azide, dimethyl sulfoxide, histidine, mannitol, sucrose, glucose, salicylate, and L-cysteine. "Hydroperoxide removing agents" include, but are not limited to catalase, pyruvate, glutathione,

and glutathione peroxidases. "Reducing agents" include, but are not limited to, cysteine and mercaptoethylene. "Metal chelators" include, but are not limited to, EDTA, EGTA, o-phenanthroline, and citrate. "Detergents" include, but are not limited to, SDS and sodium lauroyl sarcosyl. "Chaotropes" include, but are not limited to guandinium hydrochloride, isothiocyanate, urea, and formamide. As discussed herein, stabilizers can be present in 0.0001%-50% by weight, including greater than 0.0001%, greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 1%, greater than 5%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 1%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% by weight.

Useful additives can include, for example, gelatin, gelatin hydrosylates, recombinant gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, polysaccharides or carbohydrates such as gum arabica, chitin, chitosan, xanthan gum, agar, gum ghatti, chondroitin sulfate, dextran, carrageenans, gum karaya, hyaluronic acid, curdian, alginic acid, gum tragacanth, pullulan, laminarin, khaya, zanflo, albizia gums, guar gum, Baker's yeast, locust bean gum, glycan, starch, schizophyllan, amylase, lentinan, cellulose, krestin, pectin, scleroglucan, larch gum, potato starch, pea starch, hetastarch, starch acetate, starch phosphates,inulin, and pectin, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVA/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin,

shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; or other similar polymers.

Stabilizers can include nanoparticulate stabilizers, such as a dispersant layer around a nanoparticulate surface. *See, e.g.*, Langmuir 2007, (23)3, 1081-1090, December 20, 2006, doi.org/10.1021/la062042s. Stabilizers can include stabilizer ligands, e.g., monomers bearing functional groups that can get chemisorbed on nanoparticles to form polymerizable monolayers. *See, e.g.,* Jadhav et al https://doi.org/10.1002/ppsc.201400074. Stabilizers can include surface stabilizers. *See, e.g.*, U.S. Pat. No. 6428814 and Japanese Pat. JP 4598399B2. Surface stabilizers can include tyloxapol (U.S. Pat. No. 5,429,824), polyalkylene block copolymers (U.S. Pat. No. 5,565,188), sulfated non-ionic block copolymers (U.S. Pat. No. 5,569,448), high molecular weight, linear, poly(ethylene oxide) polymers (U.S. Pat. No. 5,580,579), butylene oxide-ethylene oxide block copolymers (U.S. Pat. No. 5,587,143), hydroxypropyl cellulose (U.S. Pat. No. 5,591,456), and sugar based surface stabilizers (U.S. Pat. No. 5,622,938). Stabilizers can include peptide stabilizers. See, e.g., WO2006097748A2. Stabilizers can include for example, L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulfite, citric acid, tartaric acid, and L-cystine dihydrochloride. See, e.g., U.S. Pat. 6,153,223. Stabilizers can include natural compounds. Stabilizers can include synthetic compounds. Stabilizers can include a blend of one of more compounds or categories of compounds described above. Stabilizers can be function to protect the metabolism of a prodrug until a desired time or until it reaches a specific target, tissue or environment.

The additional components can range up to about 80%, desirably about 0.005% to 50% and more desirably within the range of 1% to 20% based on the weight of all composition components, including greater than 1%, greater than 5%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, about 80%, greater than 80%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, about 3%, or less than 1%. Other additives can include anti-tacking, flow agents and opacifiers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.005% to about 5% by weight and desirably about 0.02% to about 2% based on the weight of all film components, including greater than 0.02%, greater than 0.2%, greater than 0.5%, greater than

1%, greater than 1.5%, greater than 2%, greater than 4%, about 5%, greater than 5%, less than 4%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.02%.

In certain embodiments, the composition can include plasticizers, which can include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sugar alcohols sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, phytoextracts, fatty acid esters, fatty acids, oils and the like, added in concentrations ranging from about 0.1% to about 40%, and desirably ranging from about 0.5% to about 20% based on the weight of the composition including greater than 0.5%, greater than 1%, greater than 1.5%, greater than 2%, greater than 4%, greater than 5%, greater than 10%, greater than 15%, about 20%, greater than 20%, less than 20%, less than 15%, less than 10%, less than 5%, less than 4%, less than 2%, less than 1%, or less than 0.5%. There may further be added compounds to improve the texture properties of the film material such as animal or vegetable fats, desirably in their hydrogenated form. The composition can also include compounds to improve the textural properties of the product. Other ingredients can include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, natural gums, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, or polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable pharmaceutically active components may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or unstable pharmaceutically active components to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide. Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, including greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 0.5%, greater than 1%, greater than 2%, greater than 5%, about 10%, greater than 10%, less than 10%, less than 5%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.01%, or less than 0.001%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors. Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), or 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: saccharides, glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof, saccharin and its various salts such as the sodium salt; dipeptide based sweeteners such as aspartame, neotame, advantame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other suitable anti-foam and/or de-foaming agents may be used. Simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Patent No. 8,765,167, referred to above, also may be included in the films described herein.

The film compositions further desirably contain a buffer so as to control the pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired pH level encountered as the pharmaceutically active component is released from the composition. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the pharmaceutically active component. In some embodiments, the buffer may include sodium citrate, citric acid, bitartrate salt and combinations thereof.

The pharmaceutical films described herein may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 8,652,378, 7,425,292 and 7,357,891, which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix and a therapeutically effective amount of a pharmaceutically active component. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages.

The pharmaceutical composition can adhere to a mucosal surface. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina,

organs, or other types of mucosal surfaces. The composition carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the pharmaceutical to the treatment site, the surrounding tissues, and other bodily fluids. The composition provides an appropriate residence time for effective drug delivery at the treatment site, given the control of erosion in aqueous solution or bodily fluids such as saliva, and the slow, natural erosion of the film concomitant or subsequent to the delivery.

The residence time of the composition depends on the erosion rate of the water erodible polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using water soluble organic and inorganic salts; by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the film. Upon application, the pharmaceutical composition film adheres to the mucosal surface and is held in place. Water absorption softens the composition, thereby diminishing the foreign body sensation. As the composition rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 5 seconds to about 24 hours. More preferably, the residence time is adjusted from about 5 seconds to about 30 minutes. In addition to providing drug delivery, once the composition adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodible bandage. Lipophilic agents can be designed to slow down erodibility to decrease disintegration and dissolution.

It is also possible to adjust the kinetics of erodability of the composition by adding excipients which are sensitive to enzymes such as amylase, very soluble in water such as water

soluble organic and inorganic salts. Suitable excipients may include the sodium and potassium salts of chloride, carbonate, bicarbonate, citrate, trifluoroacetate, benzoate, phosphate, fluoride, sulfate, or tartrate. These excipients can be used for other purposes in the composition as well. The amount added can vary depending upon how much the erosion kinetics is to be altered as well as the amount and nature of the other components in the composition.

An ion exchange resin, for example, and anion exchange resin, or a buffer can be used to modulate the behavior of the excipient in the film and when released from the film. Suitable ion exchange resins can include a gel, resin or other polymer functionalized with anionic or cationic groups, for example, a polyamine, a polysulfonic acid, or a polycarboxylic acid. Examples of suitable ion exchange resins can include Duolite A143, Amberlite IRC 50, Indion 204, Purolite C102D, Kyron-T-104, Tulsion-355, Doshion P 544, Amberlite IR 120, Dowex 50, Indion 244, Purolite C100HMR, Kryon-T- 154, Dowex M-43, or Dowex G-55.

Emulsifiers typically used in the water-based emulsions described above are, preferably, either obtained in situ if selected from the linoleic, palmitic, myristoleic, lauric, stearic, cetoleic or oleic acids and sodium or potassium hydroxide, or selected from the laurate, palmitate, stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols, allyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and/or sorbitan monopalmitate.

The amount of pharmaceutically active component to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001% to about 99%, more preferably from about 0.003 to about 75%, and most preferably from about 0.005% to about 50% by weight of the composition, including, more than 0.005%, more than 0.05%, more than 0.5%, more than 1%, more than 5%, more than 10%, more than 15%, more than 20%, more than 30%, about 50%, more than 50%, less than 50%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, less than 0.05%, or less than 0.005%. The amounts of other components may vary depending on the drug or other components but typically these components comprise no more than 50%, preferably no more than 30%, and most preferably no more than 15% by total weight of the composition.

The thickness of the film may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted in order to vary the erosion kinetics. Preferably, if the composition has only two layers, the thickness ranges from 0.005 mm to 2 mm, preferably from 0.01 to 1 mm, and more preferably from 0.1 to 0.5 mm, including greater than 0.1 mm, greater than 0.2 mm, about 0.5 mm, greater than 0.5 mm, less than 0.5 mm, less than 0.2 mm, or less than 0.1 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered composition, and preferably varies from 30 to 60%, including greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 70%, greater than 90%, about 90%, less than 90%, less than 70%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, or from 0.03 to 0.5 mm.

As one skilled in the art will appreciate, when systemic delivery, e.g., transmucosal or transdermal delivery is desired, the treatment site may include any area in which the film is capable of delivery and/or maintaining a desired level of pharmaceutical in the blood, lymph, or other bodily fluid. Typically, such treatment sites include the oral, esophageal, aural, ocular, anal, nasal, or vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site, then usually larger areas of the skin wherein movement will not disrupt the adhesion of the film, such as the upper arm or thigh, are preferred.

The pharmaceutical composition can also be used as a wound dressing. By offering a physical, compatible, oxygen and moisture permeable, flexible barrier which can be washed away, the film can not only protect a wound but also deliver a pharmaceutical in order to promote healing, aseptic, scarification, to ease the pain or to improve globally the condition of the sufferer. Some of the: examples given below are well suited for an application to the skin or a wound. As one skilled in the art will appreciate, the formulation might require incorporating a specific hydrophilic/hygroscopic excipient which would help in maintaining good adhesion on dry skin over an extended period of time. Another advantage of the present invention when utilized in this manner is that if one does not wish that the film be noticeable on the skin, then no dyes or colored substances need be used. If, on the other hand, one desires that the film be noticeable, a dye or colored substance may be employed.

While the pharmaceutical composition can adhere to mucosal tissues, which are wet tissues by nature, it can also be used on other surfaces such as skin or wounds. The pharmaceutical film can adhere to the skin if prior to application the skin is wet with an aqueous-based fluid such as water, saliva, wound drainage or perspiration. The film can adhere to the skin until it erodes due to contact with water by, for example, rinsing, showering, bathing or washing. The film may also be readily removed by peeling without significant damage to tissue.

EXAMPLES

IM study in Minipig-Dipivefrin/Prodrugs

This study was conducted to compare the pharmacokinetic profile of epinephrine following intramuscular (IM) administration of L-dipivefrin and epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) in male Yucatan miniature swine. Yucatan minipigs (n=4 males per group) were weighed and weights were recorded. The morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections.

Dosing of L-Dipivefrin or other epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) solution was done (2mg/animal) through IM route. All the formulations were prepared fresh on the day of dosing and maintained on wet ice until dosing. The dose was injected in the rear hind limb. Prior to administering, the plunger of the syringe was aspirated and observed for any blood that may flow into the syringe. If no blood was observed, it was verified that the needle was in proper placement, and the test articles were administered.

Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing K_2EDTA as the anticoagulant and sodium metabisulfite as stabilizer. Sodium metabisulfite was at a concentration of 8.9mM, pH 3 (60µL/6 mL of whole blood of the 890 mM stock solution). SigmaFast (600 µL of SigmaFast 1x solution to 6 mL of whole blood) was added immediately to the tubes as the enzyme arresting agent. The tubes were inverted several times for mixing upon addition of SigmaFast solution. All blood samples were centrifuged within 30 minutes of collection at 3000 RPM for 15 minutes at ~4°C. The resulting plasma was obtained and

stored at approximately -70 degrees. The analysis of epinephrine was done using LC-MS/MS method.

Example 1

Referring to **Fig. 1A** and **Fig. 1B**, dipivefrin, a prodrug for epinephrine was tested in a 24 mg soluble film (DSF) and compared to Epipen in terms of achieving epinephrine plasma concentrations (in pg/ml) over time in humans. The study showed that surprisingly, the prodrug achieved comparable epinephrine concentrations were achieved in less than 0.6 hour, for example between 0.4-0.6 hours.

Example 2

Referring to **Fig. 2A** and **Fig. 2B**, the figures show results from projected increase in prodrug dosing from 24 mg, to 30 mg and 36 mg of dipivefrin soluble film as compared to the Epipen. As shown in the figure, the increased dose provides a curve shift to the left, resulting in achieving similar epinephrine plasma concentrations in a shorter time compared to lower doses.

Example 3 - In vitro Human Whole Blood Hydrolysis Assay

To identify epinephrine prodrugs with faster hydrolysis using human whole blood in vitro, epinephrine levels in plasma was measured. Fresh healthy human whole blood was collected in blood collection tubes and preincubated for 30 min at 37°C. After incubation, in the presence of stabilizer, the whole blood was fortified at a final concentration of 1 μM of dipivefrin or prodrugs (AQEP-03, AQEP-04, AQEP-05, AQEP-06, AQEP-07, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-12, and AQEP-13 for each time point separately. After addition, samples were mixed thoroughly and incubated at 37°C for different time points up to 6 hours. After incubation, whole blood samples at each time point was removed, quenched, and centrifuged to separate the plasma. Plasma samples were analyzed for epinephrine concentrations using established LC-MS/MS method

Referring to **Fig. 3A** and **3B**, the results show that the newly synthesized prodrug AQEP-10 has achieved significantly higher plasma levels of epinephrine in much less time including less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 10 minutes, and less than 5 minutes. Note that in this study, t=0 is not a true zero as there is an approximately 3-5min lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis.

In general, prodrugs AQEP-05, AQEP-08, AQEP-09 and AQEP-10 and AQEP-11 having ester groups showed faster hydrolysis in human whole blood compared to L-Dipivefrin. The data indicates that one or more of these prodrugs can be used in place of or in addition to L-Dipivefrin as a combination of prodrugs. Surprisingly, increasing the number of carbons did not affect the rate of hydrolysis. Unexpectedly, prodrugs AQEP-12 with carbonate group showed faster hydrolysis in human whole blood compared to L-Dipivefrin, in a manner similar to AQEP-10 with ester group. Unpredictably, prodrug AQEP-04 having ester groups showed faster hydrolysis in human whole blood, but did not permeate as well, compared to L-Dipivefrin. Prodrugs AQEP-06 or AQEP-07 with carbamate groups did not show any hydrolysis in the blood. This is consistent with literature that carbamate compounds are resistant to plasma esterases, Finally, prodrug AQEP-03 (with dimethyl amino group) showed minimal hydrolysis and increased gradually at later timepoints.

Example 4

Referring to **Fig. 4**, Prodrugs AQEP-04 and AQEP-05 were tested similarly in the manner of Example 31. Using human whole blood in vitro, epinephrine levels in plasma was measured. Whole blood was collected from 2 donors. Compounds were incubated at 1μM conc with Stabilizer. Plasma was separated after stopping the enzyme reaction at different timepoints. Samples were extracted and analyzed by LC-MS method. Rapid conversion and higher levels of epinephrine was seen for Prodrugs AQEP-04 and AQEP-05, compared to L-Dipivefrin. This shows that AQEP-04 or AQEP-05 can be combined with L-Dipivefrin ('Combo' drug) to achieve faster and sustained exposure to epinephrine in plasma and achieve improved results over Epipen.

Example 5

Referring to **Fig. 5**, Prodrugs AQEP-03, AQEP-06, and AQEP-07 were tested similarly in the manner of Example 3. Using human whole blood in vitro, epinephrine levels in plasma was measured. Whole blood was collected from 2 donors. Compounds were incubated at 1μM conc with Stabilizer. Plasma was separated after stopping the enzyme reaction at different timepoints. Samples were extracted and analyzed by LC-MS method. Prodrugs AQEP-03, AQEP-06, and AQEP-07 did not show faster hydrolysis in human blood, compared to L-Dipivefrin.

Example 6 – Intramuscular Study in Minipig for Prodrugs

Applicants sought to identify epinephrine prodrugs with higher permeability and slower hydrolysis after intramuscular (IM) administrations. This study was conducted to compare the pharmacokinetic profile of epinephrine following intramuscular (IM) administration of L-dipivefrin and epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) in male Yucatan miniature swine. Yucatan minipigs were weighed and in the morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections. .

Dosing of L-Dipivefrin or other epinephrine prodrugs (AQEP-01 (A), AQEP-02 (B), AQEP-03 (C) and AQEP-04 (D)) solution was done (2mg/animal) through IM route. The dose was injected in the rear hind limb. Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing anticoagulant and stabilizer. Protease inhibitor cocktail was added and the tubes were inverted several times for mixing. All blood samples were centrifuged and the resulting plasma was analyzed for epinephrine using LC-MS/MS method.

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level (mg/animal)	Dipi Dose Conc. (mg/mL)	Target Dose Amount (mL /animal)
1	4	L-Dipivefrin Solution	IM	2	2	1 mL
2	4	Prodrug A Solution	IM	2	2	1 mL
3	4	Prodrug B Solution	IM	2	2	1 mL
4	4	Prodrug C Solution	IM	2	2	1 mL
5	4	Prodrug D Solution	IM	2	2	1 mL

The following conversion was observed

	Actual Dose used	**Conversion ratio**	**Epinephrine Dose Equivalence (mg)**
L-Dipivefrin	2mg (0.1mg/kg)	0.52	1.04
AQEP-01	2mg (0.1mg/kg)	0.39	0.78

AQEP-02	2mg (0.1mg/kg)	0.44	0.88
AQEP-03	2mg (0.1mg/kg)	0.51	1.01
AQEP-04	2mg (0.1mg/kg)	0.43	0.86

Referring to **Fig. 6A** and **Fig. 6B**, the figures show normalization to epinephrine equivalent dose of L-dipivefrin and showing average epinephrine plasma concentration. Prodrug, AQEP-04 had higher Cmax and AUC compared to Prodrugs 01, 02 and 03 (AQEP-04>AQEP-02>AQEP-03>AQEP-01). L-dipivefrin showed Cmax (1.94 ng/ml) and AUC (256.8 ng/ml*min) compared to other Epinephrine prodrugs. Faster hydrolysis (Tmax=5 min), with sufficient plasma levels (0.5ng/ml) up to 4 hrs was seen. Faster hydrolysis was seen (Tmax=5 min) with AQEP-04, but Cmax and AUC was less compared to L-Dipivefrin.

Example 7 – Hydrolysis Testing after IV Exposure

Referring to **Figs. 7A** and **7B**, hydrolysis assay was performed with the following prodrugs as test articles: L-dipivefrin, AQEP-03, and AQEP-05. Hydrolysis was analyzed after intravenous (IV) administrations. All Groups were tested at the following time intervals: 0 (predose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes and 3hr, 4 hr, 6hr and 8hr post dose.

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level* (mg/animal)	Dipivefrin Dose Conc. (mg/mL or mg/DF)	Target Dose Amount (mL or DF/animal)
1	3	L-Dipivefrin Solution	IV	2.0	2.0	1 mL
2	3	Prodrug AQEP-03 Solution	IV	2.06	2.06	1 mL
3	3	Prodrug AQEP-05 Solution	IV	2.05	2.05	1 mL

The following pharmacokinetic (PK) parameters were observed.

	L-Dipivefrin	**AQEP-03**	**AQEP-05**
AUC_{0-t} (ng/ml*min)	243.8	60.4	457.8
AUC_{0-30} (ng/ml*min)	109.1	8.1	137.8
Cmax (ng/ml)	7.3	0.46	11.4
Tmax (min)	2	17	2

Rapid conversion of Prodrug AQEP-05 to epinephrine was seen after IV administration, compared to L-Dipivefrin. Approximately 2-fold increase in the AUC and Cmax was observed. Similar Tmax (2 minutes) was seen.

Example 8 - Intramuscular (IM) and subcutaneous (SC) administrations of L-Dipivefrin

This study was conducted to compare the pharmacokinetic profile of L-dipivefrin administered through intramuscular (IM) and subcutaneous (SC) routes to epinephrine (Epipen, 0.3 mg) (Mfg: Mylan) in male Yucatan miniature swine.. . The study measured epinephrine exposure, conversion of dipivefrin to epinephrine and pharmacokinetic (PK) parameters.

Yucatan minipigs were weighed and in the morning of the study, the vascular access port (VAP) of each animal was checked for proper functioning. Minipigs with viable VAP were removed from the home cage and placed in a holding sling. The animals were fasted overnight prior to dose administration and for the duration of PK blood collections.

Dosing of L-Dipivefrin (0.6, 1 and 2 mg/animal) solution was administered through IM or SC routes, whereas Epipen was injected through IM route. For IM route, L-Dipivefrin solutions or Epipen were injected in the rear hind limb. For SC route, L-Dipivefrin solutions were dosed on the animal's neck, just behind the right ear.

Pharmacokinetic blood sample collections were done through vascular access port at 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes, 3hr, 4 hr, 6hr and 8hr post dose. At each specified time-point, 6 mL of whole blood was collected into blood collection tubes containing anticoagulant and stabilizer. Protease inhibitor cocktail was added and the tubes were inverted several times for mixing. All blood samples were centrifuged and the resulting plasma was analyzed for dipivefrin and epinephrine using LC-MS/MS method.

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level (mg/animal)	Epi/Dipivefrin Dose Conc. (mg/mL)	Target Dose Amount (mL /animal)
1	1	Placebo	IM	0	0	1 mL
2	3	Epipen	IM	0.3	1 mg/ml	0.3 ml
3	3	Dipivefrin (Alc-L) Solution	IM	0.6	0.6 mg/mL	1 mL
4	3	Dipivefrin (Alc-L) Solution	IM	1	1 mg/mL	1 mL
5	3	Dipivefrin (Alc-L) Solution	IM	2	2 mg/mL	1 mL
6	3	Dipivefrin (Alc-L) Solution	SC	0.6	0.6 mg/mL	1 mL
7	3	Dipivefrin (Alc-L) solution	SC	1	1 mg/mL	1 mL
8	3	Dipivefrin (Alc-L) Solution	SC	2	2 mg/mL	1 mL

PK Blood /Plasma Sample Collections were collected for all Groups: 0 (predose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes and 3hr, 4 hr, 6hr and 8hr post dose.

Referring to **Fig. 8A**, average epinephrine plasma concentration was collected over time for intramuscular and subcutaneous administration of L-dipivefrin (0.6 mg, 1 mg and 2 mg) and compared to the Epipen.

Referring to **Fig. 8B**, intramuscular (IM) administration was performed and average epinephrine plasma concentration was measured.

Referring to **Fig. 8C**, subcutaneous (SC) administration, and average epinephrine plasma concentration was measured.

Example 9

Referring to **Fig. 9A**, a comparison of IM & SC administration of L-dipivefrin 0.6 mg was performed and average epinephrine plasma concentration was measured, using the same protocol as in Example 38. Referring to **Fig. 9B**, the same comparison was drawn using 1 mg of L-dipivefrin. Referring to **Fig. 9C**, the same comparison was drawn using 2 mg of L-dipivefrin.

Example 10

Referring to **Fig. 10**, average dipivefrin plasma concentration vs time profiles were obtained over time for 0.6 mg, 1 mg and 2 mg of dipivefrin using intramuscular (IM) administration and subcutaneous (SC) administration.

Example 11

Referring to **Fig. 11A**, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using intramuscular (IM) administration.

Referring to **Fig. 11** B, conversion of dipivefrin to epinephrine was measured for 0.6 mg, 1 mg and 2 mg of dipivefrin using subcutaneous (SC)administration.

The following PK parameters were observed.

	EPI AUC 0-t (min* ng/ml)	**EPI Tmax (min)**	**EPI Cmax (mean, ng/ml)**	**DIPI AUC 0-t (min* ng/ml)**	**DIPI Tmax (min)**	**DIPI Cmax (mean, ng/ml)**
Placebo	0	-	-	0	-	-
Epipen	71.02	5	0.403	-	-	-
L-Dipivefrin IM 0.6mg	62.85	20	0.387	2.6	5	0.285

L-Dipivefrin IM 1 mg	123.1	10	0.851	15.63	10	0.632
L-Dipivefrin IM 2 mg	208.2	10	1.35	29.79	5	0.882
L-Dipivefrin SC 0.6mg	83.13	2	0.48	18.25	17	0.602
L-Dipivefrin SC 1 mg	248.2	17	1.17	80.14	10	2.34
L-Dipivefrin SC 2 mg	490.9	17	2.89	197.6	17	5.2

Example 12- Alternative Administration of Dipivefrin

Referring to **Fig. 12A**, a comparison was performed for IM and SC administration of dipivefrin as compared to the Epipen. It was determined that 0.6mg dipivefrin was equivalent to 0.3mg epinephrine. No apparent difference in IM vs SC vs EpiPen.

Referring to **Fig. 12B**, the dose response (epinephrine plasma levels) was obtained as a function of route of administration.

Referring to **Fig. 12C**, dose response (epinephrine plasma levels) as a function of route of administration.

The results show that dose response varies by route of administration. It was found that ~2.5X higher dose response in AUC and Cmax for SC vs. IM. Statistically significant only at 2mg in this data set ($p<0.05$). Equivalent at dose of interest 0.6mg Dipivefrin (equivalent to EpiPen). Effect at dose of EpiPen Jr (0.15mg Epi = 0.3mg Dipivefrin).

Comparable plasma Epinephrine levels were observed after IM and SC administrations of L-Dipivefrin at all doses tested, except 2 mg dose where SC administration showed higher levels of Epinephrine than IM administration. It is expected that a threshold is crossed at 1 mg changing the distribution to the body (depo effect)

Conversion of Dipivefrin to Epinephrine was seen after IM and SC administrations of L-Dipivefrin at all doses tested. Dose dependent effects were seen in the plasma epinephrine

exposure (AUC) after IM and SC administrations of L-Dipivefrin. The onset of epinephrine response was very similar in both IM and SC administrations and comparable to Epipen.

Example 13–In Vitro Human Whole Blood Assay

Referring to **Fig. 13A**, prodrugs AQEP-08, AQEP-09 and AQEP-10 were tested against L-dipivefrin for their resulting epinephrine concentration in human plasma (ng/ml) over time (min). Note: t=0 is not a true zero as there is an approximately 3-5min lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis. Prodrugs AQEP-08, AQEP-09, and AQEP-10 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

Further, as shown in **Fig. 13B**, Prodrugs AQEP-11, AQEP-12, and AQEP-13 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

Referring to **Fig. 13C**, the graph indicates a comprehensive comparison of various prodrugs tested against dipivefrin for resulting epinephrine concentration in human plasma (ng/ml) over time (min). Note: t=0 is not a true zero as there is an approximately 3-5min lag for mixing of the components prior to addition of the stabilizer that stops enzymatic hydrolysis. Prodrugs AQEP-08, AQEP-09, and AQEP-10 showed faster hydrolysis in human blood, compared to L-Dipivefrin.

The results showed prodrug AQEP-04 (with similar ester groups) showed faster hydrolysis in human whole blood, but did not permeate higher than L-Dipivefrin. However, prodrugs AQEP-05, AQEP-08, AQEP-09 and AQEP-10 (with ester groups) showed surprisingly faster hydrolysis in human whole blood while also showing effective permeation.

Prodrugs AQEP-06 or AQEP-07 (with carbamate groups) did not show any hydrolysis in the blood (consistent with literature that carbamate compounds are resistant to plasma esterases, Imai et al, 2012). Prodrug AQEP-03 (with dimethyl amino group) showed minimal hydrolysis and increased gradually at later timepoints.

The data indicates that the a pharmaceutically effective composition can include prodrugs AQEP-05, AQEP-08, AQEP-09, AQEP-10, AQEP-11, AQEP-11, AQEP-12, and AQEP-13 alone or in combination with each other and/or L-Dipivefrin.

Example 14– Prodrug Selection

Referring to **Fig. 14A**, of the various prodrugs tested for permeation and hydrolysis, AQEP-05, AQEP-08, AQEP-09 and AQEP-10. **Fig. 14B** shows the ex vivo permeation data for AQEP-09 compared to L-dipivefrin. **Fig. 14C** and **Fig. 14D** show the ex vivo permeation data for AQEP-09 compared to L-dipivefrin and varying polysaccharide or starch content. Higher permeation was exhibited with formulations containing pullulan (**Fig. 14C**). **Fig. 14D** shows the ex vivo permeation data for AQEP-09 formulations compared to L-dipivefrin and and the effect of starch in the AQEP-09 formulation.

Example 15 – Hydrolysis Comparison

Referring to **Fig. 15**, the graph indicates a study comparing in vitro human whole blood hydrolysis data for those prodrugs having acceptable levels of permeation.

Example 16 – Carbon Length Effect on Permeation

Conventionally, it would be expected that increasing lipophilicity would increase permeation of a compound based in increasing ability to cross a transmucosal barriers including surface epithelial cells, intercellular space, and a basement membrane.

Referring to **Fig. 16**, the graph indicates the results from a study of flux vs. carbon chain length. An unexpected result was obtained in that increasing lipophilicity did not result in enhanced permeation. The prodrug AQEP-11 having 5 carbon straight chain was tested, and unexpectedly permeation dropped. Thus, permeation was not always enhanced with increased lipophilicity.

Example 17 – Effect of NaF

Referring to **Fig. 17**, the graph indicates the effect of sodium fluoride on drug absorption. In this example, addition of NaF to a AQEP-09 formulation (squares) increased the absorption of AQEP-09 relative to compositions that did not include NaF (triangles).

Example 18 – Use of combination of two prodrugs

Referring to Fig.18A, the graph demonstrates the utility of using two prodrugs in a film formulation and and the epinephrine levels in minipigs. Early onset of epinephrine levels was seen when a combination of dipivefrin and AQEP-09 was used presumabably due to the faster conversion of AQEP-09 in the blood. Fig 18B demonstrates the utility of using a combination of AQEP-14 (monopivaloyl epinephrine) and dipivefrin. The epinephrine levels were higher compared to film formulation using AQEP-14 alone.

Other embodiments are within the scope of the following claims.

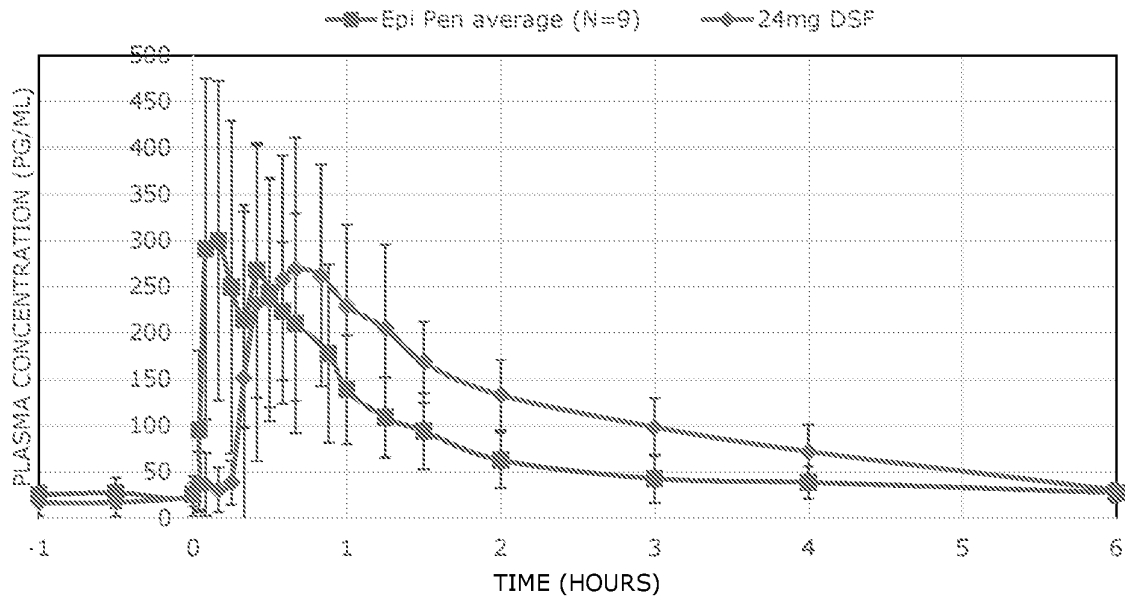

Epi Pen average (N=9)
24mg DSF
PLASMA CONCENTRATION (PG/ML)
500
450
400
350
300
250
200
150
100
50
0
-1
0
1
2
3
4
5
6
TIME (HOURS)

Fig. 1A

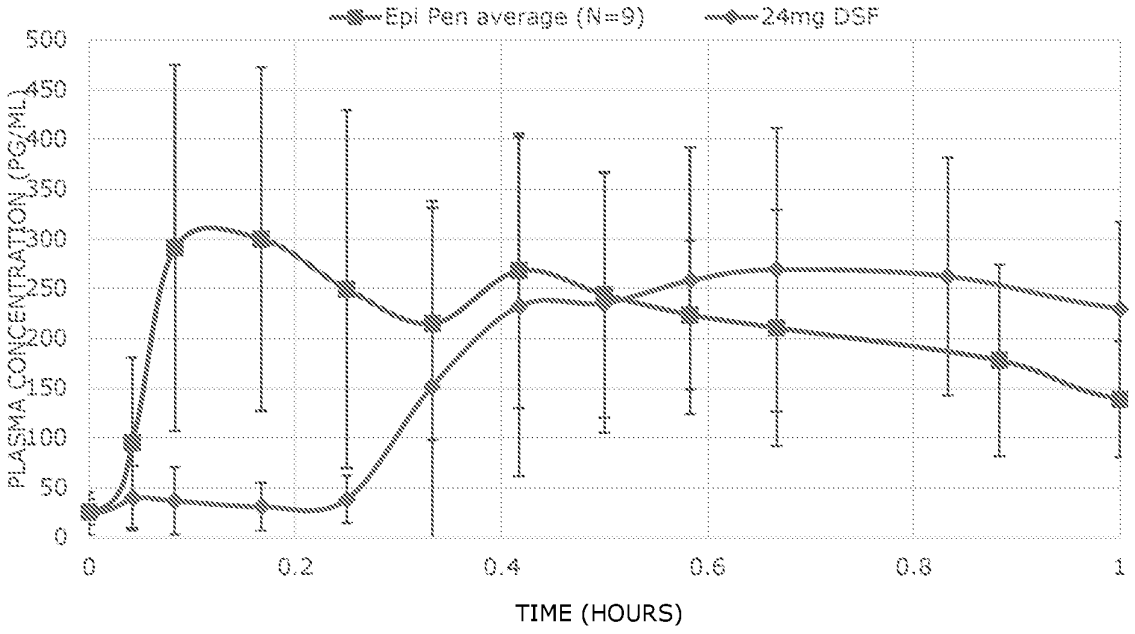

Epi Pen average (N=9)
24mg DSF
PLASMA CONCENTRATION (PG/ML)
500
450
400
350
300
250
200
150
100
50
0
0
0.2
0.4
0.6
0.8
1
TIME (HOURS)

Fig. 1B

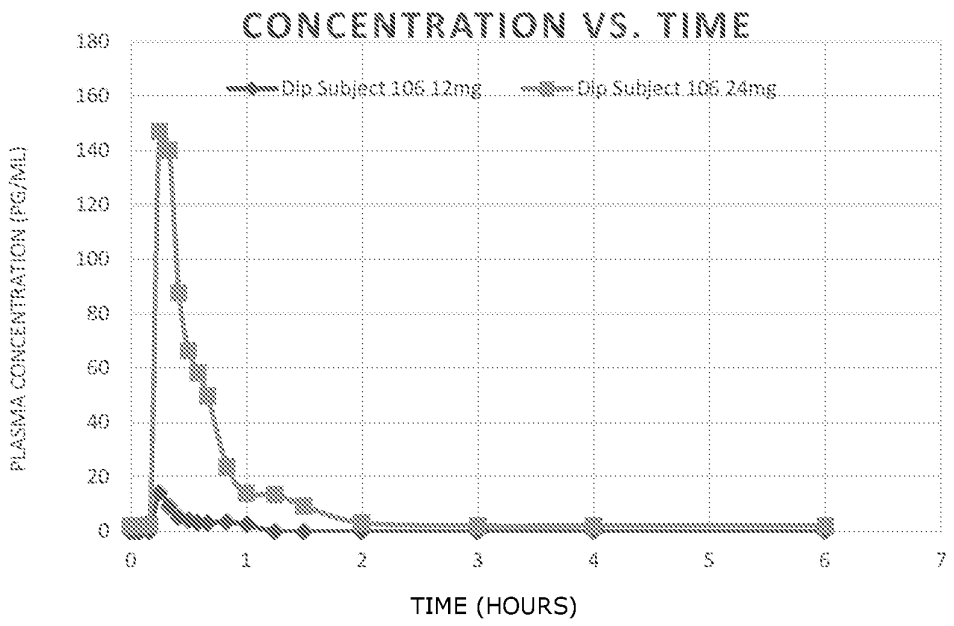

CONCENTRATION VS. TIME
Dip Subject 106 12mg
Dip Subject 106 24mg
PLASMA CONCENTRATION (PG/ML)
TIME (HOURS)
0
20
40
60
80
100
120
140
160
180
0
1
2
3
4
5
6
7

Fig. 2A

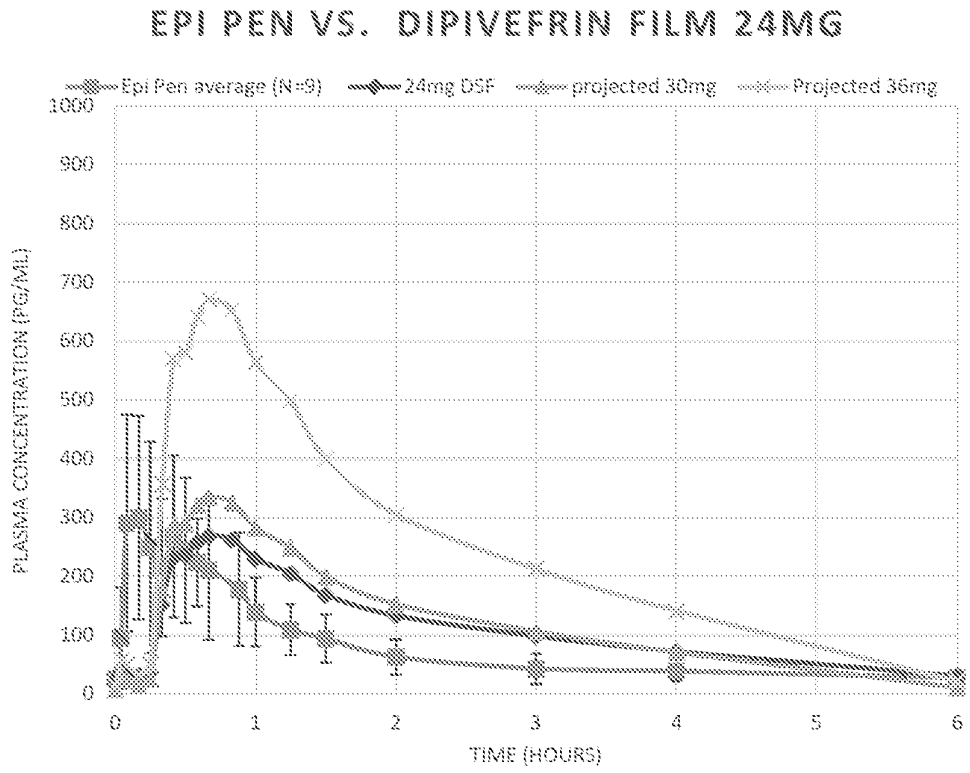

EPI PEN VS. DIPIVEFRIN FILM 24MG
Epi Pen average (N=9)
24mg DSF
projected 30mg
Projected 36mg
PLASMA CONCENTRATION (PG/ML)
TIME (HOURS)
0
100
200
300
400
500
600
700
800
900
1000
0
1
2
3
4
5
6

Fig. 2B

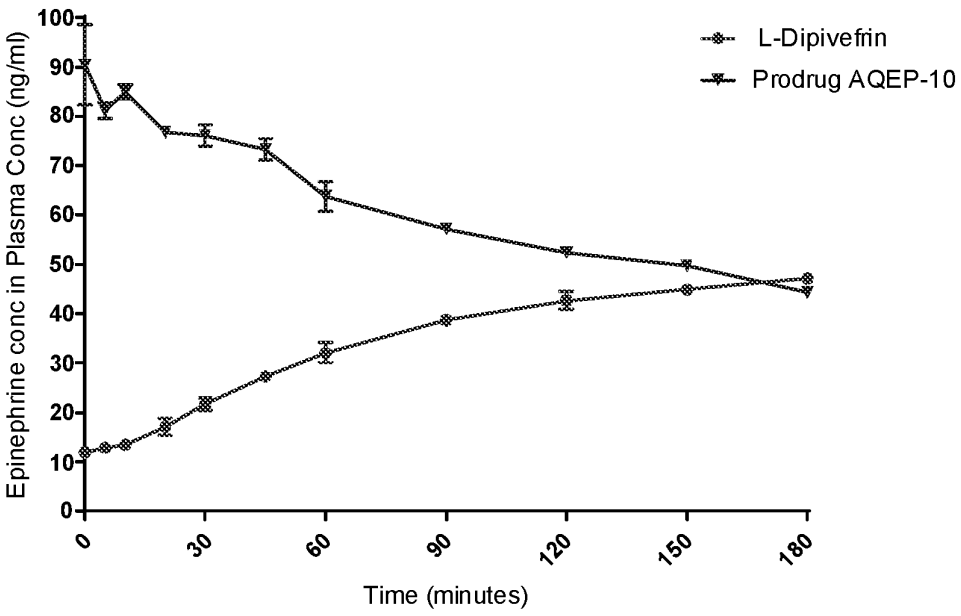

L-Dipivefrin
Prodrug AQEP-10
Epinephrine conc in Plasma Conc (ng/ml)
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
Time (minutes)

Fig. 3A

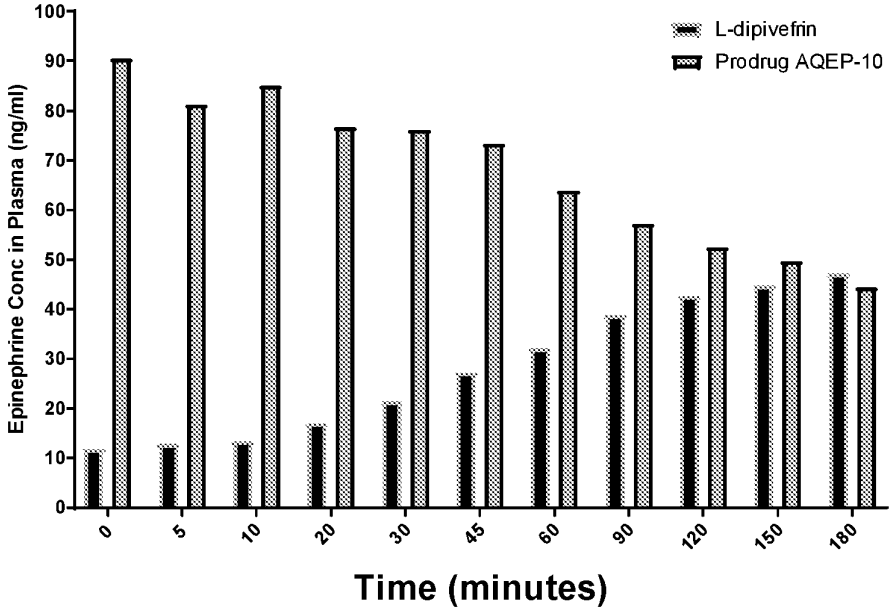

L-dipivefrin
Prodrug AQEP-10
Epinephrine Conc in Plasma (ng/ml)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
20
30
45
60
90
120
150
180
Time (minutes)

Fig. 3B

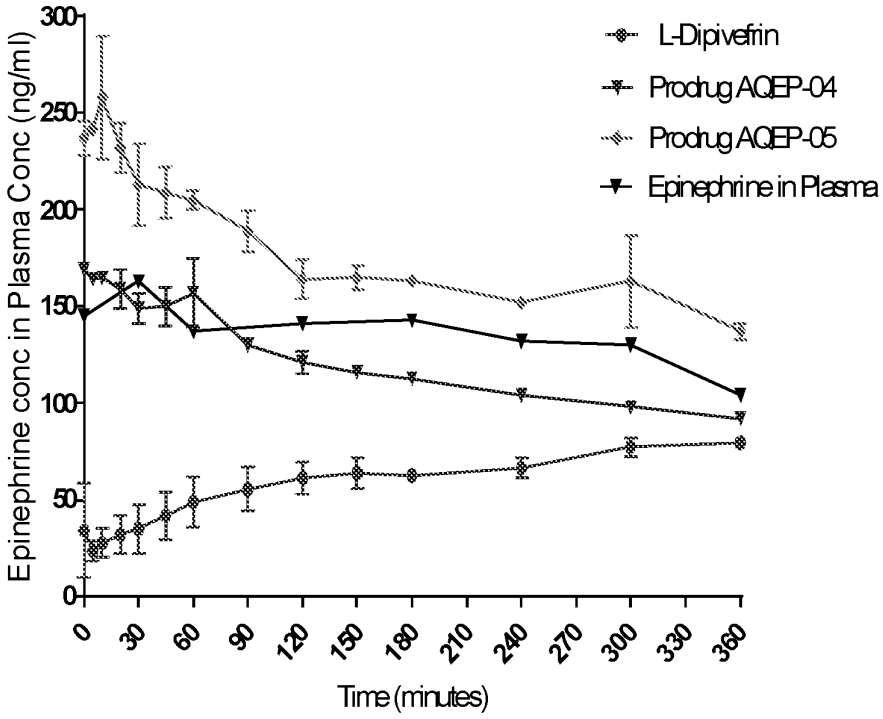

L-Dipivefrin
Prodrug AQEP-04
Prodrug AQEP-05
Epinephrine in Plasma
Epinephrine conc in Plasma Conc (ng/ml)
300
250
200
150
100
50
0
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (minutes)

Fig. 4

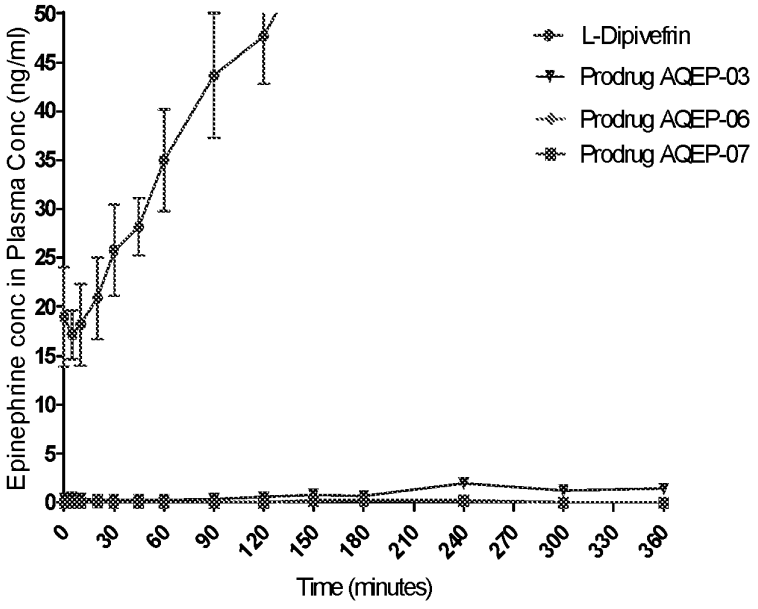

L-Dipivefrin
Prodrug AQEP-03
Prodrug AQEP-06
Prodrug AQEP-07
Epinephrine conc in Plasma Conc (ng/ml)
50
45
40
35
30
25
20
15
10
5
0
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (minutes)

Fig. 5

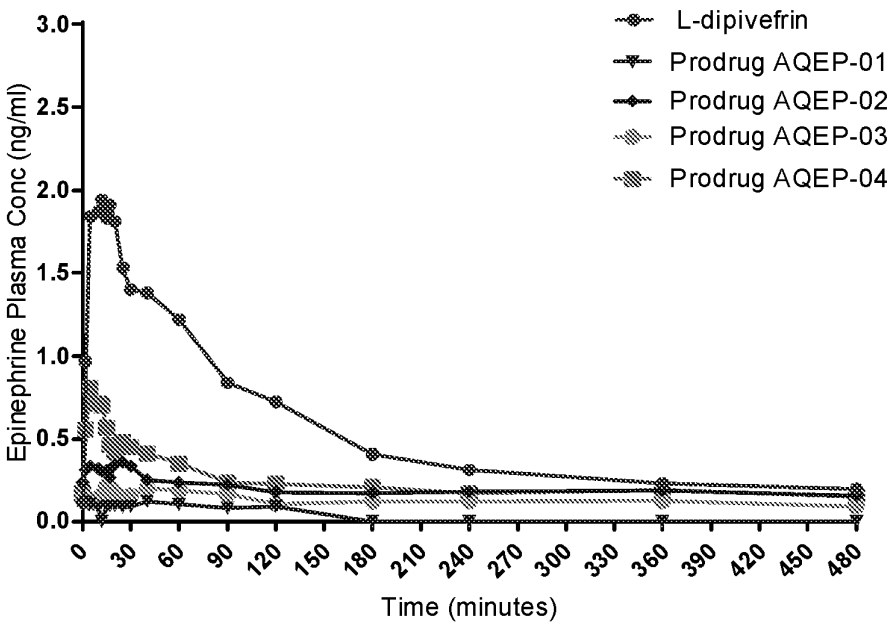

L-dipivefrin
Prodrug AQEP-01
Prodrug AQEP-02
Prodrug AQEP-03
Prodrug AQEP-04
Epinephrine Plasma Conc (ng/ml)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
Time (minutes)

Fig. 6A

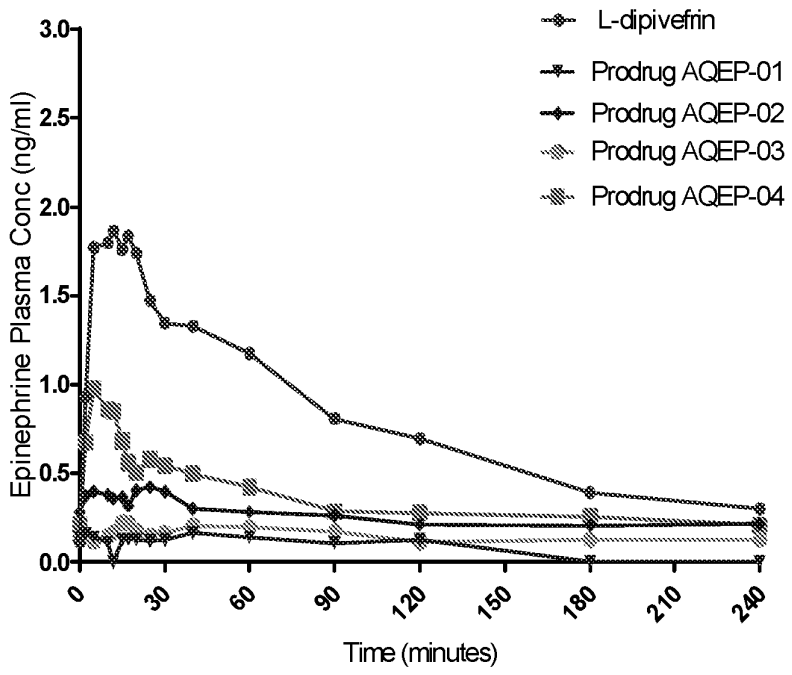

L-dipivefrin
Prodrug AQEP-01
Prodrug AQEP-02
Prodrug AQEP-03
Prodrug AQEP-04
Epinephrine Plasma Conc (ng/ml)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
30
60
90
120
150
180
210
240
Time (minutes)

Fig. 6B

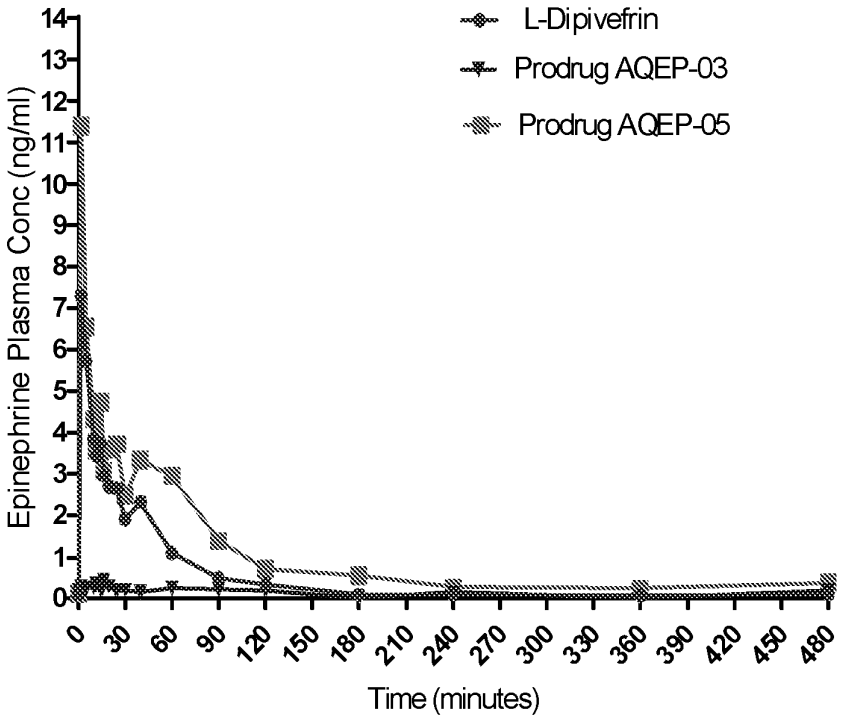

L-Dipivefrin
Prodrug AQEP-03
Prodrug AQEP-05
Epinephrine Plasma Conc (ng/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
Time (minutes)

Fig. 7A

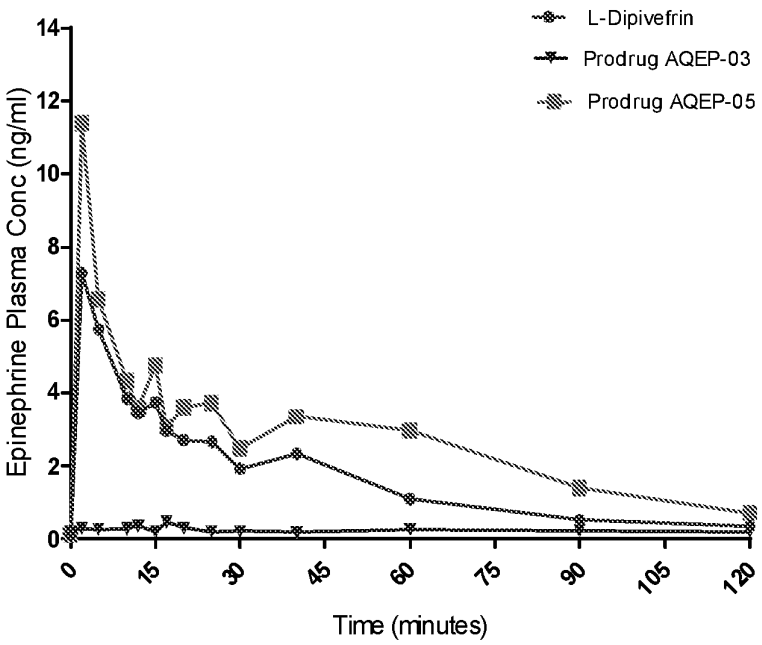

L-Dipivefrin
Prodrug AQEP-03
Prodrug AQEP-05
Epinephrine Plasma Conc (ng/ml)
0
2
4
6
8
10
12
14
0
15
30
45
60
75
90
105
120
Time (minutes)

Fig. 7B

Average Epinephrine Plasma Concentration vs Time

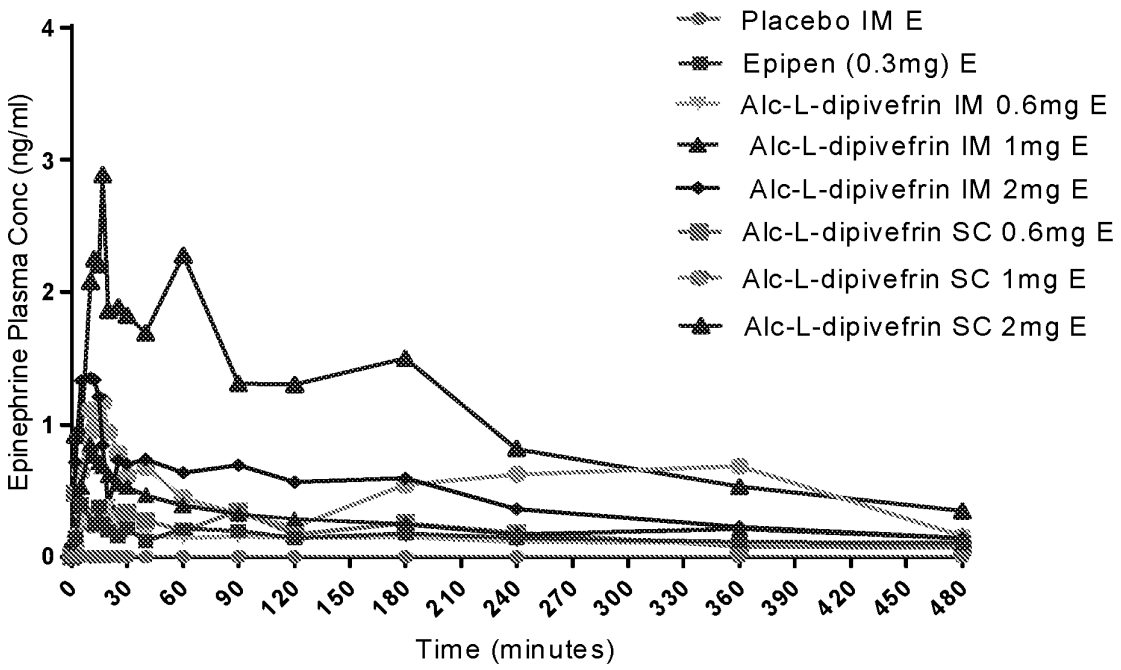


Fig. 8A

IM administration-Average Epinephrine Plasma Concentration

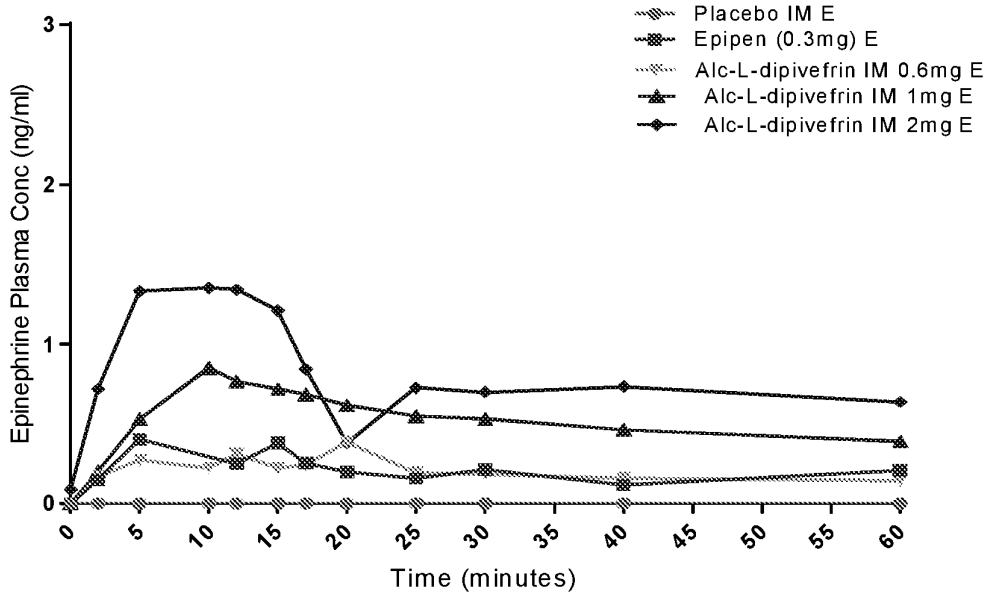


Fig. 8B

SC administration-Average Epinephrine Plasma Concentration

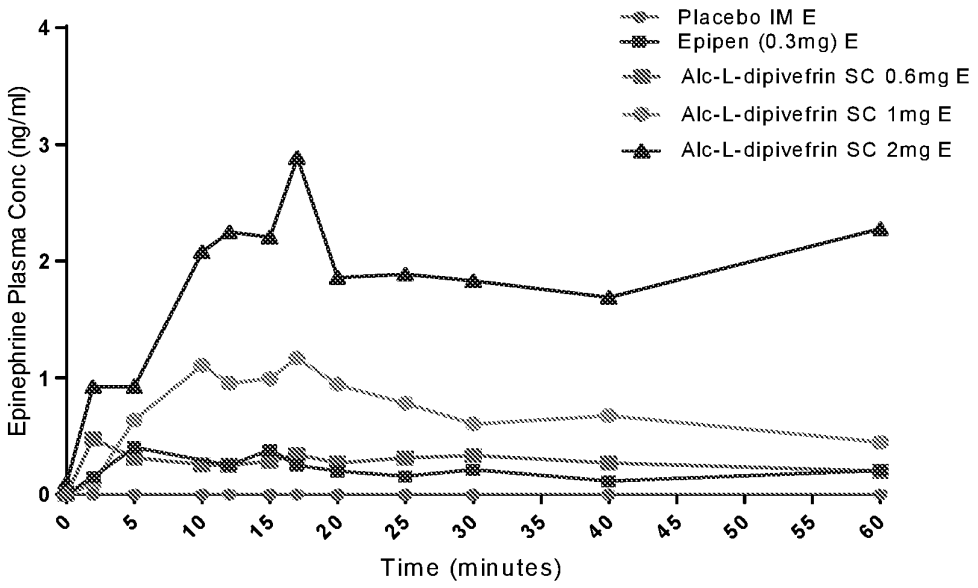


Fig. 8C

Comparison of IM & SC administration L-dipivefrin 0.6 mg-Average Epinephrine Plasma Concentration

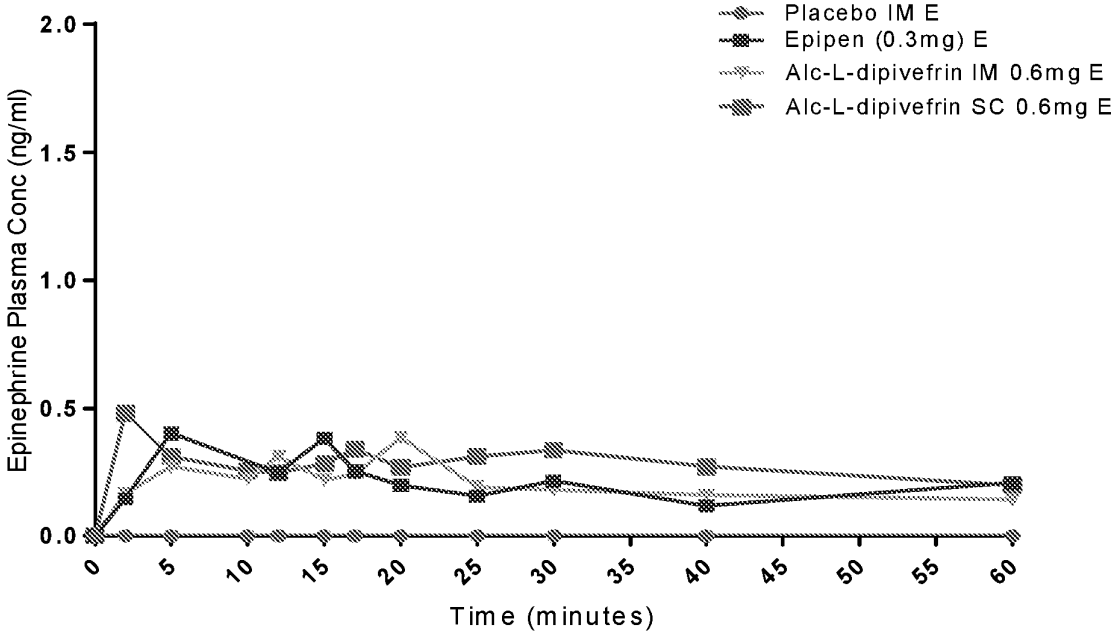


Fig. 9A

Comparison of IM & SC administration L-dipivefrin 1 mg-Average Epinephrine Plasma Concentration

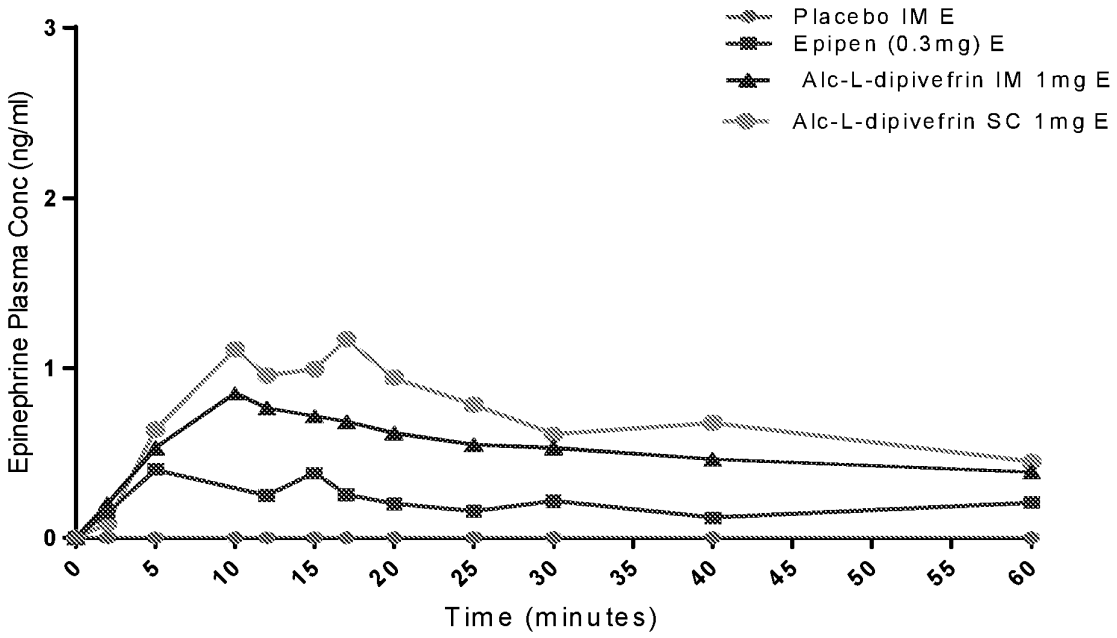


Fig. 9B

Comparison of IM & SC administration L-dipivefrin 2 mg-Average Epinephrine Plasma Concentration

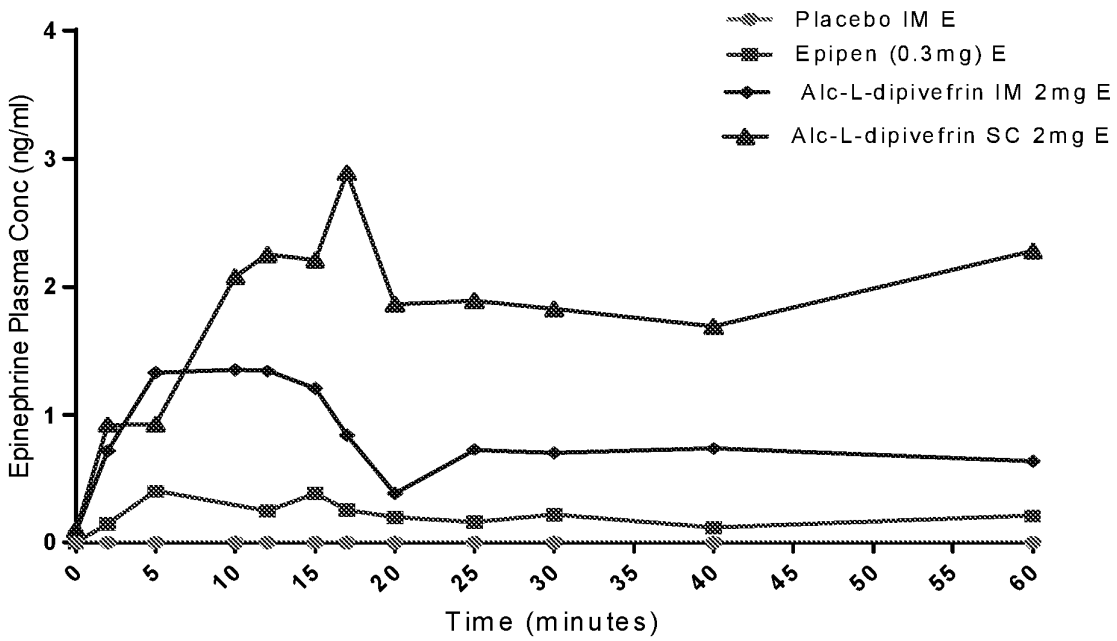


Fig. 9C

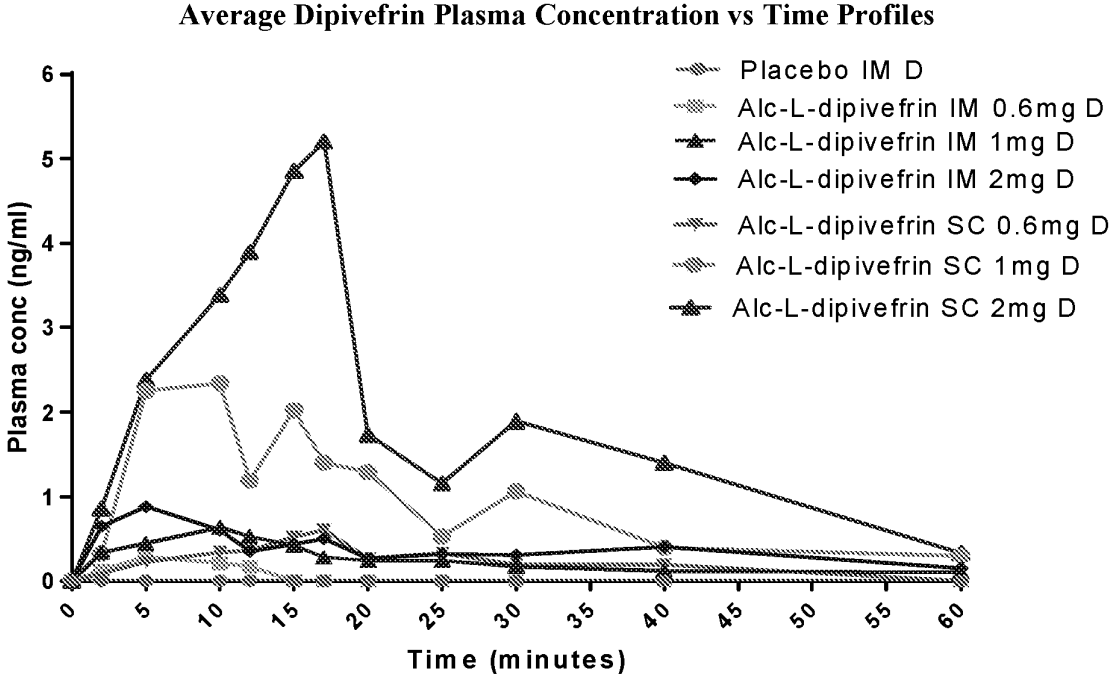


Fig. 10

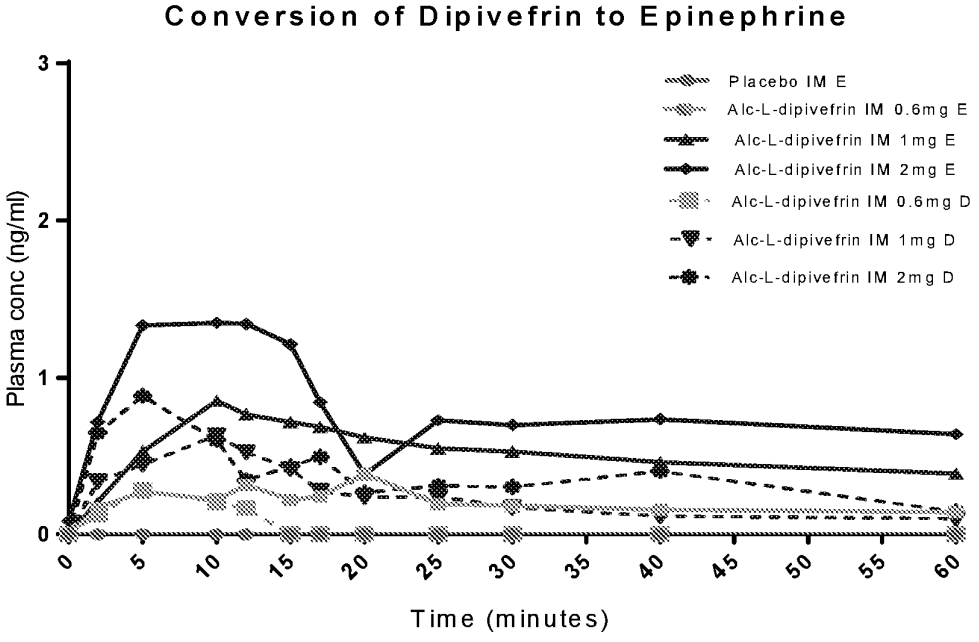


Fig. 11A

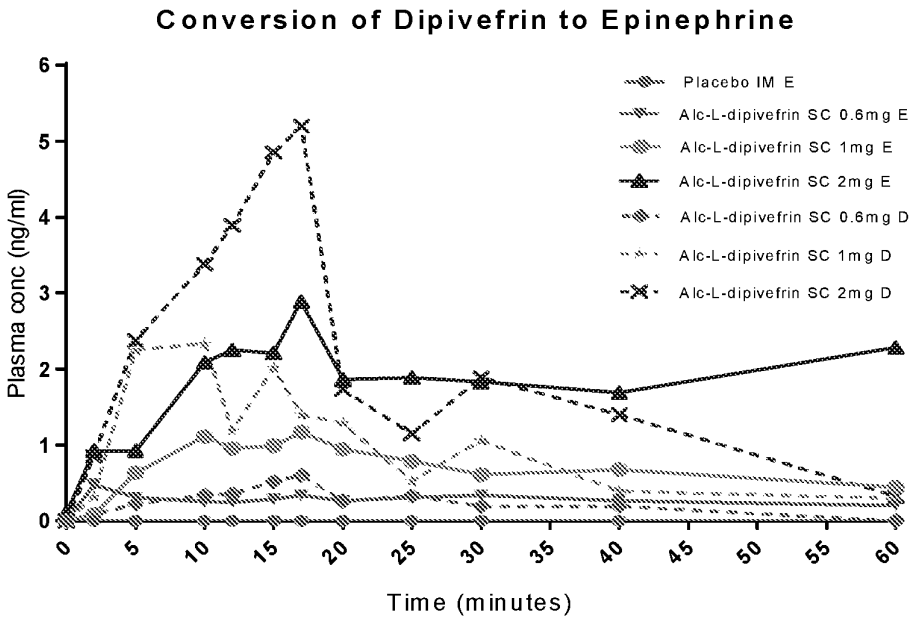


Fig. 11B

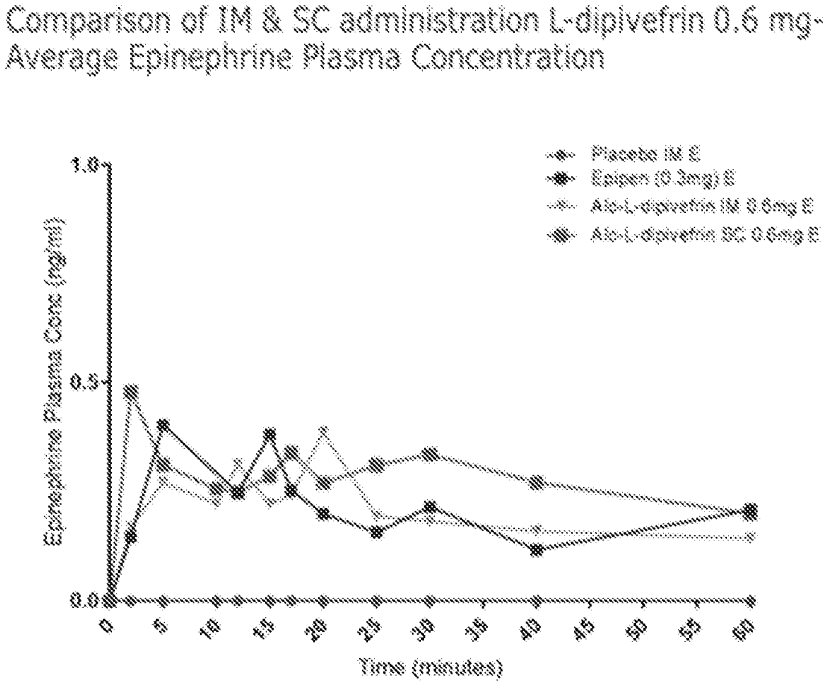


Fig. 12A

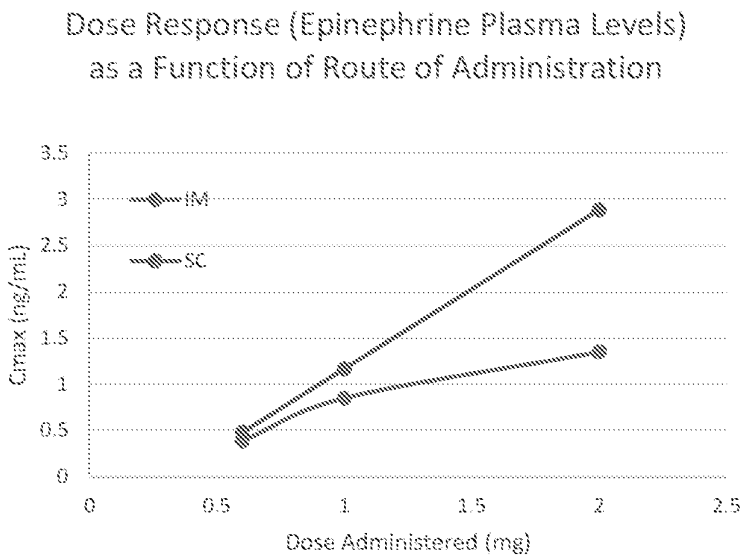


Fig. 12B

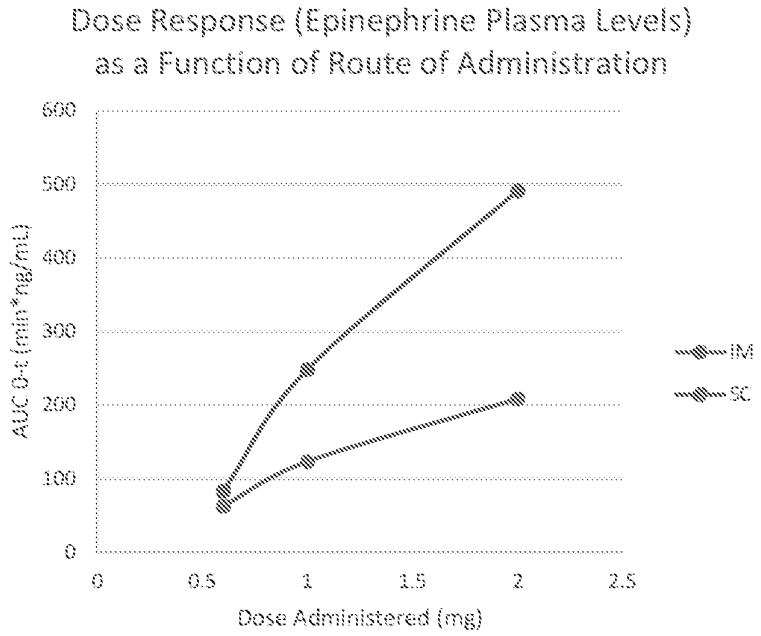


Fig. 12C

Epinephrine Concentration in Plasma

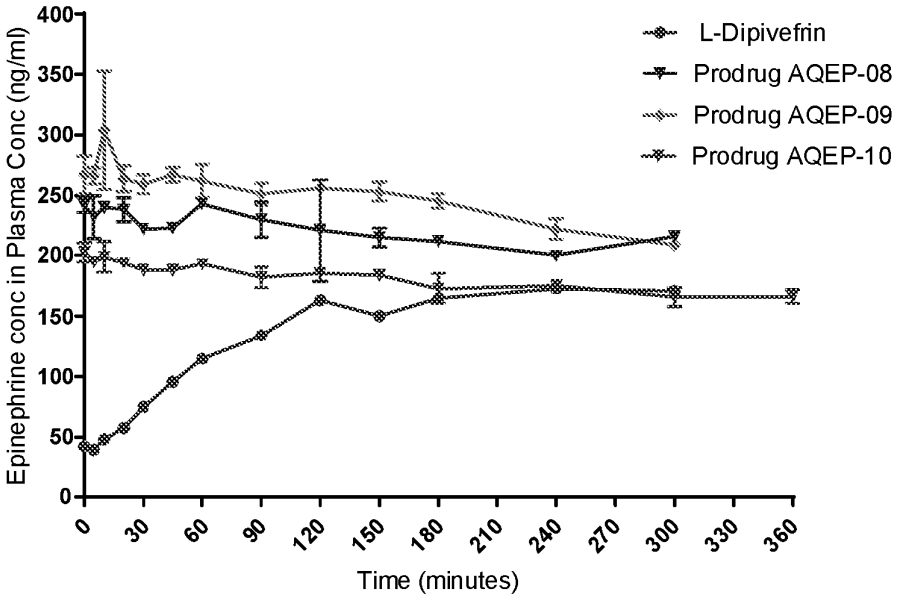


Fig. 13A

Epinephrine Concentration in Plasma

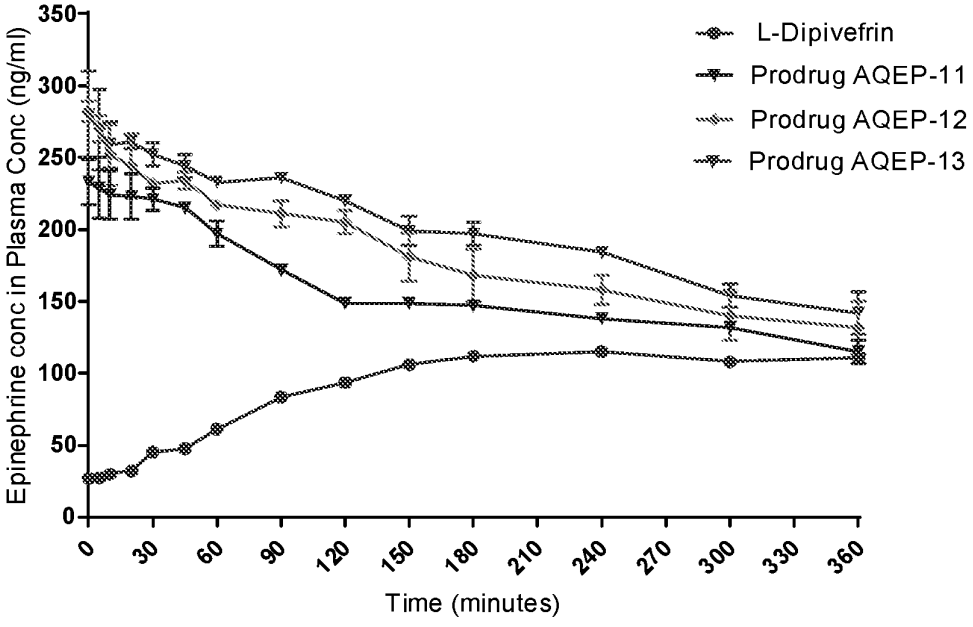


Fig. 13B

Epinephrine Concentration in Plasma

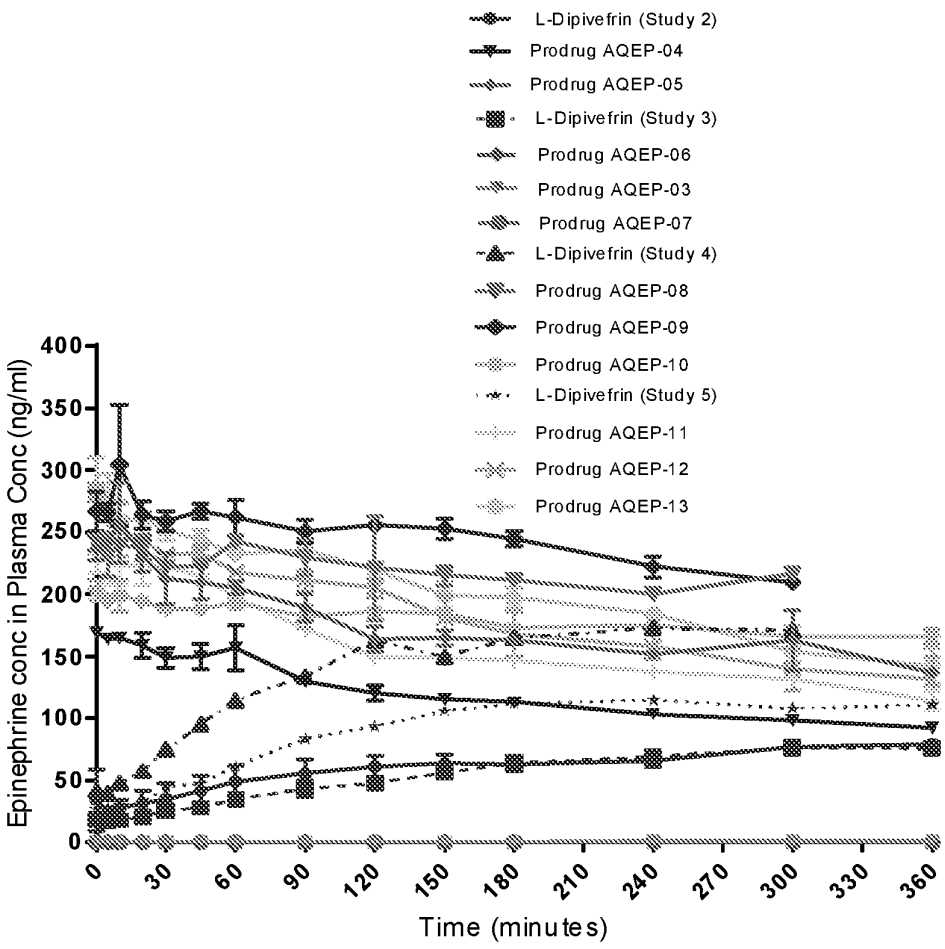


Fig. 13C

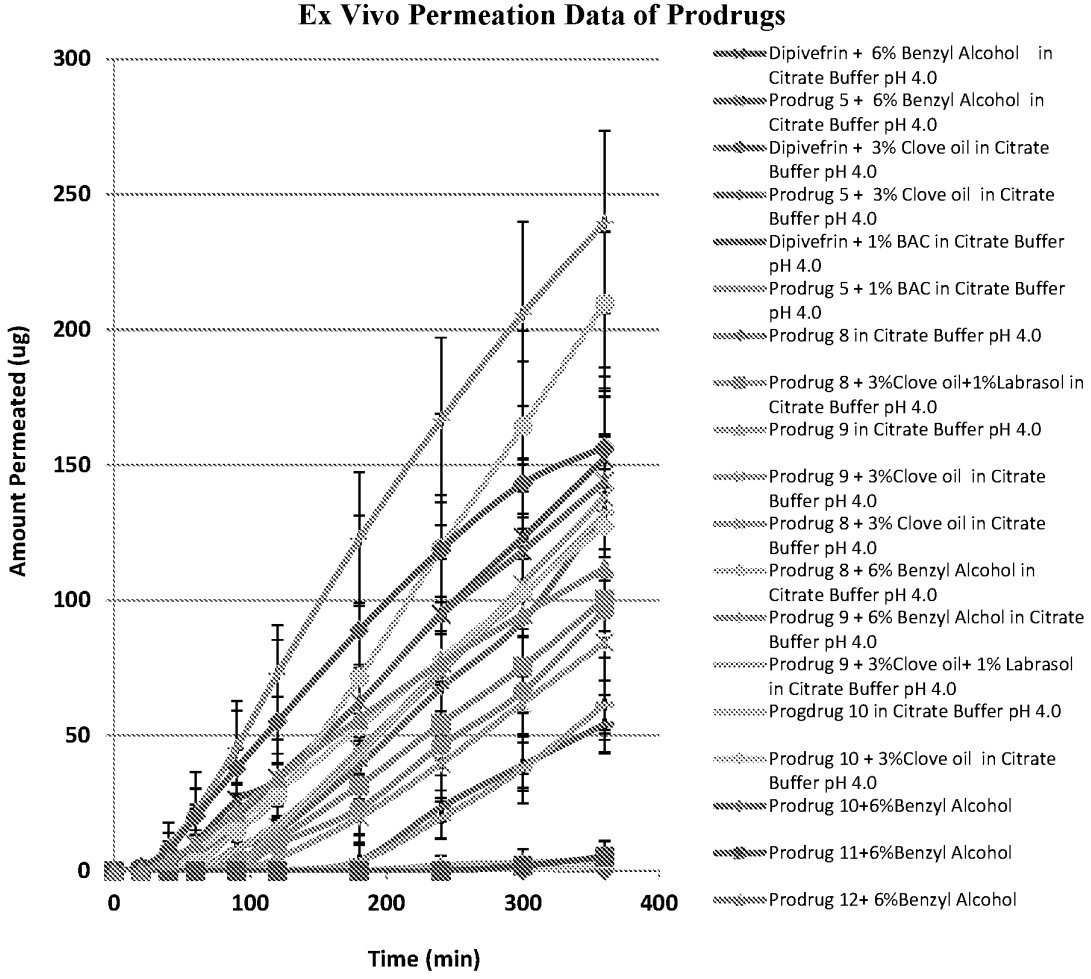

Ex Vivo Permeation Data of Prodrugs
Amount Permeated (ug)
Time (min)
0
50
100
150
200
250
300
0
100
200
300
400
Dipivefrin + 6% Benzyl Alcohol in Citrate Buffer pH 4.0
Prodrug 5 + 6% Benzyl Alcohol in Citrate Buffer pH 4.0
Dipivefrin + 3% Clove oil in Citrate Buffer pH 4.0
Prodrug 5 + 3% Clove oil in Citrate Buffer pH 4.0
Dipivefrin + 1% BAC in Citrate Buffer pH 4.0
Prodrug 5 + 1% BAC in Citrate Buffer pH 4.0
Prodrug 8 in Citrate Buffer pH 4.0
Prodrug 8 + 3%Clove oil+1%Labrasol in Citrate Buffer pH 4.0
Prodrug 9 in Citrate Buffer pH 4.0
Prodrug 9 + 3%Clove oil in Citrate Buffer pH 4.0
Prodrug 8 + 3% Clove oil in Citrate Buffer pH 4.0
Prodrug 8 + 6% Benzyl Alcohol in Citrate Buffer pH 4.0
Prodrug 9 + 6% Benzyl Alchol in Citrate Buffer pH 4.0
Prodrug 9 + 3%Clove oil+ 1% Labrasol in Citrate Buffer pH 4.0
Progdrug 10 in Citrate Buffer pH 4.0
Prodrug 10 + 3%Clove oil in Citrate Buffer pH 4.0
Prodrug 10+6%Benzyl Alcohol
Prodrug 11+6%Benzyl Alcohol
Prodrug 12+ 6%Benzyl Alcohol

Fig. 14A

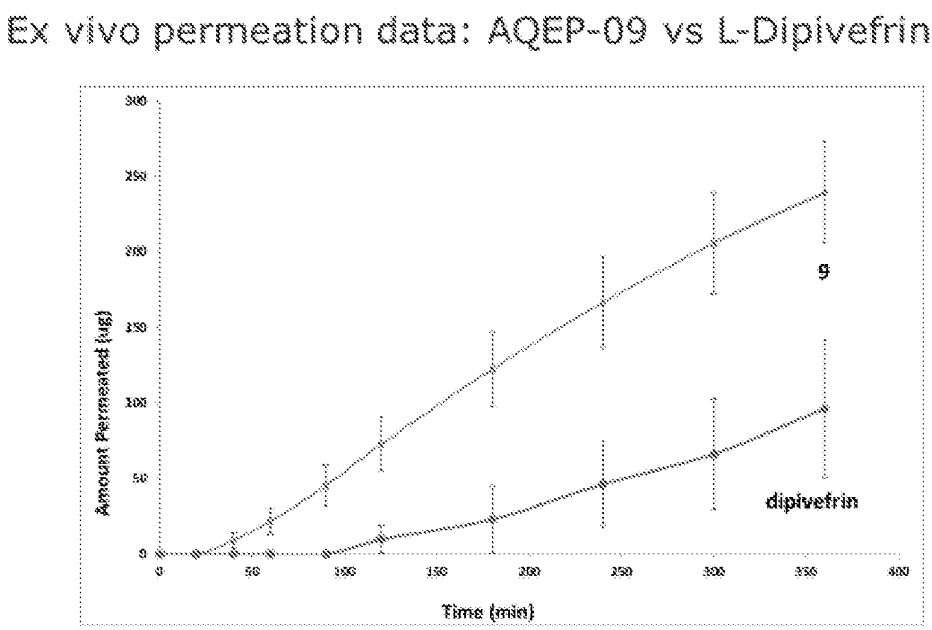

Ex vivo permeation data: AQEP-09 vs L-Dipivefrin
Amount Permeated (ug)
Time (min)
9
dipivefrin
Prodrug AQEP-09 has faster onset and better absorption than Dipivefrin

Fig. 14B

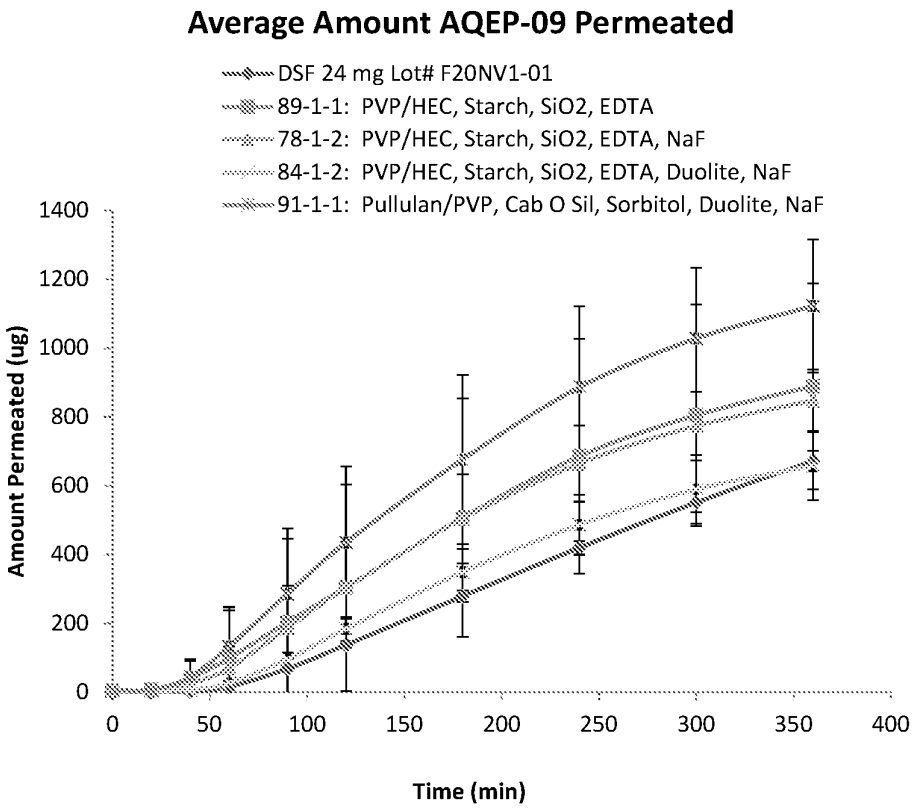

Average Amount AQEP-09 Permeated
DSF 24 mg Lot# F20NV1-01
89-1-1: PVP/HEC, Starch, SiO2, EDTA
78-1-2: PVP/HEC, Starch, SiO2, EDTA, NaF
84-1-2: PVP/HEC, Starch, SiO2, EDTA, Duolite, NaF
91-1-1: Pullulan/PVP, Cab O Sil, Sorbitol, Duolite, NaF
Amount Permeated (ug)
1400
1200
1000
800
600
400
200
0
0
50
100
150
200
250
300
350
400
Time (min)

Fig. 14C

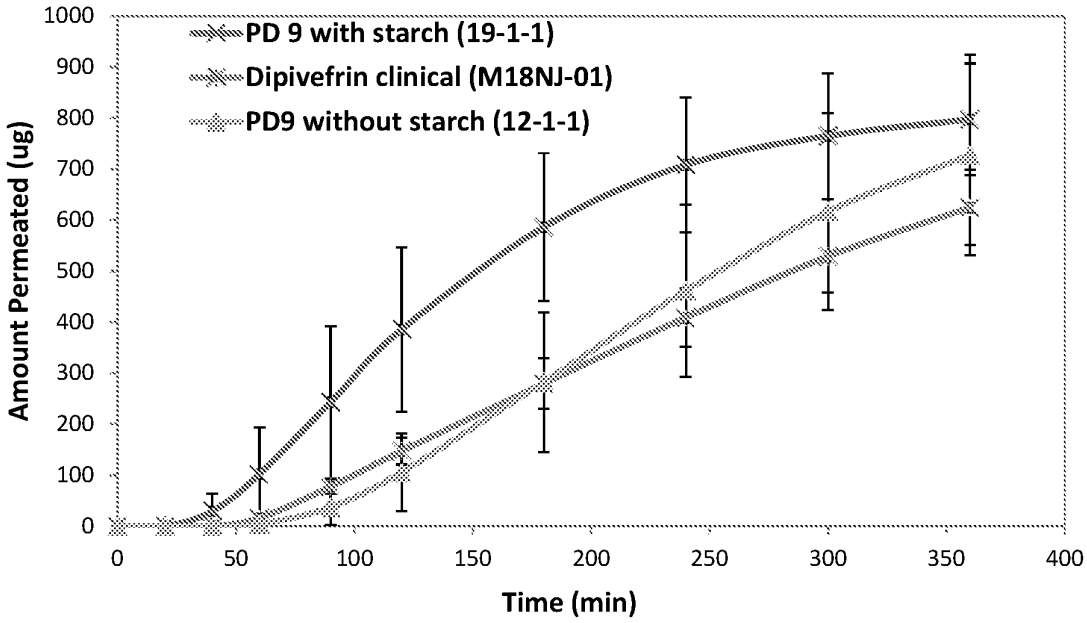

PD 9 with starch (19-1-1)
Dipivefrin clinical (M18NJ-01)
PD9 without starch (12-1-1)
Amount Permeated (ug)
Time (min)
0
100
200
300
400
500
600
700
800
900
1000
0
50
100
150
200
250
300
350
400

Fig. 14D

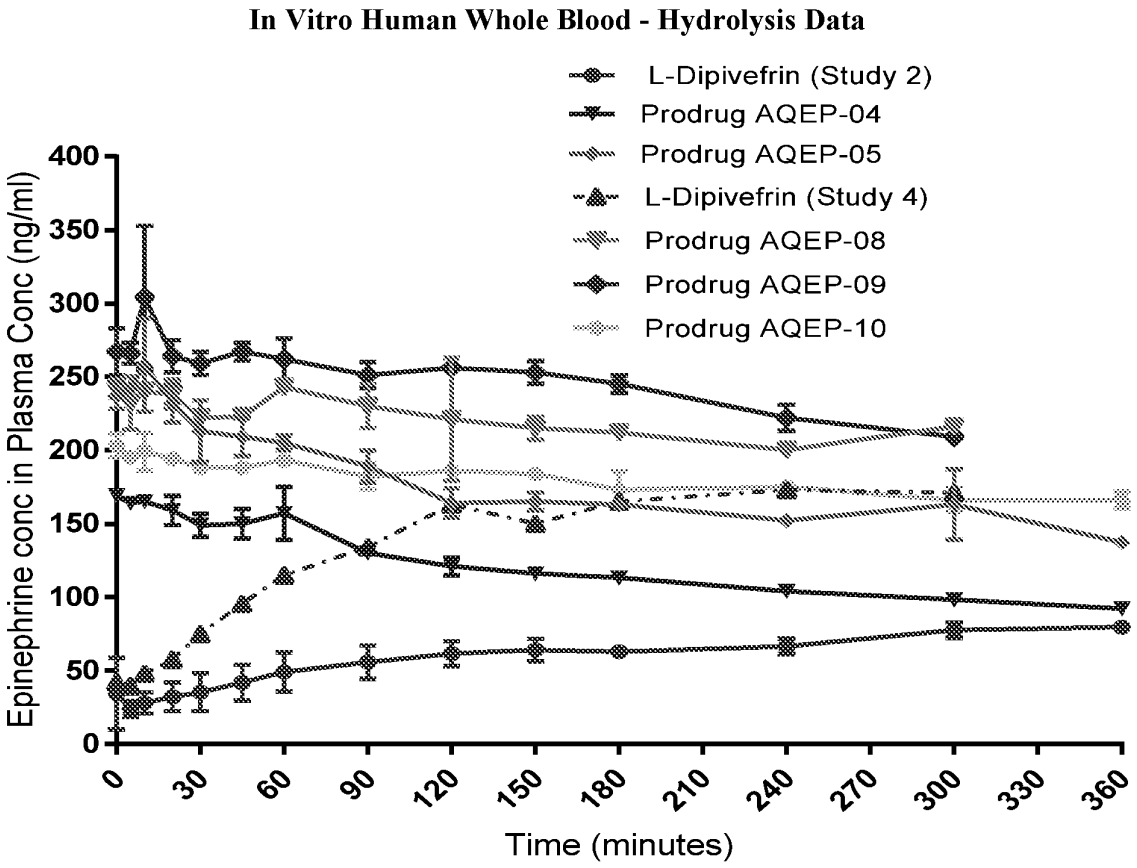

In Vitro Human Whole Blood - Hydrolysis Data
L-Dipivefrin (Study 2)
Prodrug AQEP-04
Prodrug AQEP-05
L-Dipivefrin (Study 4)
Prodrug AQEP-08
Prodrug AQEP-09
Prodrug AQEP-10
Epinephrine conc in Plasma Conc (ng/ml)
400
350
300
250
200
150
100
50
0
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (minutes)

Fig. 15

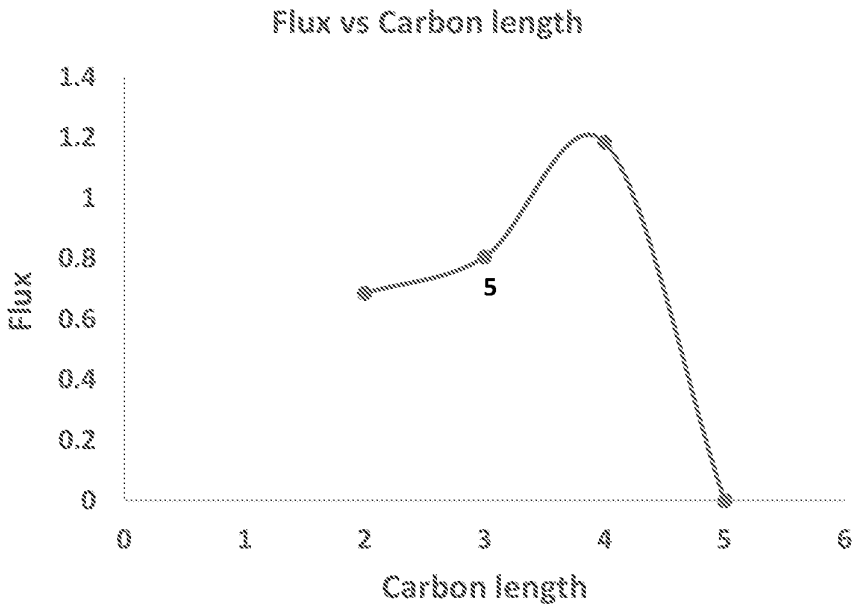

Flux vs Carbon length
Flux
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
Carbon length
5

Fig. 16

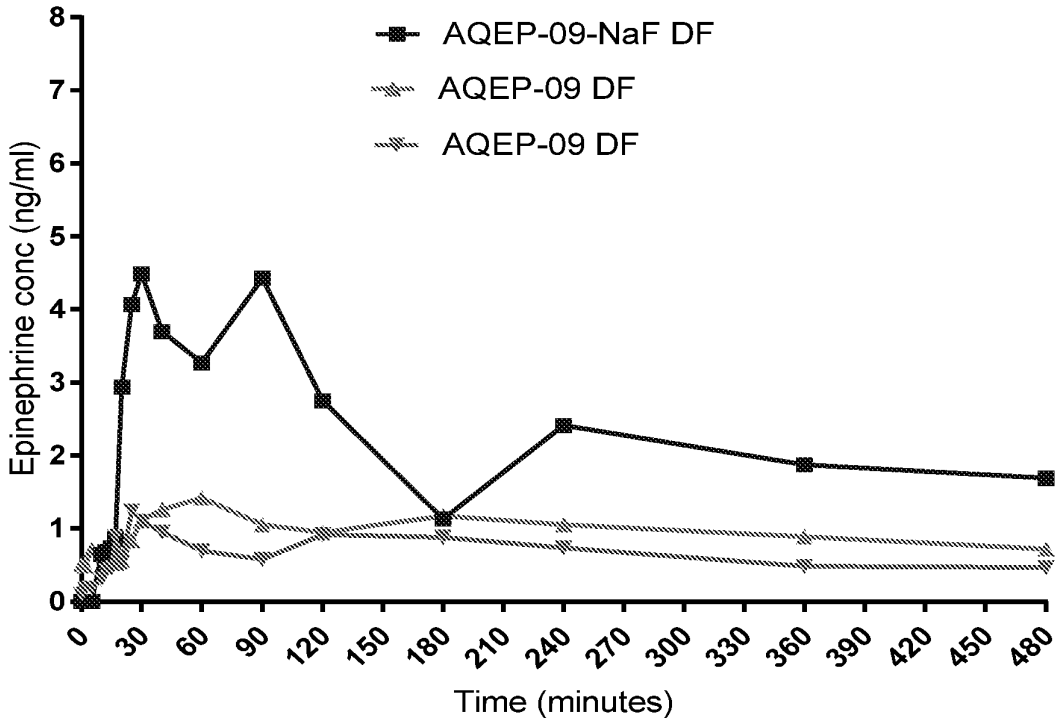

AQEP-09-NaF DF
AQEP-09 DF
AQEP-09 DF
Epinephrine conc (ng/ml)
8
7
6
5
4
3
2
1
0
0
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
Time (minutes)

Fig. 17

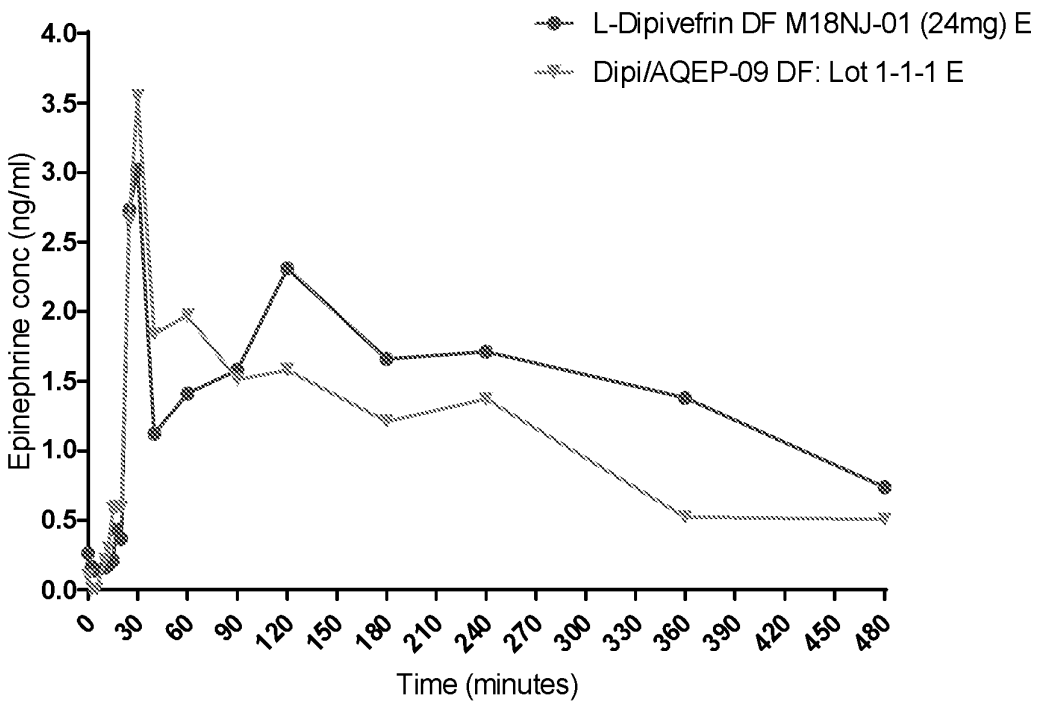


Fig. 18A

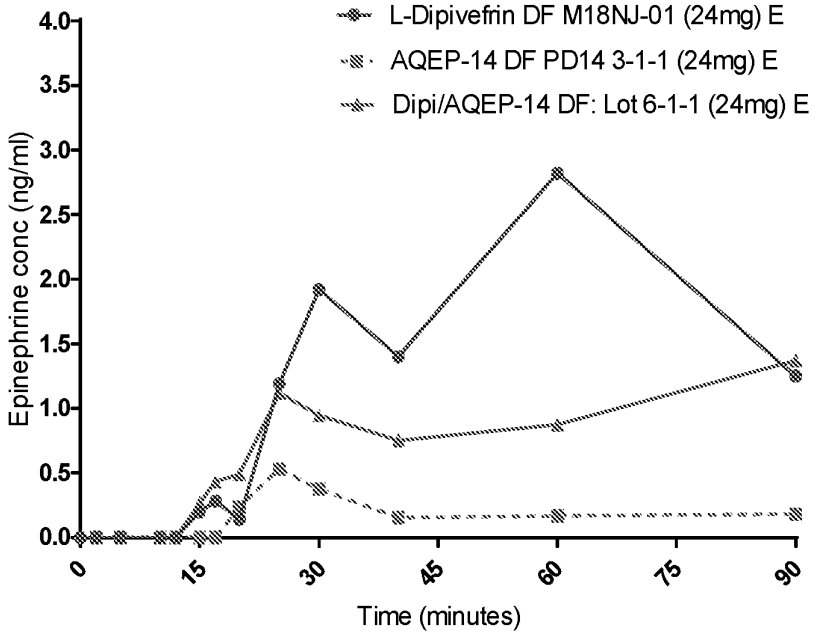


Fig. 18B

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	17086409

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance
1	11021437	437 patent shows the same subject matter set out in claims 1, 20, 21, 22, 23, 24, 25, 60-62 of the 511 patent ref is made to para 511 of patent 437. AQEP-02 is covered in structures 2A, 6I, 5G", 4F, 4E in Almoazen AQEP-03 is covered in structures in claim 1 in Almoazen AQEP-04 is covered in structures in claim 1 in Almoazen AQEP-05 is covered in structures in claim 1 in Almoazen AQEP-08 is covered in structures in claim 1 in Almoazen AQEP-09 is covered in structures in claim 2 and 3 in Almoazen AQEP-10 is covered in claim 2 and 3 in Almoazen AQEP-11 is covered in claim 1 in Almoazen AQEP-13 is covered in claim 1 and 2 in Almoazen AQEP-15 is covered in Bodor structure I and claim 1 and 7
2	4145441	441 patent shows similar subject matter set out in claims 1,60 and 61 of the 511 patent ref is made to para 511 of patent 441. AQEP-01 is covered in Bodor structure I AQEP-06 is covered in Bodor structure I AQEP-07 is covered in Bodor structure I AQEP-12 is covered in Bodor structure I AQEP-14 is covered in Bodor structure I and claim 1 and 7 AQEP-15 is covered in Bodor structure I and claim 1 and 7
3	3809714	AQEP-10 is covered in Hussain AQEP-13 is covered in Hussain

U.S. PATENT APPLICATION PUBLICATION		
Cite No	**Publication Number**	**Concise Description of Relevance**

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**

1	Almoazen et. Al. published an article about incorporating epinephrine in a fast-dissolving film Title: Development of fast dissolving film of epinephrine hydrochloride as a potential treatment for anaphylactic in pediatrics Journal of Pharmaceutical Development and Technology, Published online on January 6, 2016, vol 22:8, p 1012-1016Published online on January 6, 2016, vol 22:8, p 1012-1016. https://doi.org/10.3109/10837450.2015.1131715	Shows the use of incorporating epinephrine in a fast-dissolving film as a potential treatment for anaphylactic in pediatrics

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	17086409

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor
1	3809714	B2		
2	4145441	B2	1979-03-20	Bodor
3	11021437	B2	2021-06-01	Hassan Almoazen

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	17086409

Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]
1	Almoazen et. Al. published an article about incorporating epinephrine in a fast-dissolving film Title: Development of fast dissolving film of epinephrine hydrochloride as a potential treatment for anaphylactic in pediatrics Journal of Pharmaceutical Development and Technology, Published online on January 6, 2016, vol 22:8, p 1012-1016Published online on January 6, 2016, vol 22:8, p 1012-1016. https://doi.org/10.3109/10837450.2015.1131715	☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☒ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☐ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	17086409

Signature	/susan fentress/		
Name/Print	susan fentress	Registration Number (if applicable)	31327

Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/086,409	11/01/2020	Alexander Mark Schobel	270712/ AQU-039US/480541	1047

138831 7590 09/29/2022

Honigman LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/29/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

THuschilt@honigman.com
hfox@honigman.com
patent@honigman.com

Office Action Summary	Application No. 17/086,409	Applicant(s) Schobel et al.	
	Examiner SAN MING R HUI	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-78 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 1-78 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 37, drawn to a method of treating spectrum of anaphylaxis, classified in A61K 31/24.

II. Claim 38, drawn to a method of treating allergic reaction, classified in A61K 31/24.

III. Claim 39, drawn to a method of treating cardiac abnormality, classified in A61K 31/24.

IV. Claim 40, drawn to a method of treating pulmonary abnormality, classified in A61K 31/24.

Claims 1-36, 41-78 link(s) inventions I, II, III, and IV. The restriction requirement among the linked inventions is **subject to** the nonallowance of the linking claim(s), claim 1-36, 41-78. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the

claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are independent or distinct, each from the other because:

Inventions I-IV are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have different functions. The identified inventions function to treat different and distinct conditions. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

The inventions relate to different areas of technical endeavor. A search for each invention will require searches of different areas of non-patent literature, different patent classes and subclasses, and different commercial database resources. Furthermore, it does not appear likely that prior art found to be relevant to the patentability of one group of claims will also be relevant to the patentability of the other groups of claims. Finally, each group of claims presents its own unique questions of enablement, and therefore evaluating the independent factors of enablement for each group together presents an examination burden.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

Election of Species

Claim(s) 1-78 is/are generic to the following disclosed patentably distinct species: various combinations of a prodrug and a penetration enhancer. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed combination of a prodrug and a penetration enhancing agent, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

Due to the structural dissimilarities among the species within combinations, searching for all of the distinct combinations would impose undue burden to the examiners.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species** or grouping of patentably indistinct species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN MING R HUI whose telephone number is (571)272-0626. The examiner can normally be reached Mon - Fri 9:30-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached on 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAN MING R HUI/
Primary Examiner, Art Unit 1627

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Alexander Mark Schobel et al	Art Unit :	1627
Serial No. :	17/086,409	Examiner :	HUI, SAN MING R
Filing Date:	November 1, 2020	Confirmation No.:	1047
Title :	PRODRUG COMPOSITIONS AND METHODS OF TREATMENT		

United States Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria VA 22314

RESPONSE TO RESTRICTION REQUIREMENT

In response to the Restriction Requirement mailed September 29, 2022 ("Restriction Requirement"), Applicant submits the following amendments and remarks.

Amendments to the claims

The following listing of claims replaces all previous listings of claims.

1. (Currently Amended) A method of treating an allergic reaction ~~medical condition~~ in a human subject comprising:

administering a composition including a prodrug and a permeation enhancer from a matrix;

the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

2. (Original) The method of claim 1, wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight.

3. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight.

4. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50 by weight.

5. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight.

6. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

7. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

8. (Original) The method of claim 1, further including administering a pharmaceutically active ingredient with the prodrug.

9. (Currently Amended) A method of treating an allergic reaction ~~medical condition~~ in a human subject comprising:

administering a composition including a prodrug from a matrix;

delivering the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

10. (Original) The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by % weight.

11. (Original) The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by % weight.

12. (Original) The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.

13. (Original) The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight

14. (Original) The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.

15. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.

16. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.

17. (Original) The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

18. (Original) The method of claim 1, wherein prodrug has particle size of no more than 100 microns.

19. (Original) The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

20. (Original) The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.

21. (Original) The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

22. (Original) The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

23. (Original) The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

24. (Original) The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

25. (Original) The method of claim 1, wherein the prodrug includes an ester of epinephrine.

26. (Currently Amended) The method of claim 1, wherein at least half of the administered prodrug is converted ~~inless~~ in less than 240 minutes.

27. (Currently Amended) The method of claim 1, wherein at least half of the administered prodrug is converted ~~inless~~ in less than 120 minutes.

28. (Currently Amended) The method of claim 1, wherein at least half of the administered prodrug is converted ~~inless~~ in less than 60 minutes ~~60minutes~~.

29. (Currently Amended) The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of [[of]] 20 pg/ml to about 40 ng/ml of active compound in a period of less than 120 minutes.

30. (Original) The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

31. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.

32. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

33. (Original) The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.

34. (Original) The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.

35. (Original) The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.

36. (Original) The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.

37.-40. (Cancelled)

42. (Original) The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.

43. (Original) The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

44. (Original) The method of claim 1, wherein the phenylpropanoid is a chavicol.

45. (Original) The method of claim 1, wherein the phenylpropanoid is a safrole.

46. (Original) The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.

47. (Original) The method of claim 1, wherein the permeation enhancer is synthetic.

48. (Original) The method of claim 1, wherein the permeation enhancer is biosynthetic.

49. (Original) The method of claim 1, wherein the permeation enhancer is natural.

50. (Currently Amended) The method of claim 1, wherein the permeation enhancer includes [[150]] 50-95% eugenol.

51. (Original) The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or a sesquiterpene.

52. (Original) The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.

53. (Original) The method of claim 1, wherein the permeation enhancer includes farnesol.

54. (Original) The method of claim 1, wherein the permeation enhancer includes a self-emulsifying excipient.

55. (Original) The method of claim 1, wherein the matrix includes a mucoadhesive water soluble polymer.

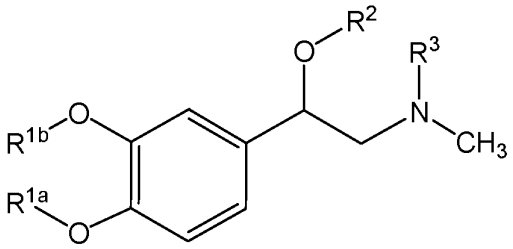
56. (Original) The method of claim 1, wherein the permeation enhancer includes linoleic acid.

57. (Original) The method of claim 1, wherein the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.

58. (Original) The method of claim 1, wherein one of the prodrugs is dipifevrin.

59. (Original) The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

60. (Original) The method of claim 1, wherein the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

61. (Original) The method of claim 60, wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

62. (Currently Amended) A method of treating an allergic reaction ~~medical condition~~ comprising

administering a prodrug from a matrix, the prodrug being converted to provide a concentration of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes.

63. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes.

64. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 100 minutes.

65. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 60 minutes.

66. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 45 minutes.

67. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 ng/ml of active compound in less than 30 minutes.

68. (Original) The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml.

69. (Original) The method of claim 62, further including administering a pharmaceutically active ingredient with the prodrug.

70. (Original) The method of claim 62 in which less than 100% of the prodrug is converted.

71. (Original) The method of claim 62 in which 100% of the prodrug is converted.

72. (Currently Amended) A method of treating an allergic reaction ~~medical condition~~ comprising

administering a prodrug, the prodrug converting to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 240 minutes.

73. (Original) The method of claim 72 in which less than 100% of the prodrug is converted.

74. (Original) The method of claim 72 in which 100% of the prodrug is converted.

75. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 15 minutes.

76. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 30 minutes.

77. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hours.

78. (Original) The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 4 hours.

REMARKS

Claims 1, 9, 26-29, 50, 62 and 72 have been amended for clarification. Claims 37-40 have been cancelled without prejudice. No new matter has been added. Claims 1-36 and 41-78 are pending.

In response to the outstanding Restriction Requirement mailed September 29, 2022, Applicant elects for prosecution the claims of Group II, the subject matter of claim 38, directed to a method of treating an allergic reaction. Independent claims 1, 9, 62 and 72 have been amended to include the features of claim 38, which has been cancelled without prejudice. Accordingly, pending claims 1-36 and 41-78 fall within the elected Group II.

Applicant also elects the species of diisobutyl esters of epinephrine as the prodrug and an essential oil extract of a clove plant as a permeation enhancer. Applicants understand these elections is for initial searching only and that the broader genus will be examined when the species is deemed allowable. Claims 1-36 and 41-78 read on the elected species.

Four months extension fees are filed concurrently with this submission. It is believed no other fees are due. However, if there are any charges or credits please apply them to Deposit Account No. 50-3145.

Respectfully submitted,

Date: March 29, 2023

/Harold H. Fox, Reg. # 41,498/
Harold H. Fox
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/086,409	11/01/2020	Alexander Mark Schobel	270712/ AQU-039US/480541	1047

138831 7590 06/29/2023

Honigman LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/29/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

THuschilt@honigman.com
hfox@honigman.com
patent@honigman.com

Office Action Summary	**Application No.** 17/086,409	**Applicant(s)** Schobel et al.	
	Examiner SAN MING R HUI	**Art Unit** 1627	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 3/29/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-78 is/are pending in the application.

5a) Of the above claim(s) 23-24,42-45,47-48,50-54,56-57 and 59 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-22,25-41,46,49,55,58 and 60-78 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

Applicant's election of the invention of group II, claims 1-36 and 41-78, in the reply filed on 3/29/2023 is acknowledged. Applicant's election of the species of diisobutyl esters of epinephrine as the prodrug and an essential oil extract of a clove plant as a permeation enhancer, in reply filed on 3/29/2023 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)).

Claims 23-24, 42-45, 47, 48, 50-54, 56-57, 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/2023.

Claims 1-22, 25-41, 46, 49, 55, 58, 60-78 have been examined to the extent they read on the elected inventions and species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 1-22, 25-41, 46, 49, 55, 58, 60-78 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 10,806,709 ('709) in view of US2017/0290776 ('776).

'709 teaches a method of treating anaphylaxis by administering anti-anaphylactic agents, including dipivefrin, intranasally (see the abstract, col. 9, line 20 for example). '709 teaches theparticle size of the active as 20-50μm (see col. 16, lines 3-16). '709 teaches penetration or permeation enhancers being included to facilitate the absorption of the anti-anaphylactic agent in the amount of 1-30% (see col. 10, line 52 bridging col. 12, line 13). The dosage of the epinephrine in the instant invention is 0.05mg to 10mg (see claim 9). '709 teaches the volume intended to be administered as 100μl (see col. 26, lines 30-34). The examiner notes that the ratio between the actives and the permeation enhanceing agent would meet the limitations of claims 2-7.

'709 does not expressly teach the permeation enhancer as the extract of a clove plant. '709 does not expressly teach the concentration of the permeation enhancer in the matrix. '709 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN MING R HUI whose telephone number is (571)272-0626. The examiner can normally be reached Mon - Fri 9:30-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached on 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAN MING R HUI/
Primary Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 17/086,409	Applicant(s)/Patent Under Reexamination Schobel et al.	
	Examiner SAN MING R HUI	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-10806709-B2	10-2020	Fleming; Nigel Ten	A61K31/277	1/1
*	B	US-20170290776-A1	10-2017	Schobel; Alexander Mark	A61K31/5513	1/1
	C					
	D					
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	J					
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	L					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
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	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/086,409	Schobel et al.
	Examiner	Art Unit
	SAN MING R HUI	1627

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/24, 47/10, 9/006, 9/7007, 31/222	06/24/2023	SH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E, Google, inventor search in PALM	06/24/2023	SH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L6	6779	Dipivefrin	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/20 10:47 AM
L7	93567	anaphylaxis	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/20 10:47 AM
L11	36	6 SAME 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/20 10:55 AM
L12	575	6 SAME (allergy OR allergic)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2023/06/20 12:14 PM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L13	283	6 AND 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/20 07:24 PM
L14	7	6 NEAR 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/20 07:39 PM
L15	178	6 AND 7 AND intranasal	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN,	OR	ON	ON	2023/06/21 12:09 PM

			WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L16	227726	(A61K31/24 OR A61K47/10 OR A61K9/006 OR A61K9/7007 OR A61K31/222).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/21 12:16 PM
L17	15	15 AND 16	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/21 12:16 PM
L18	63924	clove ADJ oil	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/21 12:23 PM
L19	5388430	penetration OR permeation	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2023/06/21 12:23 PM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
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L21	147	19 SAME 18 AND (intranasal OR transmucosal)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/06/21 12:23 PM
L22	60	19 near4 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2023/06/21 12:48 PM

			IBM_TDB)				

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
6/20/2023 9:06:37 AM	Google Scholar	[before:2014] clove oil extracts penetration enhancer
6/20/2023 9:19:42 AM	Google Scholar	[before:2014] dipifevrin
6/20/2023 9:20:22 AM	Google Scholar	[before:2014] dipivefrin
6/20/2023 9:59:08 AM	Google	dipivefrin
6/20/2023 9:59:35 AM	Google Scholar	[before:2014] Dipivefrin "clove oil"
6/20/2023 9:59:47 AM	Google Scholar	[before:2014] Dipivefrin allergic
6/20/2023 9:59:52 AM	Google Scholar	[before:2014] Dipivefrin allergy
6/20/2023 10:00:04 AM	Google Scholar	Dipivefrin allergy [before:2014]
6/20/2023 10:00:27 AM	Google Scholar	[before:2014] Dipivefrin conversion
6/20/2023 10:00:53 AM	Google Scholar	Dipivefrin conversion
6/20/2023 10:01:01 AM	Google Scholar	Dipivefrin allergy
6/20/2023 10:01:23 AM	Google Scholar	Dipivefrin hypersensitive
6/20/2023 4:33:35 PM	Google	dipivefrin for allergic reaction
6/20/2023 7:21:48 PM	Google Scholar	Dipivefrin allergic reaction
6/20/2023 7:22:09 PM	Google Scholar	Dipivefrin allergic reaction not glaucoma
6/20/2023 7:23:31 PM	Google Scholar	epinephrine allergic reaction not glaucoma
6/20/2023 7:23:36 PM	Google Scholar	epinephrine allergic reaction
6/21/2023 11:27:21 AM	Google Scholar	clove oil mucosal
6/21/2023 11:27:34 AM	Google Scholar	clove oil nasal
6/21/2023 11:27:49 AM	Google Scholar	clove oil intranasal
6/21/2023 11:44:10 AM	Google Scholar	clove oil intranasal [before:2019]

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11021437	B2	2021-06-01	Almoazen, Hassan	
	2	10149810	B2	2018-12-11	Perusse et al.	
	3	9125836	B2	2015-09-08	Nagaso et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100297232	A1	2010-11-25	Myers et al.	
	2	20110189259	A1	2011-08-04	Vasisht et al.	
	3	20110257096	A1	2011-10-20	Maggio	

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	4	20110262520	A1	2011-10-27	Dormady et al.	
	5	20110262522	A1	2011-10-27	Finn et al.	
	6	20120009260	A1	2012-01-12	Schobel et al.	
	7	20120058158	A1	2012-03-08	Booles	
	8	20130085105	A1	2013-04-04	Deasy et al.	
	9	20130267585	A1	2013-10-10	Ljusberg-Wahren	
	10	20130337022	A1	2013-12-19	Pillay et al.	
	11	20140316333	A1	2014-10-23	Kwon	
	12	20170087077	A1	2017-03-30	Perusse et al.	
	13	20170119660	A1	2017-05-04	Temtsin-Krayz et al.	
	14	20190022023	A1	2019-01-24	Schobel et al.	

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	15	20170290776	A1	2017-10-12	Schobel et al.	
	16	20040265353	A1	2004-12-30	Zhang et al.	
	17	20110192863	A1	2011-08-11	Barrass et al.	
	18	20070293582	A1	2007-12-20	Hill, Malcolm	
	19	20160051494	A1	2016-02-25	GULFO, Adele	
	20	20100150986	A1	2010-06-17	Nagaso et al.	
	21	20050147653	A1	2005-07-07	Yasuda et al.	
	22	20220401456	A1	2022-12-22	Rabinowicz et al.	
	23	20140128379	A1	2014-05-08	Bergenhem et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	1	2000027618	WO	A1	2000-05-18	Marius, Frederick		☐
	2	0024647	WO	A1	2000-05-04	Novartis AG		☐
	3	0042992	WO	A2	2000-07-27	Lavipharm Laboratories, Inc		☐
	4	2000057858	WO	A1	2000-10-05	Cima Labs Inc		☐
	5	2001003917	WO	A2	2001-01-18	Gruenenthal GmbH		☐
	6	0130288	WO	A1	2001-05-03	Anesta Corp		☐
	7	2001034121	WO	A2	2001-05-17	Lohmann Therapie Syst Lts		☐
	8	0143728	WO	A1	2001-06-21	Lohmann Therapie Syst Lts		☐
	9	0156904	WO	A1	2001-08-09	J R Crompton Ltd		☐
	10	0168452	WO	A1	2001-09-20	Stanelco Fibre Optics Ltd		☐
	11	0170194	WO	A1	2001-09-27	Warner Lambert Co		☐

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	Attorney Docket Number	270712-480541

	12	0170197	WO	A2	2001-09-27	Collaborative Technologies, Inc		☐
	13	0191721	WO	A2	2001-12-06	Staley Mfg Co A E		☐
	14	0205789	WO	A2	2002-01-24	Scs Skin Care Systems GmbH		☐
	15	0207711	WO	A1	2002-01-31	Union Carbide Chem Plastic		☐
	16	2002005820	WO	A1	2002-01-24	Lavipharm Laboratories, Inc		☐
	17	2006017462	WO	A2	2006-02-16	R.p.scherer Technologies, Inc		☐
	18	0243657	WO	A2	2002-06-06	Wrigley W M Jun Co		☐
	19	2002064148	WO	A2	2002-08-22	Shimizu Pharmaceutical Co., Ltd		☐
	20	02062315	WO	A1	2002-08-15	Pharmacia Corp		☐
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	22	02091965	WO	A1	2002-11-21	Chalmers, Susanna		☐

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	Attorney Docket Number	270712-480541

	23	03011259	WO	A1	2003-02-13	Wrigley W M Jun Co		☐
	24	03015749	WO	A1	2003-02-27	Colgate Palmolive Co		☐
	25	03030881	WO	A1	2003-04-17	Kosmos Pharma		☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Filing Date	2020-11-01
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Filing Date	2020-11-01
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	12	473268	JP		2445-05-24			☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2020-11-01
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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	13	5147140	JP	B2	2013-02-20	Sammy Corp		☐
	14	7322812	JP		2446-03-29			☐
	15	11255247	JP		2447-04-30			☐
	16	2000159658	JP	A	2000-06-13	Lion Corp		☐
	17	2001048196	JP	A	2001-02-20	Dainippon Printing Co Ltd		☐
	18	2001225851	JP	A	2001-08-21	Okayama Taiho Pharmaceutical C		☐
	19	2001279100	JP	A	2001-10-10	Kobayashi Pharma		☐
	20	2003312688	JP	A	2003-11-06	Okayama Taiho Pharmaceutical C		☐
	21	2004222663	JP	A	2004-08-12	Ni Corportion Co Ltd		☐
	22	2006143335	JP	A	2006-06-08	Dainippon Printing Co Ltd		☐
	23	2008501019	JP	A	2008-01-17			☐

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	24	2008011194	JP	A	2008-01-17	Fujifilm Corp		☐
	25	2012524771	JP	A	2012-10-18			☐
	26	2014532482	JP	A	2014-12-08			☐
	27	2019519487	JP	A	2019-07-11			☐
	28	2019519488	JP	A	2019-07-11			☐
	29	1988007103	WO	A1	1988-09-22	Valmet Paper Machinery Inc		☐
	30	9105540	WO	A1	1991-05-02	Desitin Arzneimittel GmbH		☐
	31	1992012704	WO	A1	1992-08-06	Eastman Kodak Co		☐
	32	9215289	WO	A1	1992-09-17	Noven Pharmaceuticals, Inc		☐
	33	9505416	WO	A2	1995-02-23	Cygnus Therapeutic Systems		☐
	34	9518046	WO	A1	1995-07-06	Frank, Richard		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	35	1995023596	WO	A1	1995-09-08	Boots Co PLC		☐
	36	9530601	WO	A1	1995-11-16	Sales Spa		☐
	37	9615903	WO	A1	1996-05-30	Grace W R & Co		☐
	38	9625150	WO	A1	1996-08-22	Nanosystems LLC		☐
	39	1996025638	WO	A1	1996-08-22	Johansson, Sonny		☐
	40	9731621	WO	A1	1997-09-04	Warner Lambert Co		☐
	41	9732573	WO	A1	1997-09-12	Nycomed Danmark A S		☐
	42	1997044016	WO	A1	1997-11-27	Samyang Corp		☐
	43	9810993	WO	A1	1998-03-19	Unifill Int AG		☐
	44	9817251	WO	A1	1998-04-30	Virotex Corp		☐
	45	1998014179	WO	A1	1998-04-09	Cima Labs Inc		☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	46	9935051	WO	A1	1999-07-15	Lohmann Therapie Syst Lts		☐
	47	9955312	WO	A2	1999-11-04	Virotex Corp		☐
	48	200002536	WO	A1	2000-01-20	Fmc Corp		☐
	49	2000002955	WO	A1	2000-01-20	Kimberly-clark Worldwide, Inc		☐
	50	0018365	WO	A2	2000-04-06	Warner Lambert Co		☐

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	1	U.S. Appl. No. 11/092,217, filed Mar. 29, 2005.	☐
	2	U.S. Appl. No. 11/237,525, filed Sep. 28, 2005.	☐
	3	U.S. Appl. No. 11/473,356, filed Jun. 22, 2006.	☐
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	5	U.S. Appl. No. 11/526,996, filed Sep. 26, 2006.	☐
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	8	U.S. Appl. No. 11/674,223, filed Feb. 13, 2007.	☐
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	11	U.S. Appl. No. 12/128,950, May 29, 2008.	☐
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	14	U.S. Appl. No. 12/411,505, filed Mar. 26, 2009.	☐
	15	U.S. Appl. No. 12/411,835, filed Mar. 26, 2009.	☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	16	U.S. Appl. No. 12/575,261, filed Oct. 7, 2009.	☐
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	18	U.S. Appl. No. 12/779,316, filed May 13, 2010.	☐
	19	U.S. Appl. No. 13/035,328, filed Feb. 25, 2011.	☐
	20	U.S. Appl. No. 13/052,655, filed Mar. 21, 2011.	☐
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	Attorney Docket Number	270712-480541

	27	U.S. Appl. No. 13/853,290, filed Mar. 29, 2013.	☐
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	31	U.S. Appl. No. 13/974,401, filed Aug. 23, 2013.	☐
	32	U.S. Appl. No. 13/974,413, filed Aug. 23, 2013.	☐
	33	U.S. Appl. No. 14/032,588, filed Sep. 20, 2013.	☐
	34	U.S. Appl. No. 14/195,362, filed Mar. 3, 2014.	☐
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	39	U.S. Appl. No. 14/844,810, filed Sep. 3, 2015.	☐
	40	U.S. Appl. No. 14/945,181, filed Nov. 18, 2015.	☐
	41	U.S. Appl. No. 14/980,836, filed Dec. 28, 2015.	☐
	42	U.S. Appl. No. 15/058,056, filed Mar. 1, 2016.	☐
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	50	PCT/US02/32542, Oct. 11, 2002.	☐

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☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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	1	Lahlou, Saad et al. "Cardiovascular effects of eugenol, a phenolic compound present in many plant essential oils, in normotensive rats." Journal of cardiovascular pharmacology vol. 43,2 (2004): 250-7.	☐
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	6	International Search Report and Written Opinion dated Jul. 10, 2017 in International Application No. PCT/ US2017/031170.	☐
	7	Restriction Requirement dated Oct. 7, 2019 in U.S. Appl. No. 15/724,234.	☐
	8	Non-Final Rejection dated Mar. 13, 2020 in U.S. Appl. No. 15/724,234.	☐
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	Attorney Docket Number	270712-480541

	12	Office Action dated Mar. 4, 2021 in European Application No. 17723616.3.	☐
	13	First Examination Report dated Jul. 24, 2020 in Indian Application No. 201817045308.	☐
	14	Non-Final Rejection dated Aug. 27, 2018 in U.S. Appl. No. 15/791,249.	☐
	15	Final Rejection dated Jun. 19, 2019 in U.S. Appl. No. 15/791,249.	☐
	16	Advisory Action dated Oct. 21, 2019 in U.S. Appl. No. 15/791,249.	☐
	17	Non-Final Rejection dated Dec. 12, 2019 in U.S. Appl. No. 15/791,249.	☐
	18	Final Rejection dated Jun. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
	19	Advisory Action dated Oct. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
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	23	Final Rejection dated May 13, 2020 in U.S. Appl. No. 16/143,036.	☐
	24	Advisory Action dated Aug. 27, 2020 in U.S. Appl. No. 16/143,036.	☐
	25	Non-Final Rejection dated Jan. 6, 2021 in U.S. Appl. No. 16/143,036.	☐
	26	Final Rejection dated Jun. 7, 2021 in U.S. Appl. No. 16/143,036.	☐
	27	Non-Final Rejection dated Nov. 4, 2020 in U.S. Appl. No. 16/143,821.	☐
	28	Office Action dated Jun. 1, 2021 in Japanese Application No. 2018-558224.	☐
	29	Final Rejection dated May 4, 2021 in U.S. Appl. No. 16/143,821.	☐
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	34	English Translation of Office Action dated Aug. 3, 2021 in Chinese Application No. 201780037588.X	☐
	35	Alayoubi et al., "Development of a fast dissolving film of epinephrine hydrocholoride as a potential anaphylactic treatment for pediatrics", Journal of Pharmaceutical Development and Technology, vol. 22:8, Jan. 6, 2016, pp. 1012-1016. <https://doi.org/10.3109/10837450.2015.1131715>.	☐
	36	First Examination Report dated Oct. 13, 2021 in Indian Application No. 202017016896.	☐
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	39	Notice of Allowance issued on August 20, 2021 in US Application No. 15/587,364	☐
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	41	Hussain, Anwar et al., "Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug," Journal of Pharmaceutical Sciences (1976) Vol. 65, No. 10 pp. 1510-1512	☐
	42	Non-Final Rejection issued on November 5, 2021 in US Application No. 15/724,234	☐
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	45	Final Rejection issued on January 13, 2022 in US Application No. 15/791,249	☐
	46	Non-Final Rejection issued on March 1, 2022 in US Application No. 16/143,678	☐
	47	Non-Final Rejection issued on February 4, 2022 in US Application No. 16/143,821	☐
	48	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037588.X	☐
	49	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037587.5	☐
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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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SIGNATURE

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Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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	1	2006039264	WO	A1	2006-04-13	Monosolrx, LLC		☐
	2	2006085210	WO	A1	2006-08-17	Warner Lambert Co		☐
	3	2006133948	WO	A2	2006-12-21	Novartis AG		☐

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	4	2007015105	WO	A2	2007-02-08	Rademacher, Thomas		☐
	5	2007067494	WO	A1	2007-06-14	Monosolrx, LLC		☐
	6	2007070632	WO	A2	2007-06-21	Biodelivery Sciences International, Inc		☐
	7	2008011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc		☐
	8	2008025791	WO	A1	2008-03-06	Euro Celtique SA		☐
	9	2008036299	WO	A2	2008-03-27	Monosol Rx LLC		☐
	10	2008040534	WO	A2	2008-04-10	Labtec GmbH		☐
	11	2009044118	WO	A2	2009-04-09	Bioprogress Technology Ltd		☐
	12	2009052421	WO	A1	2009-04-23	Innozen, Inc		☐
	13	2009027625	WO	A2	2009-03-05	Eastman Kodak Co		☐
	14	2009105540	WO	A1	2009-08-27	Univ Syracuse		☐

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	15	2010122355	WO	A1	2010-10-28	Londonpharma Ltd		☐
	16	2013063614	WO	A1	2013-05-02	Kwon, Sung-yun		☐
	17	2015078893	WO	A1	2015-06-04	Seppic SA		☐
	18	2017192921	WO	A1	2017-11-09	Monosol Rx, LLC		☐
	19	2017192923	WO	A1	2017-11-09	Monosol Rx, LLC		☐
	20	2019067667	WO	A1	2019-04-04	Aquestive Therapeutics, Inc		☐
	21	2019067670	WO	A1	2019-04-04	Aquestive Therapeutics, Inc		☐
	22	2014-0084176	KR	A	2014-07-04	Kwon		☐
	23	0791575	EP	A1	1997-08-27	Nakano		☐
	24	2015533155	JP	A	2015-11-19	Chin Beng Stephen Lim		☐
	25	2014057351	WO	A1	2014-04-17	Chin Beng Stephen Lim		☐

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	26	2009084177	JP	A	2014-03-05	Hisanobu Nishikawa		☐
	27	2008149440	WO	A1	2010-08-19	IIMURA YOSHIO et al.		☐
	28	2004043450	JP	A	2004-02-12	Hanayo Yasuda et al.		☐
	29	2006-507277	JP	A	2006-03-02	Lenaerts et al.		☐
	30	2011/010732	WO	A1	2013-01-07	Kyoko Endo		☐
	31	2013-530193	JP	A	2016-10-12	Ramesh Sesha		☐
	32	2004/037222	WO	A2	2004-05-06	Lenaerts et al.		☐
	33	2457581	EP	A1	2012-05-30	Kyoko Endo		☐
	34	2012/003968	WO	A1	2012-01-12	Ramesh Sesha		☐

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	1	Save, T. and Vankitachalam, P., "Studies on Solid Dispersions of Nifedipine," Drug Development and Industrial Pharmacy 18(15):1663-1679 (1992).	☐
	2	Roy, G.M., "Taste Macking in Oral Pharmaceuticals," Pharmaceutical Technology, pp. 84-99 (Apr. 1994).	☐
	3	Guo, J.H. and Cookock, K.M., "Bioadhesive Polymer Buccal Patches for Buprenorphine Controlled Delivery: Solubility Consideration," Drug Development and Industrial Pharmacy 21(7): 2013-2019 (1995).	☐
	4	Mixing in the Process Industries (2nd Ed.) Harnby, N. et al. (eds.)), pp. 3, 115 (Butterworth Heinemann 1997).	☐
	5	Himics, R, and Pineiro, R., "The Importance of Particle Size in Liquid Coatings," Products Finishing 63(2):00329940 (1998).	☐
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	7	Ilango, R. et al., "In-Vitro Studies on Buccal strips of Glibenclamide using Chitosan," Indian J. Pharm. Sci. 59 (5):232-235 (1997).	☐
	8	Ishikawa, T. et al., "Preparation and Evaluation of Tablets Rapidly Disintegrating in Saliva Containing Bitter-Taste-Masked Granules by the Compression Method," Chem. Pharm. Bull. 47(10):1451-1454 (1999).	☐
	9	Kaya, S. and Kaya, A., "Microwave drying effects on properties of whey protein isolate edible films," J. Food Engineering, 43: 91-96 (2000).	☐
	10	Al-Ghananeem et al., "Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride", AAPS PharmSciTech; Article 23, 7(1) (2006) (http://www.aapspharmscitec.org).	☐
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	12	Bowen P., "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", Journal of Dispersion Science and Technology; 23(5): 631-662 (2002).	☐
	13	Trademark Reg. No. 2,944,841—registered Apr. 26, 2005 to Reynolds Metal Co for "EZ SLIDE".	☐
	14	Hariharan et al., "Thin Film Technology, Orally Dissolving Film Strips (ODFS): The Final Evolution of Orally Dissolving Dosage Forms," Drug Delivery Technology; 9(2): 24-29 (2009).	☐
	15	Joshi et al., "Gold Nanoparticles as Carrier for Efficient Transmucosal Insulin Delivery", Langmuir; 22: 300-305 (2006).	☐
	16	Ojeda et al., "Preparation of multifunctional glyconanoparticles as a platform for potential carbohydrate-based anticancer vaccines", Carbohydrate Research; 342: 448-459 (2007).	☐
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	18	Boo, Woong Jae, "Characterization of Thin Film Properties of Melamine Based Dendrimer Nanoparticles", Thesis for Texas A&M University, Dec. 2003.	☐
	19	"Suboxone Subligualtabletten" in: Verlag Rote Liste Service GmbH: "Rote Liste 2008" 2008, Verlag Rote Liste Service GmbH, Frankfurt/Main, XP00264986, p. 39018, the whole document.	☐
	20	Transaction History for Ex Parte Reexamination Control No. 90/012,098, current as of.	☐
	21	Index of Documents for Inter Partes Review Case No. IPR2013-00316, current as of Aug. 29, 2017.	☐
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	37	Index of Documents for Inter Partes Review Case No. IPR2017-01557, current as of Aug. 29, 2017.	☐
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	45	Cholewinski et al., Pharmaceutica Acta Helvetiae, 71:405-419, 1996.	☐
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	47	Delsym Product Label (Feb. 13, 2007).	☐
	48	Di Donato et al., J. Biol. Chem, 268(7): 4745-4751, 1993.	☐
	49	Eiamtrakarn et al., "Gastrointestinal Mucoadhesive Path System (GI-MAPS) for oral administration of G-CSF, a model protein", Bipmaterials 23: 145-152 (2002).	☐
	50	Endo and Ueda, Fabad J. Pharm. Sci., 29:27-38, 2004.	☐

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(**Not for submission under 37 CFR 1.99)**

Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11191737		2021-12-07	Schobel et al.	
	2	0026401		1859-12-06	Brashear et al.	
	3	0307537		1884-11-04	Foulks	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	98	4460532		1984-07-17	Cornell	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
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	Attorney Docket Number	270712-480541

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	Filing Date	2020-11-01
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	6	1777411	CN	A	2006-05-24	Pharmaceutical Productions Inc		☐
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	First Named Inventor	Alexander Mark Schobel
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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	12	19646392	DE	A1	1998-05-14	Lts Lohmann Therapie-systeme GmbH, 56567 Neuwied		☐
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	21	0241178	EP	A1	1987-10-14	Rohto Pharmaceutical Co., Ltd		☐
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	23	0274431	EP	A2	1988-07-13	Medaphore Inc		☐
	24	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
	25	0259749	EP	A1	1988-03-16	Desitin Arzneimittel GmbH		☐
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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	34	0636364	EP	A1	1995-02-01	Mcneil-ppc, Inc		☐
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	Attorney Docket Number	270712-480541

	45	1674078	EP	A2	2006-06-28	Mcneil-ppc, Inc		☐
	46	1852041	EP	A2	2007-11-07	Baldan, Ferdinando		☐
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	37	U.S. Pat. No. 8,603,514, IPR2016-00281, Inter Partes Review.	☐
	38	U.S. Pat. No. 8,652,378, IPR2014-00794, Inter Partes Review.	☐
	39	U.S. Pat. No. 8,765,167, IPR2015-00165, Inter Partes Review.	☐
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	Attorney Docket Number	270712-480541

	48	U.S. Appl. No. 10/074,272, filed Feb. 14, 2002.	☐
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☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

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☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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	27	English Translation of Examination Report issued on December 12, 2022 in IL Application No 273477	☐
	28	Restriction Requirement issued on January 20, 2023 in US Application 17/973,345	☐
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☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Alexander Mark SCHOBEL et al.
Application No.: 17/086,409
Filing Date: November 1, 2020
Art Unit No.: 1627
Examiner: HUI, SAN MING R
Confirmation No.: 1047

For: PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO OFFICE ACTION OF JUNE 29, 2023

In response to the Non-Final office action dated June 29, 2023 ("Office Action"), Applicant submits the following amendments and remarks.

IN THE CLAIMS:

The listing of claims replaces all prior versions and listings of claims in the application.

1. (Currently amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine and a permeation enhancer from a matrix wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight;

the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

2. (Canceled) ~~The method of claim 1, wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight~~.

3. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight.

4. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50 by weight.

5. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight.

6. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

7. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

8. (Original) The method of claim 1, further including administering a pharmaceutically active ingredient with the prodrug.

9. (Currently amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine from a matrix;

delivering the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

10. (Original) The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by % weight.

11. (Original) The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by % weight.

12. (Original) The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.

13. (Original) The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight

14. (Original) The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.

15. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.

16. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.

17. (Original) The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

18. (Original) The method of claim 1, wherein prodrug has particle size of no more than 100 microns.

19. (Original) The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

20. (Original) The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.

21. (Original) The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

22. (Original) The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

23. (Withdrawn) The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

24. (Withdrawn) The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

25. (Original) The method of claim 1, wherein the prodrug includes an ester of epinephrine.

26. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 240 minutes.

27. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 120 minutes.

28. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 60 minutes.

29. (Previously Presented) The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of 20 pg/ml to about 40 ng/ml of active compound in a period of less than 120 minutes.

30. (Original) The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

31. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.

32. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

33. (Original) The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.

34. (Original) The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.

35. (Original) The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.

36. (Original) The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.

37.-40. (Cancelled)

42. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.

43. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

44. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a chavicol.

45. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a safrole.

46. (Original) The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.

47. (Withdrawn) The method of claim 1, wherein the permeation enhancer is synthetic.

48. (Withdrawn) The method of claim 1, wherein the permeation enhancer is biosynthetic.

49. (Original) The method of claim 1, wherein the permeation enhancer is natural.

50. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes 50-95% eugenol.

51. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or a sesquiterpene.

52. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.

53. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes farnesol.

54. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a self-emulsifying excipient.

55. (Original) The method of claim 1, wherein the matrix includes a mucoadhesive water soluble polymer.

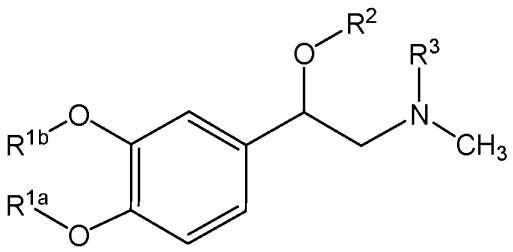
56. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes linoleic acid.

57. (Withdrawn) The method of claim 1, wherein the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.

58. (Original) The method of claim 1, wherein one of the prodrugs is dipifevrin.

59. (Withdrawn) The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

60. (Original) The method of claim 1, wherein the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

61. (Original) The method of claim 60, wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

62. (Currently amended) A method of treating an allergic reaction comprising

administering a prodrug from a matrix, the prodrug <u>of epinephrine</u> being converted to provide a concentration of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes.

63. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes.

64. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 100 minutes.

65. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 60 minutes.

66. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 45 minutes.

67. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 ng/ml of active compound in less than 30 minutes.

68. (Original) The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml.

69. (Original) The method of claim 62, further including administering a pharmaceutically active ingredient with the prodrug.

70. (Original) The method of claim 62 in which less than 100% of the prodrug is converted.

71. (Original) The method of claim 62 in which 100% of the prodrug is converted.

72. (Currently amended) A method of treating an allergic reaction comprising administering a prodrug, the prodrug <u>of epinephrine</u> converting to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 240 minutes.

73. (Original) The method of claim 72 in which less than 100% of the prodrug is converted.

74. (Original) The method of claim 72 in which 100% of the prodrug is converted.

75. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 15 minutes.

76. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 30 minutes.

77. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hours.

78. (Original) The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 4 hours.

REMARKS

Claims 1-36 and 42-78 are pending. Claims 1, 9, 62 and 72 have been amended for clarification. Support can be found throughout the specification and claims as filed. No new matter has been added and no new issues have been raised.

Rejections under U.S.C. §103

Claims 1-22, 25-41, 46, 49, 55, 58, 60-78 were rejected under 35 U.S.C. §103 as being unpatentable over US 10,806,709 ("Fleming") in view of US2017/0290776 ("Schobel"). Applicants respectfully disagree. Not in acquiescence, but to advance prosecution, the claims have been amended thereby mooting this rejection.

Fleming is directed to a nasal formulation of epinephrine. It does not teach or suggest administering a composition including a prodrug of epinephrine and a permeation enhancer from a matrix, the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

Moreover, Schobel is directed to pharmaceutical compositions having enhanced component permeation properties. It does not teach or suggest administering a composition including a prodrug of epinephrine and a permeation enhancer from a matrix wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight. See claim 1.

Moreover, apart from the knowledge gleaned from Applicants' disclosure, nothing in the cited references have motivated a person of ordinary skill to combine these teachings to arrive at the claimed subject matter.

For at least these reasons, the claims are not obvious over the cited references. Applicants respectfully request withdrawal of this ground of rejection.

CONCLUSION

For at least the reasons set forth above, Applicant respectfully submits that all grounds for patentability are met in the pending claims. Please apply any necessary charges or credits to deposit account 50-3145. Should the Examiner deem that any further action by the Applicant would be desirable to place this application in even better condition for issue, the Examiner is invited to telephone Applicant's undersigned representative.

Respectfully submitted,

Date: September 21, 2023

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/086,409	11/01/2020	Alexander Mark Schobel	270712/ AQU-039US/480541	1047

138831 7590 01/04/2024

Honigman LLP
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Kalamazoo, MI 49002

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
01/04/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

THuschilt@honigman.com
hfox@honigman.com
patent@honigman.com

Office Action Summary	Application No. 17/086,409	Applicant(s) Schobel et al.	
	Examiner SAN MING R HUI	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/21/2023.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,3-36 and 42-78 is/are pending in the application.

5a) Of the above claim(s) 23-24,42-45,47-48,50-54,56-57 and 59 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3-22,25-36,46,49,55,58 and 60-78 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 7/21/2023.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's amendments filed 9/21/2023 have been entered. Claims 1, 3-36, 42-78 are pending.

Claims 23-24, 42-45, 47, 48, 50-54, 56-57, 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/2023.

Claims 1, 3-22, 25-36, 46, 49, 55, 58, 60-78 have been examined to the extent they read on the elected inventions and species.

The examiner notes that claim 41 is not listed in the claims. Apparently claim 41 is also cancelled. Appropriate correction is required.

The rejection under 35 USC 103a is modified in response to the amendments made in amendments filed 9/21/2023.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 1-22, 25-41, 46, 49, 55, 58, 60-78 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 10,806,709 ('709) in view of US2017/0290776 ('776).

'709 teaches a method of treating anaphylaxis by administering anti-anaphylactic agents, including dipivefrin, intranasally (see the abstract, col. 9, line 20 for example). '709 teaches the particle size of the active as 20-50μm (see col. 16, lines 3-16). '709 teaches penetration or permeation enhancers being included to facilitate the absorption of the anti-anaphylactic agent in the amount of 1-30% (see col. 10, line 52 bridging col. 12, line 13). The dosage of the epinephrine in the instant invention is 0.05mg to 10mg (see claim 9). '709 teaches the volume intended to be administered as 100μl (see col. 26, lines 30-34). The examiner notes that the ratio between the actives and the permeation enhancing agent would meet the limitations of claims 2-7.

'709 does not expressly teach the permeation enhancer as the extract of a clove plant. '709 does not expressly teach the concentration of the permeation enhancer in the matrix. '709 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition. The examiner notes that the penetration enhancers is taught to be 3% in amount and the anti-anaphylactic agents to be 1-30% in amount. Accordingly, ratio between the penetration enhancer/ anti-anaphylactic agents (i.e., dipifevrin/epinephrine) meets the limitation recited in claim 1.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final

Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1-22, 25-41, 46, 49, 55, 58, 60-78 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24, 40-60 of copending Application No. 17/576,923 ('923) in view of '776.

'923 teaches a method of treating allergic reaction using epinephrine and its prodrug (see claims 1 and 38 for example). '923 teaches the Cmax and Tmax properties of the administration of the epinephrine/prodrug composition (see claims 59-60).

'923 does not expressly teach the permeation enhancer as the extract of a clove plant. '923 does not expressly teach the concentration of the permeation enhancer in the matrix. '923 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of

clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-allergic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the adjustment of penetration enhancer

amount would produce the desired serum concentration of the active agent and thereby treating the allergic condition.

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

This is a provisional nonstatutory double patenting rejection.

Response to Arguments

Applicant's arguments filed 9/21/2023 averring the cited prior art's failure to teach the epinephrine prodrug in a matrix in the weight ratio to be 1000:1 to 1:1000 of penetration enhancing agents to the prodrug, have been fully considered but they are not persuasive. The examiner notes that those deficiencies have been acknowledged in the outstanding rejection under 35 USC 103a. taking the teachings of the cited prior art together, one of ordinary skill in the art would readily envision that the penetration enhancers suitable for use for epinephrine would be reasonably expected to also be used for dipifevrin since dipifevrin is a well-known prodrug with similar structure of epinephrine. As for the weight ratio, it has been discussed in the rejection under 35 USC 103a that the known concentration of the penetration enhancing agents is 3% and that of the actives (epinephrine and dipifevrin) as 1-30%. Therefore, the ratio is well within the herein claimed range of 1000:1 to 1:1000.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN MING R HUI whose telephone number is (571)272-0626. The examiner can normally be reached Mon - Fri 9:30-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached on 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/SAN MING R HUI/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/086,409	Schobel et al.
	Examiner	Art Unit
	SAN MING R HUI	1627

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/24, 47/10, 9/006, 9/7007, 31/222	06/24/2023	SH
A61K 31/24, 47/10, 9/006, 9/7007, 31/222	12/29/2023	SH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
PE2E, Google, inventor search in PALM	06/24/2023	SH
PE2E, Google, inventor search in PALM	12/29/2023	SH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

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EXAMINER SIGNATURE

Examiner Signature	/SAN MING R HUI/	Date Considered	12/28/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	1	11021437	B2	2021-06-01	Almoazen, Hassan	
	2	10149810	B2	2018-12-11	Perusse et al.	
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	1	20100297232	A1	2010-11-25	Myers et al.	
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	2	0024647	WO	A1	2000-05-04	Novartis AG		☐
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	34	2004045537	WO	A2	2004-06-03	Zengen, Inc		☐
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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	Attorney Docket Number	270712-480541

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11191737		2021-12-07	Schobel et al.	
	2	0026401		1859-12-06	Brashear et al.	
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	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Attorney Docket Number	270712-480541

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	Attorney Docket Number	270712-480541

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	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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	47	U.S. Pat. No. 8,603,514, IPR2017-01582, Inter Partes Review.	☐

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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
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	48	U.S. Appl. No. 10/074,272, filed Feb. 14, 2002.	☐
	49	U.S. Appl. No. 10/768,809, filed Jan. 30, 2004.	☐
	50	U.S. Appl. No. 10/856,176, filed May 28, 2004.	☐

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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	1	2006039264	WO	A1	2006-04-13	Monosolrx, LLC		☐
	2	2006085210	WO	A1	2006-08-17	Warner Lambert Co		☐
	3	2006133948	WO	A2	2006-12-21	Novartis AG		☐

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	4	2007015105	WO	A2	2007-02-08	Rademacher, Thomas		☐
	5	2007067494	WO	A1	2007-06-14	Monosolrx, LLC		☐
	6	2007070632	WO	A2	2007-06-21	Biodelivery Sciences International, Inc		☐
	7	2008011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc		☐
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	9	2008036299	WO	A2	2008-03-27	Monosol Rx LLC		☐
	10	2008040534	WO	A2	2008-04-10	Labtec GmbH		☐
	11	2009044118	WO	A2	2009-04-09	Bioprogress Technology Ltd		☐
	12	2009052421	WO	A1	2009-04-23	Innozen, Inc		☐
	13	2009027625	WO	A2	2009-03-05	Eastman Kodak Co		☐
	14	2009105540	WO	A1	2009-08-27	Univ Syracuse		☐

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	15	2010122355	WO	A1	2010-10-28	Londonpharma Ltd		☐
	16	2013063614	WO	A1	2013-05-02	Kwon, Sung-yun		☐
	17	2015078893	WO	A1	2015-06-04	Seppic SA		☐
	18	2017192921	WO	A1	2017-11-09	Monosol Rx, LLC		☐
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	20	2019067667	WO	A1	2019-04-04	Aquestive Therapeutics, Inc		☐
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	22	2014-0084176	KR	A	2014-07-04	Kwon		☐
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	24	2015533155	JP	A	2015-11-19	Chin Beng Stephen Lim		☐
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	26	2009084177	JP	A	2014-03-05	Hisanobu Nishikawa		☐
	27	2008149440	WO	A1	2010-08-19	IIMURA YOSHIO et al.		☐
	28	2004043450	JP	A	2004-02-12	Hanayo Yasuda et al.		☐
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	30	2011/010732	WO	A1	2013-01-07	Kyoko Endo		☐
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	34	2012/003968	WO	A1	2012-01-12	Ramesh Sesha		☐

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	1	Save, T. and Vankitachalam, P., "Studies on Solid Dispersions of Nifedipine," Drug Development and Industrial Pharmacy 18(15):1663-1679 (1992).	☐
	2	Roy, G.M., "Taste Macking in Oral Pharmaceuticals," Pharmaceutical Technology, pp. 84-99 (Apr. 1994).	☐
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	7	Ilango, R. et al., "In-Vitro Studies on Buccal strips of Glibenclamide using Chitosan," Indian J. Pharm. Sci. 59 (5):232-235 (1997).	☐
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	10	Al-Ghananeem et al., "Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride", AAPS PharmSciTech; Article 23, 7(1) (2006) (http://www.aapspharmscitec.org).	☐
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	12	Bowen P., "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", Journal of Dispersion Science and Technology; 23(5): 631-662 (2002).	☐
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	21	Index of Documents for Inter Partes Review Case No. IPR2013-00316, current as of Aug. 29, 2017.	☐
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Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L23	6893	Dipivefrin	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L24	95547	anaphylaxis	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L25	37	6 SAME 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L26	587	6 SAME (allergy OR allergic)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2023/12/28 10:45 PM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L27	285	6 AND 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L28	7	6 NEAR 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L29	178	6 AND 7 AND intranasal	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN,	OR	ON	ON	2023/12/28 10:45 PM

			WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L30	233376	(A61K31/24 OR A61K47/10 OR A61K9/006 OR A61K9/7007 OR A61K31/222).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L31	15	15 AND 16	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L32	65386	clove ADJ oil	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L33	5516981	penetration OR permeation	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2023/12/28 10:45 PM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L34	959	19 SAME 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L35	153	19 SAME 18 AND (intranasal OR transmucosal)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/12/28 10:45 PM
L36	65	19 near4 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2023/12/28 10:45 PM

			IBM_TDB)				

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

PTO/SB/08a (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

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	Examiner Name	S. M. R. Hui
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	1	Lahlou, Saad et al. "Cardiovascular effects of eugenol, a phenolic compound present in many plant essential oils, in normotensive rats." Journal of cardiovascular pharmacology vol. 43,2 (2004): 250-7.	☐
	2	Feddersen, C O et al. "Arachidonic acid causes cyclooxygenase-dependent and -independent pulmonary vasodilation." Journal of applied physiology (Bethesda, Md.: 1985) vol. 68,5 (1990): 1799-808.	☐
	3	International Search Report and Written Opinion dated Mar. 1, 2021 in International Application No. PCT/ US2020/060464.	☐
	4	International Search Report and Written Opinion dated Feb. 9, 2021 in International Application No. PCT/ US2020/058357.	☐
	5	International Search Report and Written Opinion dated Jul. 17, 2017 in International Application No. PCT/ US2017/031167.	☐
	6	International Search Report and Written Opinion dated Jul. 10, 2017 in International Application No. PCT/ US2017/031170.	☐
	7	Restriction Requirement dated Oct. 7, 2019 in U.S. Appl. No. 15/724,234.	☐
	8	Non-Final Rejection dated Mar. 13, 2020 in U.S. Appl. No. 15/724,234.	☐
	9	Final Rejection dated Aug. 17, 2020 in U.S. Appl. No. 15/724,234.	☐
	10	Restriction Requirement dated Jun. 18, 2021 in U.S. Appl. No. 15/724,234.	☐
	11	Office Action dated Jun. 1, 2021 in Brazilian Patent Application No. 112018072467-0.	☐

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	First Named Inventor	Alexander Mark Schobel
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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	12	Office Action dated Mar. 4, 2021 in European Application No. 17723616.3.	☐
	13	First Examination Report dated Jul. 24, 2020 in Indian Application No. 201817045308.	☐
	14	Non-Final Rejection dated Aug. 27, 2018 in U.S. Appl. No. 15/791,249.	☐
	15	Final Rejection dated Jun. 19, 2019 in U.S. Appl. No. 15/791,249.	☐
	16	Advisory Action dated Oct. 21, 2019 in U.S. Appl. No. 15/791,249.	☐
	17	Non-Final Rejection dated Dec. 12, 2019 in U.S. Appl. No. 15/791,249.	☐
	18	Final Rejection dated Jun. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
	19	Advisory Action dated Oct. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
	20	Non-Final Rejection dated Mar. 29, 2021 in U.S. Appl. No. 15/791,249.	☐
	21	Restriction Requirement dated May 1, 2019 in U.S. Appl. No. 16/143,036.	☐
	22	Non-Final Rejection dated Nov. 18, 2019 in U.S. Appl. No. 16/143,036.	☐

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	23	Final Rejection dated May 13, 2020 in U.S. Appl. No. 16/143,036.	☐
	24	Advisory Action dated Aug. 27, 2020 in U.S. Appl. No. 16/143,036.	☐
	25	Non-Final Rejection dated Jan. 6, 2021 in U.S. Appl. No. 16/143,036.	☐
	26	Final Rejection dated Jun. 7, 2021 in U.S. Appl. No. 16/143,036.	☐
	27	Non-Final Rejection dated Nov. 4, 2020 in U.S. Appl. No. 16/143,821.	☐
	28	Office Action dated Jun. 1, 2021 in Japanese Application No. 2018-558224.	☐
	29	Final Rejection dated May 4, 2021 in U.S. Appl. No. 16/143,821.	☐
	30	Restriction Requirement dated Feb. 19, 2020 in U.S. Appl. No. 16/143,821.	☐
	31	Aqil, Mohammed et al. "Status of terpenes as skin penetration enhancers." Drug discovery today vol. 12,23-24 (2007): 1061-7.	☐
	32	Office Action dated Jun. 29, 2021 in Japanese Application No. 2018-558225.	☐
	33	English Translation of Office Action dated Aug. 3, 2021 in Chinese Application No. 201780037587.5	☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	34	English Translation of Office Action dated Aug. 3, 2021 in Chinese Application No. 201780037588.X	☐
	35	Alayoubi et al., "Development of a fast dissolving film of epinephrine hydrocholoride as a potential anaphylactic treatment for pediatrics", Journal of Pharmaceutical Development and Technology, vol. 22:8, Jan. 6, 2016, pp. 1012-1016. <https://doi.org/10.3109/10837450.2015.1131715>.	☐
	36	First Examination Report dated Oct. 13, 2021 in Indian Application No. 202017016896.	☐
	37	Office Action issued on July 21, 2021 in European Application No. 17723617.1	☐
	38	Restriction Requirement issued on August 5, 2021 in US Application No. 16/143,678	☐
	39	Notice of Allowance issued on August 20, 2021 in US Application No. 15/587,364	☐
	40	Issue Notification issued on February 24, 2022 in US Application No. 15/724,234	☐
	41	Hussain, Anwar et al., "Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug," Journal of Pharmaceutical Sciences (1976) Vol. 65, No. 10 pp. 1510-1512	☐
	42	Non-Final Rejection issued on November 5, 2021 in US Application No. 15/724,234	☐
	43	Non-Final Rejection issued on December 21, 2021 in US Application No. 16/143,036	☐
	44	Final Rejection issued on June 9, 2022 in US Application No. 16/143,036	☐

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	45	Final Rejection issued on January 13, 2022 in US Application No. 15/791,249	☐
	46	Non-Final Rejection issued on March 1, 2022 in US Application No. 16/143,678	☐
	47	Non-Final Rejection issued on February 4, 2022 in US Application No. 16/143,821	☐
	48	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037588.X	☐
	49	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037587.5	☐
	50	English Translation of Final Rejection issued on June 30, 2022 in CN Application No. 201780037587.5	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/SAN MING R HUI/	Date Considered	12/28/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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(**Not for submission under 37 CFR 1.99)**

Application Number	17086409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	1	English Translation of Office Action issued on November 29, 2021 in KR Application No. 1020187035240	☐
	2	English Translation of FER issued on October 7, 2021 in IN Application No. 202017016904	☐
	3	English Translation of OA issued on January 26, 2022 in JP Application No. 2018-558224	☐
	4	English Translation of FER issued on October 26, 2021 in IN Application No. 202017016905	☐
	5	English Translation of OA issued on April 6, 2022 in IL Application No. 262751	☐
	6	English Translation of OA issued on May 31, 2022 in JP Application No. 2018-558225	☐
	7	Kesharwani, Payal et al. "Biomedical applications of hydrogels in drug delivery system: An update." Journal of Drug Delivery Science and Technology (2021): n. pag.	☐
	8	Tangri, Pranshu et al. "ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS: A REVIEW." (2011).	☐
	9	Debotton, Nir and Arik Dahan. "Applications of Polymers as Pharmaceutical Excipients in Solid Oral Dosage Forms." Medicinal Research Reviews 37 (2017): n. pag.	☐
	10	English Translation of Final Rejection issued on July 20, 2022 in CN Application No. 201780037588.X	☐
	11	English Translation of Final Rejection issued on July 8, 2022 in CN Application No. 201780037587.5	☐

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	12	English Translation of OA issued on April 22, 2022 in KR Application No. 10-2018-7035236	☐
	13	English Translation of OA issued on July 26, 2022 in BR Application No. BR112020005875-0	☐
	14	English Translation of OA issued on August 16, 2022 in BR Application No. BR112020005948-0	☐
	15	English Translation of OA issued on August 16, 2022 in BR Application No. BR112020005967-6	☐
	16	English Translation of Official Hearing issued on July 15, 2022 in IN Application No. 202017016904	☐
	17	Restriction Requirement issued on September 29, 2022 in US Application No. 17/086,409	☐
	18	English Translation of OA issued on October 28, 2022 in JP Application No. 2020-517419	☐
	19	English Translation of OA issued on October 28, 2022 in JP Application No. 2020-517586	☐
	20	Non-Final Rejection issued on October 28, 2022 in US Application No. 15/791,249	☐
	21	English Translation of Official Notification issued on September 28, 2022 in IL Application No. 273485	☐
	22	English Translation of Official Notification issued on September 28, 2022 in IL Application No. 292487	☐

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	Attorney Docket Number	270712-480541

	23	English Translation of OA issued on November 1, 2022 in JP Application No. 2020-538776	☐
	24	Final Rejection issued on November 17, 2022 in US Application No. 16/143,821	☐
	25	Final Rejection issued on November 18, 2022 in US Application 16/143,678	☐
	26	English Translation of Official Notification issued on October 27, 2022 in IL Application No. 273479	☐
	27	English Translation of Examination Report issued on December 12, 2022 in IL Application No 273477	☐
	28	Restriction Requirement issued on January 20, 2023 in US Application 17/973,345	☐
	29	English Translation of Office Action issued on December 20, 2022 in CN Application 201880063175.3	☐
	30	English Translation of Office Action issued on December 22, 2022 in CN Application 201880062678.9	☐

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EXAMINER SIGNATURE

Examiner Signature	/SAN MING R HUI/	Date Considered	12/28/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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Art Unit	1617
Examiner Name	S. M. R. Hui
Attorney Docket Number	270712-480541

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5766525		1998-06-16	Andersen et al.	
	2	5766620		1998-06-16	Heiber et al.	
	3	5766839		1998-06-16	Johnson et al.	
	4	5771353		1998-06-23	Eggleston et al.	
	5	5785180		1998-07-28	Dressel et al.	
	6	5792494		1998-08-11	Kanca et al.	
	7	5800832		1998-09-01	Tapolsky et al.	
	8	5806284		1998-09-15	Gifford	

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	9	5815398		1998-09-29	Dighe et al.	
	10	5822526		1998-10-13	Waskiewicz	
	11	5830437		1998-11-03	Ascione et al.	
	12	5830884		1998-11-03	Kasica et al.	
	13	5846557		1998-12-08	Eisenstadt et al.	
	14	5847023		1998-12-08	Viegas et al.	
	15	5862915		1999-01-26	Plezia et al.	
	16	5864684		1999-01-26	Nielsen	
	17	5879690		1999-03-09	Perricone	
	18	5881476		1999-03-16	Strobush et al.	
	19	5891461		1999-04-06	Jona et al.	

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	20	5891845		1999-04-06	Myers	
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	24	5930914		1999-08-03	Johansson et al.	
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	28	5948430		1999-09-07	Zerbe et al.	
	29	5955097		1999-09-21	Tapolsky et al.	
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	35	6024975		2000-02-15	D'Angelo et al.	
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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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EFS Web 2.1.18

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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EFS Web 2.1.18

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
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	24	2008011194	JP	A	2008-01-17	Fujifilm Corp		☐
	25	2012524771	JP	A	2012-10-18			☐
	26	2014532482	JP	A	2014-12-08			☐
	27	2019519487	JP	A	2019-07-11			☐
	28	2019519488	JP	A	2019-07-11			☐
	29	1988007103	WO	A1	1988-09-22	Valmet Paper Machinery Inc		☐
	30	9105540	WO	A1	1991-05-02	Desitin Arzneimittel GmbH		☐
	31	1992012704	WO	A1	1992-08-06	Eastman Kodak Co		☐
	32	9215289	WO	A1	1992-09-17	Noven Pharmaceuticals, Inc		☐
	33	9505416	WO	A2	1995-02-23	Cygnus Therapeutic Systems		☐
	34	9518046	WO	A1	1995-07-06	Frank, Richard		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17086409
	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	35	1995023596	WO	A1	1995-09-08	Boots Co PLC		☐
	36	9530601	WO	A1	1995-11-16	Sales Spa		☐
	37	9615903	WO	A1	1996-05-30	Grace W R & Co		☐
	38	9625150	WO	A1	1996-08-22	Nanosystems LLC		☐
	39	1996025638	WO	A1	1996-08-22	Johansson, Sonny		☐
	40	9731621	WO	A1	1997-09-04	Warner Lambert Co		☐
	41	9732573	WO	A1	1997-09-12	Nycomed Danmark A S		☐
	42	1997044016	WO	A1	1997-11-27	Samyang Corp		☐
	43	9810993	WO	A1	1998-03-19	Unifill Int AG		☐
	44	9817251	WO	A1	1998-04-30	Virotex Corp		☐
	45	1998014179	WO	A1	1998-04-09	Cima Labs Inc		☐

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	46	9935051	WO	A1	1999-07-15	Lohmann Therapie Syst Lts		☐
	47	9955312	WO	A2	1999-11-04	Virotex Corp		☐
	48	200002536	WO	A1	2000-01-20	Fmc Corp		☐
	49	2000002955	WO	A1	2000-01-20	Kimberly-clark Worldwide, Inc		☐
	50	0018365	WO	A2	2000-04-06	Warner Lambert Co		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	U.S. Appl. No. 11/092,217, filed Mar. 29, 2005.	☐
	2	U.S. Appl. No. 11/237,525, filed Sep. 28, 2005.	☐
	3	U.S. Appl. No. 11/473,356, filed Jun. 22, 2006.	☐
	4	U.S. Appl. No. 11/517,982, filed Sep. 8, 2006.	☐

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	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	5	U.S. Appl. No. 11/526,996, filed Sep. 26, 2006.	☐
	6	U.S. Appl. No. 11/634,280, filed Dec. 5, 2006.	☐
	7	U.S. Appl. No. 11/639,013, filed Dec. 14, 2006.	☐
	8	U.S. Appl. No. 11/674,223, filed Feb. 13, 2007.	☐
	9	U.S. Appl. No. 11/775,484, filed Jul. 10, 2007.	☐
	10	U.S. Appl. No. 12/102,071, filed Apr. 14, 2008.	☐
	11	U.S. Appl. No. 12/128,950, May 29, 2008.	☐
	12	U.S. Appl. No. 12/107,389, filed Apr. 22, 2008.	☐
	13	U.S. Appl. No. 12/171,692, filed Jul. 11, 2008.	☐
	14	U.S. Appl. No. 12/411,505, filed Mar. 26, 2009.	☐
	15	U.S. Appl. No. 12/411,835, filed Mar. 26, 2009.	☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	16	U.S. Appl. No. 12/575,261, filed Oct. 7, 2009.	☐
	17	U.S. Appl. No. 12/614,928, filed Nov. 9, 2009.	☐
	18	U.S. Appl. No. 12/779,316, filed May 13, 2010.	☐
	19	U.S. Appl. No. 13/035,328, filed Feb. 25, 2011.	☐
	20	U.S. Appl. No. 13/052,655, filed Mar. 21, 2011.	☐
	21	U.S. Appl. No. 13/342,614, filed Feb. 12, 2012.	☐
	22	U.S. Appl. No. 13/096,996, filed Apr. 28, 2011.	☐
	23	U.S. Appl. No. 13/853,237, filed Mar. 29, 2013.	☐
	24	U.S. Appl. No. 13/853,223, filed Mar. 29, 2013.	☐
	25	U.S. Appl. No. 13/853,253, filed Mar. 29, 2013.	☐
	26	U.S. Appl. No. 13/853,276, filed Mar. 29, 2013.	☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	27	U.S. Appl. No. 13/853,290, filed Mar. 29, 2013.	☐
	28	U.S. Appl. No. 13/890,542, filed May 9, 2013.	☐
	29	U.S. Appl. No. 13/974,376, filed Aug. 23, 2013.	☐
	30	U.S. Appl. No. 13/974,389, filed Aug. 23, 2013.	☐
	31	U.S. Appl. No. 13/974,401, filed Aug. 23, 2013.	☐
	32	U.S. Appl. No. 13/974,413, filed Aug. 23, 2013.	☐
	33	U.S. Appl. No. 14/032,588, filed Sep. 20, 2013.	☐
	34	U.S. Appl. No. 14/195,362, filed Mar. 3, 2014.	☐
	35	U.S. Appl. No. 14/284,019, filed May 21, 2014.	☐
	36	U.S. Appl. No. 14/492,874, filed Sep. 22, 2014.	☐
	37	U.S. Appl. No. 14/572,173, filed Dec. 16, 2014.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2020-11-01
	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	38	U.S. Appl. No. 14/599,803, filed Jan. 19, 2015.	☐
	39	U.S. Appl. No. 14/844,810, filed Sep. 3, 2015.	☐
	40	U.S. Appl. No. 14/945,181, filed Nov. 18, 2015.	☐
	41	U.S. Appl. No. 14/980,836, filed Dec. 28, 2015.	☐
	42	U.S. Appl. No. 15/058,056, filed Mar. 1, 2016.	☐
	43	U.S. Appl. No. 15/144,191, filed May 2, 2016.	☐
	44	U.S. Appl. No. 15/398,398, filed Jan. 4, 2017.	☐
	45	U.S. Appl. No. 15/342,448, filed Nov. 3, 2016.	☐
	46	U.S. Appl. No. 15/438,406, filed Feb. 21, 2017.	☐
	47	U.S. Appl. No. 15/438,458, filed Feb. 21, 2017.	☐
	48	U.S. Appl. No. 15/634,776, filed Jun. 27, 2017.	☐

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	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

	49	U.S. Appl. No. 15/672,228, filed Aug. 8, 2017.	☐
	50	PCT/US02/32542, Oct. 11, 2002.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/SAN MING R HUI/	Date Considered	12/28/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	First Named Inventor	Alexander Mark Schobel
	Art Unit	1617
	Examiner Name	S. M. R. Hui
	Attorney Docket Number	270712-480541

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. # 41,498/	Date (YYYY-MM-DD)	2023-07-21
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Web Search History

date, time	web site	search string
12/28/2023 10:46:44 PM	Google Scholar	dipivefrin
12/28/2023 10:46:52 PM	Google Scholar	dipivefrin conversion
12/28/2023 10:46:57 PM	Google Scholar	dipivefrin prodrug
12/28/2023 10:47:01 PM	Google Scholar	dipivefrin intranasal
12/28/2023 10:47:17 PM	Google Scholar	dipivefrin anaphylaxis
12/28/2023 10:47:26 PM	Google Scholar	dipivefrin epinephrine anaphylaxis
12/28/2023 10:47:32 PM	Google Scholar	dipivefrin clove oil
12/28/2023 10:47:39 PM	Google Scholar	dipivefrin clove oil intranasal
12/28/2023 10:47:54 PM	Google Scholar	dipivefrin "clove oil" intranasal
12/28/2023 10:48:03 PM	Google Scholar	epinephrine "clove oil" intranasal
12/28/2023 10:56:24 PM	Google Patents	Search Term 1 (dipivefrin)
12/28/2023 10:56:30 PM	Google Patents	Search Term 1 (dipivefrin intranasal)
12/28/2023 10:56:34 PM	Google Patents	Search Term 1 (dipivefrin intranasal matrix)

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Request for Continued Examination (RCE) Transmittal

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/086,409
Filing Date	2020-11-01
First Named Inventor	Alexander Mark Schobel
Art Unit	1627
Examiner Name	SAN MING R HUI
Attorney Docket Number	270712/AQU-039US/480541

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-3145 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Harold H. Fox, Reg. # 41,498/	Date	2024-07-02
Name (Print/Type)	Harold H. Fox, PhD.	Registration No.	41,498

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature	/Tabitha Huschilt/		
Name (Print/Type)	Tabitha Huschilt	Date	2024-07-02

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Alexander Mark SCHOBEL et al.
Application No.: 17/086,409
Filing Date: November 1, 2020
Art Unit No.: 1627
Examiner: HUI, SAN MING R
Confirmation No.: 1047

For: PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO OFFICE ACTION OF JANUARY 4, 2024

In response to the Final office action dated January 4, 2024 ("Office Action"), Applicant submits the following amendments and remarks.

IN THE CLAIMS:

The listing of claims replaces all prior versions and listings of claims in the application.

1. (Currently amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine and a permeation enhancer from a matrix wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight to the human subject in need of treatment for the allergic reaction;

the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

2. (Cancelled)

3. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight.

4. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50 by weight.

5. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight.

6. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

7. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

8. (Original) The method of claim 1, further including administering a pharmaceutically active ingredient with the prodrug.

9. (Currently Amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine from a matrix to the human subject in need of treatment for the allergic reaction;

delivering the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

10. (Original) The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by % weight.

11. (Original) The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by % weight.

12. (Original) The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.

13. (Original) The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight

14. (Original) The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.

15. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.

16. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.

17. (Original) The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

18. (Original) The method of claim 1, wherein prodrug has particle size of no more than 100 microns.

19. (Original) The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

20. (Original) The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.

21. (Original) The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

22. (Original) The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

23. (Withdrawn) The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

24. (Withdrawn) The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

25. (Original) The method of claim 1, wherein the prodrug includes an ester of epinephrine.

26. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 240 minutes.

27. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 120 minutes.

28. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 60 minutes.

29. (Previously Presented) The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of 20 pg/ml to about 40 ng/ml of active compound in a period of less than 120 minutes.

30. (Original) The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

31. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.

32. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

33. (Original) The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.

34. (Original) The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.

35. (Original) The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.

36. (Original) The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.

37.-40. (Cancelled)

42. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.

43. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

44. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a chavicol.

45. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a safrole.

46. (Original) The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.

47. (Withdrawn) The method of claim 1, wherein the permeation enhancer is synthetic.

48. (Withdrawn) The method of claim 1, wherein the permeation enhancer is biosynthetic.

49. (Original) The method of claim 1, wherein the permeation enhancer is natural.

50. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes 50-95% eugenol.

51. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or a sesquiterpene.

52. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.

53. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes farnesol.

54. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a self-emulsifying excipient.

55. (Original) The method of claim 1, wherein the matrix includes a mucoadhesive water soluble polymer.

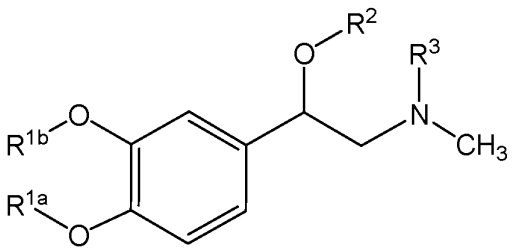
56. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes linoleic acid.

57. (Withdrawn) The method of claim 1, wherein the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.

58. (Original) The method of claim 1, wherein one of the prodrugs is dipifevrin.

59. (Withdrawn) The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

60. (Original) The method of claim 1, wherein the prodrug is a compound of formula (I), wherein



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

61. (Original) The method of claim 60, wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

62. (Currently Amended) A method of treating an allergic reaction comprising

administering a prodrug from a matrix to a subject in need of treatment for the allergic reaction, the prodrug of epinephrine being converted to provide a concentration of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes.

63. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes.

64. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 100 minutes.

65. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 60 minutes.

66. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 45 minutes.

67. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 ng/ml of active compound in less than 30 minutes.

68. (Original) The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml.

69. (Original) The method of claim 62, further including administering a pharmaceutically active ingredient with the prodrug.

70. (Original) The method of claim 62 in which less than 100% of the prodrug is converted.

71. (Original) The method of claim 62 in which 100% of the prodrug is converted.

72. (Currently Amended) A method of treating an allergic reaction comprising administering a prodrug to a subject in need of treatment for the allergic reaction, the prodrug of epinephrine converting to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 240 minutes.

73. (Original) The method of claim 72 in which less than 100% of the prodrug is converted.

74. (Original) The method of claim 72 in which 100% of the prodrug is converted.

75. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 15 minutes.

76. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 30 minutes.

77. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hours.

78. (Original) The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 4 hours.

REMARKS

Claims 1, 3-36 and 42-78 are pending. Claims 1, 9, 62 and 72 have been amended for clarification. Support can be found throughout the specification and claims as filed, e.g., at [para. 0034]. No new matter has been added and no new issues have been raised.

Rejections under U.S.C. §103

Claims 1-22, 25-41, 46, 49, 55, 58, and 60-78 were rejected under 35 U.S.C. §103 as being unpatentable over US 10,806,709 ("Fleming") in view of US2017/0290776 ("Schobel")

The '709 reference is directed lowering the epinephrine loading dose by addition of a reversible topically-acting COMT inhibitor (to prevent epinephrine enzymatic degradation at the nasal mucosa), which is co-administered with a low dose of a topically-acting vasodilator (phentolamine, to stop inhibition of mucosal transport by gross vasodilation) with epinephrine at the same time in the same dose. The Examiner concluded that the '709 reference does not teach the claimed concentration of permeation enhancers or the claimed pharmacokinetic properties of the dipivefrin composition.

The '776 reference teaches a general pharmaceutical composition and e.g., 3% clove oil. However, this reference does not specifically teach treating an allergic reaction.

The pharmaceutical field is complex and unpredictable. There is nothing in any of the cited references that would have motivated a person of ordinary skill to modify the references and arrive at the claimed subject matter, let alone the claimed pharmacokinetic properties of the dipivefrin composition. This is particularly true for epinephrine. Conventionally, the systemic administration of epinephrine was limited by the fact that it causes vasoconstriction, which limits the effectiveness of its delivery. It was not until Applicants' work that such delivery was effectively carried out. The claimed subject matter relies on a permeation enhancer promoting permeation of a prodrug through a mucosal tissue to achieve an effective plasma concentration of a drug.

For at least these reasons, the claims are not obvious over the cited references. Applicants respectfully request withdrawal of this ground of rejection.

Non-Statutory Double Patenting

Claims 1-22, 25-41, 46, 49, 55, 58, and 60-78 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24, 40-60 of copending Application No. 17/576,923 in view of Schobel.

This rejection is provisional, and will be addressed when the claims are deemed allowable.

CONCLUSION

For at least the reasons set forth above, Applicant respectfully submits that all grounds for patentability are met in the pending claims. Please apply any necessary charges or credits to deposit account 50-3145. Should the Examiner deem that any further action by the Applicant would be desirable to place this application in even better condition for issue, the Examiner is invited to telephone Applicant's undersigned representative.

Respectfully submitted,

Date: July 2, 2024

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/086,409	11/01/2020	Alexander Mark Schobel	270712/ AQU-039US/480541	1047

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/01/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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hfox@honigman.com
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Office Action Summary	Application No. 17/086,409	Applicant(s) Schobel et al.	
	Examiner SAN MING R HUI	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,3-22,25-41,46,49,55,58 and 60-78 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3-22,25-41,46,49,55,58 and 60-78 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/2/2024 has been entered.

Claims 1, 3-36, 42-78 are pending.

Claims 23-24, 42-45, 47, 48, 50-54, 56-57, 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/2023.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 1, 3-22, 25-41, 46, 49, 55, 58, 60-78 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 10,806,709 ('709) in view of US2017/0290776 ('776).

'709 teaches a method of treating anaphylaxis by administering anti-anaphylactic agents, including dipivefrin, intranasally (see the abstract, col. 9, line 20 for example). '709 teaches the

particle size of the active as 20-50μm (see col. 16, lines 3-16). '709 teaches penetration or permeation enhancers being included to facilitate the absorption of the anti-anaphylactic agent in the amount of 1-30% (see col. 10, line 52 bridging col. 12, line 13). The dosage of the epinephrine in the instant invention is 0.05mg to 10mg (see claim 9). '709 teaches the volume intended to be administered as 100μl (see col. 26, lines 30-34). The examiner notes that the ratio between the actives and the permeation enhancing agent would meet the limitations of claims 2-7.

'709 does not expressly teach the permeation enhancer as the extract of a clove plant. '709 does not expressly teach the concentration of the permeation enhancer in the matrix. '709 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably

expected to impart beneficial effect for the dipivefrin composition. The examiner notes that the penetration enhancers is taught to be 3% in amount and the anti-anaphylactic agents to be 1-30% in amount. Accordingly, ratio between the penetration enhancer/ anti-anaphylactic agents (i.e., dipifevrin/epinephrine) meets the limitation recited in claim 1.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where

the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the

form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1-22, 25-41, 46, 49, 55, 58, 60-78 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24, 40-60 of copending Application No. 17/576,923 ('923) in view of '776.

'923 teaches a method of treating allergic reaction using epinephrine and its prodrug (see claims 1 and 38 for example). '923 teaches the Cmax and Tmax properties of the administration of the epinephrine/prodrug composition (see claims 59-60).

'923 does not expressly teach the permeation enhancer as the extract of a clove plant. '923 does not expressly teach the concentration of the permeation enhancer in the matrix. '923 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-allergic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the adjustment of penetration enhancer amount would produce the desired serum concentration of the active agent and thereby treating the allergic condition.

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

This is a provisional nonstatutory double patenting rejection.

Response to Arguments

Applicant's arguments filed 7/2/2024 averring the cited prior art's failure to teach the treatment of an allergic reaction, have been considered, but are not found persuasive. The examiner notes that '709 teaches a method of treating anaphylaxis by administering anti-anaphylactic agents, including dipivefrin. Therefore, the patient being treated in '709 is indeed in need of the treatment for the allergic reaction. Accordingly, the claims are properly rejected under 35 USC 103a.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN MING R HUI whose telephone number is (571)272-0626. The examiner can normally be reached Mon - Fri 9:30-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached on 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format.

For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAN MING R HUI/
Primary Examiner, Art Unit 1627

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L37	7088	Dipivefrin	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L38	98440	anaphylaxis	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L39	39	6 SAME 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L40	617	6 SAME (allergy OR allergic)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2024/07/15 09:37 AM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L41	295	6 AND 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L42	7	6 NEAR 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L43	182	6 AND 7 AND intranasal	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2024/07/15 09:37 AM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L44	240166	(A61K31/24 OR A61K47/10 OR A61K9/006 OR A61K9/7007 OR A61K31/222).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L45	17	15 AND 16	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L46	67374	clove ADJ oil	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L47	5696385	penetration OR permeation	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2024/07/15 09:37 AM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L48	1003	19 SAME 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L49	168	19 SAME 18 AND (intranasal OR transmucosal)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L50	77	19 near4 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN,	OR	ON	ON	2024/07/15 09:37 AM

			WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
7/27/2024 2:41:44 AM	Google Scholar	dipivefrin mechanism
7/27/2024 2:41:51 AM	Google Scholar	dipivefrin conversion
7/27/2024 2:41:57 AM	Google Scholar	dipivefrin prodrug
7/27/2024 2:42:02 AM	Google Scholar	dipivefrin intranasal
7/27/2024 2:42:14 AM	Google Scholar	dipivefrin clove oil

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Alexander Mark SCHOBEL et al.	**Art Unit No.:** 1627
Application No.: 17/086,409	**Examiner:** HUI, SAN MING R
Filing Date: November 1, 2020	**Confirmation No.:** 1047

For: PRODRUG COMPOSITIONS AND METHODS OF TREATMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO OFFICE ACTION OF AUGUST 1, 2024

In response to the Non-Final office action dated August 1, 2024 ("Office Action"), Applicant submits the following amendments and remarks.

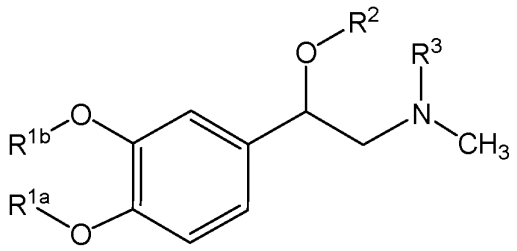
IN THE CLAIMS:

The listing of claims replaces all prior versions and listings of claims in the application.

1. (Currently amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine and a permeation enhancer from a matrix wherein the matrix has a permeation enhancer to prodrug ratio is 1000:1 to 1:1000 by weight to the human subject in need of treatment for the allergic reaction;

wherein the prodrug is a compound of formula (I)



(I)

wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl,

the permeation enhancer promoting permeation of the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour.

2. (Cancelled)

3. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 100:1 to 1:100 by weight.

4. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:50 by weight.

5. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 1:1 by weight.

6. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 50:1 to 10:1 by weight.

7. (Original) The method of claim 1, wherein the permeation enhancer to prodrug ratio is 10:1 to 1:10 by weight.

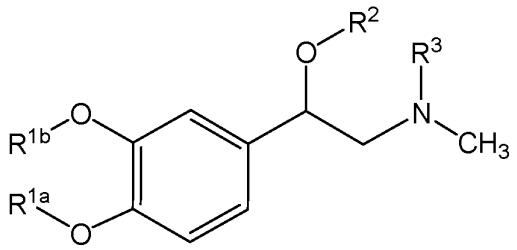
8. (Original) The method of claim 1, further including administering a pharmaceutically active ingredient with the prodrug.

9. (Currently Amended) A method of treating an allergic reaction in a human subject comprising:

administering a composition including a prodrug of epinephrine from a matrix to the human subject in need of treatment for the allergic reaction;

delivering the prodrug through a mucosal tissue to achieve an effective plasma concentration of a pharmaceutically active form of the prodrug in the human subject in less than one hour,

wherein the prodrug is a compound of formula (I)



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together,

R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

10. (Original) The method of claim 1, wherein the prodrug comprises 0.01-90% of the matrix by % weight.

11. (Original) The method of claim 1, wherein the prodrug comprises 0.1-50% of the matrix by % weight.

12. (Original) The method of claim 1, wherein the permeation enhancer comprises 1-50% of the matrix by % weight.

13. (Original) The method of claim 1, wherein the permeation enhancer comprises 5-25% of the matrix by % weight

14. (Original) The method of claim 1, wherein the pharmaceutically active form of the prodrug has a Tmax of less than 240 minutes.

15. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 120 minutes.

16. (Original) The method of claim 1, wherein the prodrug has a Tmax of less than 60 minutes.

17. (Original) The method of claim 1, wherein the prodrug has a Cmax of 0.1 pg/ml-50,000 pg/ml.

18. (Original) The method of claim 1, wherein prodrug has particle size of no more than 100 microns.

19. (Original) The method of claim 1, wherein the prodrug and permeation enhancer concurrently penetrate the mucosal tissue.

20. (Original) The method of claim 1, wherein the prodrug is an ester of a pharmaceutically active form of the prodrug.

21. (Original) The method of claim 1, wherein the prodrug includes an alkyl ester of a pharmaceutically active form of the prodrug.

22. (Original) The method of claim 1, wherein the prodrug includes a butyl ester of a pharmaceutically active form of the prodrug.

23. (Withdrawn) The method of claim 1, wherein the prodrug includes an isopropyl ester pharmaceutically active form of the prodrug.

24. (Withdrawn) The method of claim 1, wherein the prodrug includes an ethyl ester pharmaceutically active form of the prodrug.

25. (Original) The method of claim 1, wherein the prodrug includes an ester of epinephrine.

26. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 240 minutes.

27. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 120 minutes.

28. (Previously Presented) The method of claim 1, wherein at least half of the administered prodrug is converted in less than 60 minutes.

29. (Previously Presented) The method of claim 1, wherein the prodrug converts to produce a concentration of active compound of 20 pg/ml to about 40 ng/ml of active compound in a period of less than 120 minutes.

30. (Original) The method of claim 1, wherein the matrix is applied as chewable or gelatin based dosage form, inhalation dosage form, capsule, lyophilized solid dosage unit, mist, powder, spray, liquid, gum, gel, cream, film or tablet.

31. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 90 minutes in an oral cavity.

32. (Original) The method of claim 1, wherein the matrix is pharmaceutical film as a residence time of less than 60 minutes in an oral cavity.

33. (Original) The method of claim 1, wherein the matrix is pharmaceutical film has a residence time of less than 15 minutes in an oral cavity.

34. (Original) The method of claim 1, wherein administering the prodrug stimulates one or more adrenergic receptors.

35. (Original) The method of claim 1, wherein administering the prodrug does not activate the alpha 1 adrenergic receptor.

36. (Original) The method of claim 1, wherein administering the prodrug minimizes a side effect of epigastric pain.

37.-40. (Cancelled)

42. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a eugenol or eugenol acetate.

43. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

44. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a chavicol.

45. (Withdrawn) The method of claim 1, wherein the phenylpropanoid is a safrole.

46. (Original) The method of claim 1, wherein the permeation enhancer includes an essential oil extract of a clove plant.

47. (Withdrawn) The method of claim 1, wherein the permeation enhancer is synthetic.

48. (Withdrawn) The method of claim 1, wherein the permeation enhancer is biosynthetic.

49. (Original) The method of claim 1, wherein the permeation enhancer is natural.

50. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes 50-95% eugenol.

51. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a terpenoid, terpene or a sesquiterpene.

52. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a benzyl alcohol.

53. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes farnesol.

54. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes a self-emulsifying excipient.

55. (Original) The method of claim 1, wherein the matrix includes a mucoadhesive water soluble polymer.

56. (Withdrawn) The method of claim 1, wherein the permeation enhancer includes linoleic acid.

57. (Withdrawn) The method of claim 1, wherein the composition including a prodrug includes more than one prodrug with each prodrug being a derivative of a pharmaceutically active ingredient.

58. (Original) The method of claim 1, wherein one of the prodrugs is dipifevrin.

59. (Withdrawn) The method of claim 54, wherein the first prodrug is a first ester of epinephrine and the second prodrug is a second ester of epinephrine, the first ester of epinephrine and the second ester of epinephrine being different.

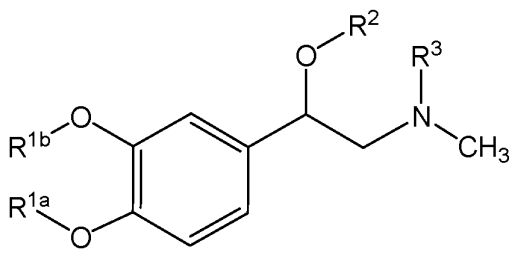
60. (Canceled)

61. (Currently Amended) The method of claim [[60]] 1, wherein R^2 and R^3 are H and each R^{1a} and R^{1b}, independently, is ethanoyl, n-propanoyl, isopropanoyl, n-butanoyl, isobutanoyl, sec-butanoyl, tert-butanoyl, n-pentanoyl, isopentanoyl, sec-pentanoyl, tert-pentanoyl, or neopentanoyl.

62. (Currently Amended) A method of treating an allergic reaction comprising

administering a prodrug from a matrix to a subject in need of treatment for the allergic reaction, the prodrug of epinephrine being converted to provide a concentration of 20 pg/ml to about 40 ng/ml of active compound in less than 240 minutes,

wherein the prodrug is a compound of formula (I)



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

63. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 120 minutes.

64. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 1200 pg/ml of active compound in less than 100 minutes.

65. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 60 minutes.

66. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 pg/ml of active compound in less than 45 minutes.

67. (Original) The method of claim 62, wherein the prodrug is converted to provide a concentration of 200 pg/ml to about 600 ng/ml of active compound in less than 30 minutes.

68. (Original) The method of claim 62, wherein the prodrug converts to create a sustained concentration of 200 pg/ml to about 600 pg/ml.

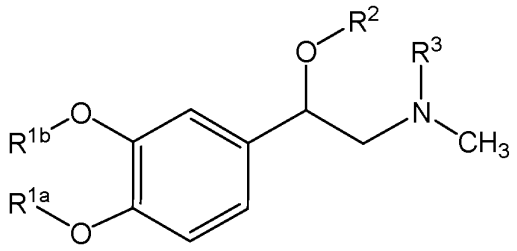
69. (Original) The method of claim 62, further including administering a pharmaceutically active ingredient with the prodrug.

70. (Original) The method of claim 62 in which less than 100% of the prodrug is converted.

71. (Original) The method of claim 62 in which 100% of the prodrug is converted.

72. (Current Amended) A method of treating an allergic reaction comprising administering a prodrug to a subject in need of treatment for the allergic reaction, the prodrug of epinephrine converting to produce a concentration of active compound of between 20 pg/ml to about 40 ng/ml in a period of less than 240 minutes,

wherein the prodrug is a compound of formula (I)



(I)

each of R^{1a}, R^{1b}, R^2 and R^3, independently, can be H, C1-C16 acyl, alkyl aminocarbonyl, alkyloxycarbonyl, phenacyl, sulfate or phosphate, or R^{1a} and R^{1b} together, R^{1a} and R^2 together, R^{1a} and R^3 together, R^{1b} and R^2 together, R^{1b} and R^3 together, or R^2 and R^3 together form a cyclic structure including a dicarbonyl, disulfate or diphosphate moiety, provided that one of R^1, R^2 and R^3 is not H, or a pharmaceutically acceptable salt thereof.

73. (Original) The method of claim 72 in which less than 100% of the prodrug is converted.

74. (Original) The method of claim 72 in which 100% of the prodrug is converted.

75. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 15 minutes.

76. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 30 minutes.

77. (Original) The method of claim 59, wherein prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 1 hours.

78. (Original) The method of claim 59, wherein the prodrug produced therapeutic levels over 100 pg/ml of epinephrine for a duration of at least 4 hours.

REMARKS

Claims 1, 3-36 and 42-78 are pending. Claim 1, 9, 61, 62 and 72 have been amended for clarification. Claim 60 has been canceled without prejudice.

Support can be found throughout the specification and claims as filed. No new matter has been added and no new issues have been raised.

Applicant notes box 5 of the Office Action states claims 1, 3-22, 25-42, 46, 49, 55, 58, and 60-78 are pending and box 5a does not list any withdrawn claims. As claims 1, 3-36, and 42-78 remain pending in the application and claims 23-24, 42-45, 47-48, 50-54, 56-57, and 59 have been withdrawn from consideration applicant believes this is merely a typographical error. Corrective action is requested in the next communication.

Rejections under U.S.C. §103

Claims 1, 3-22, 25-41, 46, 49, 55, 58, 60-78 were rejected under 35 U.S.C. §103 as being unpatentable over US 10,806,709 ("Fleming") in view of US2017/0290776 ("Schobel").

Fleming does not teach or suggest a prodrug of epinephrine and teaches a composition with epinephrine itself.

For at least these reasons, the claims are not obvious over the cited references. Applicants respectfully request withdrawal of this ground of rejection.

Non-Statutory Double Patenting

Claims 1-22, 25-41, 46, 49, 55, 58, 60-78 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24, 40-60 of copending Application No. 17/576,923 in view of Schobel.

Not in acquiescence, but to advance prosecution, the claims have been amended thereby mooting this rejection.

Moreover, as this rejection is provisional, Applicants will address it when the claims are deemed allowable.

CONCLUSION

For at least the reasons set forth above, Applicant respectfully submits that all grounds for patentability are met in the pending claims. Please apply any necessary charges or credits to

deposit account 50-3145. Should the Examiner deem that any further action by the Applicant would be desirable to place this application in even better condition for issue, the Examiner is invited to telephone Applicant's undersigned representative.

Respectfully submitted,

Date: January 31, 2025

/Harold H. Fox, Reg. # 41,498/
Harold H. Fox
Reg. No. 41,498

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/086,409	11/01/2020	Alexander Mark Schobel	270712/ AQU-039US/480541	1047

138831 7590 05/15/2025

Honigman LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/15/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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hfox@honigman.com
patent@honigman.com

Office Action Summary	**Application No.** 17/086,409	**Applicant(s)** Schobel et al.	
	Examiner SAN MING R HUI	**Art Unit** 1627	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/31/2025.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,3-36,42-59 and 61-78 is/are pending in the application.

5a) Of the above claim(s) 23-24,42-45,47-48,50-54,56-57 and 59 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3-22,25-36,46,49,55,58 and 61-78 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's amendments filed 1/31/2025 have been entered.

Claims 1, 3-36, 42-59, 61-78 are pending.

Claims 23, 24, 42-45, 47, 48, 50-54, 56, 57, 59 are withdrawn from further consideration as non-elected specie. Election was made **without** traverse in the reply filed on 3/29/2023.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 1, 3-22, 25-36, 46, 49, 55, 58, 61-78 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 10,806,709 ('709) in view of US2017/0290776 ('776).

'709 teaches a method of treating anaphylaxis by administering anti-anaphylactic agents, including dipivefrin, intranasally (see the abstract, col. 9, line 20 for example). '709 teaches the particle size of the active as 20-50μm (see col. 16, lines 3-16). '709 teaches penetration or permeation enhancers being included to facilitate the absorption of the anti-anaphylactic agent in the amount of 1-30% (see col. 10, line 52 bridging col. 12, line 13). The dosage of the epinephrine in the instant invention is 0.05mg to 10mg (see claim 9). '709 teaches the volume intended to be administered as 100μl (see col. 26, lines 30-34). The examiner notes that the ratio between the actives and the permeation enhancing agent would meet the limitations of claims 2-7.

'709 does not expressly teach the permeation enhancer as the extract of a clove plant. '709 does not expressly teach the concentration of the permeation enhancer in the matrix. '709 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition. The examiner notes that the penetration enhancers is taught to be 3% in amount and the anti-anaphylactic agents to be 1-30% in amount. Accordingly, ratio between the penetration enhancer/ anti-anaphylactic agents (i.e., dipifevrin/epinephrine) meets the limitation recited in claim 1.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to

control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761

(CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1, 3-22, 25-36, 46, 49, 55, 58, 61-78 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16, 18, 21, 22, 24, 40-60 of copending Application No. 17/576,923 ('923) in view of '776.

'923 teaches a method of treating allergic reaction using epinephrine and its prodrug (see claims 1 and 38 for example). '923 teaches the Cmax and Tmax properties of the administration of the epinephrine/prodrug composition (see claims 59-60).

'923 does not expressly teach the permeation enhancer as the extract of a clove plant. '923 does not expressly teach the concentration of the permeation enhancer in the matrix. '923 does not expressly teach the herein claimed pharmacokinetic properties of the dipivefrin composition (e.g., Cmax, Tmax, the conversion time).

'776 teaches mucosal permeation systems for delivering an adrenergic-receptor modulators such as epinephrine (see for example claims and 19). '776 teaches a permeation enhancer as clove oil from clove leaf, bud, and/or stem (see Fig. 11 and example 1 for example). '776 teaches 3% of clove oil (see for example [0178]). '776 teaches the matrix comprising a water soluble polymer (see for example claim 21). '776 also teaches the pharmaceutical dosage form includes film (see claim 23).

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-anaphylactic dipivefrin composition. It would have been obvious to one of ordinary skill in the art to adjust the Cmax and Tmax of the dipivefrin composition.

One of ordinary skill in the art would have been motivated to incorporate the extract of clove plant as permeation enhancer and a matrix into the anti-allergic dipivefrin composition. Since the penetration/permeation enhancers are known to be suitable and compatible with adrenergic modulator such as epinephrine for transmucosal administration, incorporating the extract of clove

plant such as clove oil and the matrix of water-soluble polymer would be reasonably expected to impart beneficial effect for the dipivefrin composition.

One of ordinary skill in the art would have been motivated to adjust the Cmax and Tmax of the dipivefrin composition. By adjusting the amount of the matrix would be reasonably expected to control the rate of the release and thereby the Cmax and Tmax. Therefore, the optimization of result effect parameters (e.g, amount of the excipients that affect the Cmax and Tmax) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the adjustment of penetration enhancer amount would produce the desired serum concentration of the active agent and thereby treating the allergic condition.

In addition, the herein claimed pharmacological and pharmacokinetic properties such as how fast the conversion from prodrug to active or whether the prodrug activate or not activate certain receptors is considered as an intrinsic property of the prodrug.

This is a provisional nonstatutory double patenting rejection.

Response to Arguments

Applicant's arguments filed 1/31/2025 averring the cited prior art's failure to teach the prodrug dipivefrin have been fully considered but they are not persuasive. The examiner notes that '709 clearly teaches the anti-anaphylactic agents epinephrine derivative include dipivefrin. Employing dipivefrin in the nasal composition would be reasonably expected to be effective in treating anaphylaxis.

Applicant's remarks with regard to the provisional double patenting rejection are acknowledged. Accordingly, the rejection is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any nonprovisional extension fee (37 CFR 1.17(a)) pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN MING R HUI whose telephone number is (571)272-0626. The examiner can normally be reached Mon - Fri 9:30-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAN MING R HUI/
Primary Examiner, Art Unit 1627

Web Search History

date, time	web site	search string
5/12/2025 4:19:09 PM	Google Scholar	dipivefrin anaphylaxis
5/12/2025 4:21:46 PM	Google Scholar	dipivefrin anaphylaxis intranasal
5/12/2025 4:21:49 PM	Google Scholar	dipivefrin intranasal
5/12/2025 4:21:53 PM	Google Scholar	dipivefrin pharmacokinetics
5/12/2025 4:21:58 PM	Google Scholar	dipivefrin pharmacokinetics intranasal
5/12/2025 4:22:11 PM	Google Scholar	dipivefrin pharmacokinetics intranasal penetration enhancer

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L37	7088	Dipivefrin	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L38	98440	anaphylaxis	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L39	39	6 SAME 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L40	617	6 SAME (allergy OR allergic)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2024/07/15 09:37 AM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L41	295	6 AND 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L42	7	6 NEAR 7	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L43	182	6 AND 7 AND intranasal	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2024/07/15 09:37 AM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L44	240166	(A61K31/24 OR A61K47/10 OR A61K9/006 OR A61K9/7007 OR A61K31/222).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L45	17	15 AND 16	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L46	67374	clove ADJ oil	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L47	5696385	penetration OR permeation	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2024/07/15 09:37 AM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L48	1003	19 SAME 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L49	168	19 SAME 18 AND (intranasal OR transmucosal)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/15 09:37 AM
L50	77	19 near4 18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN,	OR	ON	ON	2024/07/15 09:37 AM

			WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.